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INSIDE

CT Coronary Angiography

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

Source: Mollet NR, et al. High-Resolution Spiral Computed Tomography Coronary Angiography in Patients Referred for Diagnostic Conventional Coronary Angiography. *Circulation*. 2005;112:2318-2323.

THE NEWEST GENERATION SPIRAL CT SCANNER WITH 64 SLICES, thin detectors and faster X-ray tube rotation provides high-resolution, near motion-free coronary artery images. In 52 patients with acute chest pain syndromes referred for invasive coronary angiography, CT scans with contrast were performed before cardiac catheterization. All were in sinus rhythm, had normal renal function, and had never had revascularization before. Patients with resting heart rates > 70 beats per minute received beta-blockers. The CT scans were compared to quantitative coronary angiography by readers blinded to the other test results. A reduction in lumen of ≥ 50% in diameter was considered a significant lesion.

Results: Mean scan time was 13 seconds. One CT scan was classified as inconclusive. Using invasive angiography as the gold standard, on a segment to segment analysis CT scanning had a sensitivity of 99%, a specificity of 95%, a positive predictive value of 76%, and a negative prediction value of 99%. CT images were judged of good quality in 90%. Poor images were most often due to motion artifacts (60%) and severe calcification (20%). Intra and interobserver variability was .73 and .79, respectively. The presence of coronary calcium tended to lead to overestimation of severity of lesions by CT. Vessel-to-vessel agreement was .85 and patient-to-patient was .95. Mollet and colleagues concluded that a 64-slice CT coronary angiogram accurately detects coronary artery disease in patients with a variety of chest pain syndromes.

COMMENTARY

Earlier studies of coronary CT scanning looked at selective larger coronary segments and were not really comparable to conventional coronary angiography. This study examined all clinically relevant segments, as defined by the American Heart Association coronary artery disease grading sys-

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tem. In this study, CT angiography came out very well by analysis of coronary artery segments, vessels, or patients. Unlike noninvasive perfusion imaging, the results didn't vary by vessel. All but one patient with normal coronary arteries was correctly identified for a negative predictive value of 99%. No person with significant coronary artery disease was missed, and only one significant lesion was missed. Indeed, sensitivity was 99% and the investigators admitted they read for maximum sensitivity, as most radiologists do. Of course this caused specificity to fall a bit to 95%, but the positive predictive value was only 76%. So clearly this test is most valuable when negative.

Before we rush off and install one in every emergency room, there were some significant limitations to this study. The major problem is the selection bias of patients going to catheterization. Mollet et al claim that their study evaluated patients from a wide spectrum of clinical settings, but in fact most of the patients had a high pre-test likelihood of disease. To whit, only 12% had atypical chest pain, most had stable angina (63%), and 28% had unstable angina or nonST-elevation MI. Accordingly only 13% were found to have no coronary artery disease. The ability of any test to detect disease when the pre-test likelihood of disease is high, is enhanced by this selection bias. However to be fair, it is very difficult to define a gold standard that does not involve a selection bias. Regardless, expect CT angiography to perform less well in a truly broad patient population.

The second major problem is patient exclusions for renal dysfunction, cardiac rhythm disturbances, prior revascularization, etc. Again, expect a weaker performance when such patients are included in real world situations. Third, the more coronary calcium that was present the more CT angiography tended to overestimate the degree of stenosis. So don't expect CT angiography to solve the problem of who with coronary calcium present has significant lesions. Fourth, patients with heart rates > 70 had to have beta blockers to slow their heart rate to minimize motion artifacts. This is a logistical and clinical issue that may impede usefulness. Finally, CT angiography exposes the patient to much more radiation than cardiac catheterization. When presented with this fact, many patients decline the test. Despite these limitations, the current results with this technique are impressive, and it is being installed in my hospital's emergency room as you read this. Thus, it is time to pull our heads out of the sand and face the reality of this technique in our armamentarium. ■

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Questions & Comments

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Effective Aspirin Dose

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

Synopsis: *The majority of chronic stable coronary artery disease patients given 75 mg of EC aspirin daily have adequate inhibition of COX, but younger, heavier, and post MI patients may not.*

Source: Maree AO, et al. Platelet Response to Low-Dose Enteric-Coated Aspirin in Patients With Stable Cardiovascular Disease. *J Am Coll Cardiol*. 2005;47:1258-1263.

