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INSIDE

Cardiac-Resynchronization Therapy in Advanced Chronic Heart Failure

ABSTRACT & COMMENTARY

Synopsis: *In selected patients, cardiac resynchronization therapy with a pacemaker or pacemaker-defibrillator improves their clinical course and the addition of a defibrillator with cardiac resynchronization therapy alone further reduces mortality.*

Source: Bristow MR, et al. *N Engl J Med.* 2004;350:2140-2150.

PREVIOUS STUDIES ON CARDIAC RESYNCHRONIZATION THERAPY (CRT) have used an improvement in heart failure symptoms or a decrease in hospitalization as their primary end points and have not had adequate statistical power to detect changes in mortality. In this paper, Bristow and colleagues report the results of the Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure (COMPANION) Trial. This was a multicenter trial conducted in North America to evaluate the effects of CRT with and without defibrillation on both symptoms and mortality. Patients were eligiblefor inclusion if they had New York Heart Association class III or class IV heart failure due to either an ischemic or nonischemic cardiomyopathy, a left ventricular ejection fraction of 0.35 or less, and a QRS duration of at least 120 msec. All patients had sinus rhythm.

Patients could not have a documented bradycardia or tachycardia indication for a pacemaker or defibrillator and were required to have had a hospitalization for heart failure within the preceding 12 months. Patients were randomly assigned in a 1:2:2 ratio to treatment with either contemporary pharmacologic therapy for heart failure, pharmacologic therapy plus CRT with a pacemaker, or pharmacologic therapy plus CRT with a pacemaker-defibrillator. The pharmacologic therapy used in all groups was designed to include diuretics, angiotensin converting enzyme (ACE) inhibitors or angiotensin II receptor blockers, beta blockers, and spironolactone. Digoxin could be used at the investigators' discretion. Patients who underwent CRT with a pacemaker received right atrial, right ventricular and left ventricular epicardial pacing leads and were programmed in the VDD mode with a lower rate

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below the patient's lowest intrinsic heart rate. Patients who received a defibrillator used similar pacing settings, but therapy for ventricular arrhythmias was programmed.

The primary end point was a composite of death from any cause or hospitalization from any cause from the time of randomization to the time of the first event. Hospitalization for implant was not included. Unscheduled intravenous administration of inotropic or vasoactive drugs from more than 4 hours in an emergency department or outpatient setting was considered to be the equivalent of a hospitalization. Death from any cause was a secondary end point.

Enrollment began in January 2000 and was stopped in November 20002 when the Data Safety Monitoring Board reported that a prespecified target of 1000 events had been reached. At that time, 1520 patients had undergone randomization.

The average age was 67 years and 67% of the patients were male. Eighty-five percent of the patients were in New York Heart Association class III at the time of randomization and heart failure had been present for a mean of 3.6 years. The mean left ventricular ejection fraction was 21%. The median QRS interval was 159 msec and 56% of the patients had an ischemic cardiomyopathy.

Of the patients who were assigned to CRT, implantation was successful in 87% of the patients in the pacemaker group and in 91% of the patients in the pacemaker-defibrillator group. There were 5 deaths in the pacemaker group and 3 in the pacemaker-defibrillator group that were thought to be related to procedural complications. However, the mortality rate during the 30 days after randomization was similar among the 3 groups: 1% in the CRT pacemaker group, 1.8% in the CRT pacemaker-defibrillator group, and 1.2% in the pharmacologic therapy group. CRT devices become available for routine clinical use during the trial. As a result, follow-up was complicated by the fact that 13% of the pharmacologic therapy group withdrew from the study, primarily to receive an out-of-study resynchronization device. Because of this, complete outcome data through the end of the study was known for only 91% of the patients in the pharmacologic therapy group vs 99% of the patients in the other groups. Mortality data, however, were complete for 96% of the pharmacologic therapy patients. A total of 1020 primary end points were analyzed. The 12-month rate of the primary composite end point of death from any cause or hospitalization from any cause was 68% in the pharmacologic therapy group as compared with 56% in the pacemaker group and 56% in the pacemaker-defibrillator group. The 1-year mortality rate in the pharmacologic therapy group was 19% and there was a total mortality during the entire study of 25%. Implantation of a pacemaker was associated with a trend toward improved survival (hazard ratio, 0.76; 95% confidence interval, 0.58-1.01) whereas the implantation of the pacemaker-defibrillator was associated with a significant 36% reduction in risk (hazard ratio, 0.64; 95% confidence interval, 0.48-0.86).

