AMERICAN HEALTH CONSULTANTS®

Providing Evidence-based Clinical Information for 21 Years

CLINICAL CARDIOLOGY ALERT

A monthly update of developments in cardiovascular disease

American Health Consultants Home Page—http://www.ahcpub.com

CME for Physicians—http://www.cmeweb.com

C-Reactive Protein Hits the Big Time

ABSTRACT & COMMENTARY

THERE HAS BEEN A DRUM ROLL OF REPORTS OVER THE PAST SEVeral years regarding high-sensitivity c-reactive protein (hs-CRP) in the evaluation of primary and secondary cardiovascular prevention. Driven by the remarkable output of reports from Paul Ridker, MD, of the Brigham and Women's Hospital at Harvard, many data indicate that measurement of this stable protein should be of use in the risk assessment of patients with and without coronary artery disease (CAD). Many studies have indicated that hs-CRP levels are independently predictive of CAD events in diverse patient populations and in apparently healthy individuals. The robust hs-CRP data have been highly consistent in relating an elevated level to subsequent cardiovascular events.

A recent report from the January 21, 2003, issue of *Circulation* correlates the elevation with exercise-induced ischemia. In the same issue, there is a study suggesting that statins reduce cardiovascular deaths in those with high CRPs and positive serology for cytomegalic virus.[1] Two important studies from Ridker's group include a long-term evaluation of women with metabolic syndrome, where CRP measurement "adds clinically important prognostic information," indicating an interaction between inflammatory markers and outcome in individuals who meet the criteria for this high-risk condition.[2] In another important observation, a study of 28,000 healthy subjects in the Women's Health Study with a mean 8-year follow-up, CRP levels were predictive of vascular events, even more so than LDL cholesterol.[3] Furthermore, the data suggest that women who had a below-median LDL level and an elevated CRP (> 3 mg/L) had a greater hazard than an elevated LDL without an elevation of CRP. The combination of a high CRP and high LDL had the worst outcome, whereas a low LDL and low CRP (< 1 mg/L) had the best prognosis.

In Ridker's expert opinion mini-review, he concludes that CRP levels should be part and parcel of everyday practice. In healthy populations, "the primary use of CRP should be at the time of cholesterol screening . . . as an adjunct of global risk assessment."[4] He suggests that low and intermediate levels of LDL cholesterol and an ele-

VOLUME 22 • NUMBER 3 • MARCH 2003 • PAGES 17-24

INSIDE

vated CRP increase the long-term risk of healthy individuals, and this should influence the aggressiveness of risk factor interventions, including lifestyle changes, as well as pharmacotherapy. He suggests an alternative approach to only measure CRP in individuals felt to be at an intermediate risk (eg, 5-20% cardiac event 10-year Framingham Risk Score). He reports on increasing use of CRP measurements in the emergency room setting in individuals with chest pain syndromes and negative troponin, citing literature evidence that an elevated CRP in such an environment is associated with an increased risk of events.

In the same issue of *Circulation*, an important Task Force report from the AHA/CDC workshop on Inflammatory Markers and Cardiovascular Disease—Applications to Clinical and Public Health Practice was published.[5] This workshop was held almost 1 year ago, focusing on inflammatory markers and cardiovascular disease and dealing with a wide variety of issues in this emerging area. The new document reports the major findings and conclusions of the workshop with more information coming in future publications. A writing group of the workshop members reviewed the evidence that inflammation is a key pathophysiologic phenomenon in atherosclerosis, and they reviewed the vascular aspects of this process, which involves activation of cytokines and other bioactive substances related to inflammation at all levels of the atherogenic process. While there are a wide variety of pro-inflammatory risk factors that can be measured, the Task Force concluded that hs-CRP is "far and away the best and the most reliable substance that can be used outside of the research laboratory." They go on to ask whether CRP is a risk marker or risk factor; they reach no conclusion. However, it seems clear from data in the literature that an elevated CRP is an active factor increasing vascular events. The Task Force concludes that there is a risk increase of 2-fold in individuals for major coronary events in populations that are at the highest tertile of CRP levels (> 3 mg/L).

They cite a "dose-response relationship between the level of hs-CRP and the risk of incident heart disease," and emphasize that there are data that suggest a relationship between the inflammatory marker and sudden death and peripheral arterial disease and that hs-CRP levels are predictive in men and women, in the elderly as well as the young. It should be pointed out that ethnic minorities, particularly blacks, are not well represented in the overall CRP database, and more research needs to be done in these individuals. The Task Force lists a variety of CVD events and death that are associated with elevated CRP, including unstable angina and acute myocardial infarction. A high CRP may be a marker for restenosis following PCI and may predict stroke. Increased body weight and the metabolic syndrome are associated with an increased CRP, as are some of the classic CAD risk factors, including hypertension, cigarette smoking, metabolic syndrome, diabetes, female hormonal state, and chronic infections and inflammatory processes. There is ample evidence to recommend obtaining a hs-CRP as a marker of risk in individuals at intermediate risk by global assessment (ie, 10-20% risk of CAD over a 10-year period). This approach has been given a IIa rating. The group report recommends that individuals with stable or unstable coronary syndromes might benefit from measurements of hs-CRP as an "independent marker of prognosis for recurrent events, including death and MI, and restenosis after PCI." Last, they stress that the CRP measurements in patients with established vascular disease may not have significant clinical value in terms of choice of therapy, other than by perhaps underscoring a more aggressive approach to risk factor modification.

The Task Force recommends obtaining 2 CRP measurements, similar to cholesterol guidelines, to make sure that individuals do not have a systemic inflammatory condition, trauma, or active infection. They stress that levels > 10 mg/L should be disregarded and to look for nonvascular infection or inflammation in such individu-

Clinical Cardiology Alert, ISSN 0741-4218, is published monthly by American Health Consultants, 3525 Piedmont Rd., NE, Bldg. 6, Suite 400, Atlanta, GA 30305.

VICE PRESIDENT/GROUP PUBLISHER: Brenda Mooney.
EDITORIAL GROUP HEAD: Glen Harris.
MANAGING EDITOR: Robin Mason.
ASSISTANT MANAGING EDITOR: Robert Kimball.
SENIOR COPY EDITOR: Christie Messina.
MARKETING PRODUCT MANAGER: Schandale Kornegay.

GST Registration Number: R128870672.

Periodicals postage paid at Atlanta, GA.

