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CLINICAL CARDIOLOGY ALERT

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INSIDE

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Clinical Cardiology Alert's physician editor, Michael H. Crawford, MD, is on the speaker's bureau for Pfizer.
The peer reviewer, Rakesh Mishra, MD, reports no consultant, stockholder, speaker's-bureau, or other financial relationship with any company related to this field of study.

Statins in Nonischemic Cardiomyopathy

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

Source: Sola S, et al. Atorvastatin Improves Left Ventricular Systolic Function and Serum Markers of Inflammation in Nonischemic Heart Failure. *J Am Coll Cardiol*. 2006;47:332-337.

Inflammatory cytokines are a feature of heart failure from any cause. Since statins inhibit the synthesis of inflammatory cytokines, Sola and colleagues hypothesized that they may benefit patients with nonischemic cardiomyopathy. They enrolled 108 stable patients with nonischemic heart failure and left ventricular ejection fraction (EF) < 35%, and randomized them to atorvastatin 20 mg a day or placebo (double blind) for 12 months. Diabetics were excluded. The primary end point was change in echocardiographic EF. Secondary end points included changes in inflammatory and oxidation markers.

Results: In the atorvastatin group, EF increased from a mean of 0.33 to 0.37 ($P = 0.01$), whereas EF declined in the placebo group (0.33 to 0.31). This was due to reductions in left ventricular systolic and diastolic dimensions in the atorvastatin group. Left ventricular size increased in the placebo group. Erythrocyte superoxide dismutase (E-SOD) increased, and serum high sensitivity C-reactive protein (hsCRP) interlukin-6 (IL-6) and tumor necrosis factor-alpha receptor II (TNF-x RII) decreased in the atorvastatin group (all $P <$ .01). These markers were unchanged in the placebo group. As expected, there were significant reductions in LDL cholesterol and triglyceride in the atorvastatin group. Sola et al concluded that atorvastatin use in nonischemic cardiomyopathy abrogates adverse remodeling and improves EF. LDL cholesterol and inflammatory marker reductions may play a role in these effects.

COMMENTARY

Prior observational studies have shown an association between statin therapy and mortality in heart failure. A smaller, randomized trial of simvastatin also showed increased ejection fraction and reduced

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inflammatory markers. Since inflammatory markers are associated with a worse outcome in large studies, this effect of statins may be the mechanism of the improved survival noted in observational studies and the improved EF noted in the Sola study (*see following article*). It is noteworthy that the Mozaffarian study did not show improvements in either the 6-minute walk test or the symptoms questionnaire. However, neither of the studies reported here were large enough nor long enough to adequately evaluate clinical outcomes.

Although cholesterol levels changed as expected with statin, those in the Sola study did not meet guidelines for treatment and, in the Mozaffarian study, the changes in cholesterol did not correlate with the changes in inflammatory markers. Interestingly, both trials focused on patients with nonischemic cardiomyopathy (100% Sola, > 90% Mozaffarian), which makes a cholesterol-related beneficial effect less likely. Also, in observational studies, lower cholesterol is associated with increased mortality in heart failure. Thus, the role of changes in lipid profile is unclear.

Should dilated cardiomyopathy patients be treated with statins regardless of lipid levels? Perhaps not at this time without any outcomes data, but if a patient were not doing well, I would consider it.

Statins in Heart Failure

Source: Mozaffarian D, et al. The Effects of Atorvastatin (10 mg) on Systemic Inflammation in Heart Failure. *Am J Cardiol*. 2005;96:1699-1704.

Statins have improved outcomes in heart failure patients in observational studies, but the mechanism is unknown. Thus, Mozaffarian and colleagues randomized 22 patients with nonischemic (20) and ischemic cardiomyopathy to atorvastatin 10 mg per day or placebo (double blind) for 16 weeks using a cross-over design at 8 weeks. The primary end points were inflammatory markers at baseline vs 8 weeks of therapy. Secondary end points included a heart failure symptoms questionnaire, a 6-minute walk, and various blood tests. Atorvastatin therapy reduced TNF 8%, CRP 37%, and endothelin 17%. IL-6 and brain natriuretic peptide were unchanged. Total cholesterol, LDL cholesterol, and triglycerides were decreased. There was no change in HDL cholesterol. Changes in cholesterol were not correlated with changes in inflammatory markers. Atorvastatin did not change serum catecholamine levels. Mozaffarian et al concluded that short-term atorvastatin therapy reduced levels of important inflammatory markers in patients with heart failure. ■

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Questions & Comments

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Rescue Angioplasty: The REACT Trial

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

Synopsis: *Event-free survival after failed thrombolytic therapy was significantly higher with rescue PCI than with repeated thrombolysis or conservative treatment.*

Source: Gershlick AH, et al. Rescue Angioplasty After Failed Thrombolytic Therapy for Acute Myocardial Infarction. *N Engl J Med*. 2005;353:2758-2768.