Aspirin resistance is a concern for the long-term treatment of patients with cardiovascular disease. Maree and colleagues from Dublin, Ireland, tested the hypothesis that low-dose enteric-coated (EC) aspirin provides inadequate drug bioavailability and incomplete inhibition of platelet aggregation in 131 stable patients with atherosclerotic coronary artery disease who were taking 75 mg a day of EC aspirin. Serum thromboxane (TX) B2 was measured to assess cyclooxygenase (COX) activity. A subgroup also had arachidonic acid (AA) stimulated TX B2

production from platelet-rich plasma and platelet aggregation measured. If platelet aggregation was detected, the assay was repeated after adding aspirin to the platelet-rich plasma.

Results: Forty-four percent of the patients had elevated TX B2 levels, which indicates a suboptimal response to aspirin. Patients with a suboptimal response to aspirin were more likely to exhibit platelet aggregation to AA (21% vs 3% of those with low TX B2 levels, $P = .004$). When platelet aggregation was shown with AA, it was always abolished by addition of aspirin in vitro. Patients who showed suboptimal aspirin responses were younger, heavier, and more likely to have had a previous myocardial infarction (MI) on multiple regression analysis. Maree et al concluded that the majority of chronic stable coronary artery disease patients given 75 mg of EC aspirin daily have adequate inhibition of COX, but younger, heavier, and post MI patients may not.

COMMENTARY

Aspirin irreversibly inhibits COX and prevents the conversion of AA to TX, which is required for platelet aggregation. In healthy volunteers, 30-40 mg of aspirin will effectively cease platelet aggregation in vitro. In patients, studies have shown that such inhibition is easily obtained with 75-150 mg of plain aspirin, because the average bioavailability of aspirin is about 50%. This study tested the effect of EC aspirin in patients, and found a high level of inadequate responses (44%). The reason for this suboptimal response is not known, but enteric coating may inhibit absorption of aspirin or hasten its breakdown. This is supported by the association of a suboptimal response with heavier and younger individuals. More importantly, those with a previous MI were also more likely not to respond to 75 mg of EC aspirin for reasons that are unclear. However, these data suggest that patients with chronic stable coronary atherosclerosis, especially if they are post MI, should receive at least 150-162 mg of EC aspirin or plain aspirin if they can tolerate it. Low-dose (75-81 mg) aspirin is probably adequate for primary prevention, especially if plain aspirin is used. The practice of using lower doses of aspirin in the elderly is supported by this study, since younger patients seemed to be more resistant. Also, larger doses should be given to larger individuals. It seems that aspirin preparations and doses need to be tailored to the individual patient. ■

Colchicine for Acute Pericarditis

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

Synopsis: *Colchicine added to conventional therapy for acute pericarditis reduced the recurrence rate and corticosteroids increased it.*

Source: Imazio M, et al. Colchicine in Addition to Conventional Therapy for Acute Pericarditis: Results of the COlchicine for Acute PEricarditis (COPE) Trial. *Circulation*. 2005:112: 2012-2016.

COLCHICINE IS AN ANTI-INFLAMMATORY AGENT THAT has been used successfully to treat recurrent pericarditis. Imazio and colleagues from Italy, hypothesized that if colchicine was started during acute pericarditis, it may reduce recurrences. They studied 120 patients with a first episode of acute pericarditis. The only exclusion criteria were infective and neoplastic causes and contraindications to colchicine therapy. Acute pericarditis was diagnosed by 2 of the following: typical chest pain, friction rub, or characteristic ECG changes. The patients were randomly assigned to conventional therapy with high-dose aspirin (800 mg po 6-8 hours for 7-10 days then tapering off over 1 month) or aspirin plus colchicine, 1-2 mg the first day followed by 0.5-1.0 mg daily for 3 months. Corticosteroids were only used in those [who were] aspirin intolerant. The primary end point was recurrent pericarditis, defined as pain plus evidence of pericardial inflammation (blood tests, ECG, echocardiogram).