POSTMASTER: Send address changes to ***Clinical Cardiology Alert,*** P.O. Box 740059, Atlanta, GA 30374.

Back issues: $40. Missing issues will be fulfilled by Customer Service free of charge when contacted within one month of the missing issue's date.

THOMSON
AMERICAN HEALTH CONSULTANTS™

Subscriber Information

Customer Service: 1-800-688-2421.
Customer Service E-Mail: customerservice@ahcpub.com
Editorial E-Mail: christie.messina@ahcpub.com

Subscription Prices

United States
1 year *with* Free AMA Category 1 credits: $287
(Student/Resident rate: $145).
Multiple Copies
2-9 additional copies: $213 each. 10 or more copies: $190 each.
Canada
Add GST and $30 shipping.
Elsewhere
Add $30 shipping.

Accreditation

American Health Consultants (AHC) designates this educational activity for a maximum of 25 hours in category 1 credit toward the AMA Physician's Recognition Award. Each physician should claim only those credits that he/she actually spent in the activity.

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

AHC is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

Questions & Comments

Please call **Robin Mason,** Managing Editor, at (404) 262-5517, or **Christie Messina**, Senior Copy Editor, at (404) 262-5416 or e-mail at christie.messina@ahcpub.com between 8:30 a.m. and 4:30 p.m. ET, Monday-Friday.

Statement of Financial Disclosure

In order to reveal any potential bias in this publication, and in accordance with Accreditation Council for Continuing Medical Education guidelines, we disclose that Dr. Abrams serves on the speaker's bureau for Merck, Pfizer, and Parke-Davis. Dr. DiMarco is a consultant for Bayer and Novartis, is on the speaker's bureau for Medtronic and Guidant, and does research for Medtronic and Guidant. Drs. Crawford and Vernon report no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study.

als. In clinical practice, CRP should be best used to assist risk assessment in individuals being considered for lipid-lowering, antiplatelet, or other drug therapies, as well as recommendations for an enhanced emphasis on lifestyle modifications. Several studies suggest that patients with elevated hs-CRP vs normal levels may enjoy a greater actual risk reduction from targeted pharmacotherapy, including aspirin and statins. "The writing group endorses the optional use of hs-CRP to identify patients without known CVD who may be at higher absolute risk than estimated by major risk factors, specifically, those with an intermediate 10-20% 10-year CAD risk." They emphasize that traditional cardiovascular risk factors must be assessed prior to hs-CRP determination, which they accept as "an independent predictor of increased coronary risk." Also, the writing group concurs with Ridker that the use of CRP testing in individuals with established vascular disease is uncertain and at the present time does not seem to be of obvious benefit. Finally, the writing group cites the "striking lack of level A evidence" related to randomized clinical trials supporting CRP data (Beattie MS, et al. *Circulation*. 2003;107:245-250).

COMMENT BY JONATHAN ABRAMS, MD

While many questions remain, it appears that CRP has finally broken through the prevention community barrier against recommending this test for screening. However, the writing group "recommends against screening of the entire adult population," rather using the assay "as an adjunct to the major risk factors to further assess absolute risk for coronary disease primary prevention." Tightening of pharmacotherapy and enhancement of motivation are clearly major benefits derived from defining an individual at a high risk because of a CRP > 3 mg/L. The Task Force recommends the use of hs-CRP testing, albeit with a number of stipulations. Physicians should be certain that their hospital or laboratory uses one of the accredited devices; the cost, however, should be low, and the stability of the measurements are quite good, with relatively modest intra-individual variation over time. Finally, it behooves the physician to remember that what is being measured is one of a variety of inflammatory markers and to keep in mind that a low CRP value indicates little to no inflammation, whereas a high value (ie, > 3 mg/L) clearly indicates an ongoing inflammatory process, whether it be in the coronary arterial circulation, aorta, or elsewhere. Such observations should trigger extremely aggressive and sustained risk modification approachs to such individuals. ■

References

1. Horne BD, et al. *Circulation*. 2003;107:258-263.
2. Ridker PM, et al. *Circulation*. 2003;107:391-397.
3. Ridker PM, et al. *N Engl J Med*. 2002;347:1557-1565.
4. Ridker PM. *Circulation*. 2003;107:363-369.
5. Pearson TA, et al. *Circulation*. 2003;107:499-511.

Recommended Reading

1. Libby P. *Atherosclerosis: The New View. Scientific American*. 2002;286:46.

Coated Stents for In-Stent Restenosis

ABSTRACTS & COMMENTARY

Synopsis: *Sirolimus-eluting stents markedly reduce in-stent restenosis and clinical events over 1 year in patients with restenosis in conventional stents.*

Sources: Sousa JE, et al. *Circulation*. 2003;107:24-27; Degertekin M. *J Am Coll Cardiol*. 2003;41:184-189.

SIROLIMUS-ELUTING STENTS (SES) HAVE SHOWN much promise in reducing restenosis rates when implanted in de novo coronary lesions. However, in 2003, treating in-stent restenosis (ISR) remains a significant challenge in clinical practice, and, at present, little is known about the potential effects of drug-eluting stents on the prevention of recurrent restenosis or on clinical outcomes of patients receiving them for ISR. Reports from 2 small, nonrandomized patient series published last month begin to shed some light on this issue and raise questions about the efficacy of this technology when applied beyond the patient population studied in clinical trials.

Sousa and colleagues present outcomes from a pilot study of 25 consecutive patients with ISR who were treated with ≤ 2 18-mm slow-release (> 28-day) sirolimus-eluting Bx VELOCITY stents. This series excluded patients with lesions > 36 mm in length, lesions in saphenous vein grafts, and patients previously treated with intravascular brachytherapy. All patients were successfully treated with 1 (n = 16) or 2 (n = 9) SES. Antiplatelet therapy consisted of aspirin (ASA) given at least 12 hours preprocedure and indefinitely postprocedure, as well as clopidogrel 300 mg immediately postprocedure and then 75 mg/d for 60 days. Follow-up consisted of clinical evaluation, quantitative coronary angiography (QCA), and intravascular ultrasound (IVUS) at 4 and 12 months. In-stent and in-lesion (5 mm proximal to and 5 mm distal to stent margins)

segments were analyzed.