THROMBOLYSIS THERAPY OF ACUTE MYOCARDIAL INFARCtion (MI) results in TIMI 3 flow in about 60% of patients. What to do with the remaining patients is controversial. Thus, the results of the Rescue Angioplasty versus Conservative Treatment or Repeat Thrombolysis (REACT) trial are of interest. The multi-center, randomized, parallel group trial was conducted in the United Kingdom between 1999 and 2004. Patients with acute ST-segment elevation MI treated with thrombolytics within 6 hours of pain onset, in whom ST-segment elevation failed to decrease > 50% in 90 minutes, were eligible for inclusion. Crossovers were allowed if the clinical results were unfavorable. Over half of the 35 centers participating had no cardiac catheterization facilities, so patients were transported to a center that did, if randomized to rescue angioplasty. The primary end point was the combination of major adverse cardiac and cerebral events at 6

months (death, recurrent MI, stroke, heart failure). Secondary end points included revascularization and bleeding. The 427 patients were randomized to the 3 groups (about 140 in each group). Event-free survival was 85% for rescue angioplasty, 70% for conservative therapy, and 69% for repeat thrombolysis ($P = .004$). There was no difference in mortality for all causes. Freedom from revascularization was more frequent with rescue angioplasty; 86% vs 78% conservative therapy and 74% repeat thrombolysis ($P = .05$). Nonfatal bleeding was more common with rescue angioplasty, mainly from the sheath site. The results were the same whether intention to treat or actual therapy were used. The median transfer time for rescue angioplasty, if necessary, was 85 minutes (range, 55-120). Rescue angioplasty was accomplished in a median of 414 minutes after pain onset (range, 350-505). Stents were used in 67%, and 43% received platelet glycoprotein IIb/IIIa receptor inhibitors.

There was a trend for lower mortality at 6 months with rescue angioplasty (5% vs 13% for both other groups combined $P < .05$). Stroke and heart failure were not different between groups. Recurrent MI was less with rescue angioplasty (2% vs 11% and 9%, $P = .004$).

Gershlick and colleagues concluded that rescue angioplasty, even if intra-hospital transfer is required, is superior to repeat thrombolytic therapy or conservative therapy for preventing major adverse cardiac and cerebral events.

COMMENTARY

Rescue angioplasty has been controversial, and the recently published MERLIN trial (*J Am Coll Cardiol*. 2004;44:287) showed only a decrease in subsequent revascularization with rescue angioplasty. This study showed a reduction in the composite end point of major cardiac and cerebral events, recurrent MI and revascularization compared to conservative therapy and repeat thrombolysis. There was a trend toward lower mortality in the rescue group. These beneficial effects occurred despite the necessity to transfer about 40% of the patients to another facility for angioplasty, which cost a median of 84 minutes.

Why this study showed more benefit than the MERLIN study is probably related to study details that change with time. The MERLIN study is at least 2 years older, and streptokinase was the thrombolytic used in 96% vs 59% in this study. Also, less stents and IIb/IIIa agents were used in MERLIN. In addition, there was considerable cross-over from the conservative arm to the repeat thrombolysis arm, which did not happen in this study, which only had 4% of patients who did not receive their assigned treatment. Finally, only 8% of rescue angioplasty attempts failed in this study. This is important because observational data suggest that patients with failed rescue angioplasty have a worse prognosis.