When only death or hospitalization for cardiovascular causes was considered CRT with or without defibrillation produced significant reductions in risk. The risk reductions were 25% in the pacemaker group and 28% in the pacemaker-defibrillator group. A variety of subgroups were analyzed to test the applicability of the data to select populations. Favorable trends were noted for most subgroups. In particular, CRT reduced the risk of primary end points among patients with both ischemic and nonischemic cardiomyopathy to approximately the same extent. Both CRT groups experienced an improvement in 6-minute walk distance, quality of life and New York Heart Association class symptoms. Median systolic blood pressures were increased with resynchronization therapy and were decreased with pharmacologic therapy.

Bristow et al conclude that in selected patients, cardiac CRT with a pacemaker or pacemaker-defibrillator improves their clinical course and that the addition of a defibrillator with cardiac resynchronization therapy

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alone further reduces mortality.

COMMENT BY JOHN P. DiMARCO, MD, PhD

COMPANION is an important trial because it addresses several key questions about the use of biventricular pacemakers and ICDs. Although the results might have been more definitive if the trial had been allowed to run further, the results are adequate for making several clinical conclusions. First, resynchronization therapy with biventricular pacing improves a number of important outcomes in patients with prolonged QRS durations and depressed left ventricular ejection fractions. Second, the effects of CRT and ICD therapy on mortality appear to be additive. Third, there is no apparent difference between patients with ischemic vs nonischemic cardiomyopathies. These conclusions are well justified by the data and should be used for clinical decision making. They should also form the basis for a revision of current reimbursement guidelines.

However, many questions still remain. The event rates, particularly for hospitalization, in COMPANION remain quite high even with CRT. Is there some way that CRT can be optimized to further improve therapy? Why do some patients not improve? Is QRS duration a valuable predictor of response or is there at least some minimum value—130 or 140 msec—below which improvement should not be expected?

COMPANION also illustrates an interesting problem facing those who design clinical trials in patients with heart failure. Pharmacologic therapy has improved prognosis for patients with heart failure dramatically. The COMPANION investigators therefore selected a very high risk group by requiring all patients to have had a recent heart failure hospitalization. Although this resulted in a high rate of events, it also meant that the clinical release of CRT devices for general use after the trial was under way had 2 unfortunate consequences: many desperate control patients withdrew from the trial to receive an out-of-study CRT device and enrollment dramatically declined in the later phases of the study. These 2 developments almost caused the trial to stop because of the poor enrollment and the withdrawals to cross-over made data analysis much more difficult. These problems will continue in future trials if the clinical availability of the device under study changes during the course of the study.

As of June 2004 the Centers for Medicare & Medicaid Services has not yet revised there reimbursement guidelines on the basis of the COMPANION data. As clinicians, we should demand that new guidelines that allow appropriate use of CRT devices in patients likely to benefit be issued soon.

Prophylactic Defibrillator Implantation in Patients with Nonischemic Dilated Cardiomyopathy

ABSTRACT & COMMENTARY

Synopsis: *Data showed a strong trend toward benefit with ICD therapy in patients with nonischemic cardiomyopathy.*

Source: Kadish A, et.al. *N Engl J Med.* 2004;350: 2151-2158.

Most prior trials involving implantable cardioverter defibrillators (ICDs) for the primary prevention of sudden cardiac death have focused on patients with coronary artery disease and prior myocardial infarction. In this study, Kadish and colleagues report the results of a randomized clinical trial in patients with nonischemic cardiomyopathy. The Defibrillators in Nonischemic Cardiomyopathy Treatment Evaluation (DEFINITE) trial reported here is the first large study in this population.

Patients were eligible for the trial if they had a left ventricular ejection fraction of less than 36%, either nonsustained ventricular tachycardia or at least 10 premature ventricular complexes per hour during 24-hour Holter monitoring, a history of symptomatic heart failure and a nonischemic dilated cardiomyopathy. All patients were treated with currently recommended heart failure medication. These included angiotensin converting enzyme inhibitors unless they were contraindicated, beta blockers, and digoxin and diuretics as necessary. Antiarrhythmic drugs were discouraged but could be used to treat symptomatic supraventricular arrhythmias.

Patients were randomly assigned to either ICD therapy or control with 229 patients in each group. The ICD used was a single chamber device which was programmed for back-up ventricular pacing at a rate of 40 bpm and a ventricular fibrillation detection zone at 180 bpm. Patients in the control group who developed either a cardiac arrest or an episode of unexplained syncope could receive an ICD if deemed necessary.

