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TMR Revisited

ABSTRACTS & COMMENTARY

Synopsis: *In patients with refractory angina who were not candidates for percutaneous or surgical revascularization, transmyocardial revascularization resulted in more relief of angina, increased freedom from cardiac events, and a better quality of life.*

Sources: Frazier OH, et al. *N Engl J Med* 1999;341:1021-1028; Allen KB, et al. *N Engl J Med* 1999;341:1029-1036.

In the april 1999 *Clinical Cardiology Alert*, we reported the disappointing results of a randomized controlled trial of surgical transmyocardial revascularization (TMR) and speculated that perhaps catheter-based systems would be the answer (Schofield PM, et al. *Lancet* 1999;353:519-524). However, two studies were reported in a recent issue of the *New England Journal of Medicine* of successful results with surgical TMR. Of note, one study used carbon dioxide laser and one used holmium laser. Both were prospective randomized trials in refractory angina patients who were not candidates for percutaneous or surgical revascularization. Patients were randomized to surgical TMR or medical therapy. Both studies required documented ischemia and a left ventricular ejection fraction greater than 20%. Also, both studies allowed medically randomized patients who developed angina refractory to intravenous medications to cross over to TMR. End points in both studies included angina severity, exercise thallium imaging, and quality of life over 12 months.

The CO_2 laser study (Frazier and colleagues) randomized 192 patients and 60 of 101 initially assigned to medical therapy crossed over to TMR. After one year, angina class was significantly improved in 72% of TMR patients and 13% of the medical patients, ($P < 0.001$) as was quality of life (38% vs 6%; $P < 0.001$). The number of thallium scan nonischemic segments increased 20% with TMR and fell 27% in medical patients ($P = 0.002$). Hospitalizations for unstable angina occurred in 2% of TMR patients in one year vs. 69% of medical patients ($P < 0.001$). Perioperative mortality was 3% with TMR. One-year survival was 85% in the TMR group and 79% in the medical patients (NS).

The holmium laser study (Allen and colleagues) randomized 275 patients and 46 of the 143 medical patients (32%) crossed over to

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TMR. Significant reductions in angina occurred in 76% of the TMR patients vs. 32% of the medical patients ($P < 0.001$). Although survival at one year was not different (84 vs 89%), survival free of cardiac events was better with TMR (54% vs 31%; $P < 0.001$). Exercise tolerance was better after TMR (5 MET vs 4 MET; $P = 0.05$), as was quality of life score (21 vs 12; $P = 0.003$). However, myocardial perfusion by thallium scintigraphy was not different between the two groups and perioperative mortality was 5%.

Both studies concluded that in patients with refractory angina who were not candidates for percutaneous or surgical revascularization, TMR resulted in more relief of angina, increased freedom from cardiac events, and a better quality of life. One study concluded that myocardial perfusion was also improved (CO_2 laser study).

COMMENT BY MICHAEL H. CRAWFORD, MD

These two studies represent a significant advance since the negative results of the previous controlled study (*Lancet* 1999). Also, they dispel the notion that CO_2 laser is better than other types since their results were similar. The major difference between these studies and the *Lancet* study is that the patients were sicker in these studies: 70-100% were excluded in the *Lancet* study. Perhaps unstable patients stand to gain more from TMR. Although there was no difference in exercise tolerance at 12 months in the *Lancet* study, angina frequency, hospitalization, and use of medications decreased with TMR vs. medical therapy. Also, fixed defects on thallium scintigraphy remained stable after TMR but increased in the medical group, suggesting scarring of ischemic areas since there was no change in total defects. Thus, taken together, these three studies suggest benefit for highly selected patients for TMR.

The real concern is whether this is just another Vineberg operation and we are observing the placebo effect of cardiac surgery. This cannot be answered unless a sham operation control group is included in the next study, which is unlikely. This raises the issue of mechanism of any benefit. Originally it was thought that these channels would stay open and create a reptilian heart with sinusoids for perfusion of the myocardium, hence the idea that CO_2 laser was better because the channels were cleaner with it. Now we know the channels close. So what is the benefit? Perhaps denervation is the mechanism. This would explain the decrease in angina, but not the reduction in fixed defects in one study and improved perfusion observed in another study. The most popular explanation now is that these laser channels stimulate angiogenesis.

Another concern is the initial mortality associated with surgery and the lack of survival gain in these small studies. In the CO_2 laser study, it was noted that if surgery was delayed, two weeks mortality decreased from 3% to 1%. In the holmium laser study, it was noted that mortality for the last 100 patients decreased from 5% overall to 2%. Thus, careful management of these sick patients may make perioperative mortality acceptable.