Nonfatal bleeding, mainly from the sheath site, was more common in the rescue group, but fatal bleeding was more common in the other 2 groups ($P = .005$). Also, when the rescue group was compared to both other groups combined, the lower mortality in the rescue group was significant. This trial was stopped early because of falling enrollment and a finite funding period by the steering committee. The 80% power calculation suggested that about 156 patients per group would be required, but when the study ended there were 141-144 patients in each group. Had the trial continued, more robust results may have occurred, but certainly the direction of the results would not have changed. These results suggest that rescue angioplasty is now the treatment of choice for failed thrombolysis in acute ST elevation MI. ■

Value of Electrophysiologic Testing in Post MI Patients with Low EF

ABSTRACT & COMMENTARY

By John P. DiMarco, MD

Professor of Medicine, Division of Cardiology, University of Virginia, Charlottesville

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

Synopsis: *In the MADIT II study patients, inducibility was associated with an increased likelihood of VT.*

Source: Daubert JP, et al. Predictive Value of Ventricular Arrhythmia Inducibility for Subsequent Ventricular Tachycardia or Ventricular Fibrillation in Multicenter Automatic Defibrillation Implantation Trial (MADIT) II Patients. *J Am Coll Cardiol*. 2006;47:98-107.

THE MULTICENTER AUTOMATIC DEFIBRILLATION Implantation Trial (MADIT) II enrolled patients with coronary artery disease, prior myocardial infarction, and an ejection fraction of less than 0.30. MADIT II included an evaluation of the prognostic value of inducibility of ventricular arrhythmias by programmed electrical stimulation as a pre-specified secondary objective. The MADIT II protocol strongly encouraged, but did not require, patients randomized to the ICD arm to undergo electrophysiologic (EP) testing. This report describes the predictive value of the results of the EP study results.

MADIT II randomized 742 patients to the ICD arm of the trial, and 720 received an ICD. Of these, 593 underwent electrophysiologic testing, and the results from this cohort are the subject of this report. The study used a standard EP testing protocol. One to 3 extrastimuli were delivered at 2 basic cycle lengths. The protocol specified that stimulation be preformed via an electrode catheter at 2 right ventricular sites but, in 13% of the patients, inducibility was determined only through the ICD lead at the apex. The EP study end points included the induction of a sustained episode of monomorphic ventricular tachycardia (VT), polymorphic VT, ventricular fibrillation (VF) episode, or completion of the protocol. Daubert and colleagues examined 3 different criteria for inducibility. The standard inducibility definition included sustained monomorphic VT or polymorphic VT initiated by 3 or fewer extrastimuli and ventricular fibrillation with 2 or fewer extrastimuli. The narrow inducibility criterion included only sustained monomorphic VT as a significant response. The broad definition of inducibility included any sustained arrhythmia with any portion of the protocol.

Patients in the MADIT II study underwent quarterly ICD interrogation, as well as interim visits after ICD shocks. ICD interrogation data were reviewed by an ICD end point committee. The committee was blinded to the results of the initial EP study. Only appropriate ICD therapy was included in the data analyzed in this report.

At baseline electrophysiologic study, sustained monomorphic VT was induced in 169 of 593 patients (29%), sustained polymorphic VT in 26 (4%) patients, VF with one or 2 extrastimuli in 16 (3%) patients, and VF with triple extrastimuli in 32 (5%) patients. Only minor differences in clinical characteristics were seen in patients with inducible arrhythmias and those who did not have inducible arrhythmias. At least one appropriate ICD therapy was delivered in 141 (24%) of the 593 patients who underwent EP testing. By log rank analysis, patients with inducible arrhythmias were not more likely to receive appropriate ICD therapy, either shock or antitachycardia pacing (ATP), than patients without inducible arrhythmias using the standard definition. The 2-year point estimates for appropriate ICD therapy were 29.4% and 25.5%, respectively in the 2 groups. Inducibility at electrophysiologic study did predict ICD treatment for VT only but noninducibility predicted ICD treatment for a VF episode. The alternate inducibility definitions were also examined. The narrow definition of inducibility was a better predictor of ICD therapy for VT, and there was still a trend for less VF among patients with induced monomorphic VT. The broad definition, which included induction of VF with triple extrastimuli, performed less well as a predictor for any combination of events than either the narrow definition or the standard inducibility definition.

Daubert et al also examined whether the cycle length of the induced VT was a valuable predictor. Induction of VT with a cycle length of less than 240 m/sec (> 250 bpm) did not predict subsequent occurrence of VT better than noninducibility. Additional analyses which concluded ICD therapy for VT, ICD therapy for VF, or sudden death without ICD interrogation showed similar results to those described above. Overall, patients with inducible arrhythmias had a lower mortality than patients without inducible arrhythmias. Even after multivariate analysis, inducibility was independently, although weakly, associated with improved survival.