The trial follow-up was 29.0 ± 14.4 months. The total group had a mean age of 58.3 years with a range of 20.3

to 83.9 years. Seventy-one percent were male. Thirtythree percent of the patients were minorities. There was a history of diabetes in 23% and atrial fibrillation in 25% of the patients. Twenty-two percent of the patients were in New York Heart Association class I, 57% in NYHA class II and 21% in NYHA class III. Left bundle branch block was noted in 19.7% and right bundle branch block in 3.3%. The mean left ventricular ejection fraction was 21.4. ACE inhibitors were used in 86% of the patients and beta blockers in 85%. Eighty-seven percent of the patients received a diuretic and 11% an angiotensin II receptor blocker. Amiodarone was used in 5.2% of the patients because of symptomatic arrhythmias. Digoxin was used in 42% of the patients.

There were 229 patients randomized to the ICD group. However, 2 patients declined to undergo ICD implantation and, in response-to-patient requests, 1 patient had the ICD explanted and one patient had the device inactivated. There were 3 implant complications: 1 hemothorax, 1 pneumothorax and 1 cardiac tamponade. All complications resolved with appropriate therapy. There were 10 late complications including 6 lead dislodgements or lead fractures, 3 cases of venous thrombosis and 1 infection. After implant, 2 patients received ICD upgrades to dual chamber devices and eleven received biventricular devices to treat heart failure. Of the 229 patients in the control group, 23 (10%) received ICDs during follow-up primarily for syncope or heart failure with a prolonged QRS duration.

There were 28 deaths in the ICD group vs 40 deaths in the standard therapy group but the difference in survival was not significant (P = 0.08). The unadjusted hazard ratio for deaths among patients who received an ICD was 0.65 (95% confidence interval, 0.4-1.06). Survival analysis showed that the rate of death from any cause at one year was 6.2% in the standard therapy group and 2.6% in the ICD group. At 2 years, it was 14.1% in the standard therapy group and 7.9% in the ICD group. Analysis of mechanism of death suggested that the benefit from the ICD was related to a decrease in arrhythmic deaths. There were 3 sudden deaths from arrhythmia in the ICD group compared with 14 deaths in the standard therapy group. There were 11 deaths due to heart failure in the standard therapy group and 9 in the ICD group. During follow-up, 41 patients received 91 appropriate ICD shocks. In addition, 49 patients received inappropriate ICD shocks for either atrial fibrillation or other supraventricular arrhythmias. A subgroup analysis was performed. There appeared to be increased benefit among patients with class III congestive heart failure and among men.

Kadish et al conclude that their data showed a strong trend toward benefit with ICD therapy in patients with nonischemic cardiomyopathy. They suggest that since the study did not achieve statistical significance for the entire population, they consider that implantation be approached on a case by case basis.

COMMENT BY JOHN P. DiMARCO, MD, PhD

The DEFINITE Trial is the first large study that has shown at least a trend toward benefit with ICD insertion in patients with nonischemic cardiomyopathy. Several studies have shown benefit in patients with ischemic heart disease. However, in 2 prior studies, the Cardiomyopathy Trial (CAT) and the AMIOVIRT Study showed no benefit. However, both of these latter studies were quite small with only about 100 patients in each group.

The findings in DEFINITE are what one should expect. There was a decrease in arrhythmic mortality. The subgroup analysis may however be misleading. There was no benefit demonstrated among women and no benefit demonstrated among patients with class II congestive heart failure. However, the point estimates for both patients with class I and class II heart failure were quite similar at about 0.5 even though the confidence interval for class I heart failure crossed one. We therefore should interpret these data as showing a strong trend toward benefit among all patients with nonischemic cardiomyopathy. As recently reported from the Sudden Cardiac Death Heart Failure Trial, a similar survival benefit was noted in that study in patients with nonischemic cardiomyopathy. ■

Pre-Discharge Beta Blockers for Heart Failure

ABSTRACT & COMMENTARY

Synopsis: *The pre-discharge initiation of beta blocker therapy for decompensated heart failure patients increased the number of patients on beta blockers at 60 days without an increase in length of stay or adverse effects.*

Source: Gattis WA, et al. *J Am Coll Cardiol*. 2004;43: 1534-1541.