Another limitation to these studies is the allowance of crossovers to TMR. Naturally it was high (30-60%) because the patient had to be medically refractory to be candidates for the studies. However, in both studies the crossover group did almost as well as the TMR groups and better than the medical group.

Morbidity was not inconsequential in the TMR groups: ventricular tachyarrhythmias in 8% of the CO_2 laser patients and 12% of the holium laser patients; heart failure in 11% and 4%; and myocardial infarction in 7% and 6%, but does not appear excessive vs. bypass surgery. Complications were similar in the crossover groups despite their acuity.

What about the catheter-based approach, percutaneous myocardial revascularization (PMR)? Although still being studied, its development was hampered by difficulty in directing the laser beam by catheter in the beating heart. A new system has now been developed with better steering capabilities called directed myocardial revascularization (DMR). This field, like most, is a moving target. At this

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point, TMR appears more promising, PMR has faded, but DMR raises hopes for a percutaneous approach. ❖

Amiodarone for Resuscitation of Cardiac Arrest

ABSTRACT & COMMENTARY

Synopsis: *Amiodarone improves the probability of admission to the hospital after failure of initial resuscitation in victims of out-of-hospital cardiac arrest.*

Source: Kudenchuk PJ, et al. *N Engl J Med* 1999; 341:871-878.

It has not been conclusively shown that antiarrhythmic drugs during cardiopulmonary resuscitation improve outcome. Kudenchuk and colleagues conducted a randomized, double-blind, placebo-controlled trial using intravenous amiodarone in patients with out-of-hospital cardiac arrest. Victims of cardiac arrest were initially treated by first responders who initiated basic life support measures including the delivery of shocks using an automatic external defibrillator. Adults with nontraumatic out-of-hospital cardiac arrest could be included in the study if ventricular fibrillation or pulseless ventricular tachycardia was still present after three or more precordial shocks had been delivered, if intravenous access had been established, and if a paramedic team with study drug arrived on the scene. At this point, patients underwent endotracheal intubation and received 1 mg of epinephrine intravenously according to the standard advanced cardiac life support protocol. Eligible patients then were randomly assigned to receive either 300 mg of intravenous amiodarone or its diluent, polysorbate 80, as placebo. The primary end point for the study was admission to the hospital with a spontaneously perfusing rhythm. This was defined as a rhythm and blood pressure sufficiently stable to allow assignment to an inpatient hospital bed. Deaths in the emergency room were not considered to have been admissions to the hospital. Secondary end points were adverse effects, number of shocks required after the administration of amiodarone or placebo, duration of resuscitation, survival to discharge, and functional neurologic status at discharge.

Fifteen hospitals participated in the study. During the study period (November 1994-February 1997), 3954 consecutive patients without a possible cardiac arrest were considered for enrollment in the trial. A total of 504 patients were appropriately randomized and received either amiodarone or placebo. The group was predominantly male, with a mean age of 66 years. Slightly more than 70% of the arrests were witnessed and approximately 60% of the patients received bystander cardiopulmonary resuscitations. The initial cardiac arrest rhythm was ventricular fibrillation in 83% of the study patients. The remaining patients either had asystole or pulseless electrical activity converting to ventricular fibrillation or had pulseless ventricular tachycardia. Arrival time for first responders was similar between the two groups (4.4 minutes), as was arrival time for paramedics (8.6 minutes). However, time to administration of study drug was approximately 21 minutes because of the previous resuscitation efforts.

An average of five shocks were delivered before the administration of amiodarone or placebo. Twenty-one percent of the patients had transient return of spontaneous circulation before administration of study drug. Bradycardia requiring treatment occurred in about one-fifth of the patients before study drug administration.

Of the 544 patients in the study, 197 (39%) survived to be admitted to the hospital. Admission to the hospital was more likely among recipients of amiodarone (44% vs 34%; P = 0.03). After adjustment for relevant clinical factors, the risk ratio for survival to admission to the hospital favored amiodarone by a factor of 1.6 (95% confidence interval, 1.1 to 2.24; P = 0.02). Patients whose cardiac arrest was due to ventricular fibrillation were more likely to survive to be admitted to the hospital than were those whose initial rhythm was asystole or pulseless electrical activity (44% vs 14%). Early transient return of spontaneous circulation was also a predictor of survival. After admission to the hospital, patients were managed by their physicians with conventional methods. A total of 67 patients (13%) were discharged alive from the hospital. One hundred seventeen of the patients admitted to the hospital never regained consciousness. There was no difference in survival to hospital discharge between the amiodarone and placebo groups (13.4% vs 13.2%). However, 35 of the 67 patients discharged after treatment resumed independent living or returned to their former employment after discharge.