Results: Over a mean follow-up of 24 months, a higher recurrence rate was observed in the aspirin-alone group vs the colchicine group (33% vs 12%; $P = .009$). Almost all recurrences occurred within 18 months. Colchicine-treated patients had a longer symptom-free interval (23 vs 17 months; $P = .007$). Corticosteroids were given to 16% of the patients; in this subgroup, recurrence rates were 87% in the corticosteroid group vs 11% in the corticosteroid plus colchicine group ($P < .001$). Multivariate analysis confirms that early steroid use increased the recurrent rate significantly, and colchicine use lowered it. Overall adverse effects were mild: 8% had diarrhea on colchicine and 7% had GI side effects on aspirin (P = NS). Imazio et al concluded that colchicine added to conventional therapy for acute pericarditis reduced the recurrence rate and corticosteroids increased it.

COMMENTARY

This paper advances the concept that colchicine should

be standard therapy along with NSAIDs, such as aspirin, for acute pericarditis and, that after the first few weeks, only the colchicine should be continued for 3 months. It hastened the resolution of symptoms, and deceased recurrences of 2 years, compared to early aspirin therapy alone. There is a good biologic rationale for the drug since it affects the secretory function of leukocytes, which should reduce inflammation. The drug dose was weight adjusted, but GI side effects still occurred in about 8% of those treated with colchicine. This may limit therapy. Although used for years to treat recurrent pericarditis, this study recommends it for early treatment and late prophylaxis against recurrence. Predictably steroids increased the number of recurrences.

It is tempting to change our practice based upon this study, but it had several weaknesses. It was open label, so treatment biases could have occurred. The primary end point of pericarditis recurrence required symptoms which are subjective. Theoretically, acute pericarditis is viral, and etiology and recurrences are due to autoimmune phenomena. They excluded infective and neoplastic causes, but included patients with autoimmune diseases. How much these later patients would have affected the early beneficial effect is unclear. Finally, colchicine therapy alone was not studied, and only one duration of therapy was tested. ■

Outcomes and the Volume of Cardioverter-Defibrillator Implants Performed

ABSTRACT & COMMENTARY

By John P. DiMarco, MD, PhD

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Dr. DiMarco is a consultant for Novartis, and does research for Medtronic and Guidant.

Synopsis: *ICDs implanted by higher volume physicians are associated with lower rates of mechanical complications and infection.*

Source: Al-Khatib SM, et al. The Relation Between Patients' Outcomes and the Volume of Cardioverter-Defibrillator Implantation Procedures Performed By Physicians Treating Medicare Beneficiaries. *J Am Coll Cardiol*. 2005;46:1536-1540.

It has been previously well documented that greater operation volume is associated with improved outcomes for several cardiac procedures. In this paper Al-Khatib and colleagues analyzed the Medicare Provider Analysis and Review (MEDPAR) files and correlated patient short-term outcomes with the volume of implantable cardioverter defibrillator (ICD) insertions performed by the individual implanting physicians. Al-Khatib et al sampled 20% of Medicare part B claims and correlated them with valid physician identifiers for the period between January 1, 1999 and December 30, 2001. Hospital admission and discharge dates that covered the period of implantation were identified, and the hospitalization was classified as elective, urgent or emergent. Patient co-morbidities were assessed using the Charlson Co-Morbidity Score. Outcomes were identified on the claim forms for the initial procedure or for subsequent claims available within 90 days of the index procedure. Al-Khatib et al specifically looked for the presence of codes for device related infections and mechanical complications within this period. Individual physician volumes were estimated using a 5-fold multiplier to calculate an average annual volume of ICD placement. A frequency distribution of physician procedure volumes was created and used to test the relationship between implanter volume and outcomes.

In the 20% sample selected for study, 1672 physicians submitted Medicare claims for ICD implantation in 9854 patients. Adjusted for the sample size, the average annual volume ranged from 1 to 87, with a median of 7 procedures per year. Over 60% of the physicians performed between 1 and 10 ICD implants per year, about 20% performed between 11 and 18, 15% between 19 and 28, only 7% more than 29 implants per year. Of the patients included in the sample, 19.3% were over age 80, 21.6% were women, and 92.4% were white. The Charlson Co-Morbidity Score was 0 or 1 in 79.9%. There were only small differences in patient characteristics across quartiles of physician volume. The overall mortality rate in the entire population was 2.4% within 30 days and 5.8% within 90 days. Mortality rates were not affected by physician volume. There was, however, a significant increase in mechanical complications between the highest volume and the lowest volume implanters, and a significant decrease in infections among the highest volume implanters. The 90-day mechanical complication rate was 7% among physicians who had implanted 1 to 10 ICDs vs 4.4-4.9% in the other 3 quartiles. For 90-day infection, the rate was 1.2% to 1.4% in the 3 lower volume quartiles, and only 0.6% in the highest volume quartile. These observations held true after adjustment for the urgency of the implantation.