BETA BLOCKERS ARE OF PROVEN BENEFIT FOR THE long-term management of heart failure, but current guidelines suggest that they should not be started during hospitalization for heart failure decompensation. Thus, Gattis and coworkers conducted the Initiation Management Pre-discharge: Process for Assessment of

Carvedilol Therapy in Heart Failure (IMPACT-HF) trial to study whether in patients admitted for heart failure and stabilized, carvedilol initiation predischarge would result in more patients treated with beta blockers at 60 days post-discharge without increasing length of stay or adverse effects. In 45 centers across the United States, 363 patients were randomized to pre-discharge carvedilol vs usual care, which meant beta blocker initiation within 2 weeks after discharge. All had left ventricular ejection fraction < 0.40 and had no contraindications to beta blockers, including class IV status. Carvedilol could be started whenever feasible during hospitalization, but not after 12 hours before discharge. Those in the outpatient beta blocker group could be put on any beta blocker any time deemed appropriate by their physician. The primary end point of the study was the number of patients treated with any beta blocker 60 days after randomization. Several secondary end points were pre-specified. At 60 days, 91% of patients randomized to carvedilol pre-discharge were on beta blockers vs 73% of the usual care patients (P < .001). Also, pre-dischargepatients were more likely to be at target doses of beta blocker (36 vs 28%; P = .02). About 10% of the early and late beta blocker groups had therapy discontinued. Hospital length of stay was not affected. Finally, a composite clinical outcome score was similar for both groups, but there was a trend toward lower death and rehospitalization in the early initiation group. Gattis et al concluded that the pre-discharge initiation of beta blocker therapy for decompensated heart failure patients increased the number of patients on beta blockers at 60 days without an increase in length of stay or adverse effects.

COMMENT BY MICHAEL H. CRAWFORD, MD

One of the reasons beta blocker use in heart failure patients is generally < 50% is that there is concern about the potential for short-term worsening of heart failure. Although the concern is legitimate, data show that 80-90% of patients will tolerate beta blockers long term. However, to avoid problems the drug manufacturers and current guidelines recommend cautious outpatient titration in very stable patients only. Gattis et al in this study believe that this has stifled the use of this highly beneficial therapy. Thus, the important finding in this study is that in-hospital initiation of therapy results in more longer-term use without an increase in adverse effects. Of note, these were sick patients. Not only were these patients admitted for heart failure decompensation, but they were discharged relatively early (5 days) and before they had experienced any significant decrease in congestion as estimated by weight. Also, the 60-day death or rehospitalization rate was 25%.

The study increased the use of beta blockers in the usual care group as well since the rate of 73% is much higher than that reported in other surveys. Thus, it is not surprising that little difference in outcome was seen between the 2 groups. Gattis et al point out that these were the so-called "wet and warm" patients; volume overloaded, but not in a low output state. Those needing isotropic support were excluded.

There were limitations to the study. Although prospective, it was not blinded, but it is not clear how any biases influenced the results other than increasing beta blocker use in the usual care group. Also, the study only evaluated the patients after 60 days of follow-up. It is conceivable that after 6 months or a year, beta blocker use might have been the same, abrogating the value of starting early. Despite these limitations, the study fits with the growing trend to start all beneficial cardiac drugs as early as possible. Decompensated heart failure patients seem to be the last group to move toward the more aggressive approach we are taking today. ■

COX-2 Inhibitor Controversy

ABSTRACTS & COMMENTARY

Synopsis: *Current rofecoxib use was associated with a higher risk of acute myocardial infarction or admission for heart failure compared to celecoxib.*

Sources: Soloman DH, et al. *Circulation*. 2004;109: 2068-2073; Mamdani M, et al. *Lancet*. 2004;363: 1751-1756.

Cyclooxygenase-2 inhibitors are associated with less gastrointestinal bleeding than nonselective non-steroidal anti-inflammatory drugs (NSAIDs), but concern about their cardiovascular effects have arisen. Thus, Solomon and colleagues conducted a case controlled study of 54,475 patients older than 65-years-old identified in a state-sponsored pharmaceutical benefits program for elderly or disabled low-income individuals from 1998-2000. Patients with diseases that may have obscured the relationship between COX-2 drugs and cardiovascular disease were excluded. The case defining event was hospitalization for acute myocardial infarction (AMI), determined by chart review, which was found in 10,895. For each AMI, 4 controls were found and matched for age and sex. Logistic regression analyses were used to assess the relative risk of AMI in patients taking rofecoxib, celecoxib or no NSAIDs. The relative