Kudenchuk et al conclude that amiodarone improved the probability of admission to the hospital after failure of initial resuscitation in victims of out-of-hospital cardiac arrest. They also propose that further studies with amiodarone in this setting are indicated.

COMMENT BY JOHN P. DiMARCO, MD, PhD

Although antiarrhythmic drugs are frequently used in the setting of cardiac arrest, no study has shown benefit with such therapy. In part, this is due to the difficulty in performing randomized clinical trials in out-of-hospital cardiac

arrest. However, the limited data available have not shown benefit with lidocaine, bretylium, or other antiarrhythmic drugs. The present study that used amiodarone can be interpreted in several ways. An optimistic interpretation would be to say that a single dose of amiodarone in the setting of refractory cardiac arrest demonstrated an improvement in the survival rate to hospital admission. A conservative interpretation would say that survival to hospital discharge was not affected by drug therapy. In the later interpretation, the use of amiodarone only increased hospital admissions and costs without producing significant patient benefit. The real value of this paper probably lies somewhere in between. Amiodarone did produce a change in the primary end point of the study. However, amiodarone was administered relatively late during the resuscitation. The data suggest that earlier, more aggressive administration is worthy of study since this is the time in which real effects on long-term survival would be most likely.

The mechanism by which amiodarone produced its effect is unknown. A single dose of intravenous amiodarone probably results in relatively little change in the repolarization properties of the ventricle. In other studies, one of the first effects seen with intravenous amiodarone has been noncompetitive beta adrenergic blockade. Some authorities have recommended use of intravenous beta blockers to prevent early recurrence of ventricular fibrillation after an initial defibrillation. Thus, it is possible that some of the effects seen with amiodarone in this study are due to just beta blockade. In that case, use of intravenous beta adrenergic blockers would be easier and less expensive than adding amiodarone to the resuscitation algorithm.

Studies in out-of-hospital cardiac arrest victims are difficult both from a logistical and an ethical standpoint. However, it is clear that further studies need to be done. This paper by Kudenchuk et al should encourage further clinical trials in this important field. ❖

Interruption of the Renin-Angiotensin Access

ABSTRACT & COMMENTARY

Synopsis: *Combination therapy with candesartan and enalapril was the most effective approach with respect to remodeling and neurohormones.*

Source: McKelvie RS, et al. *Circulation* 1999;100: 1056-1064.

The randomized evaluation of strategies for Left Ventricular Dysfunction (RESOLVD) Trial pilot study was reported at the annual American Heart Association meeting one year ago and has finally been published. This controversial study assessed the effects of an angiotensin II receptor blocker (ARB) (candesartan) and an angiotensin converting enzyme (ACE) inhibitor, enalapril, and their combination in almost 800 individuals with heart failure. RESOLVD was a relatively short-term study of 43 weeks duration that was not powered to look at major morbidity and mortality results. It was a multicenter, double-blind, randomized parallel trial of 768 patients with an ejection fraction of less than 40%, NYHA class II-IV; most were in functional class II. They were evaluated by serial six-minute walk test, echocardiographic left ventricular function and volume data, neurohormones, and quality of life/functional class assessment at weeks 17 and 43. Patients had to terminate a six-minute walk distance in less than 500 meters. All individuals were submitted to a run-in period with enalapril, candesartan, and the combination. Three groups were studied: candesartan, 327 subjects; enalapril, 109 subjects; and the combination, 332 subjects. There was no placebo group. In addition, candesartan patients were individually randomized to three dosing strategies—4, 8, and 16 mg daily; the enalapril group received 10 mg bid; and combination patients received enalapril, 10 mg bid plus candesartan 4 or 8 mg.