Al-Khatib et al conclude that ICDs implanted by higher volume physicians are associated with lower rates of mechanical

complications and infection. They suggest that ICD implantation should be directed towards high volume physicians.

COMMENTARY

The data in this paper confirm previous observations that, as a general rule, higher volume operators have better outcomes than low volume operators. This has been shown for percutaneous interventions, CABG surgery, and other cardiac procedures.

ICD implantation and follow-up, however, requires 2 separate skills. The surgical skills for placing a lead and making the pocket are now not much different than the skills required for a routine single or dual chamber pacemaker insertion. Programming the devices optimally and trouble shooting during acute defibrillation testing and chronic follow-up, however, require more than just surgical skills. These latter skills are best learned during formal training in clinical cardiac electrophysiology, or by frequent clinical practice in that discipline. This paper really deals with only the surgical part of the issue.

Recently, the Heart Rhythm Society has proposed that experienced pacemaker implanters, either cardiologists or cardiac surgeons, could gain competency in ICD implantation under certain circumstances. The guidelines suggest that physicians who implant more than 35 pacemakers per year, with over 100 within 3 years, could gain competency in ICD implantation after a minimum of 10 mentored initial implants and 5 follow-up procedures. In contrast, clinical cardiac electrophysiology fellowship training programs require at least 25 ICD initial implants, and training in most programs would provide several times this number. The data presented here suggest that both groups need to maintain a reasonable volume to minimize surgical complications. Optimal trouble-shooting and follow-up should also be related to the number of patients followed, and this will usually favor follow-up by electrophysiologists whenever problems arise.

There are several possible limitations of the data presented here that should also be recognized. During the period under study, cardiac resynchronization therapy was just being introduced. These procedures are considerably more involved and risky, and I would expect that they were performed only by the highest volume operators during this time period. MEDPAR coding during this period probably did not allow these procedures to be separately analyzed. This may well have artificially increased the rate of mechanical complications and infections for the highest volume implanter group. We are also not told the specialty training of the operators in this survey. Over the last 15 years, ICD implantation has gradually passed from cardiac surgeons to electrophysiologists in most centers. However, certain complicated cases may still be done by surgeons, and the reasons for the complicated procedure may not be reflected in a co-morbidity index. Few surgeons do many ICD implants per year, yet the cases they do may be the most hazardous. This may account for some of the excess complications noted in the low implanter volume group. ■

High Sensitivity C-Reactive Protein Predicts Recurrence of Atrial Fibrillation

ABSTRACT & COMMENTARY

By John P. DiMarco, MD, PhD

Synopsis: *These data, indicating that high levels of CRP are associated with an increased risk of recurrence, support the concept that systemic inflammation is important for the pathogenesis of atrial fibrillation.*

Source: Malouf JF, et al. High Sensitivity C-Reactive Protein: A Novel Predictor for Recurrence of Atrial Fibrillation After Successful Cardioversion. *J Am Coll Cardiol*. 2005;46: 1284-1287.

In this paper, Malouf and colleagues from the Mayo Clinic looked at the significance of C-reactive protein (CRP) levels on the recurrence of atrial fibrillation or atrial flutter after a successful cardioversion. In 67 patients referred for cardioversion, high-sensitivity CRP was measured in patients prior to the procedure. Patients with previous cardioversions, recent infections, recent coronary surgery, or an acute coronary syndrome were excluded. CRP values were then included with other variables in a logistic regression model to identify univariate and multivariate predictors for recurrence of arrhythmia within one month after cardioversion. A large number of patient characteristics were included in the model, and stepwise linear regression was used first to identify univariate predictors of recurrence. Variables that were determined to be associated with recurrence in the first step were then included in a multivariate analysis. In the final step, the association of CRP levels was assessed after adjusting for the variables determined to show a relationship in the first and second steps.