risk of AMI in those on rofecoxib compared to celecoxib was 1.24 (95% CI, 1.05-1.46; P < .02) and compared to no NSAID was 1.14 (1.0-1.3; P = .054). The effect was related to drug dose: rofecoxib 25 mg or less vs celecoxib 200 mg or less (OR, 1.21; 1.01-1.44; P = .036) or rofecoxib > 25 mg vs celecoxib > 200 mg (OR, 1.7; 1.07-2.71; P = .026). Also, risk of AMI with rofecoxib was related to duration of therapy: 1-30 days (OR, 1.4; 1.12-1.75; P = .005) and > 90 days (OR, .96; 0.72-1.25; P = 0.8) compared to celecoxib for a similar duration. Celecoxib was not associated with a higher risk of AMI vs no NSAIDs. Soloman and colleagues concluded that current rofecoxib use was associated with a higher risk of acute myocardial infarction compared to celecoxib or no NSAID use. The risk was greatest during the first 90 days of use, but not thereafter and was higher with doses > 25 mg/day.

COMMENT BY MICHAEL H. CRAWFORD, MD

Although a boon to those with arthritic conditions, concern about adverse cardiac effects based upon the VIGOR study has been a source of continued controversy. In the VIGOR study, rofecoxib 50 mg was compared to naproxen 1000 mg in patients with rheumatoid arthritis. The risk of AMI was elevated in the rofecoxib-treated patients, but aspirin use was prohibited. Other studies have either confirmed or denied this finding, but all had significant limitations. Studies of celecoxib have been generally neutral on AMI risk with a few exceptions. This large observational study certainly puts the onus back on rofecoxib (Merck) to prove that AMI risk is not increased vs celecoxib (Pfizer). Mechanistically, it is not clear why one drug would be more of a problem than the other. Both inhibit COX-2, which decreases the beneficial vasodilatory and platelet effects of prostacyclin, leaving intact the platelet aggregation and vasoconstriction effects of COX-1. Perhaps rofecoxib is just more potent since other studies have shown increased blood pressure on rofecoxib vs celecoxib. The dose relationship would support this as well. Also, the increased risk associated with initial therapy probably has to do with ferreting out the susceptible patients, suggesting that avoiding these drugs in high-risk cardiac patients would make sense

There are limitations to this study. First, Medicare databases are not always accurate, especially with disease classification. Second, this is a retrospective observational study that could be biased by unrecognized confounders. Third, some patients may have taken their coxib PRN. Finally, the generalizability of a low-income elderly or disabled population may be suspect. However, until a definitive randomized controlled study is completed, it would be advisable to avoid coxibs and especially high doses of rofecoxib in high risk ischemic heart disease patients.

The second study by Mamdani and colleagues is also a retrospective observational study of subjects older than 65-years-old in Ontario Canada who were divided into 3 cohorts: users of rofecoxib, celecoxib, or non-selective NSAIDs. The case defining event was hospital admission for congestive heart failure. Using a community control group of non-NSAID users proportional hazzard models were constructed accounting for comorbidity. Compared to the controls, rofecoxib and non-selective NSAID users had a higher rate of admissions for heart failure (RR, 1.8; 1.5-2.2; and 1.4; 1.0-1.9, respectively) but not celecoxib (1.0, 0.8-1.3). Among patients with no heart failure admissions for 3 years, only rofecoxib increased the risk of subsequent admission relative to the controls (1.8, 1.4-2.3). Of note, COX-2 users were more likely to have pre-existing cardiovascular disease based upon their history of other drug use. Also, patients without previous use of cardiovascular medications were more likely to be put on them in all the NSAID groups. Soloman et al concluded that there is a higher risk of admission for heart failure among users of rofecxib and non-selective NSAIDs, but not with celecoxib.

COMMENT BY MICHAEL H. CRAWFORD, MD

The Mamdani study is interesting because this same group using the same database were unable to demonstrate a difference in AMI rates between refecoxib and celecoxib, but in that study patients with NSAID use < 30 days were excluded. This is likely the most vulnerable timeframe based upon the Solman study above. In this study, they avoided that mistake and found that the risk of heart failure admission was higher on relecoxib and non-selective NSAIDs vs celecoxib (number needed to harm 14, 14, 24, respectively). Also, patients with no history of cardiovascular medication use were more likely to end up on them in the NSAID users. These are important findings given that 28% of Ontario seniors were prescribed these medications.

We have known for many years that non-selective NSAIDs may exacerbate heart failure by causing salt and water retention, but this study suggests that heart failure may even by precipitated for the first time with these drugs, especially rofecoxib. They suggest that rofecoxib may be more risky because of its long half-life and tendency to accumulate in the body, but believe caution is advised with all NSAIDs in patients at risk for heart failure. Also, their data are consistent with other studies showing that rofecoxib increases blood pressure more than other NSAIDs. This may contribute to heart failure

initiation or decompensation.