The external safety and efficacy monitoring committee stopped the trial early because of a differential mortality in the candesartan group vs. enalapril. The enalapril patients had a mortality of 3.7%, the candesartan patients 6%, and the combination group 8.7%. Congestive heart failure (CHF) hospitalizations included 10.7% for candesartan, 3.7% for enalapril, and 7.2% for the combination. The combination of death plus CHF hospitalization was roughly 2.5 times higher for the combination group than for enalapril alone (15.1% vs 6.4%). No available data in the literature or from other ARB trials have suggested an adverse result with an ARB, but the study was terminated against the wishes of the investigators. Nevertheless, this occurred only six weeks prior to the scheduled trial termination, and 90% of the entire cohort had completed all visits at the time of termination; approximately 9% of patients had a shortened follow-up by a mean of 16 days. The results of the trial indicated no differences among the groups for the six-minute walk distance, with no improvement over baseline. Left ventricular function showed a trend toward an increase in ejection fraction for the combination patients at the highest dose of candesartan plus enalapril. LV volumes increased with candesartan and enalapril, although there was no significant change for the combination patients at 43 weeks. Neuro-hormonal levels demonstrated a rise in renin in all groups; ANG II

increased markedly with candesartan alone and less with combination therapy. Aldosterone declined in all groups, as did norepinephrine and epinephrine levels. Pro-ANP and BNP levels showed declines. There were no significant differences among the three groups for NYHA, functional class, or quality-of-life scores at 18 or 43 weeks. There were no significant differences in mortality or morbidity among the three groups.

McKelvie and colleagues conclude that candesartan has a similar effect to enalapril on the walk test, ventricular function, and clinical status. Of interest, only the combination group demonstrated prevention of left ventricular remodeling and the most effective suppression of aldosterone and BNP. Few adverse effects were noted and were not different among the treatment groups. McKelvie et al concluded that combination therapy was the most effective approach with respect to remodeling and neurohormones. In no group was there a significant increase in neurohormonal activation. Aldosterone declined the most and renin increased the most with combination therapy; this suggests that "more complete blockade of the renin-angiotensin-aldosterone system was achieved." Furthermore, the 8 mg dose of candesartan was shown to be the most effective.

There is a problem with the major clinical event differences among the groups. The enalapril group was only 109 patients and the mortality was much lower than would be expected in a cohort of similar heart failure patients. McKelvie et al conclude that "the RESOLVD study should not be viewed as being reliable in estimating the effects of candesartan or candesartan plus enalapril vs. enalapril alone on clinical outcomes." They also conclude that candesartan was as effective, safe, and tolerable as enalapril, and that the combination may be more beneficial than either drug alone in preventing LV remodeling and suppressing neurohormones. In an accompanying editorial, Barry Greenberg, MD, goes through the physiologic rationale of ACE inhibitors and ARBs, which underlines the hypothesis that combination therapy with both classes of drugs might be better than either alone. Greenberg concludes that one cannot make any definite assumptions regarding the RESOLVD study, partly because of the relatively small numbers of patients in this pilot study and because of the multiple treatment regimens that make intergroup comparisons hazardous. In addition, some individuals were randomized to a beta blocker after 19 weeks of therapy; data were not provided. Greenberg suggests that the beneficial effects of combination therapy on remodeling may be due to a greater blood pressure lowering effect of both candesartan and enalapril together, and that the differences in LV volumes could reflect "acute unloading effects of combined therapy." He points out that many other data sets have indicated the prevention of remodeling with an ACE inhibitor, unlike the findings of RESOLVD.

COMMENT BY JONATHAN ABRAMS, MD

This study is confusing with respect to the divergence of hard clinical end points due to the failure of the ARB or the ACE inhibitor to prevent left ventricular cavity expansion, but it does suggest that combination therapy may be particularly beneficial in heart failure patients. The construct that more complete suppression of angiotensin II will be beneficial is not new. This would result in lower aldosterone levels as well; the recent RALES Trial strongly supports the clinical benefits of aldosterone lowering in heart failure patients. The prevention of LV remodeling in the RESOLVD Trial has been shown in larger trials with ACE inhibitors alone (SAVE, SOLVD) but in this study was seen only in the combination group.

Large trials, including VAL-HEFT and CHARM, are currently assessing the role of combination therapy with an ARB and an ACE inhibitor in heart failure patients. The results are eagerly anticipated. Furthermore, other studies, including ELITE-2, are asking the question as to whether an ARB or an ACE inhibitor is more beneficial in the therapy of heart failure. It is unfortunate that RESOLVD was terminated early, as it has cast a cloud of controversy over this trial. However, it is doubtful that the results were significantly altered, in that at trial cessation, only 10% of individuals had incomplete data and only for a short period.