Daubert et al conclude that for postinfarction patients with an ejection fraction of less than or equal to 0.30, inducibility of ventricular arrhythmias at electrophysiologic testing is not a useful predictor of future ICD therapy.

COMMENTARY

Electrophysiologic testing to induce ventricular arrhythmias with programmed ventricular stimulation was first introduced over 30 years ago. Stimulation protocols, then developed, had a high sensitivity for inducing sustained monomorphic VT in patients with a history of recurrent episodes of VT. Studies in cardiac arrest survivors showed a lower rate of inducibility, but EP testing was still considered to be useful for many years. Although earlier trials that studied the use of ICD therapy for primary prevention used VT induction as an entry criterion (MADIT I and MUSTT), the value of VT induction has been recently questioned. These data from the MADIT II study confirmed that VT induction is of only limited, if any, value. Similar observations have been reported by follow-up analyses from other trials such as the AVID study. Even the observation that monomorphic VT was more common in patients in whom arrhythmia could be induced is of questionable value given the possibility that changes in programming and the delivery of ATP early in an episode that may have terminated on its own, may be responsible for this finding.

VT induction is a valuable technique when used for diagnosis of tachycardias of unknown mechanism and if the goal is catheter ablation of the ventricular tachycardia. However, data from several studies now indicate that its value for either serial drug testing or for risk prediction is quite limited. ■

Outcomes After ICD Placement

ABSTRACT & COMMENTARY

By John P. DiMarco, MD, PhD

Synopsis: *A risk score using simple clinical criteria may identify patients at high risk of early mortality after ICD implantation.*

Source: Parkash R, et al. Predicting Early Mortality After Implantable Defibrillator Implantation: A Clinical Risk Score For Optimal Patient Selection. *Am Heart J*. 2006; 151:397-403.

PARKASH AND COLLEAGUES FROM BRIGHAM AND Women's Hospital have developed a scoring system for predicting outcome after defibrillator implantation. Parkash and colleagues retrospectively reviewed data from 469 patients who underwent ICD implantation at their hospital between February, 1999 and March, 2002. The patients were randomly assigned to either a prediction or a validation cohort. Baseline clinical variables were chosen to be entered into a multivariate logistic regression model. The variables selected were: age greater than 80 years, primary vs secondary prevention use of ICD therapy, ejection fraction less than 35%, QRS duration greater than 120 m/sec, history of atrial fibrillation, New York Heart Association class III or IV, presence of coronary artery disease, renal insufficiency (creatinine greater than 1.8 mg/dL), and presence of significant co-morbid illness. The logistic regression model was used to assess the independent prognostic value of each of these variables for predicting mortality during one year after ICD implantation. Factors found to be significant were included in a risk score by assigning a value of 1 to the presence of the factor and 0 to its absence. The risk scoring system was then applied to the validation cohort to test its ability to protect 6 month and one year mortality.

There were 228 patients in the prediction cohort and 241 patients in the validation cohort. In the entire group, there were 46 deaths during the first year after the ICD implant. There were 27 deaths in the prediction cohort and 19 deaths in the validation cohort with one year mortalities of 11.8% and 7.9%, respectively. Total mortality over 3.2 years of follow-up was 18% in the entire group.

In the prediction cohort, the independent predictors of one year mortality were: age greater than 80 years, history of atrial fibrillation, renal insufficiency, and presence of New York Heart Association class III or IV. One year mortality significantly increased with higher risk scores. Mortality rates for patient groups with 0, 1, 2, and greater than or equal to 3 points were: 2.1%, 8.9%, 37.5%, and 42%, respectively. The Kaplan-Meier survival estimates for one year mortality risk showed a clear separation between the patients with a risk score less than 2 compared to those with a risk score greater than or equal to 2. Six months mortality rates showed a similar trend. The six month mortality rate for 0, 1, 2, and greater than 3 were: 1.1%, 3.3%, 34%, and 36%, respectively. In the validation cohort, the risk score showed similar results. A low risk score (0 to 1) predicted a one year survival of 96%, whereas risk score greater than or equal to 2 predicted a one year mortality of 21%.