This retrospective observational study suffers from the problem of bias due to unrecognized confounders. Also, this study had recognized confounders in that the coxib users were likely to have a higher incidence of pre-existing cardiovascular disease. In addition, no dosage data were available, but interestingly, < 10% of subject on rofecoxib were on < 25 mg/day. In summary, it would appear that the use of coxib drugs should be used with caution in patients at high risk for ischemic heart disease events or heart failure. Rofecoxib doses > 25 mg/day in particular should be avoided in such patients. ■

Much More About CRP!

ABSTRACTS & COMMENTARY

Synopsis: *CPR values as a continuous variable have independent predictive value for subsequent coronary events in apparently healthy women.*

Sources: Ridker PM, Cook N. *Circulation*. 2004;109: 1955-1959; Verma S, et al. *Circulation*. 2004;109:2058-2067; Verma S, et al. *Circulation*. 2004;109:1914-1917; Khreiss T, et al. *Circulation*. 2004;109:2016-2022.

In a new analysis by Ridker from the large-Women's Health Study, levels of C-reactive protein (CRP) at baseline were correlated with first cardiovascular events over a 9-year period. The particular focus of this report was very low and very high CRP levels, as well as looking at deciles of baseline CRP with and without adjustment for diabetes and Framingham Risk Score. In this study, 28,000 low-risk women were evaluated at entry, who were "similar to that of the general population in terms of . . . lipid levels . . . and metabolic syndrome." Framingham Risk Scores (FRS) were computed and analyses were carried out adjusted for both FRS and diabetes.

Results: A graded relative risk was demonstrated for each of 10 CRP groups, all highly statistically significant. Thus, CRP has again been shown to have an independent predictive value on subsequent events in patients without clinical CAD. The analysis of very low (< 0.5 mg/L and very high (>10 mg/L) levels correlate with both crude and FRS adjusted risk groups. Thus, unadjusted event rates were 6-fold higher in individuals with an initial CRP > 10 compared to an initial CRP < 0.5; adjusted rates in FRS and diabetes were 2-fold higher for CRP >10 mg/L. In fact, even between 0.5 and 1.0 mg/L there was a near doubling of adjusted risk. The authors conclude that "there is no evidence . . . of any threshold affect." They also point out that unusually low or unusually high values generally do not represent false negatives or positives. They believe that actual CRP levels provide considerable value over and above the recommended cut points of < 1, 1-3, and > 3 established by the recent CDC/AHA guidelines for use CRP. Although the highest CRP group (> 10 mg/L) represented only 5.5% of the total population, their risk was strikingly elevated. Those women with levels of > 20 at baseline (2.2% of the total population) were at an even greater risk. Fifteen percent of the population had an initial level of < 0.5 with an extremely low event rate. The authors conclude that CRP may play a direct role in atherothrombosis, given the precisely graded increases in risk across 9 cut points, and that at very high CRP levels, the increased CV risk is consistent with the hypothesis that CRP may have direct vascular effects. They furthermore suggest that the data supports the concept that chronic inflammatory states, such as arthritis, periodontal disease, etc, may be disposed to increased CV events, rather than high CRP being considered a false positive response. Furthermore, the authors emphasize that only a high sensitivity assay should be used for evaluation of CRP and two measurements are recommended for any level of > 10 mg/L.

■ COMMENT BY JONATHAN ABRAMS, MD

This report, and many others, link vascular events to gradations of CRP. CRP has been studied in many different populations and the data are consistent. The marked differential of risk between very low and very high CRP levels suggests a pathogenetic role for CRP itself. An in vitro basic science report from Canada suggests that CRP may have an adverse effect on endothelial progenitor cells (EPC) which are believed to be responsible for (favorable) neovascularization and angiogenesis. Investigators found that adding CRP to the experimental medium reduced EPC cell counts, inhibited the expression in specific endothelial cell markers, and increased endothelial cell apoptosis. Angiogenesis was impaired and endothelial nitric oxide synthase expression was diminished. Of great interest, the diabetes drug, rosiglitazone, attenuated these effects. These authors concluded that CRP (in this case, human recombinant CRP) has inhibitor effects on EPC differentiation, survival, and function, and thus may decrease the angiogenesis response to chronic ischemia. Verma et al conclude that CRP should now be seen as a "prominent partaker in endothelial dysfunction and atherosclerosis." Verma et al address conformational modification of CRP, such that differing subunits of CRP can have a greater or lesser

pro-inflammatory phenotype, which may modulate subsequent cardiovascular risk. Furthermore, they emphasize a wide variety of cellular effects in multiple experiments which support a direct role of CRP in promoting endothelial dysfunction and a variety of pro-inflammatory and pro-atherosclerotic actions. Transgenic animals that can express human CRP have been developed; these mice are prothrombotic and atherogenic, and are associated with "adverse cardiovascular processes," including impaired NO production, and enhanced endothelin release. These authors suggested that in the future, strategies to decrease CRP and modify its structure may become available to modulate atherosclerotic plaque initiation, progression, and rupture.