It is clear that the RESOLVD study design contributed to the messiness of the data with multiple groups (three candesartan dose arms in the ARB cohort and two in the combination cohort). The failure to have a placebo arm also contributes to the uncertainty of the various data sets. The marked differences in clinical events are unexpected and in contradistinction to the recently published ELITE Trial comparing losartan to captopril, which favored the ARB. For reasons already stated, the reliability of the data is somewhat suspect because of multiple groups and the small number of individuals taking enalapril alone, as well as the short duration of the study (less than 12 months).

What is the clinician to do? It would appear that RESOLVD does support the safety of the combination of an ARB and an ACE inhibitor. For patients with heart failure who are not doing well on an ACE inhibitor alone, it may be reasonable to add an ARB to attempt to achieve a greater ANG II and aldosterone suppression and perhaps more blunting of LV cavity expansion. There are no solid clinical data as yet to support this suggestion, however. Nevertheless, no obvious adverse effects were found in RESOLVD with combination ther-

apy, so that careful clinical and laboratory monitoring would appear to allow such a strategy to be used without serious risk. We must await the results of VAL-HEFT and other trials to answer the hotly contested question of whether an ARB or an ACE inhibitor is better, or whether combination therapy is the best of all.

The efficacy of ACE inhibitors has been well shown in heart failure, asymptomatical LV dysfunction, hypertension, and diabetes. The recently released HOPE Trial, assessing more than 9000 patients who were treated with ramapril or placebo, represents a major advance in understanding the benefits of ACE inhibitors. There was a 20-25% reduction in all major clinical end points with ACE inhibitor therapy. Subjects enrolled in the study had to have coronary or peripheral vascular disease or were diabetics with one or more other risk factors. HOPE was not a hypertension or heart failure trial, but asked the question whether an ACE inhibitor would be beneficial in patients with established vascular disease and/or who are at high risk for cardiovascular problems.

In conclusion, an ACE inhibitor remains the mainstay for patients with LV systolic dysfunction, whether symptomatic or not. HOPE suggests that these drugs might be appropriate for all individuals with vascular disease, irrespective of LV function and hypertension. Clearly, diabetics should be considered for an ACE inhibitor if they have a significant vascular disease risk factor profile. The ARB story is promising but less well supported by clinical trial data. ❖

Dofetilide in Patients with Congestive Heart Failure

ABSTRACT & COMMENTARY

Synopsis: *Dofetilide has no beneficial effect on total mortality among patients with congestive heart failure.*

Source: Torp-Pedersen C, et al. *N Engl J Med* 1999; 341:857-865.

In this article, torp-pedersen and associates report the results of the Danish Investigations of Arrhythmia and Mortality on Dofetilide in Congestive Heart Failure (DIAMOND-CHF) Trial. A total of 1518 patients with advanced heart failure and left ventricular dysfunction were recruited from 34 participating hospitals in Denmark. Patients were randomly assigned to treatment with either dofetilide, a new class III antiarrhythmic drug, or placebo. Patients were hospitalized for the first three days of therapy. The initial dofetilide dose was 500 g bid for patients in sinus rhythm and 250 g bid for patients in atrial fibrillation. After enrollment of 288 patients, the protocol was changed and subsequently the initial dosage was based on creatinine clearance. If the creatinine clearance was greater than 60 mL/min, the dose was 500 g bid. If between 40-60 mL/min, the dose was 250 g bid. If between 20-40 mL/min, a single 250 g daily dose was used. The primary end point was all-cause mortality. In the prespecified atrial fibrillation subgroup, effects of dofetilide conversion rates and hospitalizations were important secondary end points.

Dofetilide had no significant effect on mortality. During a median follow-up of 18 months, 41% of the dofetilide patients and 42% of the placebo patients died. Among the atrial fibrillation patients, dofetilide resulted in conversion to sinus rhythm in 12% vs. 1% on placebo. If patients were either pharmacologically or electrically converted at any time, dofetilide was more effective for maintaining sinus rhythm. New atrial fibrillation developed less frequently during dofetilide therapy. Dofetilide decreased the hospitalization rate among treated patients with both sinus rhythm and atrial fibrillation at baseline.

The only adverse reactions more common during dofetilide treatment were QT prolongation and torsade de pointes. QT prolongation led to discontinuation of study drug in 14 dofetilide patients vs. only three placebo patients. Twenty-five cases of torsade de pointes were noted in the dofetilide group vs. none in the placebo group. Of these, 15 episodes required cardioversion and two were fatal. Nineteen of 25 (76%) occurred during the initial in-hospital loading period. Using the initial unadjusted dose of 500 g bid, the rate of torsade de pointes was 4.8%. After the dosage adjustment was included in the protocol, this rate fell to 2.9%. Female gender and class III or IV heart failure were risk factors for development of proarrhythmia.

