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INSIDE

Stem Cells: Post-Myocardial Infarction

ABSTRACT & COMMENTARY

Synopsis: *Autologous bone marrow stem cells injected into the infarct-related artery, after successful PCI, improves LVEF at 6 months, compared to controls.*

Source: Wollert KC, et al. Intracoronary Autologous Bone-Marrow Cell Transfer After Myocardial Infarction: The BOOST Randomised Controlled Clinical Trial. *Lancet*. 2004;364:141-148.

THE INHERENT TIME DELAYS IN ACHIEVING REPERFUSION IN acute myocardial infarction (MI) often result in myocardial damage. Autologous bone marrow stem cells have shown promise for repairing this damage. Thus, Wollert and colleagues designed a randomized trial of intracoronary injections of autologous bone marrow stem cells in patients with acute ST elevation MI who had successful percutaneous intervention (PCI) with stenting. Eligible patients had to have single vessel disease and evidence of left ventricular (LV) wall motion abnormalities, but also had to be stable. After the 60 patients were enrolled and randomized to either autologous bone marrow infusion into the infarct-related artery or control groups (30 each), each patient underwent cardiac MRI, with contrast. The primary end point was global LV ejection fraction (EF) change from baseline to 6 months. The enrolled subjects were mainly male, hypertensive smokers, with left anterior descending lesions. Appropriate medical therapy was 93-100% in both groups.

Results: Baseline LVEF (mean, 3.5 days post PCI) increased from 50% to 56.7% ($P < .003$) in the stem cell group, as compared to 51% to 52% in the control group (P = NS). Measures of LV volumes, mass, and infarct size (late contrast enhancement) did not change significantly in either group. The beneficial change in EF was seen across all subgroups and was unrelated to characteristics of the cells infused. Regional wall motion analysis showed that the beneficial effect was confined to the peri-infarct zone. Formal electrophysiologic (EP) testing was done in 90% of the patients, and no difference was seen in inducible arrhythmias. Also, there was no difference in clinical outcomes or in-stent restenosis between the 2 groups. Wollert et al concluded that autologous bone marrow stem

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cells injected into the infarct-related artery, after successful PCI, improves LVEF at 6 months, compared to controls.

COMMENT BY MICHAEL H. CRAWFORD, MD

Stem cells are the hot new thing in cardiac research, and the use of autologous bone marrow cells avoids ethical and legal issues. After several preliminary feasibility studies, Wollert et al from Germany have completed a randomized, controlled trial in humans. The results are encouraging for several reasons. The procedure appeared safe, as no untoward effects were observed. Of special concern are arrhythmias, since prior studies have shown that other types of cells, when incorporated into the myocardium, become disordered regions, which increase the propensity to arrhythmias. There was no increase in clinical arrhythmias, and EP testing was no different in the 2 groups. Part of the reason for this lack of arrhythmias may have been the observation that the cells were not transformed into myocytes. If they were not adding to the myocyte pool, how were they increasing LVEF? Although this was not a mechanistic study, other data suggest that these cells may have a paracrine effect that promotes angiogenesis. This may also explain why there was no effect on remodeling (no change in LV volumes). That the procedure changed EF without changing LV volumes, suggests that it improved the inotropic state of the myocardium, perhaps through these paracrine pathways. Whether such a change will be sustained in the absence of structural changes in the myocardium, will require further long-term follow-up.

The study population was somewhat unique in that 40% were referred from other hospitals for rescue angioplasty. Thus, the average duration of symptoms to PCI was 8.5 hours. This is certainly beyond the optimal time for recovery of myocardium. Yet, this procedure, done 3-5 days later, was able to show some positive benefit. Presumably, stunning was over by then, otherwise, the improvement would be expected. Finally, the controls did not have a sham procedure, which raises the question of whether just doing a bone marrow harvest and another cardiac catheterization has some positive effect on LV performance that persists. Although encouraging, this stem cell procedure is not ready for prime time. ■

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Prognosis of Women with Syndrome X

ABSTRACT & COMMENTARY

Synopsis: *An abnormal stress MRS, indicative of myocardial ischemia in symptomatic women without CAD, predicts cardiovascular events, especially hospitalization for unstable angina.*

Source: Johnson BD, et al. Prognosis in Women with Myocardial Ischemia in the Absence of Obstructive Coronary Disease: Results from the National Institutes of Health-National Heart, Lung, and Blood Institutes-Sponsored Women's Ischemia Syndrome Evaluation (WISE). *Circulation*. 2004;109:2993-2999.