Although considerable controversy remains regarding the putative role of CRP as a participant or a marker for adverse cardiovascular events, it appears that there is a great deal of evidence that C-reactive protein itself, particularly with certain structural conformational profiles, can become pro-inflammatory. Thus, the hypothesis shared by many but not all, strongly supports an active role of CRP in the early as well as late atherothrombotic process. It is well-known that LDL cholesterol lowering results in decreased CRP levels; other interventions that reduce CRP itself may result in decreased atherothrombosis ". . . and that a virtual absence CRP may in fact be protective." CRP can be produced within vascular vessel muscle of diseased coronary arteries in addition to the liver. While many of these basic science reports have no direct effect on clinical practice as yet, it does appear that CRP status, either directly or as a surrogate for an inflammatory state, is a valid and important construct relating to both healthy as well as unhealthy arteries. ■

CME Questions

1. **ICD therapy for nonischemic cardiomyopathy:**
   a. reduces total mortality.
   b. reduces arrhythmic mortality.
   c. reduces heart failure deaths.
   d. All of the above.

2. **CRP predicts cardiovascular risk:**
   a. independent of clinical risk factors.
   b. across the spectrum of CRP values.
   c. even when values are > 0.5 < 1.0.
   d. All of the above

3. **Mortality in advanced heart failure patients is reduced by:**
   a. biventricular pacing
   b. biventricular pacing, plus ICD
   c. dual chamber (AV) pacing
   d. all of the above

4. **CRP:**
   a. increases endothelial cell apoptosis.
   b. impairs angiogenesis.
   c. diminishes endothelial NO production.
   d. All of the above

5. **Beta blockers for heart failure can be safely started:**
   a. in class IV patients.
   b. in cardiogenic shock patients.
   c. in pre-discharge heart failure decompensation patients.
   d. All of the above

Answers: 1 (b); 2 (d); 3 (b); 4 (d); 5 (c)

PHARMACOLOGY WATCH

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

Britain to Allow Over-the-Counter Sales of Zocor

The British government will soon allow over-the-counter (OTC) sales of Merck's simvastatin (Zocor), marking the first time any country has allowed the OTC sale of a statin. The drug lost its patent protection in England last year, and Merck is eager to make up for some lost revenues by entering the lucrative OTC market. It is likely the drug will be available in an OTC dose of 10 mg. Pharmacists will be asked to carry out a simple screening questionnaire on the spot to screen for appropriateness and safety. Not everyone is happy about the OTC switch however. An editorial in the British journal *Lancet* stated that there is insufficient evidence to justify the OTC switch and implied that the British government is simply trying to save money by defraying prescription drugs costs. Currently over 1.8 million patients in England take statins at a cost of over $1.1 billion per year.

FDA Rejects Plan B Bid

FDA regulators have rejected a bid from Barr Pharmaceuticals to market their "morning after pill" as an OTC. The product, called Plan B, contains 0.75 mg of levonorgestrel, a progestin commonly used in birth control pills. Plan B is marketed as an emergency contraceptive that can be used up to 72 hours after unprotected intercourse or suspected contraceptive failure. The decision by the FDA was somewhat surprising as it went against the recommendation the agency's own advisers who, last December, voted overwhelmingly in favor of the over-the-counter switch for Plan B. The decision prompted some groups to suggest that political pressure from the Bush administration was responsible for the denial. The FDA, however, stated in its rejection letter that they were concerned about the safety of the product for younger women, and kept the door open by suggesting that more data may prompt a reconsideration. In the meantime, Plan B is still available by prescription.