Of the patients studied, 80% were male, 24% were diabetic, and 20% had recurrent ISR. The treated lesion was classified as focal (≤ 10 mm) in 32%, diffuse intrastent in 40%, and diffuse proliferative (involvement extending beyond stented segment) in 28%. Angiographic follow-up revealed only 1 patient with (asymptomatic) ISR. The remainder of patients demonstrated only minimal decrease (0.36 ± 0.46 mm) in in-stent minimal luminal diameter (MLD) and essentially no change (0.16 ± 0.42 mm) in in-lesion MLD at 12-months. IVUS follow-up revealed only minimal neointimal proliferation with percent volume obstruction of 0.81 ± 1.7 and 1.76 ± 3.44, at 4 and 12 months respectively. At 1 year, no clinical events, including recurrent angina, stent thrombosis, repeat revascularization, or major adverse cardiac events (MACE), defined as myocardial infarction (MI), stroke, or death, were reported.

Sousa et al conclude that, despite the limitations of a small, nonrandomized cohort of patients and the absence of a control group, the results of this study are encouraging given good angiographic, IVUS, and clinical outcomes demonstrated in this patient group. They point out that a longer period of follow-up coupled with larger randomized, controlled trials will be necessary to determine whether this approach will yield acceptable results or represent an acceptable alternative to brachytherapy in the treatment of ISR.

Degertekin and colleagues studied 16 patients with ISR in a native coronary artery (> 2.5 mm and < 3.5 mm in diameter) and objective evidence of ischemia. This series included 4 patients previously treated with brachytherapy. All patients were successfully treated with up to 5 SES. Antiplatelet therapy consisted of ASA and clopidogrel 300 mg immediately postprocedure and then 75 mg/day for 2-4 months at the discretion of the operator. Follow-up consisted of QCA and IVUS evaluation of in-stent and in-lesion segments at 4 months and clinical evaluation at 9 months.

In this series, 75% of patients were male and 25% were diabetic. Four patients (25%) had recurrent ISR after intracoronary brachytherapy. The treated lesion was classified as focal (≤ 10 mm) in 3 patients, diffuse intrastent in 5 (31.2%), diffuse proliferative in 5 (31.2%), and total occlusion in 3 (18.7%). Nine patients received a single SES, 6 received 2 SES (1 of these procedures was felt to be unsuccessful) and 1 received a total of 5 SES for treatment of a total occlusion. QCA and IVUS follow-up were completed in 15 patients. Angiography revealed 3 patients with recurrent ISR, all of which were asymptomatic. One patient demonstrated total occlusion at follow-up after an initially unsuccessful procedure due to failure to achieve adequate stent expansion. The second patient demonstrated a 59% in-lesion stenosis in a gap between 2 SESs, and the third patient, a heart transplant recipient, developed 62% stenosis proximal to the stented segment in an uncovered area of balloon injury. Overall QCA analysis revealed a minimal decrease in in-stent and in-lesion MLD at 4 months (0.26 ± 0.67 mm and 0.21 ± 0.62 mm, respectively). IVUS follow-up revealed minimal neointimal proliferation with percent volume obstruction of 1.1 ± 2.6 at 4 months. Clinical follow-up at 9 months revealed 2 deaths and 1 Q-wave MI. One patient died suddenly 3.5 months after successful implantation of 2 SES in the right coronary artery. The other death occurred in a patient who had failed brachytherapy and who did not show evidence of ISR at follow-up and who died of congestive heart failure 9 months after the index procedure. The MI occurred in the patient who received 5 SES 7 months after the index procedure. Of interest, angiography showed total vessel occlusion, which resolved with thrombus aspiration, and IVUS revealed no neointimal proliferation within the stented segment.

Degertekin et al discuss similar limitations of their small observational study, as well as the need for data from larger, randomized clinical trials. They point out that their series of patients presented with extremely complex lesions at high risk for adverse procedural and clinical outcomes, including those previously treated with brachytherapy and those with occlusive ISR. Despite this, procedural and in-hospital outcomes were uneventful and overall low rates of neointimal proliferation by IVUS follow-up at 4 months were encouraging. They acknowledge that 1 patient death and 1 MI can likely be attributed to thrombotic events, raising questions about how antithrombotic therapy should be handled in this clinical scenario. They also point out the importance of scrupulous technique and probably IVUS guidance, when SES use is extended to higher-risk patient populations, as 2 of the adverse outcomes in this series may be attributable to technical issues such as gaps between stents and unstented areas of balloon injury.

COMMENT BY SARAH M. VERNON, MD

The first "coated stent," the Cordis/J & J Cypher (sirolimus-eluting Bx VELOCITY® stent) will likely be FDA-approved early in the second quarter of this year and is expected to be released for widespread clinical use immediately afterward. To say that this is a highly anticipated event in the interventional cardiology community would be an understatement. Based on the data from RAVEL and SIRIUS, expectations are high that

drug-eluting stents will significantly impact outcomes, namely restenosis rates, of coronary stenting and start a "revolution" that will "forever change" interventional cardiology, as we know it. While all of this may eventually prove to be true, it's probably somewhat premature to assume that coated stents will represent "the Holy Grail" for every patient, lesion subset, or indication that we encounter in clinical practice. These 2 recent reports of outcomes in patients receiving SES for ISR, though small and nonrandomized, are both encouraging and sobering. They remind us that we still have a lot to learn about what the imminent coated-stent technology will have to offer to patients in "real-life" clinical practice, many of whom, in this day and age, have very complex coronary artery disease indeed. We need to remember that we have good data about the efficacy of brachytherapy and extensive experience with CABG surgery, either of which may be a very acceptable strategy for a given patient with ISR. The remarkable results of RAVEL and SIRIUS should not be extrapolated to apply to many of the patients we encounter almost daily in clinical practice, not only those who already have ISR, but to those with ostial, calcified, total occlusion, bifurcation, or vein graft lesions to name a few. The "cat will be out of the bag" soon, and it's likely to be a good thing for interventional cardiologists and their patients as a whole. However, a coated stent may not be the answer for every patient referred to the cardiac catheterization laboratory. As was the case when the first Palmaz-Schatz stent was released for clinical use almost a decade ago, we still have a lot left to learn about patient and lesion selection, so that we can achieve the best possible outcomes that coated-stent technology will have to offer. ■

Risk of Arrhythmic Events in Asymptomatic Patients with Wolff-Parkinson-White Pattern

ABSTRACT & COMMENTARY

Synopsis: *In asymptomatic patients with preexcitation, electrophysiologic testing can stratify the risk of future symptomatic and fatal arrhythmic events.*

Source: Pappone C, et al. *J Am Coll Cardiol*. 2003;41: 239-244.