Parkash et al conclude that their data provide the basis for a risk scoring system that may identify patients at increased risk of death in the first year after ICD implantation. They argue that given the high cost of ICD therapy and the ability to predict absence of long-term benefit should be an important consideration in ICD decision making.

COMMENTARY

Current indications for ICD implantation are quite liberal. Most patients with a history of a sustained ventricular arrhythmia who have structural heart disease are considered candidates for secondary prevention of sudden death. Heart failure or ventricular dysfunction are not criteria even though most benefit of the ICD over drug is seen in those with low ejection fractions. Indications for primary prevention ICDs, however, are based primarily on ventricular function and heart failure status. Both primary and secondary prevention indications are based on data from a large number of clinical trials.

In this paper, Parkash et al show that patients with early identifiable risk factors for pump failure death will still have significant mortality even with ICD implantation. This does not mean that these patients may not, as a group, derive benefit. In fact, many of these patients will receive an appropriate shock and have at least a small prolongation of life. However, the mortality benefit may be small and may not be enough to justify the expense of ICD implantation. This is true since in patients with advanced heart failure, the ratio of arrhythmic deaths to pump fail-

ure deaths is shifted to the latter mechanism. Even though the ICD therapy delivery rate in these patients is high, their mortality during chronic ICD therapy may still be substantial.

Optimal prescription of ICD therapy remains a challenge. One would hope that we could identify patients at high enough risk for arrhythmic death that they would have some chance of substantial prolongation of life after receiving the ICD. However, the ICD may not have a major effect on the long-term outcome in patients if their greatest risk is for a pump failure death. Unfortunately, predicting heart failure mortality in an individual patient can be quite difficult, but risk scores such as those outlined in this paper should prove to be helpful resources for physicians and patients. ■

Troponin vs CKMB in ACS

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

Synopsis: *Among patients with NSTE ACS, an elevated troponin level identifies patients at increased acute risk regardless of CK-MB status, but an isolated CK-MB+ status has limited prognostic value.*

Source: Newby LK, et al. Frequency and Clinical Implications of Discordant Creatine Kinase-MB and Troponin Measurements in Acute Coronary Syndromes. *J Am Coll Cardiol*. 2006;47:312-318.

Cardiac biomarker testing is part of the standard approach to evaluating patients with suspected acute coronary syndromes (ACS). Although troponin has become the diagnostic standard for myocardial infarction (MI), CKMB is often tested as well. Thus, Newby and colleagues evaluated the use of dual marker testing in patients with non-ST elevation ACS in the CRUSADE quality improvement initiative database. The end point chosen was in-hospital mortality. They specifically focused on the significance of discordant results of troponin and CKMB, which occurred in 28% of the 29,357 patients who had both measured. Most patients had concordant cardiac marker values; 12% were CKMB negative and troponin (Tn) negative and 60% were CKMB+/Tn+. CKMB+/ Tn- occurred in 10%; CKMB-/ Tn+ occurred in 18%. Hospital mortality was highest in the concordant positive (CKMB+/Tn+) patients at 5.9% and lowest in the concordant negative patients at 2.7%. Hospital mortality in the discordant patients was 3.0% in the CKMB+/Tn- patients and 4.5% in the CKMB-/Tn+ patients. Baseline characteristics showed that Tn+ patients were older, had more evidence of vascular disease, and more often had heart failure. After adjustment for baseline characteristic differences, troponin was more strongly associated with mortality than CKMB (chi square 23 for troponin and 8 for CKMB). Hospital therapy was similar for all cardiac marker groupings. Newby et al concluded that in patients with non-ST elevation ACS, an elevated troponin is associated with an increased risk of death regardless of the CKMB value, but an elevated CKMB alone is of little prognostic value.

■ COMMENTARY

The major conclusion of this study is that an elevated troponin value defines the highest risk patients among non-ST elevation ACS patients who are admitted. However, all the patients in this database were treated similarly, despite their troponin values. For example, those who were CKMB- and Tn- were most likely to have an early cardiac catheterization approach as compared to either group with discordant results. Newby et al argue that cardiac biomarker results should be used to direct the most aggressive therapy to the highest risk patients, those who were troponin positive. They believe CKMB adds little to the troponin results, yet most centers do both in ACS patients. Should CKMB be eliminated? Perhaps it should in the triage of ACS patients, but it may be useful later to estimate infarct size in selected patients.