The cardiac syndrome X, signs and symptoms of myocardial ischemia without epicardial coronary artery disease (CAD), can be associated with a stress-induced reduction in the myocardial phosphocreatine-adenosine triphosphate ratio, as measured by phosphorous-31 nuclear magnetic resonance spectroscopy (MRS). Johnson and colleagues, from the NHLBI-sponsored Women's Ischemia Syndrome Evaluation (WISE) study, sought to determine the prognostic value of an abnormal MRS, indicative of myocardial ischemia, in the absence of CAD. Women, referred for coronary angiography for suspected myocardial ischemia, underwent handgrip stress MRS and follow-up evaluation. There were 3 groups: 1) 60 with no CAD and a normal

stress MRS; 2) 14 with no CAD and an abnormal MRS; 3) 352 with CAD, 13 of whom had MRS. The primary end point was freedom from cardiovascular events—death, myocardial infarction, heart failure, stroke, and hospitalization for unstable angina. Compared to those with CAD, those without were younger, had fewer CAD risk factors, and had a higher frequency of hormone therapy. Women with an abnormal MRS were likely to be smokers. Cumulative freedom from cardiovascular events at 3 years was 87, 57, and 52% for groups 1-3, respectively ($P < .01$). Among the 74 without CAD, most of the events were hospital admissions for unstable angina. After adjustment for confounders, an abnormal MRS was an independent predictor of events ($P = .02$). Total costs were highest for CAD patients, but for the no CAD abnormal MRS women, the costs were similar to the CAD women ($11,102 vs $14,495; P = NS). Johnson et al concluded that an abnormal stress MRS, indicative of myocardial ischemia in symptomatic women without CAD, predicts cardiovascular events, especially hospitalization for unstable angina.

COMMENT BY MICHAEL H. CRAWFORD, MD

The results of this study suggest that a subgroup of women without CAD have symptoms caused by myocardial ischemia that can be detected by stress MRS. Johnson et al's experience suggests that this subgroup represents 20% of such women. Of importance, this study shows that they have almost the same number of cardiovascular events over 3 years as women with CAD. Presumably, this disorder, sometimes called Syndrome X, is due to microvascular disease. Unfortunately, as this study confirms, the usual therapy for myocardial ischemia is not particularly effective. Thus, these women are frequently hospitalized, and undergo invasive and noninvasive tests, which increase health care costs.

The implication of this study is that by using handgrip stress MRS, these women can be identified and appropriately managed, reducing health care costs. Johnson et al claim that other tests for myocardial ischemia in these women have shown inconsistent results, and therefore, are not as good as MRS. However, this remains to be proven, and there are several limitations to MRS. First, MRS only samples the anterior myocardium. So whether the MRS test is positive or negative for ischemia, you still cannot rule out CAD, nor that the microvascular disease is localized. Thus, all patients suspected of having Syndrome X require cardiac catheterization. Second, handgrip stress may not be sufficient to bring out myocardial ischemia, but this is the only type of exercise feasible in these small bore magnets. Perhaps dobutamine or other pharmacologic agents would increase the sensitivity for detecting myocardial ischemia. Finally, this is a small study that was underpowered to detect hard events. There were no deaths or MIs over the 3 years. At this point, the value of this article is that it substantiates, by sophisticated metabolic analysis, that this syndrome exists and represents a challenge to physicians who care for patients with chest pain. ■

Abdominal Aortic Aneurysm

ABSTRACT & COMMENTARY

Synopsis: *Annual, or less frequent, surveillance intervals are effective for aneurysms < 45 mm in diameter.*

Source: Brady AR, et al. Abdominal Aortic Aneurysm Expansion: Risk Factors and Time Intervals for Surveillance. *Circulation*. 2004;110:16-21.

Studies have shown that abdominal aortic aneurysms (AAA) can be safely followed until a diameter of 55 mm is reached before considering surgery. However, the size surveillance frequency is poorly understood. Thus, Brady and colleagues, from the United Kingdom (UK) Small Aneurysm Trial, analyzed repeated AAA diameter measurements by ultrasonography from a large national cohort to characterize AAA expansion and its determinants. In 93 UK hospitals, patients referred to vascular surgeons with aneurysms 40 to 50 mm in diameter, who were fit for surgery, were asked to participate in a trial comparing immediate surgery to surveillance and surgery, if the aneurysm became > 55 mm, grew by > 10 mm/year, or they had symptoms due to the aneurysm. The surveillance frequency was every 3 months for aneurysms > 50 and < 55, and 6 months for those < 50 mm. Sophisticated, statistical methods were used to eliminate bias. Among 2366 patients recruited, 1743 had more than 1 (9125 total) AAA diameter measurement over a mean of 2 years follow-up (maximum 8 years). The mean, initial AAA diameter was 43 mm, and the growth rate was 2.6 mm/year (95% range, 1.0-6.1 mm/year). The strongest predictor of growth rate was initial size. Growth rates were lower in diabetics and those with peripheral vascular disease, but higher in current smokers. Age, hypertension, and other cardiovascular disease risk factors were not related to growth. The surveillance intervals to keep < 1% at 55 mm were 36, 24, 12, and 3 months for aneurysms of 35, 40, 45, and 50 mm, respectively. Brady and colleagues concluded that annual, or less frequent, surveillance intervals are

effective for aneurysms < 45 mm in diameter.