PAPPONE AND COLLEAGUES FROM MILAN, ITALY, report a prospective study on the natural history of asymptomatic patients with preexcitation. Pappone et al recruited 212 patients with asymptomatic preexcitation who had been discovered during a routine examination that was not performed because of symptoms. The age of enrollment ranged from 7 to 63 years with a mean age of 35.8 (± 20.5) years. Patients underwent an initial electrophysiologic study, which characterized the properties of the accessory pathway, the site(s) and number of accessory pathways present, and the ability to induce both atrioventricular reciprocating tachycardia (AVRT) and atrial fibrillation (AF). Patients were not specifically treated for arrhythmias. Patients were followed clinically off antiarrhythmic drugs after the baseline electrophysiologic study. Five years later, or earlier if symptoms or arrhythmias occurred, a second electrophysiologic study was performed.

Of the 212 original patients, 3 were lost to follow-up and 47 patients who remained asymptomatic refused repeat electrophysiologic study after 5 years. There were therefore 162 patients who completed the follow-up period and provided full data for this report. At initial study, 115 (71%) of the 162 patients had no inducible arrhythmia at the baseline study and 47 (29%) did have an inducible arrhythmia. Among the latter patients, 17 had nonsustained AF, 19 had sustained AVRT, and 11 had AVRT that degenerated into preexcited AF. Multiple accessory pathways or accessory pathway insertion sites were noted in 17 of the 212 patients (8%). The presence of multiple accessory pathways was strongly correlated (93%) with ability to induce arrhythmia. Among these 162 patients who had baseline and follow-up studies, 21 (13%) showed loss of all anterograde preexcitation on their surface ECG after 5 years. Retrograde conduction over the accessory pathway was lost in 35 of 115 patients who had no inducible arrhythmia at baseline but was never lost in those with inducible AVRT.

During 38 ± 16 months of follow-up, 33 of 162 patients (20%) became symptomatic due to arrhythmia. AVRT was noted in 25 patients and AF in 8 others. Among the 8 patients with AF during follow-up, 2 had aborted sudden death with documented ventricular fibrillation and 1 died suddenly with ventricular fibrillation. Patients who became symptomatic had a shorter anterograde effective refractory period of the accessory pathway and most, 29 of these 33 (87.8%), had manifest an inducible sustained AVRT at the baseline study. None of the 17 patients with only inducible nonsustained AF developed symptoms. Among the patients who did not have an inducible arrhythmia at the baseline study, only 4 of 115 ever developed symptoms with arrhythmia.

The 3 patients who developed VF during follow-up all had 2 accessory pathways and had also developed

symptoms (palpitations) before their episode of VF. Pappone et al examined electrophysiologic and clinical predictors of arrhythmia occurrence. An inducible arrhythmia at baseline study and a younger age were both significantly associated with risk of future arrhythmic events.

Pappone et al conclude that in asymptomatic patients with preexcitation, electrophysiologic testing can stratify the risk of future symptomatic and fatal arrhythmic events. Patients who are older and have no inducible arrhythmia are at very low risk for arrhythmic events up to 5 years follow-up. Patients who are younger and have an inducible arrhythmia, particularly if they have multiple accessory pathways, are at higher risk.

They suggest that these data should be used to guide the use of electrophysiologic studies in asymptomatic patients with preexcitation.

COMMENT BY JOHN DiMARCO, MD, PhD

The prevalence of preexcitation has been estimated to be 1-2 per 1000. Many of these patients come to medical attention when they have an electrocardiogram taken for some other reason and an incidental finding of preexcitation is made. This paper by Pappone et al, which focuses on asymptomatic individuals with preexcitation, should help us manage this clinical scenario.

There are several issues that should be addressed in dealing with asymptomatic patients with preexcitation. Although it is uncommon, sudden death can be the first manifestation of Wolff-Parkinson-White syndrome. The mechanism responsible is thought to usually be AVRT that degenerates to AF with rapid rates that then deteriorates further to ventricular fibrillation. The 3 factors that have been associated in prior studies with sudden death have been a short refractory period of the accessory pathway, either measured directly or as the shortest preexcited RR interval during AF, the ability to induce AVRT, and the presence of multiple accessory pathways. Sudden death is, however, quite rare and most adult patients, as shown here, will have a history of either symptoms or documented arrhythmias before their sudden death event. The situation in children and adolecents is less certain since these individuals rarely have an ECG in the absence of symptoms and preexcitation cannot be diagnosed after death. Similarly, AVRT that does not degenerate to atrial fibrillation can usually be tolerated by the patient; thus, evaluation and therapy can be withheld until after the initial episode. Despite this, however, many patients with preexcitation either have episodes of symptoms in which it is uncertain whether there is a relationship to arrhythmia, or they may simply wish to know their risk for future arrhythmic events. The data shown here by Pappone et al suggest that patients with either multiple accessory pathways or with inducible arrhythmias are at significant risk for future arrhythmic events.

I would interpret these data to mean that if an electrophysiologic study is performed, the electrophysiologist should, in most cases, proceed to catheter ablation in patients who either have multiple accessory pathways or have an inducible AVRT. This would be particularly true in younger patients, especially children and adolescents, who are at high risk of developing symptoms. Older patients (those older than 40 or 50) who have been truly asymptomatic would rarely require a prospective study.

Despite this recommendation, the electrophysiologist must recognize that in asymptomatic individuals it is important not to place the patient at excess risk if at all possible. Therefore, I would not favor proceeding with either a difficult anteroseptal ablation where there is risk of damaging the conduction system or with a difficult posteroseptal ablation that might require coronary venous access for a successful ablation until the patient develops symptoms and the need for such a procedure is clearly demonstrated. In an experienced laboratory, the risk of ablating either a right or left free wall pathway should be acceptable. ■

Cardioversion of Recent-Onset Atrial Fibrillation: Amiodarone vs Placebo and Class 1c Drugs

ABSTRACT & COMMENTARY

Synopsis: *Amiodarone is superior to placebo for cardioversion of AF when measured at 24 hours after drug administration.*

Source: Chevalier P, et al. *J Am Coll Cardiol*. 2003;41: 255-262.