Why are we not responding more aggressively to an elevated troponin? Perhaps because of troponin desensitization. We are used to seeing elevated troponins in many hospitalized patients. We are annoyed by consultation requests to see terminally ill non-cardiac patients with slight troponin elevations. Thus, in ACS patients where an elevated troponin is of value, we may not react appropriately anymore. Also, troponin assays have been a moving target; troponin T, then I; changes in cutoff values; test inaccuracies. In this study, they used each center's test and values; there was no core laboratory. So, Newby et al note that as more centers convert to the latest troponin I system there could be changes in this ongoing database. Finally, it was pointed out that these results may not apply to lower risk patients who are not hospitalized, but held in chest pain observation units. ■

Erectile Dysfunction and Subsequent Cardiovascular Disease

ABSTRACT & COMMENTARY

By Jonathan Abrams, MD

Professor of Medicine, Division of Cardiology, University of New Mexico, Albuquerque

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

Synopsis: *Erectile dysfunction should prompt investigation and intervention for cardiovascular risk factors.*

Source: Thompson IM, et al. Erectile Dysfunction and Subsequent Cardiovascular Disease. *JAMA*. 2005;294:2996-3002.

The use of therapeutic agents for erectile dysfunction (ED) or impotence has been an enormous story since the advent of sildenafil (Viagra) some years ago. Recent data suggests that more than 10 million men in the United States have some degree of ED; approximately 30,000 men die yearly from prostate cancer. Some have suggested that ED may be a clue to occult vascular disease, given the fact that nitric oxide (NO) modulates erectile function; thus, the common sense hypothesis that vascular disease in one organ may increase the likelihood of endothelial dysfunction in other areas of the body, particularly the coronary arteries.

The Prostate Cancer Prevention Trial was a 7-year prospective RCT evaluating the drug finasteride on the prevalence of prostate cancer. Finasteride, the primary result of this trial, blocks conversion of testosterone to dihydrotestosterone (*N Engl J Med*. 2003;349:215-224) demonstrated a reduction in prostate cancer. A sub-study sought to evaluate the incidence and prevalence of ED over the duration of the trial. Thus, in addition to yearly PSA levels and digital rectal examinations, a standardized yearly survey addressing sexual function was included to examine the issues of ED, decreased libido, and decreased ejaculation volume. Cardiovascular events were also evaluated as part of safety monitoring, and included myocardial infarction, revascularization, stroke, TIA, or congestive heart failure. The sexual function component of the Prostate Cancer Prevention Trial was carried out in the placebo group. Men who had a history of cardiovascular disease at entry were excluded from the primary analysis, but were carefully followed; a proportional hazards regression model was used to evaluate the association of ED with cardiovascular disease, with a separate analysis of each of the major cardiovascular events. Men with and without ED at baseline were followed for changes in sexual function. Two models were used to address cardiovascular events, including an unadjusted and co-variant-adjusted approach. The interval from the onset of ED to the first cardiovascular event was assessed in men with no prior history of a cardiovascular event.

Results: Eight thousand sixty-three men had no cardiovascular disease at study entry, representing 85% of the entire placebo cohort; however, 47% of these individuals reported some degree of ED at study entry. Of the 4247 men who reported no ED at study entry, 57% noted the development of incident ED by 5 years, increasing to 65% at 7 years. Seventy-six percent of all enrollees completed the 7-years protocol. Incident ED was associated with the development of angina, myocardial infarction, and stroke, (*P*-value of 0.04 for angina and 0.06 for stroke). Men with ED "had a significantly increased risk of myocardial infarction or angina, relative to men without a report of ED, after adjusting for potential confounders" (hazard ratio of 1.37, $P = 0.02$). When men with ED at study entry were added to the total population, the results were similar. The highest hazard was for TIA (HR of 1.9, $P = 0.02$) and 1.45 for any cardiovascular event ($P < 0.01$). Men who reported a reduction in libido and had no ED were excluded from the analysis but evaluated for the first report of cardiovascular disease. These individuals were defined as grade 3-4 (moderate to severe) sexual dysfunction, but represented only 1% of the entire cohort. Hazard ratios were comparable in men with a decrease in libido prior to developing overt ED. After the first year of the study, 2% of all men with ED developed a cardiovascular event, and 11% at 5 years. An evaluation of cardiovascular risk factors indicated that ED "had an equal or greater effect on subsequent cardiovascular event of the same magnitude as a family history of myocardial infarction, cigarette smoking, or measures of hyperlipidemia."