COMMENT BY MICHAEL H. CRAWFORD, MD

This study presents highly practical information that is of value to patients, physicians, and health care systems. Brady et al set the goal of keeping the discovery of patients with AAA diameter > 55 mm to 1% as their surveillance interval standard. This should be acceptable to all. They found that the growth rate of AAAs was slower than appreciated in previous studies because the earlier studies used linear regression modeling, which is biased toward larger aneurysms with higher growth rates. AAA size is the major factor in predicting aneurysm growth rates. Thus, the surveillance frequency proposed varies with initial AAA size.

Since the upper limit of the abdominal aortic diameter is 30 mm, why not operate on everyone above that limit and save the cost of all this screening? Two studies, 1 in the United States, and this study from the United Kingdom, did not show a mortality benefit of such a strategy. However, some studies have shown a low rupture rate up to a diameter of 60 mm. Thus some have recommended advising surgery based upon AAA size and the risk of surgery. For example, a healthy 60-year-old with an aneurysm of 55 mm would get surgery, but in a more risky patient, one might wait until 60 or 65 mm. This approach makes some sense, but has not been studied prospectively.

Interestingly, traditional atherosclerosis risk factors do not seem to be a factor in aneurysm growth, with the exception of smoking. However, the effect of smoking on AAAs may not be related to its effect on atherosclerosis. Pathologic studies have shown that AAAs are not typically atherosclerotic, and the main findings are inflammation and proteolysis. Thus, we don't fully understand the pathogenesis of AAAs, but smoking cessation would make sense since it increases the growth rate of AAAs by up to 20%. Because we don't understand the pathogenesis of AAAs, some have suggested that every 70-year-old man should have 1 abdominal ultrasound screening or other imaging study. The effectiveness of this recommendation is not proven, but it makes some sense. We are not told how the patients in this study were identified. Some may have had symptoms, a positive abdominal physical exam, or routine screening.

Again, because of our ignorance about the pathogenesis of AAA, Brady et al have suggested that surveillance be applied to post-stent graft and post-operative patients, under the theory that the untreated segments of aorta may expand over time and cause leaks. ■

Cryoablation of Supraventricular Tachycardia

ABSTRACT & COMMENTARY

Synopsis: *Cryoablation offers an alternative approach to radiofrequency ablation.*

Source: Friedman PL,et.al. Catheter Cryoablation of Supraventricular Tachycardia: Results of the Multicenter Prospective "Frosty" Trial. *Heart Rhythm*. 2004;1: 129-138.

For many years, radiofrequency energy delivery has been the standard tool for catheter ablation. Recently, a cryoablation catheter was introduced. This report details the clinical results using this catheter in a large clinical trial. Patients were eligible for inclusion in the trial if they were older than age 18 and had a clinical history of supraventricular tachycardia (SVT), suspected to be due to atrioventricular nodal reentry (AVNRT) or AV reentry using an accessory pathway (AVRT). Patients who were undergoing AV junctional ablation for atrial fibrillation, with excess ventricular rates, were also eligible. The study was conducted in 11 hospitals in the United States and 3 in Canada. The ablation catheter used is a 7 French quadripolar steerable catheter with a 4 mm tip. The catheter has an outer shaft that is maintained under constant vacuum, and an inner injection tube through which liquid N_2O is injected. When the liquid N_2O escapes at the end of the injection tube into the outer shaft, it evaporates, resulting in cooling at the tip. A thermocouple at the catheter tip allows temperature to be monitored. In operation, the operator can use either a cryomapping mode, in which temperature is maintained at or above -30° Centigrade, or a cryoablation mode, in which the coldest possible temperature tip is achieved generally less than or equal to -68° Centigrade. The standard period of application for cryoablation is 4 minutes. In this study, cryoablation was performed at sites chosen on the basis of electrical mapping, anatomic landmarks, or the results of cryomapping. No limit was placed on the number of cryomapping or cryoablation attempts. If cryoablation proved unsuccessful, patients could be crossed over to radiofrequency energy for their ablation.