THE USE OF AMIODARONE FOR MAINTENANCE OF sinus rhythm in patients with a history of atrial fibrillation is now well established. However, the role of amiodarone for converting recent-onset atrial fibrillation is less well defined. Chevalier and associates did a literature search of all clinical trials dealing with conversion of recent-onset atrial fibrillation with amiodarone. For inclusion, the study had to be a prospective, randomized trial of amiodarone vs placebo or amiodarone vs a class

1c drug. The primary end point analyzed was conversion to sinus rhythm within the first 24 hours but intermediate time points were also analyzed.

Although 79 potentially relevant articles were identified, 69 were excluded for various reasons. Only 10 met the criteria as stated above. Six studies including 595 patients compared amiodarone with placebo. Seven studies including 579 patients compared amiodarone with a class 1c drug. Three included both a placebo and 1c drug comparison. Five of the 6 amiodarone vs placebo studies used intravenous amiodarone and 1 used a single 30 mg/kg oral dose. Studies that used intravenous propafenone used a 2 mg/kg intravenous bolus followed by a second dose of 1 mg/kg or an infusion of 5-10 mg/kg per 24 hours. Oral propafenone when studied was given as a single 600-mg dose. For flecainide, either a 2 mg/kg intravenous bolus or a single 300-mg oral dose was administered.

None of the studies of amiodarone vs placebo reported drug efficacy at 3-5 hours but at 6-8 hours and at 24 hours, amiodarone was more effective than placebo. Overall, 82% of the patients who received amiodarone vs 56% of the patients who received placebo had converted after 24 hours. Class 1c drugs were more effective than amiodarone at the early time points up to 8 hours, but at 24 hours, there was no difference. The overall conversion rate was 66% for amiodarone and 71% for 1c drugs at the 24-hour time point.

Side effects were minor in the trials. Nonsustained ventricular tachycardia was reported in 2 amiodarone patients and in 1 patient given propafenone. Sustained ventricular tachycardia was observed in 1 patient receiving placebo. Four episodes of 1:1 atrial flutter were reported—3 in patients on flecainide and 1 in a placebo patient.

Chevalier et al conclude that amiodarone is superior to placebo for cardioversion of AF when measured at 24 hours after drug administration. Faster initial rates of conversion are noted with 1c agents, but overall efficacy at 24 hours is similar.

COMMENT BY JOHN DiMARCO, MD, PhD

Atrial fibrillation of recent onset remains a major clinical problem. Amiodarone has been shown in a number of trials to be the most effective single agent for maintaining sinus rhythm during chronic therapy, but the literature on the effects of amiodarone for converting recent-onset atrial fibrillation have been uncertain. This paper by Chevalier et al suggests to us the optimal ways to use drugs to convert atrial fibrillation. In patients who do not have ischemic heart disease or congestive heart failure, propafenone and flecainide are the initial drugs of choice for both converting atrial fibrillation and maintaining sinus rhythm thereafter. Patient response to these drugs is relatively rapid, and they can be used in the emergency room setting. However, many patients with particularly problematic atrial fibrillation have either ischemic heart disease or congestive heart failure with ventricular dysfunction, both contraindications to therapy with a 1c agent. Intravenous ibutilide, the most effective rapidly acting agent for converting AF, is also associated with a high incidence of side effects in patients with severe left ventricular dysfunction. In these patients, use of amiodarone has the benefit that it not only may convert the patient back to sinus rhythm and avoid the need for cardioversion, but it also may provide effective long-term prophylactic therapy. Even if conversion is not rapid, the ability to cardiovert with intravenous or oral amiodarone is significant. This is particularly important in critically ill patients in intensive care units in whom the expense of intravenous amiodarone can be justified. In the emergency room setting where the goal is still to discharge the patient quickly, amiodarone does not have a rapid enough action to justify its use. Further studies using oral loading regimens in the outpatient or emergency room setting should be performed to further clarify the role of amiodarone in these situations. ■

The New Natural History of Marfan's Syndrome

ABSTRACT & COMMENTARY

Synopsis: *Death due to cardiac structural complications is rare in young Marfan's patients followed carefully on medical therapy, but arrhythmogenic sudden death occurs and is more common in those with LV dilatation.*

Source: Yetman AT, et al. *J Amer Coll Cardiol*. 2003;41:329-332.

It is believed that sudden death in Marfan's syndrome is usually due to aortic dissection and rupture. The ubiquitous use of pharmacologic therapy to abrogate this complication and the routine use of echo- cardiography to detect dangerous levels of aortic dilatation raises the issue of the natural history of Marfan's syndrome in the modern era. Thus, Yetman and colleagues retrospectively reviewed the experience at 1 institution with 70 consecutive Marfan's patients followed in a special clinic for up to 24 years. The patients were seen biannually, and echocardiograms were done every 6-12 months. In addition, ambulatory ECG monitoring was performed initially off medication and subsequently if clinically indicated.

Patients were divided into those with ventricular premature beats (VPBs) > 10 per hour and compared to those with < 10 VPBs/hr. The 70 patients, 34 men and 36 women, had a median age of 10 years (range, birth to 52 years) at diagnosis and 17 years (range, 1.5-55 years) at final follow-up. The median follow-up was 6 years (range, 20 months to 25 years). A family history of Marfan's syndrome was present in 24 patients, and 13 of these had a family history of sudden death. Although all patients were started on blood pressure-lowering medications, 83% were still on such therapy at final follow-up due to adverse effects. Drug therapy was mainly beta blockers (37%) and angiotensin receptor blockers (26%) Six patients (8%) underwent aortic surgery; all but 1 were elective. None had valve surgery. All 3 deaths were sudden and none of these patients had structural failure at autopsy. Thus, all were believed to be arrhythmogenic. All patients had echocardiographic evidence of cardiovascular involvement: 90% aortic root dilatation, 68% left ventricular (LV) dilatation, and 11% LV systolic dysfunction. On ECG all were in sinus rhythm, 16% had prolonged QTc, and 60% had prominent u waves. On ambulatory ECG monitoring, 13 (21%) had > 10 VPBs and 4 had nonsustained ventricular tachycardia. Ventricular ectopy was univariately associated with mitral valve prolapse (100% of the 13 patients with VPBs), mitral regurgitation, LV dilatation, prolonged QTc, and u waves. Interestingly beta-blocker use was more common in the frequent VPB group. Multiple logistic regression analysis showed that only LV size was independently associated with frequent ventricular ectopy. All 3 of the deaths were in the frequent VPB group. Also, of the 4 patients with nonsustained VT, 2 died suddenly, and 2 were alive, 1 on amiodarone and 1 on beta blocker. Yetman et al concluded that death due to cardiac structural complications is rare in young Marfan's patients followed carefully on medical therapy, but arrhythmogenic sudden death occurs and is more common in those with LV dilatation.