Thompson and colleagues comment that up to half of all deaths from CAD occur in men without a history of vascular disease. They note that patients with cardiovascular disease frequently report preexisting ED, as also demonstrated in other studies. Risk factors for ED and cardiovascular disease are well known, and include obesity, cigarette smoking, physical inactivity, diabetes, hypertension, and hyperlipidemia. Some patients have ED without cardiovascular disease or cardiovascular risk factors, and presumably have a defect in the peripheral penile vasculature "independent of other systemic vascular disease." Reports in literature have suggested that

ED "is a harbinger of cardiovascular disease"; peripheral vascular disease has also been found to be markedly increased in patients with preexisting ED.

This study of asymptomatic healthy men utilizing a yearly questionnaire for ED indicates that half (47%) had some degree of ED at the time of study entry; 57% of those who had no ED at entry developed sexual symptoms after 5 years. Thompson et al point out that the use of the Sexual Problems Scale may be somewhat outdated methodology for evaluating ED, and also recognize they do not have adequate data on medications that could be related to ED. Thompson et al cite the Massachusetts Male Aging Study estimate that more than 600,000 American men develop ED annually; men over 70 with ED have a 2-fold greater risk of cardiovascular disease than men without ED.

Thus, "this analysis suggests that the initial presentation of a man with ED should prompt the evaluating physician to screen for standard cardiovascular risk factors." Nevertheless, there is no evidence that lifestyle or behavioral interventions, including PDE-5 agents, can "reduce or delay the onset on ED." Thompson et al conclude that this study provides the first evidence "of a strong association between ED and subsequent development of clinical cardiovascular events." They suggest that symptoms of ED "should prompt an assessment of cardiovascular risk factors and vigorous interventions as appropriate."

COMMENTARY

The remarkable success of the PDE-5 inhibitors attests to the widespread prevalence of some degree of abnormal sexual function in males. One wonders if a decline in sexual function is truly abnormal, in that at least 50% ultimately develop ED. Several years ago at one of the national heart meetings, a poster was presented regarding a small cohort of men that had ED and a substantial burden of cardiovascular risk factors; Thompson et al suggested enhanced clinical observation of such individuals and vigorous treatment of risk factors. This makes common sense. It would appear reasonable that sexual dysfunction or ED be included in the routine cardiovascular risk assessment of middle-aged or older men, with a report of ED stimulating aggressive risk factor identification as well as treatment. Thus, it is appropriate to initiate a search for cardiovascular risk factors, as well as behavioral and pharmacologic therapies for ED, in those men who might otherwise slip through the cracks of prevention. ■

CME Questions

13. Patients with erectile dysfunction often have:
a. cardiovascular disease.
b. risk factors for cardiovascular disease.
c. cardiomyopathy
d. a & b

14. Independent predictors of death in ICD patients include:
a. age > 80.
b. renal insufficiency.
c. class III or IV heart failure.
d. All of the above

15. Decisions regarding ICD placement rely on:
a. EF determination.
b. electrophysiologic testing.
c. etiology of heart disease.
d. All of the above

16. Statins are of demonstrated benefit in patients with:
a. coronary artery disease.
b. elevated LDL cholesterol.
c. dilated cardiomyopathy.
d. All of the above

17. Rescue angioplasty after failed thrombolysis results in:
a. reduced stroke.
b. reduced heart failure.
c. reduced major cardiac and cerebral events.
d. reduced bleeding.

18. In hospitalized ACS patients, which group had the highest mortality?
a. CKMB negative /troponin positive
b. CKMB positive/troponin negative
c. CKMB negative/troponin negative
d. Early invasively managed patients

Answers: 13. (d); 14. (d); 15. (a); 16. (d); 17. (c); 18. (a)

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Correction

In the January issue, we included a letter which marked the beginning of the next semester of CME. In the letter we stated that once the CME activity was complete, the activity would be valid for 6 months. It should have read that the CME activity would be valid for 36 months. We apologize for any inconvenience. ■

CME Objectives

The program's objectives are:

• To present the latest information regarding diagnosis and treatment of cardiac disease;

• To discuss the pros and cons of these interventions, as well as possible complications;

• To discuss the pros, cons, and cost-effectiveness of new and traditional diagnostic test; and

• To present current data regarding outpatient care of cardiac patients. ■

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.