Recombinant Erythropoietin Products May Stimulate Tumor Growth

Two recent studies have raised the question of whether recombinant erythropoietin products may stimulate tumor growth in cancer patients. One study, published in the October 2003 *Lancet*, reviewed 351 adult patients with head neck cancer who were randomized to subcutaneous erythropoietin or placebo 3 times weekly prior to radiation therapy and continuing throughout radiation therapy. Patients treated with erythropoietin had improved hemoglobin concentrations, but otherwise had poor outcomes. Median locoregional progression-free survival was 745 days with placebo and 406 days with erythropoietin (relative risk, 1.62; [95% CI, 1.22-2.14]; P = .0008). Overall,

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over the 4 years of study, 52% of placebo-treated patients died, compared to 61% of erythropoietin treated patients (RR 1.39; [95% CI, 1.05-1.82]; P = .02). A second study in Europe of erythropoietin in breast cancer patients was terminated early because patients receiving the drug had lower 12 month survival rates than patients receiving placebo (70% vs 76%; P = .0117). An editorial in the December 17th Journal of the National Cancer Institute reviewed this issue and raised the plausibility of the findings. The authors noted that erythropoietin receptors have been found on head and neck cancer cells, prostate cancer cells, and ovarian cancer cells, as well as breast, renal, and uterine cancer cells. They also noted that the preliminary data suggest that some of these cancers may proliferate in the presence of erythropoietin.

The editorial concluded by calling for more research into the possible relationship between erythropoietin and poor outcomes in the treatment of cancer patients. The FDA's Oncologic Drugs Advisory Committee recently met in May, and backed a proposal by Johnson & Johnson (makers of Procrit) and Amgen (makers of Aranesp) to study this issue. The exact design of these studies is still to be delineated, but both companies have pledged to collaborate on such research.

Rosuvastatin: Market's Most Potent Statin

Rosuvastatin (Crestor-Astra Zeneca) appears to be the most potent statin currently marketed. In a study of 3140 patients with CAD, atherosclerosis, or type 2 diabetes, patients were randomized to rosuvastatin 10 mg, atorvastatin 10 or 20 mg, simvastatin 20 mg, or pravastatin 40 mg for 8 weeks. Patients either remained on these treatments or were switched from other statins to rosuvastatin. The primary pinpoint was a LDL cholesterol of < 116 mg/dL. Significant improvement in LDL cholesterol goal achievement was found for patients who were switched to rosuvastatin 10 mg compared with patients who remained on atorvastatin 10 mg (86% vs 80%; P < 0.5), simvastatin 20 mg (86% vs 72%, P <.001), and pravastatin 40 mg (88% vs 66%, P < .0001). For patients who were switched from atorvastatin 20 mg to rosuvastatin 20 mg, the rate at goal was 90% vs 84% (P < .01) (*Am Heart J*. 2004;147:705-712). But while rosuvastatin appears to be the most potent statin, it may carry a higher dose related risk of muscle toxicity including myositis and rhabdomyolysis. Astra Zeneca has recently acknowledged 4 cases of rhabdomyolysis in patients who were taking 40 mg of rosuvastatin, and has urged physicians in England to avoid initial high dose therapy with the drug, instead starting at 10 mg and titrating with appropriate follow-up.

FDA Actions

Immunex Corp.'s etanercept (Enbrel) has been approved for use in patients older than the age of 18 with moderate-to-severe plaque psoriasis. Enbrel is currently marketed for use in patients with ankylosing spondylitis, psoriatic arthritis, moderate to severe rheumatoid arthritis, and juvenile rheumatoid arthritis. The expansion of indications to treat psoriasis was expected after 2 phases.

All studies showed improvement with treatment up to 1 year. Etanercept, which is a tumor necrosis factor inhibitor, joins the biologics alefcept (Amevive) and efalizumab (Raptiva) in the suddenly rather crowded market for the treatment of psoriasis.

The FDA has approved Indevus Pharmaceutical's trospium chloride (Sanctura), for the treatment of overactive bladder with symptoms of the urge urinary incontinence, urgency and frequency. The drug is a muscarinic receptor antagonist, and as such, has side effects that include dry mouth and constipation. It is, however, relatively well-tolerated with fewer drug-drug interactions than currently available medications.

Fondaparinux (Arixtra-Fonda BV), the synthetic selective factor Xa inhibitor, has been given the expanded indication for treatment of acute pulmonary embolism and acute deep venous thrombosis without PE when coadministered with warfarin. Previously, the drug had been approved for prevention of DVT in the setting of orthopedic surgery.

Salix Pharmaceuticals has received approval to market rifaximin (Xifaxan) for the treatment of travelers diarrhea caused by noninvasive strains of *Escherichia coli*. The drug is unique in that it is minimally absorbed (< 0.5%) after oral administration, and exerts its action only in the gut. It is not for use in patients with diarrhea associated with fever or bloody stools, or pathogens other than *E. coli*. The drug is approved for patients age 12 and older and appears to be well-tolerated. ■