COMMENT BY MICHAEL H. CRAWFORD, MD

Most cardiologists are well aware of the need to perform routine echocardiograms in Marfan's patients to detect increasing aortic size. Also, we recognize that mitral valve prolapse and aortic regurgitation can be a problem in some patients. However, ventricular tachyarrhythmias have not been prominent in our thinking. This modern natural history study suggests that sudden death due to ventricular arrhythmia is now the most common cause of death in young Marfan's patients. Although some of the patients in this study had aortic surgery (8%), none died of aortic rupture, and none had mitral valve surgery.

This study represents intensive management of these patients in 1 center. Patients were seen at 6-month intervals with echoes every 6-12 months and routine ambulatory ECG monitoring at the time of diagnosis and during follow-up as necessary. Pharmacologic antihypertensive therapy was liberally used with 83% remaining on it long term. Despite the use of ambulatory ECG monitoring, apparently antiarrhythmic drugs other than beta blockers were not given, and none of the patients were given implantable defibrillators. Given the results, this decision is being questioned by the investigators.

By multivariate analysis only, LV dilatation was independently associated with frequent ventricular ectopy. Unfortunately, the study population is too small to assess the role of beta blockers and ACEI to prevent LV dilatation, but clearly this needs to be studied in this population. Apparently LV dilatation is common in Marfan's patients even in the absence of regurgitation. Perhaps all Marfan's patients should be on ACEI. Beta blockers can improve LV function in heart failure and prevent ventricular tachyarrhythmias in patients with ischemic heart disease. However, these beneficial effects may not occur in Marfan's patients. Beta blockers may play a role in preventing shear forces in the aorta leading to dilatation and dissection, so they should probably remain as desirable therapy. This study suggests that in addition to beta blockers and ACEI, consideration should be given to antiarrhythmia therapy in those with demonstrated ventricular arrhythmias and those with LV dilatation that does not respond to ACEI and beta-blocker therapy. The role of defibrillators in Marfan's patients remains to be elucidated, but this study suggests that they should be considered in patients with nonsustained VT on monitoring. ■

CME Questions

12. In-stent restenosis may be treated with:

a. CABG.
b. brachytherapy.
c. sirolimus-eluting stents.
d. All of the above

13. High-sensitivity CRP testing should be considered in:

a. asymptomatic individuals at intermediate clinical risk for a coronary event.
b. stable CAD patients.
c. unstable coronary syndrome patients.
d. All of the above

14. Factors favoring ablation therapy in asymptomatic WPW patients include:

a. multiple accessory pathways.
b. inducible AV node reentrant tachyarrhythmias.
c. older age.
d. a and b

Answers: 12(d); 13(d); 14(d)

AMERICAN HEALTH CONSULTANTS®

Clinical Briefs in Primary Care™

The essential monthly primary care update

By Louis Kuritzky, MD

Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Infectious Disease Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports,* and *Sports Medicine Reports.*

VOLUME 8, NUMBER 3 PAGES 5-6 MARCH 2003

The Metabolic Syndrome and Total and Cardiovascular Disease Mortality in Middle-Aged Men

Source: Lakka HM, et al. *JAMA*. 2002;288:2709-2716.

THE METABOLIC SYNDROME (MBS) HAS 2 currently popular definitions. According to the National Cholesterol Education Program, MBS exists when a patient has at least 3 of the following characteristics: fasting glucose (FPG) > 110 mg/dL, abdominal obesity, triglycerides > 150, HDL < 40 mg/dL, and elevated blood pressure (> 130/85). The World Health Organization (WHO) definition stratifies things just a bit differently, defining MBS as either hyperinsulinemia (upper quartile of the adult, nondiabetic population) or FPG, and any 2 or more of abdominal obesity, dyslipidemia (triglycerides > 150 mg/dL or HDL < 35), and BP > 140/90. Despite these modest differences, the criteria basically define the same group of individuals. Lakka and associates prospectively studied for a mean of 11.6 years a random, age-stratified sample of men in Finland (n = 2682) aged 42 and older, to examine cardiovascular and overall mortality in relation to MBS.

MBS patients had reduced (79%) Kaplan-Meier estimates of overall survival when compared with patients without MBS. Similarly, CHD mortality was 2.4-3.4 times higher in persons with MBS. The prevalence of MBS at baseline was 9-14%. The public health impact of MBS is substantial. Whether specific treatment of MBS will reduce mortality has not been determined. ■

Amlodipine Fosinopril Combination on Microalbuminuria in Hypertensive Type 2 Diabetic Patients

Source: Fogari R, et al. *Am J Hypertens*. 2002;15:1042-1049.

NUMEROUS STUDIES HAVE CONfirmed the role of ACE inhibitors in modulation of microalbuminuria. The data on effects of calcium channel blockers (CCB) have been conflicting, especially as concerns dihydropyridine CCB (eg, amlodipine, felodipine, nifedipine). Fogari and associates addressed the effects of fosinopril (FOS) and amlodipine (AML), alone or in combination (COM), in an open-labeled, randomized, prospective, parallel group study for 4 years (n = 309).

By 3 months' time, the FOS group had demonstrated a decline in urinary albumin excretion (UAE), which decreased slightly further in the first year, and then stabilized. The AML group also demonstrated a decline in UAE, but not until 18 months into the study, after which point the UAE stabilized. COM therapy produced an impact at 3 months, which increased at 12 months and again at 36 months, and was statistically significantly greater than either monotherapy.

The mechanism by which COM therapy is superior to either monotherapy is uncertain, but the greater reduction in BP achieved (approximately 12/5 greater reduction by the former) is thought to have figured prominently. ■

Relation Between Alcohol Consumption and C-Reactive Protein Levels in the Adult United States Population

Source: Stewart SH, et al. *J Am Board Fam Pract*. 2002;15:437-442.

EPIDEMIOLOGIC DATA CONSISTENTLY indicate that moderate intake of alcohol (ETOH) is associated with reductions in cardiovascular mortality. Though the mechanism by which this effect is achieved is uncertain, increases in HDL by alcohol may explain as much as 50% of the protective effect.