A total of 166 patients were enrolled in the study. The group included 103 patients with AVNRT, 51 patients with AVRT, and 12 patients with atrial fibrillation. In 2 patients, the cryoablation catheter was not activated because of technical difficulties, and 1 patient had discovery of a left atrial tachycardia

after the catheter was introduced. An additional 7 patients did not have a qualifying cryoablation due to inability to achieve target temperature. By intention to treat analysis, acute procedural success was achieved in 91% of the patients with AVNRT, 69% of the patient with AVRT, and 67% of the patients who underwent attempted AV junctional ablation. The increased success rate in patients with AVNRT was statistically significant compared to the other 2 groups. Among the patients with accessory pathways, the success rate was lower (65%) for those with left lateral accessory pathways, compared to those with accessory pathways in other positions. There were 27 patients in whom acute procedural success was not achieved with cryoablation. Twenty-five of these underwent an attempted ablation with radiofrequency energy. Radiofrequency ablation was successful in 23 of these 25 subjects. Cryomapping was attempted before cryoablation in 135 of the patients, and successfully identified a suitable site of ablation in 87 of the 135 subjects. In selective patients, rewarming was performed to see if changes, seen during cryomapping, were reversible. In 58 of the 62 cases, electrophysiologic changes, noted during cryomapping, completely resolved within 6 minutes. All patients showed at least partial recovery of conduction. There were 8 acute major complications related to catheter placement in the trial. None of the complications were specifically related to the cryoablation delivery. There were 10 subjects who had transient abnormalities of AV conduction noted during the procedure. All these conduction abnormalities resolved within 1 minute. No patient had persistent AV block, or required permanent pacemaker insertion. Among the patients in whom acute procedural success rate was achieved, the long-term success was 91% for all subjects, and 94% for those with AVNRT.

Friedman and colleagues conclude that cryoablation offers an alternative approach to radiofrequency ablation. They anticipate that improvements in catheter design in the future will increase the success rate without compromising efficacy.

COMMENT BY JOHN P. DiMARCO, MD, PhD

Since its introduction more than 15 years ago, radiofrequency ablation has become the standard approach for the catheter ablation of many types of cardiac arrhythmias. For patients with the common forms of supraventricular tachycardia, success rates should exceed 95%, with permanent complications seen in less than 0.5%, if the procedure is performed by experienced operators. Many of the complications seen in patients with radiofrequency ablation are due to catheter manipulation and positioning, and would be expected to occur with almost any type of ablation, as was seen in this report. However, radiofrequency energy ablation and cryoablation are quite different in the time required for an irreversible effect to occur. Irreversible damage may be produced within seconds of radiofrequency energy delivery, and if the catheter is not in the correct position, or if it dislodges, AV block may be inadvertently produced. In patients with AV node reentrant tachycardia, the standard approach is to start as far away from the His bundle catheter as possible, but rare patients have posteriorly positioned fast pathways, and in other patients, the slow pathway and the fast pathway are immediately adjacent. In patients with midseptal and anteroseptal accessory pathways, it may be quite difficult to separate the normal conduction system from the accessory pathway. If one ablates an accessory pathway in these positions with radiofrequency energy, one often has a His bundle potential recorded on the ablation catheter that can be seen only after preexcitation has been eliminated. In these patients, having the option to produce a reversible lesion during cryomapping has potential advantages. Freezing takes several minutes to produce irreversible conduction block. If AV block is observed during a lesion, the cryomapping or cryoablation can be stopped, and the tissue should recover. These potential advantages with cryoablation are also relevant in young children, where the area for safe ablation might be quite small and for ablation of septal atrial tachycardias. The disadvantages of cryoablation are several. The lesions do take 4 minutes to produce, and if multiple lesions are required, this can prolong procedure duration. In addition, the marker frequently used to guide slow pathway ablation, is an accelerated junctional rhythm, and this is not seen during cryoablation. One has to rewarm and then retest after every lesion. Although in theory, the catheter should adhere to the tissue at the ablation site during cryomapping and cryoablation, stabilizing the catheter for 4 minutes may be difficult. The long-term results, reported after an acute procedural success, seem to show about the same risk of recurrence of 3% to 5%, as has been reported to occur with standard radiofrequency procedures.

Cryoablation does have a place in the armamentarium of electrophysiologists. Right now, it is the preferred approach if a high risk of producing AV

block is anticipated because of the position of the structure targeted for ablation. In most patients with AVRT and AVNRT, this risk with radiofrequency ablation will remain the modality of choice. Hopefully, in the future, improved catheter design and handling will allow higher success rates to be achieved with cryoablation for all the structures we commonly target. ■

Long-Term Comparison of ICD vs Amiodarone

ABSTRACT & COMMENTARY

Synopsis: *The benefit of ICD therapy, compared to amiodarone therapy in patients with life-threatening arrhythmia, continues to increase over time, and that their long-term data support the use of an ICD as first line therapy for secondary prevention of sudden cardiac death.*

Source: Bokhari F, et al. Long-Term Comparison of the Implantable Cardioverter Defibrillator vs Amiodarone: Eleven-Year Follow-Up of a Subset of Patients in the Canadian Implantable Defibrillator Study (CIDS). *Circulation*. 2004;110:112-116.