Before cardioversion, the estimated duration of the arrhythmia was less than one month in 52% of the patients and more than one month in 48%. Only 2 patients had been in atrial fibrillation for more than one year. At

the one month follow-up, 22 patients (33%) had recurrence of atrial fibrillation or atrial flutter. Pre-cardioversion CRP levels were associated with arrhythmia recurrence, even after adjusting for age, gender, and duration of arrhythmia. Other univariate predictors of arrhythmia recurrence included a higher pre-cardioversion mean heart rate, pre-cardioversion use of class 1C antiarrhythmic drugs, or calcium channel blockers. An increase in the frequency of recurrent arrhythmia was also noted among patients discharged on nondihydropyridine channel blockers. A trend towards less arrhythmia recurrence was seen among patients discharged on beta blockers. Interestingly, Malouf and colleagues report that left ventricular ejection fraction, the presence of valvular heart disease, pre-conversion usage of angiotensin receptor blockers, angiotensin converting enzyme inhibitors, amiodarone, sotalol, and digoxin were not predictors of recurrence. Unfortunately, the influence of any post-discharge antiarrhythmic drugs is not clearly reported. On multivariate analysis, pre-cardioversion CRP was the only independent predictor of recurrence, with an odds ratio of 2.19 (95% confidence interval 1.05 to 4.55; $P = 0.036$). Malouf et al suggest that their data, indicating that high levels of CRP are associated with an increased risk of recurrence, support the concept that systemic inflammation is important for the pathogenesis of atrial fibrillation.

COMMENTARY

This is an interesting report that, although it does not provide definite data, should lead to further studies investigating the role of inflammation in the pathogenesis and maintenance of atrial fibrillation. There has been increasing interest in the role of the atrial endocardium in atrial fibrillation, and inflammation is one of the possible factors that might promote changes which favor atrial fibrillation.

The major limitation in this study is the very large number of variables examined in a relatively small population. Numerous, large studies of antiarrhythmic therapy have shown that sotalol, amiodarone, or other antiarrhythmic drugs are more effective than placebo in preventing recurrences of atrial fibrillation. Malouf et al report that there was not a relationship with amiodarone or sotalol therapy, but it seems likely that most patients were discharged on antiarrhythmics, and the study was not large enough to differentiate between 2 effective agents. The same logic may well pertain to this study's inability to show an effect from angiotensin receptor blockers and angiotensin converting enzyme inhibitors, agents shown to help prevent recurrent atrial fibrillation in other reports. One would anticipate that many of the patients were discharged on these agents and, therefore, one could not see whether these truly had an effect on recurrence.

We must also remember that merely identifying a risk factor for an adverse clinical outcome does not always mean that treatment directed against the risk factor will produce benefit. However, the observations here, and in other studies, seem promising and should lead to the next level of clinical trials. ■

More Data From PROVE IT-TIMI 22

A SPECIAL REPORT

By Jonathan Abrams, MD

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Dr. Abrams serves on the speaker's bureau for Merck, Pfizer, and Parke-Davis.

A RECENT JOURNAL OF THE AMERICAN COLLEGE OF Cardiology contains a Focus Issue section, consisting of 3 articles about PROVE IT-TIMI 22 and a state of the art paper relating to the lipid independent or pleiotropic affects of statins in the management of acute coronary syndromes (ACS). The previously reported main PROVE IT-TIMI 22 trial randomized over 4000 individuals with ACS to a moderate or intensive LDL lowering strategy. A less potent drug, pravastatin 40mg, was compared to atorvastatin 80mg. Average follow-up was 24 months (18-36 months). Patients were randomized to a statin within 10 days of hospitalization for ACS. The primary end point was reduced by 16%. The first article is a post hoc analysis of early and late events in the PROVE IT-TIMI 22 trial, focusing on the 30-day window after admission, as well as long-term follow up from 6 months to the end of the study. The analysis mirrors the data from the primary report, and somewhat arbitrarily breaks down the overall results into 2 time periods. Thus, the composite end point in the atorva patients vs prava had a risk reduction of 24%, $P = 0.0002$, with an average duration of follow-up of 2 years. When early effects alone were analyzed, there was a 15% risk reduction within 15 days (NS). At 4 months, the primary end point was achieved by 8.2% of patients in the intensive (atorva) arm vs 10.2% on prava, risk reduction of 19%, $P = 0.03$. Using a different multiple end point, risk reduction was 28% at 30 days with atorva ($P = 0.046$), CRP levels were lower at 30 days and 4 months with atorva. Late effects of statin treatment (6 months to end of study) resulted in an 18% hazard reduction with atorva, $P = 0.037$, and a separate conditional hazard analysis from 1 year to the end of the follow-up demonstrated a 28% risk reduction with atorva, $P = 0.02$. The composite triple end point was also positive for atorva, with a 28% risk reduction, $P = 0.003$ by study end. The authors suggest that the early