C-reactive protein (CRP) is increasingly recognized as an independent risk factor for cardiovascular endpoints, suggesting an important role of inflammation in promoting atherosclerotic events. To evaluate the relationship between CRP and ETOH, Mainous and associates analyzed data from the National Health and Nutrition Evaluation Survey (NHANES III), which included complete information on 11,572 US adults.

Almost half of the NHANES population were alcohol abstainers; CRP levels in abstainers were significantly greater than in those who drink alcohol, regardless of level of alcohol ingestion. The mechanism by which ETOH might reduce CRP (or inflammation) remains unknown. A small trial of ETOH in healthy volunteers has shown a reduction in CRP and is stimulus for follow-up evaluation in larger studies. ■

Prostate Cancer Screening

Source: Ransohoff DF, et al. *Am J Med*. 2002;113:663-667.

In contrast to screening for breast and colon cancer, both of which have been demonstrated to reduce mortality, prostate cancer screening (PCS) has not yet been proven to favorably affect overall mortality, although some trials have found that PCS screening reduces prostate cancer-related mortality. Hence PCS has not met the same standard as other commonly used screening tools. Because of the discordance between the relative lack of supportive data to provide justification for PCS and the very high frequency of PCS testing, Ransohoff and colleagues sought to evaluate what factors promote PCS. That PCS can result in harm (eg, postsurgical impotence, incontinence) is clear; whether PCS can provide benefit (ie, reduction in mortality) remains to be demonstrated.

Ransohoff et al describe the PCS model as "lacking negative feedback:" a patient who undergoes PCS and has no cancer-suggestive findings feels reassured by these findings and is happy to have participated; a patient who has an elevated PSA often undergoes medical or surgical intervention. Even in the face of postintervention sequelae, the screened patient may feel that, ultimately, the intervention has spared his life, and he too may be grateful for the PCS.

Currently, whether PCS is mortality-effective is uncertain. Nonetheless, public satisfaction and enthusiasm for PCS remains high. It is conceivable that, in the long run, harm from PCS-stimulated intervention may outweigh benefit. Until the relative risks and benefits of PCS are more clearly defined, clinicians are well advised to review the decision path of PCS with patients before the process is embarked upon, in order that fully informed consent, dispassionately, may be attained. ■

Clinical Briefs in Primary Care™ is published monthly by American Health Consultants. Copyright © 2003 American Health Consultants. **Vice President/Group Publisher:** Brenda Mooney. **Editorial Group Head:** Glen Harris. **Editor:** Stephen Brunton, MD. **Managing Editor:** Robin Mason. **Assistant Managing Editor:** Rob Kimball. **Senior Copy Editor:** Christie Messina This is an educational publication designed to present scientific information and opinion to health professionals, stimulate thought, and further investigation. It does not provide advice regarding medical diagnosis or treatment for any individual case. It is not intended for the layman.

Subscriber Information

Customer Service: 1-800-688-2421

E-Mail Address: robert.kimball@ahcpub.com

World Wide Web: http://www.ahcpub.com

Address Correspondence to: American Health Consultants 3525 Piedmont Road, Building Six, Suite 400 Atlanta, GA 30305.

THOMSON

AMERICAN HEALTH CONSULTANTS

Can We Trust Home BP Measurement?

Source: Bachmann LM, et al. *J Clin Hypertens*. 2002;4:405-407,412.

The window of observation of blood pressure as obtained in the typical office setting has important limitations, with both exaggerations (ie, "white-coat" hypertension), and underestimates (ie, "masked hypertension") of hypertension burden being well documented. Abnormal circadian BP patterns, such as failure to experience the normal nocturnal decline in blood pressure, predict higher cardiovascular risk yet are not discerned by simple office measurement. Twenty-four-hour Ambulatory Blood Pressure Monitoring (ABPM) can resolve all 3 of these issues but is not without significant expense, and despite the endorsement of ABPM by the JNC VI report and the WHO guidelines, this technique remains only rarely used. Whether home blood pressure measurement, perhaps an intermediate step between office measurement and ABPM, is reliable is the subject of this report.

Bachmann and colleagues included 48 hypertensive patients from a single practice, who had been referred for 24-Hour ABPM. Subjects were randomly assigned to either a group which was asked to keep a personal log of the BP measurements recorded by the ABPM, and advised that their log would be checked for accuracy against that registered by the ABPM device, or a group who were also advised to periodically record BP measurements as registered by the ABPM device, but who were unaware that the ABPM automatically records and stores BP measurements. Discrepant results occurred when patient-recorded records either had an incorrect time, an incorrect BP value, or a BP was entered as recorded when the ABPM device had not performed such a measurement. Although patients unaware of the ABPM recording capacity were found to have more "fictional" registrations than the "informed" group (10/728 vs 29/616), ultimately these discrepant recordings did not confound the overall mean accuracy of averaged home blood pressure readings. ■

Systolic and Diastolic Dysfunction

Source: Redfield MM, et al. *JAMA*. 2003;289:194-202.

Congestive heart failure (CHF) is typically classified as systolic (ie, reduced ejection fraction), diastolic (normal ejection fraction, with impaired ventricular filling), or both. Indeed, though CHF may have been generally conceptualized solely as "inadequate pumping," some degree of diastolic dysfunction accompanies almost all patients suffering systolic dysfunction. Additionally, isolated diastolic dysfunction, which may present with identical clinical symptoms as systolic dysfunction, has recently been recognized to be approximately as common as systolic dysfunction in patients with manifest CHF. Redfield and associates evaluated with doppler echocardiography adults older than 45 years of age participating in the Rochester (Minnesota) Epidemiology Project (n = 2042), none of whom entered the study with a diagnosis of CHF.