The Canadian Implantable Defibrillator Study (CIDS) was a randomized comparison of amiodarone and implantable cardioverter defibrillators (ICD) as initial therapy in patients with documented, sustained ventricular arrhythmias or syncope with inducible ventricular tachycardia. Patients in the study had to have either survived a cardiac arrest with ventricular fibrillation (VF), had hemodynamically significant sustained ventricular tachycardia (VT), or syncope with left ventricular dysfunction and inducible VT. CIDS showed a benefit with ICD therapy that did not reach statistical significance. However, a meta-analysis of 3 trials, CIDS, the Antiarrhythmics vs Implantable Defibrillators Trial (AVID), and the Cardiac Arrest Study Hamburg (CASH) showed a significant reduction in death from any cause in the ICD group, with a summary hazard ratio of 0.72. In this paper, Bokhari and colleagues from St. Michael's Hospital in Toronto, Ontario, Canada, report their single-center experience with longer follow-up of patients in CIDS. At the time the CIDS main trial results were published, Bokhari et al, for this report, with their institutional review board's approval, elected to continue patients who had enrolled in CIDS at their hospital on their previously assigned therapy. The primary end point for this extended follow-up study was all cause mortality. Secondary end points were cause specific mortality, amiodarone related side effects, amiodarone discontinuation, and ventricular arrhythmia recurrence. In patients with an ICD, each stored arrhythmia episode was reviewed and classified as appropriate or inappropriate.

There were 120 patients entered at St. Michael's Hospital in the CIDS Trial. The amiodarone group and the ICD group were well matched in terms of age, gender, ejection fraction, and other clinical parameters. Twenty-seven patients in the amiodarone group presented with VF, compared to 18 in the ICD group. In contrast, 35 patients presented with VT in the ICD group vs 23 in the amiodarone group. The mean total daily amiodarone dose was 398 ± 39 mg at 2 months and 306 ± 89 mg at last follow-up.

During follow-up, there were 28 deaths (47%) in the amiodarone group, compared with 16 deaths (27%) in the ICD group (P = 0.02)—a 43% lower risk of all cause mortality in the latter. There were only 2 presumed arrhythmic deaths in the ICD group, compared with 12 in the amiodarone group. Arrhythmic cardiac deaths, vascular deaths, and noncardiac deaths were almost evenly matched between the 2 groups.

By the end of a median follow-up 5.92 years, 40 patients assigned to amiodarone had either symptomatic nonfatal arrhythmia recurrence (n = 12) or had died. Of note, 25 of the 28 deaths were not preceded by a nonfatal symptomatic arrhythmia recurrence.

Side effects thought to be related to amiodarone were reported in 49 of 60 patients (82%). Of these, 30 patients had side effects requiring dose reduction or discontinuation. In 13 of these patients, the adverse events were considered to be serious. Among the amiodarone patients, there were 19 patients who crossed over to ICD therapy because of either adverse effects which required drug discontinuation or a nonfatal arrhythmia recurrence. In the ICD group, there were 3 pocket infections, 18 lead failures or dislodgements, 1 pneumothorax, 1 deep vein thrombosis, and 1 pocket hematoma. Amiodarone was added to ICD therapy in 26 patients in the ICD group to decrease the frequency of atrial or ventricular arrhythmias. Appropriate ICD therapy was observed during follow-up in 70% of the ICD therapy group. One or more episodes of inappropriate therapy delivery was noted in 30 patients. By using a Cox proportional hazards model, 2 variables were identified as significant independent predictors of survival, ICD therapy and

the absence of coronary artery disease. Bokhari et al conclude that the benefit of ICD therapy, compared to amiodarone therapy in patients with life-threatening arrhythmia, continues to increase over time, and that their long-term data support the use of an ICD as first line therapy for secondary prevention of sudden cardiac death.

COMMENT BY JOHN P. DiMARCO, MD, PhD

The 3 major secondary prevention trials that compared ICD's to antiarrhythmic drugs for secondary prevention of sudden cardiac death (AVID, CIDS and CASH) included relatively few patients who were followed for more than 4 years. In this paper, from a single center that enrolled in CIDS, Bokhari et al elected to keep patients in their assigned group after publication of the main trial results. They observed an increased incidence of serious adverse effects using amiodarone, and also documented a relatively high frequency of complications related to transvenous defibrillators. Another publication from CIDS, which previously showed that the benefits of the initial study, was largely seen among the oldest patients and those with the lowest ejection fractions and the poorest functional status. This led to a proposal that the ICD be the first option only in those with depressed ventricular function, with other patients selected on a case-by-case basis. The data presented here suggest that, over time, the ICD will prove superior for most, but the group is not large enough to test if outcomes for those with preserved ventricular function will be satisfactory.