Torp-Pedersen et al conclude that dofetilide has no beneficial effect on total mortality among patients with congestive heart failure. However, among patients with heart failure and atrial fibrillation, dofetilide may help restore and maintain sinus rhythm and reduce the need for repeat hospitalization. Although dofetilide may produce torsade de pointes, careful dosage adjustment during initiation of therapy with in-hospital monitoring can lower the risk to the patient.

COMMENT BY JOHN P. DiMARCO, MD, PhD

Dofetilide is a new antiarrhythmic drug that has recently been approved by the FDA for use in patients with atrial fibrillation. The data from the DIAMOND-CHF Trial and a similar study in patients with recent myocardial infarction (DIAMOND-MI) provided important evidence in support of this decision.

Atrial fibrillation is common among patients with heart failure and its prevalence increases with heart failure severity. The independent effect of atrial fibrillation on mortality in heart failure is controversial but all agree atrial fibrillation complicates management of heart failure patients. Atrial fibrillation may worsen heart failure in several ways: inappropriate and irregular ventricular rates, loss of atrial contractility, and increased thromboembolic risk. As heart failure worsens, control of ventricular rate and restoration and maintenance of sinus rhythm become more difficult.

Data from studies with class I antiarrhythmic drugs have suggested an increased mortality among patients with atrial fibrillation and heart failure (*J Am Coll Cardiol* 1992;20:527-532). In a large trial in patients with heart failure, amiodarone resulted in favorable antiarrhythmic effects in patients with atrial fibrillation even though there was no overall survival benefit (*Circulation* 1998;98:2574-2579). The data in this paper are similar, suggesting a neutral overall effect of dofetilide but some benefit in the atrial fibrillation subgroup.

However, it is important to remember that DIAMOND-CHF was not a trial designed to study the management of atrial fibrillation. An aggressive approach to drug loading and cardioversion was not required by the trial protocol. We can only speculate whether a more systematic attempt to restore and maintain sinus rhythm would have produced greater or lesser benefit.

Like other agents that prolong repolarization, dofetilide can produce torsade de pointes. It appears that careful monitoring of dosage, renal function, and ECG parameters can reduce this risk. However, even the rate of 2.9% seen later in the study is significant and considerable caution will have to be exercised when using dofetilide in high-risk patients. ❖

Obesity is a Problem!

ABSTRACT & COMMENTARY

Synopsis: *A BMI between 20-25 is optimal and is associated with the longest survival for any causes of death.*

Source: Calle EE, et al. *N Engl J Med* 1999;341: 1097-1105.

The relationship between excessive body weight and mortality is problematic. In addition to the questions of the optimal weight at different ages and gender, there has been the suggestion of a U-shaped curve regarding body weight with respect to survival; the latter has stimulated much discussion regarding the potential downside of being underweight or lean, perhaps due to unrecognized medical conditions. The Cancer Prevention Study II, a prospective study of mortality among U.S. men and women, initiated in 1982 by the American Cancer Society, recently reported 14-year follow-up data. By 1996, 20% of the entire cohort of 457,785 men and 588,369 women had died. All participants were divided into 12 categories of body mass index (BMI). The primary end points were all-cause death as well as cardiovascular disease mortality. Smoking history, status of disease at entry, and race and gender were examined. The results indicate a relationship between increasing BMI and mortality that differed by smoking status and the presence of any disease. Obesity was more strongly associated with decreased survival in nonsmokers and in those without a disease history. Leanness was most strongly associated with decreased survival in smokers with a history of disease. Intermediate survival was noted for smokers without a history of disease and for nonsmokers with concomitant disease. At a BMI of 28 and higher, the relative risk of death began to increase most steeply for the nonsmokers without a history of disease. The highest mortality rates occurred in obese men, with a relative risk of 2.7 vs. 1.9 in women. There was a small increase in risk in the leanest men and women. The nadir of the BMI curves and mortality was at a BMI between 23.5 and 25 in men and 22.0 and 23.4 in women. In nonsmokers without a disease history, the association between a high BMI and increased mortality was stronger in whites than in blacks. BMI and cancer death demonstrated a positive relationship; there was no elevation in risk among lean individuals for cancer. The cardiovascular curves were U-shaped; there was no increased risk of dying in lean men and women. A high BMI was predictive of death from cardiovascular disease; it was greater in men (relative risk 2.9) than in women; risk began to increase at a BMI of more than 25 in women and 26.5 in men. The relative risk associated with high BMI diminished with increasing age. Overall death rates increased throughout the range of moderate to severe overweight in both men and women, less so in blacks and particularly black women (about one-third lower than white women). Cancer deaths increased by 40-80% in the heaviest groups of men and women, without a concomitant increase risk in lean subjects. Calle and associates conclude that a BMI between 20 and 25 for men and women of all ages is optimal and is associated with the longest survival for any causes of death. "These data offer support for the use of a single recommended range of body weight throughout life."