In this asymptomatic (for CHF) group, validated CHF prevalence was 2.2%, approximately equally divided between systolic and diastolic dysfunction. Diastolic dysfunction, whether mild, moderate, or severe, was found by multivariate analysis to be predictive of all-cause mortality. This trial indicates that diastolic dysfunction, previously regarded as more "benign" than systolic dysfunction, portends significant adverse health outcomes. ■

PHARMACOLOGY WATCH

Smallpox Vaccination Guidelines Published by CDC

The CDC published "Smallpox Vaccination and Adverse Reactions—Guidance for Clinicians" in the Jan. 24th edition of *Morbidity and Mortality Weekly Report.* The guidance is a thorough review of the smallpox vaccine with a well-illustrated compendium of complications. Some of the highlights include:

Inoculation is administered using a multiple-puncture technique with the bifurcated needle. The inoculation site progresses from papule to vesicle, eventually becoming a pustule within 10 days. The pustule scabs over within 2-3 weeks usually leaving a pitted scar. Development of a pustular lesion is considered a major reaction and a successful vaccine take. Lesser reactions are considered equivocal and are nontakes. Large vaccination reactions may occur in 10% of first-time vaccinees. Systemic reactions are common in all vaccinees and include fatigue, headache, myalgias, chills, nausea, and fever. The vaccine is made from live vaccinia virus (it does not contain variola virus) and transmission is possible from the vaccination site up to 3 weeks after vaccination. The shedding period may be less for revaccination. The inoculation site is generally considered infectious from the time just after vaccination until the scab separates from the skin. Vaccinia is transmitted by close contact and can lead to the same adverse events in an infected contact as in the vaccinee. The inoculation sites should remain covered and vaccinees should wash their hands immediately after touching vaccination sites or changing dressings. The smallpox vaccination is generally considered safe, but is contraindicated in patients who have, or are in close contact with, those who have atopic dermatitis (eczema) regardless of the severity, skin diseases that disrupt the epidermis, pregnant women or women who plan on becoming pregnant within 1 month after vaccination, and immunocompromised patients. Others who should not receive the vaccine include those who have an allergy to a component of the vaccine, are breast-feeding, are using ocular steroids, have moderate-to-severe intercurrent illness, or are younger than 18 years of age.

The CDC has an excellent web site for health-care providers who wish to learn more about the smallpox vaccine: www.bt.cdc.gov/training/smallpox-vaccine/reactions/default.htm

Nurses: Delay Vaccination Program

Meanwhile, not everyone is happy with the national smallpox vaccination program. Recently the American Nurses Association (ANA) requested that the Bush administration delay the smallpox vaccination program until certain safety issues can be addressed. Specifically, the ANA is seeking information regarding potential transmission of vaccinia virus to family members of vaccinated nurses, coverage of medical costs related to vaccination, safety of the vaccination materials, adequate educational materials and staffing issues, and job security issues related to the vaccination program. Others such as Thomas Mack, MD, MPH, argue in the Jan. 30 edition of the *New England Journal of Medicine* that

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. Telephone: (404) 262-5517. E-mail: robin.mason@ahcpub.com. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study.

smallpox is overrated as a bioterrorist weapon. His view is that the current vaccination policy would provide little protection and the cost from vaccine complications would outweigh any benefit (*N Engl J Med*. 2003;348:460-463). However, a special article in the same issue developed scenarios of smallpox attacks and reviewed possible outcomes of control policies. Their analysis favors a program of prior vaccination of health care workers but favors vaccination of the public only in the likelihood of a national attack, or multiple attacks is very high (*N Engl J Med*. 2003;348:416-425).

Viagra Effective for Depression Treatment

Sildenafil (Viagra) is an effective treatment for antidepressant-associated sexual dysfunction in men. The drug was tested in a multicenter randomized double-blind placebo-controlled trial. Ninety men with major depression in remission on SSRI antidepressants were randomly assigned to take sildenafil (50 to 100 mg) or placebo for 6 weeks. Men who were most affected by antidepressant-associated sexual dysfunction were significantly more likely to improve with sildenafil (24/44, 54.5% response rate) vs placebo (2/45, 4.4% response rate) ($P < .001$). Erectile function, arousal, ejaculation, orgasm, and overall satisfaction measures improved significantly with sildenafil compared with placebo (*JAMA*. 2003;289:56-64). This study is important because sexual dysfunction is a common cause of noncompliance with serotonin reuptake inhibitors, and use of sildenafil may improve compliance with antidepressant treatment.

Finisteride/Doxazosin no Better than Placebo for Urinary Obstruction

Finisteride (Proscar) is no better than placebo when used in combination with doxazosin for the treatment of urinary obstruction due to benign prostatic hypertrophy, according to the recently published Prospective European Doxazosin and Combination Therapy (PREDICT) trial. These findings come in contradiction to the Medical Therapy of Prostatic Symptoms (MTOPS) trial published in May 2002, which showed a benefit of the combination of finasteride and doxazosin. In the current study, more than 1000 men were randomized to doxazocin, finisteride 5 mg per day, the combination of both, or placebo. The groups receiving doxazocin alone or in combination with finisteride had significant improvements in total maximal urinary flow rates and International Prostate Symptoms Score compared to the finisteride alone group and placebo group ($P < .05$). There was no significant difference between treatment with finisteride and placebo. Doxazosin was initiated at 1 mg per day and titrated to a maximum of 8 mg per day. All treatments were well tolerated (*Urology*. 2003;61:119-126).

Sildenafil, however, may be effective of relieving obstructive urinary symptoms in men who use the drug on a regular basis. British researchers looked at 112 men with erectile dysfunction at 1 and 3 months after taking sildenafil as needed before sexual intercourse. Only 20 of the 112 men complained of lowered urinary tract symptoms, but of those men, improved urinary scores at 3 months strongly correlated with improvement in sexual function. The authors suggest that an increase in nitric oxide associated with the resumption of normal sexual activity may be responsible for the improvement in urinary symptoms (*Br J Urol Int*. 2002;90: 836-839).

Serevent Receives 'Dear Doctor' Letter

GlaxoSmithKline has issued a "Dear Doctor" letter regarding its asthma bronchodilator salmeterol (Serevent). The warning is based on interim results from a large study of salmeterol that was initiated in 1996. The Salmeterol Multi-center Asthma Research Trial (SMART) was a postmarketing study designed to investigate reports of several asthma deaths associated with use of salmeterol. Analysis of the interim results showed a trend "toward a greater increase in asthma deaths and serious asthma episodes" with the largest increase in African-American patients. Data on almost 26,000 patients were available for analysis. While there was no significant difference for the primary end point of combined respiratory related deaths and respiratory related life-threatening experiences including incubation and mechanical ventilation between salmeterol and placebo, a higher, but not statistically significant number of asthma related life-threatening experiences including deaths occurred in the salmeterol group. The number of adverse events reached statistical significance in African-Americans who represented 17% of the study. No other ethnic group drew any conclusions. The use of inhaled corticosteroids reached only 47% in the entire population of the SMART study. Because of these findings, GlaxoSmithKline has decided to discontinue the study and continue reviewing data from the interim analysis. The FDA is involved in this process and will likely require label changes for Serevent that will reinforce guidance on appropriate and safe prescribing. ■