benefits in the high dose statin cohort "…occur before the greater reductions in LDL-C with intensive statin therapy are likely to have had any significant effect." They stress that the greater CRP reduction in the intensive therapy group supports ". . .greater early anti-inflammatory pleiotropic affects with intensive statin therapy." They conclude that all ACS patients should receive high-dose intensive statin therapy in hospital, and that the statin "should be continued long-term."

Safety of Intensive Statin Therapy

The second article by Wiviott and colleagues reports on possible adverse outcomes with intensive lipid lowering, compared to the moderate pravastatin group. This analysis only involved the intensive treatment arm, who had greater lowering of LDL cholesterol and presumably a greater degree of potential risk. The primary efficacy analysis used a composite end point with multi-variable analysis for differences in baseline characteristics, such as age, gender, and diabetes. Crude rates of safety were reported, including evaluation of hemorrhagic stroke and liver enzymes. The results in the 2100 patients randomized to atorvastatin 80mg were quite reassuring, with infrequent muscular side effects and no rhabdomyolysis. Furthermore, there was no relationship between achieved LDL and muscle symptoms. There were no ophthalmologic events. Of interest, there was no correlation between the degree of LDL reduction and increased liver enzymes. Ten percent of the entire atorvastatin cohort achieved LDL levels < 40 mg/dL, and fully 25% were < 50 mg/dL. There was no increase in adverse events in these subjects. The lowest achieved LDL levels tended to have lower baseline LDL concentrations, more commonly found in older males, diabetics, and those who had not utilized statin therapy. Wiviott et al point out that PROVE-IT-TIMI-22 "is the largest long-term specific study of the safety of high-dose atorvas- tatin published to date." They note that adverse events were few, and suggest that the data are most reassuring. Regarding efficacy, they suggest that "further LDL lowering beyond the new guideline optimal goal of less than 70 mg/dL may translate into an additional clinical benefit." Wiviott et al note that TNT, HPS, and A to Z are all comparable with respect to statin efficacy, as related to the potency of statins. Wiviott et al point out that this analysis is post-hoc, and they emphasize that PROVE-IT used single doses of 2 statins; thus, other agents or combinations might not have fared so well.

Inflammation and Statins

The third article in this series evaluated the relationship between uncontrolled risk factors and C-reactive protein (CRP) levels in patients receiving standard or intensive statin therapy for ACS. This evaluation consisted of 2885 patients on either atorvastatin or pravastatin who had metabolic markers and CRP measurements available at 4 months; these patients reflect approximately 70 % of the entire study. Four-month CRP levels were correlated with multiple variables, including BMI, systolic blood pressure, glucose, LDL, and triglycerides. Furthermore, smoking, diabetes, and "uncontrolled metabolic risk factors" were factored into the analysis. Multi-variant analyses were utilized using log CRP and multiple risk factors. The relationships between risk factors were relatively weak, although independently associated with higher CRP, and included age, female sex, BMI, smoking, LDL > 70 mg/dL, glucose > 110 mg, and HDL < 50 mg/dL. Uncontrolled risk factors demonstrated a direct relationship between CRP levels for both statins. Nevertheless, randomization to the intensive group was associated with a lower CRP in spite of uncontrolled risk factors, and this was true across all strata. Wiviott et al conclude that "a more intensive statin regimen consistently achieved lower CRP levels in 4 months. . .independent of lipid levels in the presence of CV risk factors." The highest CRP levels were noted in individuals with the greatest number of metabolic and/or lifestyle risk factors, with an approximate 0.3-0.5 mg/dL greater CRP increment for each risk factor present. Lower numbers of risk factors were associated with lower CRP. CRP levels were lower in the intensive group when compared to the standard group (pravastatin), no matter how many risk factors were present. Wiviott et al suggest that there may have been greater pleiotropic effects related to statin dose (intensive arm) via interaction with intercellular mechanisms, including Rho/Rho kinase pathways, lipid rafts, etc. They point out that although there was a weak relationship between achieved CRP and LDL, as cited in the initial publication of PROVE-IT1, there is at least some interaction between the 2 variables. The final conclusions are that high-dose statin therapy "was independently associated with significantly lower CRP levels irrespective of the number of type of risk factors present." They suggest that CRP might be valuable as a global barometer of the effectiveness of lifestyle and other interventions that modify CV risks.