We should learn several lessons from this report. The data from all the secondary prevention trials show us that neither drug therapy nor ICD therapy is the perfect option for all patients. Drug therapy was frequently limited by side effects, some of which may be dose related, and imperfect efficacy. ICD therapy will be poorly tolerated if frequent events occur. Many patients are best treated with a combined approach. The ICD is the primary treatment, and antiarrhythmics are used to modify the frequency of ventricular, and also supraventricular, arrhythmias. This is illustrated by this paper, in which 19 of the 60 patients in the amiodarone group eventually crossed over to ICD therapy and almost half of the patients (26) in the ICD group eventually had amiodarone added. Patients with rare arrhythmia episodes can be managed just with ICDs. Patients with frequent arrhythmias should have drugs added. The drugs should not be used in high doses, which will increase the frequency of side effects. Rather, the minimal dosage needed to make ICD therapy tolerated should be employed. Combining drugs and devices, in a balanced approach, should lead to the best outcomes. ■

Q-Wave or Non-Q-Wave Myocardial Infarction: Does It Make Any Difference?

ABSTRACT & COMMENTARY

Synopsis: *The Q-wave / non-Q-wave distinction is useful clinically, and the primary determinant of the presence of Q-waves is the total size of the underlying infarction, rather than its transmural extent.*

Source: Moon JCC, et al. The Pathologic Basis of Q-Wave and Non-Q-Wave Myocardial Infarction. *J Am Coll Cardiol*. 2004;44:554-561.

There has been considerable controversy regarding the dichotomous labeling of an acute myocardial infarction (AMI) as transmural vs non transmural; Q-wave vs non-Q-wave; ST elevation (STEMI) vs non-ST elevation (NSTEMI), and more recently, the microinfarcts, defined by isolated troponin elevation without CK or CKMB abnormalities. Prior pathology studies have demonstrated that many Q-wave infarctions are often non transmural, and conversely, transmurality may occur in the absence of Q-waves. The present study using a new imaging technique, late gadolinium enhancement cardiovascular magnetic residence (CMR), was used to evaluate 91 patients with previous myocardial infarction to determine the transmural extent and anatomic features of the MI. The CMR imaging technique employed a 1.5-T CMR scanner, sectioning the left ventricle (LV) into 2 long axis slices, and up to 10 short-axis slices, encompassing the entire LV myocardium. Intravenous gadolinium was injected, with imaging acquired after 10 minutes for late enhancement image analysis. LV function, volume, and mass were calculated, as well as the degree of enhancement within each of the 17 LV sections analyzed, utilizing a scoring system rating ranging from 0-25% to 100% infarction. Each segment was assessed for the presence, at any point, of transmural involvement. Anatomic regions analyzed were anterior, inferior, and lateral; the latter equivalent to posterior MI. Total size of MI was calculated for each territory. ECG analysis was made using both TIMI criteria, as well as those of the ESC/ACC. Of interest, the former were more accurate in correlating with CMR images. The results demonstrated a better correlation of

Q-waves, with total size of the prior MI vs the degree of transmurality. Furthermore, LV function, as assessed by ejection fraction (EF), also correlated with the size of the MI; receiver operating curve 0.85 for all MI (0.90 for anterior and 0.77 for inferior territory). There was no relationship for lateral MI with any parameter. Classification into Q-wave/non-Q-wave MI was a good diagnostic test for the size of MI. In addition, there was an increased likelihood of prior Q-wave MI being present, as the extent of transmural MI territory increased. This was true for both anterior and inferior MI, but not lateral. The total size of MI was a better predictor of Q-wave vs non-Q-wave classification than the transmural extent; the latter did not significantly increase the area under the ROC curve with multivariant analysis, and was not an independent predictor of Q vs non-Q MI. Systolic function was worse in patients with any Q-wave MI in the anterior region vs non-Q MI, (47% EF vs 55%; $P = 0.02$). Anterior Q-wave MI had a lower EF than anterior non-Q MI, (45% vs 55%; $P = 0.003$), but there was no difference between inferior Q-wave vs non-Q MI. Although ESC/ACC definition of Q-wave MI resulted in fewer patients classified as Q-wave MI, both TIMI and ESC/ACC ECG criteria correlated with infarct size, most prominently for anterior MI. Six of 21 anterior Q-wave MI patients were defined as non-transmural, and 34 of 48 transmural MI were classified as Q-wave MI. Thus, non transmural Q-wave infarctions were observed, as well as transmural non-Q-wave infarction. Moon et al conclude that: 1) the Q-wave/non-Q-wave distinction is useful clinically, and 2) the primary determinant of the presence of Q-waves is the total size of the underlying infarction, rather than its transmural extent. Thus, the larger the MI, the more likely Q-waves will be present; conversely Q-waves on an ECG suggest a large infarction and lower EF. Subendocardial infarction was not predicted by the presence, or absence, of Q-Waves. Moon et al opine that MIs have a complex structure, with varying transmural extent, making the transmural/non-transmural division overly simplistic. Previous silent infarctions were not uncommon, even when the index infarction was believed to be the first event. Late gadolinium enhancement CMR is suggested as an excellent technique to evaluate MI. Moon et al suggest that there should be a reinterpretation of anatomic and pathologic bases of the ECG, with new criteria resulting from further research. Although the size of an infarct correlates with outcome, there is no clear evidence that transmural extent is an independent predictor of clinical events compared to the size of the MI. As Moon et say, "MIs are rarely simply one or the other."