COMMENT BY JONATHAN ABRAMS, MD

These data, while not surprising, are of great interest because of the enormous size of the study population (> 1 million) and the long-term (14-year) follow-up. That

approximately one-third of American adults meet WHO criteria for a grade 1 overweight (BMI 25-30) and 22% are even more overweight confirms that obesity is a substantial health problem. Only 8% of the adults in the United States have a BMI less than 20. The health care burden of a high BMI is well demonstrated in this study. It is unclear why blacks carry a lower burden of mortality for comparable degrees of obesity; however, it must be stressed that moderate to high levels of BMI are adverse for all causes of death unrelated to age, gender, or ethnicity. This study did not include coronary artery risk factor measurements; one cannot conclude that increase in mortality among the healthy overweight was related to coronary events, although this is likely. Obesity is associated with insulin resistance or the "metabolic syndrome," which includes dyslipidemia, hypertension, impaired glucose tolerance, and overt diabetes. For high-BMI individuals, particularly nonsmokers without disease, the BMI curves in this study are truly alarming. ❖

Corrections

Please note the following corrections to the "Reperfusion Strategies in Elderly Patients with Acute MI: Angioplasty is the Winner" article from the September 1999 issue. In the second paragraph, please add, "the entire database **of the 80,351 subjects** did not receive. . . ." On page 66, 2nd column, 4th line, "11.8% vs. 17.2% with *none* (not more). On page 66, column 2, paragraph 2, line 6, *sheer* (not shear). ❖

CME Questions

24. Angiotensin receptor blockers are clearly indicated for:
- a. heart failure.
- b. post-myocardial infarction.
- c. diabetic nephropathy.
- d. hypertension.

25. In heart failure patients, dofetilide treatment:
- a. prevented atrial fibrillation.
- b. prevented ventricular tachyarrhythmias.
- c. prevented torsade de pointes.

26. Field use of amiodarone in refractory ventricular tachyarrhythmia patients resulted in:
- a. increased survival to hospital discharge.
- b. increased survival to hospital admission.
- c. improved neurologic outcomes.
- d. increased one-year survival.

27. Surgical transmyocardial revascularization results in:
- a. relief of angina.
- b. reduced cardiac events.
- c. better quality of life.
- d. All of the above

28. Nonsmoking, healthy, significantly overweight men and women have a lower mortality rate related to BMI than smokers.
- a. True
- b. False

Annual Statement of Ownership, Management, and Circulation

1. Publication Title	2. Publication No.	3. Filing Date
Clinical Cardiology Alert	0 7 4 1 - 4 2 1 8	9/24/99
4. Issue Frequency	5. Number of Issues Published Annually	6. Annual Subscription Price
Monthly	12	$209.00

7. Complete Mailing Address of Known Office of Publication *(Not Printer) (Street, city, county, state, and ZIP+4)*: 3525 Piedmont Road, Bldg. 6, Ste. 400, Atlanta, Fulton County, GA 30305 — Contact Person: Willie Redmond — Telephone: 404/262-5448

8. Complete Mailing Address of Headquarters or General Business Office of Publisher *(Not Printer)*: 3525 Piedmont Road, Bldg. 6, Ste. 400, Atlanta, GA 30305

9. Full Names and Complete Mailing Addresses of Publisher, Editor, and Managing Editor *(Do Not Leave Blank)*

Publisher *(Name and Complete Mailing Address)*: Donald R. Johnston, 3525 Piedmont Road, Bldg. 6, Ste. 400, Atlanta, GA 30305

Editor *(Name and Complete Mailing Address)*: Michelle Moran, same as above

Managing Editor *(Name and Complete Mailing Address)*: Glen Harris, same as above