Pleiotrophic Effects of Statins

The last paper in this Focus Issue deals with the potential relevance of multiple lipids independent or pleiotropic effects of statins. This is a thorough review of many studies that suggest the importance of such lipid independent actions, including the effect of these drugs on endothelial cells, thrombosis, markers of coagulation, and the interaction between stains and inflammation. Considerable basic science work is reviewed with excellent diagrams, demon-

strating a wide variety of putative mechanisms. It is of interest that there are indeed many potential alterations relating to the effects of statins in ACS, as formulated by Wiviott et al. Thus, in addition to the evidence for CRP lowering with statins in clinical trials, these drugs produce reductions in ICAM-1, e-selection, IL-1, IL-6, and soluble CD40-ligand. The timing of event curve separations is an issue of scrutiny, in that stable CAD patients generally have a much later curve separation and statistical evidence of benefit from LDL cholesterol lowering than in ACS, where available data indicate very rapid favorable alterations, with early statin initiation. Finally, Wiviott et al conclude that "the highest statin doses may be important for early clinical benefits in ACS patients." They suggest that the "lipid independent effects of statins. . .may contribute to the early reduction in cardiovascular risk observed with intensive statin therapy in ACS."

COMMENTARY

For those readers particularly interested in the issues of statin therapy, acute coronary syndromes, and mechanisms of benefit, it is worth reading these articles, particularly the last one, which is not a study, but a well written comprehensive review of potential pleiotropy in ACS. There is clearly some aspect of data dredging in this focused review of PROVE-IT-TIMI-22. The first 3 papers all reconfirm statin efficacy, as well as safety in the aggregate, but nothing particularly new is noted. The authors' observations and conclusions that early intensive statin therapy is particularly beneficial in ACS is of considerable interest. Nevertheless, many papers have indicated that patients who are on statin, or who are put on statin during a hospitalization for ACS, fare well, and a very recent publication even indicates day one statin use is related to favorable outcomes. Although the results of MIRACL, the first randomized controlled trail in ACS, were disappointing to many, they now seem to be more valid; the relatively modest benefits in that study has been amplified by the larger and longer studies such as PROVE IT-TIMI-22. The TNT study in stable CAD patients supports the favorable data in the core PROVE IT paper, as well as in these 3 additional publications, as does the REVERSAL trial. It would appear that in high-risk individuals, particularly those with an ACS or perhaps with a multiplicity of risk factors, very aggressive LDL lowering to achieve a target of 70 mg/dL or less, is no longer a fairy tale, and should be a reality for all practicing physicians caring for these patients. ■

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CME Questions

23. Which of the following is correct concerning enteric coated aspirin doses?
a. 75-81 mg/day in large males
b. 150-162 mg/day in post MI patients
c. 300-325 mg/day in small females
d. All of the above

24. Which is correct concerning colchicine for acute pericarditis?
a. Sole therapy is appropriate
b. Use only if recurrences occur
c. Begin early and continue for 3 months
d. Use for steroid failures

25. CT coronary angiography for CAD:
a. has a high negative predictive value.
b. has a high positive predictive value.
c. can be used with any heart rhythm.
d. does not use contrast.

26. High volume ICD implanters had:
a. lower mortality.
b. fewer infections.
c. fewer mechanical complications.
d. B and C

27. Atrial fibrillation recurrence after cardioversion is predicted by:
a. Troponin I.
b. BNP.
c. Hs-CRP.
d. All of the above

28. Which is true regarding statin therapy for ACS?
a. should be started on day one
b. the LDL target is < 70mg/dL
c. results in a high incidence of muscle problems
d. A and B

Answers: 23. (b); 24. (c); 25. (a); 26. (d); 27. (c); 28. (d)

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