COMMENT BY JONATHAN ABRAMS, MD

The terminology of MI has been a subject of many reports over the years, and remains somewhat arcane and confusing. Years ago, it was believed that "non-transmural"or "non-Q-infarction" were more benign than Q-wave MI, until it was realized that long term follow-up demonstrated a merging of survival and event curves, often with worse prognosis for non-Q MI. In the recent era, the terms STEMI and NSTEMI have become popularized; it is well known that morbidity and mortality is higher immediately with STEMI, but during long-term follow-up, NSTEMI subjects have substantial morbidity and mortality. Lytic therapy and/or direct angioplasty are accepted as the appropriate emergent therapy for STEMI, but individuals with NSTEMI or non-Q-wave MI are more complicated to treat, and are candidates for variety of anti-platelet/thrombotic medications, as well as early catherization and possibly early coronary intervention. It is well accepted that the presence of Q-waves usually indicates substantial LV dysfunction, which may or may not be true with NSTEMI without Q-waves.

The present study by Moon et al confirms that the presence of Q-waves are important with respect to predicting LV function. Transmurality of an infarct is not necessarily concordant with Q-waves on the electrocardiogram. Physicians should keep in mind the difference in pathophysiology of ST segment elevation MI compared to non-ST MI. While a large infarction is likely to be present when extensive Q-waves are found, the converse may not be true, ie, LV systolic function can be unexpectantly decreased in the absence of Q-waves. STEMI are generally associated with a total occlusion of a large coronary artery, with significant loss of myocardium. This study, as have others, indicates that the territory subserved by the left anterior descending artery is significantly greater than that supplied by the right coronary artery, helping to explain the better prognosis with interior MI, usually a smaller infarction. NSTEMIs are usually the result of non-occlusive thrombus, often with multiple complex lesions throughout the coronary tree, and leave the patient with "more to come" unless vigorous ACS therapy is instituted. On the other hand, STEMI or Q-waves MI are likely to be larger, have a higher early mortality, and less likely to be accompanied by recurrent infarction or unstable angina after the event. Finally, in spite of attempts to estimate the degree of involvement of LV with troponins, CK, and ECG findings, prompt assessment, of LV function with ultrasound, is critical for all infarctions to provide an accurate baseline ejection fraction and extent of regional wall motion abnormalities. Transmural vs non-transmural infarction is a taxonomy that should be discarded. ■

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.*

New Clinical Guidelines on Cholesterol Management

The National Cholesterol Education Program (NCEP), a product of a collaboration of the National Heart, Lung, and Blood Institutes, the American College of Cardiology, and the American Heart Association, has updated its clinical practice guideline on cholesterol management. Based on several recent studies, that suggest that aggressive lowering of LDL cholesterol benefits high-risk patients, the new guidelines recommend aggressive treatment for patients who are at risk for coronary artery disease. Specifically, patients who are defined as "very high-risk" should be considered for aggressive treatment. Very high-risk patients are defined as those who have cardiovascular disease together with multiple risk factors (especially diabetes), severe and poorly controlled risk factors (such as continued smoking), or metabolic syndrome. The guideline had previously recommended drug therapy in these patients only if the LDL cholesterol was greater than 130 mg/dL, with a goal of 100 mg/dL. The new guideline recommends a treatment threshold of 100 mg/dL, with a goal of 70 mg/dL. "High-risk patients" are defined as those who have coronary heart disease, cerebrovascular disease, peripheral vascular disease, diabetes, or 2 or more risk factors (such as smoking or hypertension) that give a greater than 20% chance of having heart attack within 10 years. The LDL goal for these patients remains 100 mg/dL or less, and the new guideline now recommends drug treatment for those high-risk patients with an LDL > 100 mg/dL. Moderately high-risk patients are defined as those with 2 or more risk factors for coronary heart disease and a 10-20% risk of heart attack within 10 years. For these patients, drug therapy is recommended to lower LDL cholesterol under 130 mg/dL, and the option is given to treat to levels under 100 kg/dL. For lower-risk patients, the guideline was not changed. Drug therapies recommended by the NCEP include statins, bile acid resins, nicotinic acid, and ezetimibe. As in previous NCEP guidelines, the role of lifestyle modification is stressed. The full guideline can be viewed in the July 13th issue of *Circulation*, and highlights can be reviewed on-line at www.nhlbi.nih.gov.