10. Owner *(Do not leave blank. If the publication is owned by a corporation, give the name and address of the corporation immediately followed by the names and addresses of all stockholders owning or holding 1 percent or more of the total amount of stock. If not owned by a corporation, give the names and addresses of the individual owners. If owned by a partnership or other unincorporated firm, give its name and address as well as those of each individual. If the publication is published by a nonprofit organization, give its name and address.)*

Full Name	Complete Mailing Address
American Health Consultants	3525 Piedmont Road, Bldg. 6, Ste 400 Atlanta, GA 30305

11. Known Bondholders, Mortgagees, and Other Security Holders Owning or Holding 1 Percent or More of Total Amount of Bonds, Mortgages, or Other Securities. If none, check box → ☐ None

Full Name	Complete Mailing Address
Medical Economics Data, Inc.	Five Paragon Drive Montvale, NJ 07645

12. Tax Status *(For completion by nonprofit organizations authorized to mail at nonprofit rates.) (Check one)*
The purpose, function, and nonprofit status of this organization and the exempt status for federal income tax purposes:
☐ Has Not Changed During Preceding 12 Months
☐ Has Changed During Preceding 12 Months *(Publisher must submit explanation of change with this statement)*

PS Form **3526**, September 1998 *See instructions on Reverse)*

13. Publication Name: Clinical Cardiology Alert — 14. Issue Date for Circulation Data Below: November 1999

15. Extent and Nature of Circulation			Average No. of Copies Each Issue During Preceding 12 Months	Actual No. Copies of Single Issue Published Nearest to Filing Date
a. Total No. Copies *(Net Press Run)*			1607	1550
b. Paid and/or Requested Circulation	(1)	Paid/Requested Outside-County Mail Subscriptions Stated on Form 3541. *(Include advertiser's proof and exchange copies)*	1401	1350
	(2)	Paid In-County Subscriptions *(Include advertiser's proof and exchange copies)*	0	0
	(3)	Sales Through Dealers and Carriers, Street Vendors, Counter Sales, and Other Non-USPS Paid Distribution	0	0
	(4)	Other Classes Mailed Through the USPS	0	0
c. Total Paid and/or Requested Circulation *(Sum of 15b(1) and 15b(2)*			1401	1350
d. Free Distribution by Mail *(Samples, Complimentary and Other Free)*	(1)	Outside-County as Stated on Form 3541	0	0
	(2)	In-County as Stated on Form 3541	0	0
	(3)	Other Classes Mailed Through the USPS	0	0
e. Free Distribution Outside the Mail *(Carriers or Other Means)*			14	14
f. Total Free Distribution *(Sum of 15d and 15e)*			14	14
g. Total Distribution *(Sum of 15c and 15f)*			1415	1364
h. Copies Not Distributed			192	186
i. Total *(Sum of 15g, and h.*			1607	1550
Percent Paid and/or Requested Circulation *(15c divided by 15g times 100)*			99	99

16. Publication of Statement of Ownership Publication required. Will be printed in the November issue of this publication. ☐ Publication not required.

17. Signature and Title of Editor, Publisher, Business Manager, or Owner: Publisher — Date: 9/24/99

I certify that all information furnished on this form is true and complete. I understand that anyone who furnishes false or misleading information on this form or who omits material or information requested on the form may be subject to criminal sanctions (including fines and imprisonment) and/or civil sanctions (including multiple damages and civil penalties).

Instructions to Publishers

1. Complete and file one copy of this form with your postmaster annually on or before October 1. Keep a copy of the completed form for your records.
2. In cases where the stockholder or security holder is a trustee, include in items 10 and 11 the name of the person or corporation for whom the trustee is acting. Also include the names and addresses of individuals who are stockholders who own or hold 1 percent or more of the total amount of bonds, mortgages, or other securities of the publishing corporation. In item 11, if none, check the box. Use blank sheets if more space is required.
3. Be sure to furnish all circulation information called for in item 15. Free circulation must be shown in items 15d, e, and f.
4. Item 15h., Copies not Distributed, must include (1) newsstand copies originally stated on Form 3541, and returned to the publisher, (2) estimated returns from news agents, and (3), copies for office use, leftovers, spoiled, and all other copies not distributed.
5. If the publication had Periodicals authorization as a general or requester publication, this Statement of Ownership, Management, and Circulation must be published; it must be printed in any issue in October or if the publication is not published during October, the first issue printed after October.
5. In item 16, indicate date of the issue in which this Statement of Ownership will be published.
6. Item 17 must be signed.

Failure to file or publish a statement of ownership may lead to suspension of second-class authorization.

PS Form **3526**, September 1999 *(Reverse)*