Hypothyroidism and Pregnancy

A new study clarifies thyroid replacement therapy during pregnancy. Researchers at Harvard followed 19 women with hypothyroidism through 20 pregnancies, of which 17 resulted in full-term births. Thyroid function, HCG levels, and estradiol were measured before conception, every 2 weeks for the first trimester, and monthly thereafter. Oral doses of levothyroxine were increased during pregnancy to maintain preconception levels. The mean levothyroxine requirements increased 47% during the first half of pregnancy, plateaued by week 16, and remained

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stable until delivery. The authors recommend that hypothyroid women, who become pregnant, should increase their levothyroxine dose by 30% as soon as pregnancy is confirmed, and should be monitored carefully throughout the duration of their pregnancy (*N Engl J Med*. 2004;351:241-249). Although simple in its design, this is an important study because it is estimated that 1 to 2% of all pregnant women are hypothyroid and need replacement therapy. Hypothyroidism during pregnancy is associated with poor fetal outcomes including impaired cognitive development and increased mortality. Clinicians now have a clear guide to levothyroxine dosing changes during pregnancy.

Anti-Depressants and the Risk of Suicide

The risk of suicidal behavior is relatively high after starting anti-depressants, however, there is no statistical difference between anti-depressants used, according to a new study. Researchers reviewed data from the UK General Practice Research Database from 1993 to 1999, and compared nearly 160,000 users of 4 anti-depressant drugs, 2 SSRIs and 2 tricyclics; fluoxetine, paroxetine, amitriptyline, and dothiepin (a trycyclic anti-depressant not marketed this country). The outcome was first-time non-fatal suicidal behavior, or suicide in treated patients vs comparable patients who did not exhibit suicidal behavior. The relative risks for non-fatal suicidal behavior were 0.83 for amitriptyline (95% CI, 0.61-1.13), 1.16 for fluoxetine (95% CI, 0.90-1.50), and 1.29 for paroxetine (95% CI, 0.97-1.70), compared to those using dothiepin. Perhaps the most startling finding in this study was the 4.07 relative risk for suicidal behavior within 9 days of starting any anti-depressant (95% CI, 2.89-5.74), compared to patients prescribed an anti-depressant 90 days or more before their suicidal behavior. Even more concerning, was a relative risk for fatal suicide among new users of anti-depressants of 38.0 (95% CI, 6.2-231). The authors found no significant associations between use of the various anti-depressants and the risk of suicide (*JAMA.* 2004;292:338-343, ed 379-380). The accompanying editorial points out the timeliness of the study, with regard to current congressional hearings in the use of anti-depressants in young adults. The authors point out that the data on patients aged 10 through 19 is limited however, and further study may be needed in this group.

FDA Actions

The FDA has approved acamprosate (Campral-Merck) for the maintenance of abstinence in patients in alcohol recovery programs. The drug, which has been available in Europe for several years, may not work if patients are still drinking or abusing other drugs when initiating therapy. Acamprosate's mechanism of action is unknown, but it appears to act in the central nervous system. Common side effects include diarrhea, nausea, vomiting, and abdominal pain.

The FDA has approved Merck and Schering-Plough's Vytorin for the treatment of hypercholesterolemia. The drug combines Merck's simvastatin (Zocor) with the jointly developed ezetimibe (Zetia), and is touted to be as potent as the so-called "super statins" atorvastatin (Lipitor) and rosuvastatin (Crestor). The new drug, which is expected to garner a hefty market share, will be priced at $2.30 a pill and should be available this fall.

Imiquimod (Aldera-3M) has received the expanded indication for treatment of superficial basal cell carcinoma. The drug, which is a topical immune modulator, was recently approved for treatment of actinic keratosis, and was initially approved for the treatment of venereal warts.

Brief Notes

The over-the-counter cough medications, dextromethorphan and diphenhydramine, are no better than placebo in suppressing cough in children (*Pediatrics.* 2004;114:e85-e90).

Many women are turning to phytoestrogens in lieu of hormone replacement therapy. The most commonly used of these, isoflavone soy protein, does not improve cognitive function, bone mineral density, or plasma lipids in healthy postmenopausal women (*JAMA.* 2004;292:65-74).

Ginseng reduces the effectiveness of warfarin in healthy volunteers. Patients on warfarin should be questioned as to their herbal supplement use (*Ann Intern Med.* 2004;141:23-27).