Treating Opioid-Dependent Patients with OAT

A Perspective article in the Jan. 17 *Annals of Internal Medicine* reviews pain management in patients with a history of opioid addiction who are receiving opioid agonist therapy (OAT) with maintenance methadone or buprenorphine. These patients present unique challenges that frequently result in suboptimal treatment of acute pain.

The authors provide an excellent review of these challenging patients and point our 4 common misconceptions: 1) Maintenance opioids provide analgesia—not only is this not the case, but OAT may reduce the effectiveness of standard pain relief measures; 2) Opioids for analgesia may result in addiction relapse—there is no evidence that treatment of acute pain triggers relapse; 3) The additive effects of opioid analgesics and OAT may cause respiratory and CNS depression—tolerance to the respiratory and CNS effects of opioids develops rapidly and is not exacerbated by acute therapy; 4) Reporting pain is drug-seeking behavior—as long as there is clinical evidence of pain, or an acute injury, pain may be safely treated. Drug seeking and manipulation is more likely characterized by vague reports of long-term pain than requests for short term pain relief. Plus, patients on OAT are less likely to experience euphoria associated with coadministered opioids, so there is less incentive to drug seek.

The authors provide specific pain treatment recommendations for patients on methadone and buprenorphine. They conclude, "Addiction elicits neurophysiologic, behavioral, and social responses that worsen the pain experience and complicate provision of adequate analgesia. These complexities are heightened for patients with opioid dependency who are receiving OAT, for whom the neural responses of tolerance or hyperalgesia may alter the pain experience. As a consequence, opioid analgesics are less effective; higher doses administered at shortened intervals are required. Opioid agonist therapy provides little, if any, analgesia for acute pain. Fears that opioid analgesia will cause addiction relapse or respiratory and CNS depression are unfounded. Furthermore, clinicians should not allow concerns about being manipulated to cloud good clinical assessment or judgment about the patient's need for pain medications. Reassurance regarding uninterrupted OAT and aggressive pain management will mitigate anxiety and facilitate successful treatment of pain in patients receiving OAT" (Alford DP, et al. *Ann Intern Med*. 2006;144:127-134).

Long-Term Effects of Warfarin Use

Warfarin use may be associated with osteoporosis and fractures in men, but not women, with atrial fibrillation, according to new study. In a retrospective cohort study of Medicare benefici-

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aries with atrial fibrillation in United States, 4461 patients on long-term warfarin therapy were compared to 7587 patients who were not prescribed warfarin. The adjusted odds ratio of fracture was 1.25 in patients who took warfarin (95% CI, 1.06-1.48). The odds ratio for men was 1.63, and a nonsignificant 1.05 for women. In patients who were prescribed warfarin for less than one year, the risk of osteoporotic fracture was not increased significantly. The authors speculate that since warfarin blocks vitamin K dependent clotting factors, it may also block vitamin K dependent osteocalcin and other bone matrix proteins. Interestingly, use of beta blockers reduced the risk of fracture in this population. The authors conclude that long-term use of warfarin was associated with osteoporotic fractures in men with atrial fibrillation, and that beta-blockers may be somewhat protective (Gage BF, et al. *Arch Intern Med*. 2006;166:241-246).

Statins' Multiple Benefits

Mounting evidence suggest that statins have benefits beyond their ability to lower LDL cholesterol. Multiple studies show that statins reduce inflammation in patients without heart failure. Now, 2 new studies suggest that they also reduce inflammation in patients with heart failure. In a study from Emory University, 108 patients with nonischemic heart failure were randomized to atorvastatin 20 mg per day or placebo. Inflammatory markers such as C reactive protein, interleukin-6, and TNF-alpha were all reduced in the atorvastatin group. Atorvastatin treated patients also showed an improvement in LVEF from 0.33-0.37 over one year (P = 0.01) (Sola S, et al. *J Am Coll Cardiol*. 2006;47:332-337).

A second study, from Harvard, in patients with heart failure showed that atorvastatin 10 mg/ day led to an 8% reduction in TNF receptor 1, a 37% reduction in C reactive protein, and a 17% reduction in endothelin-1 (Mozaffarian D, et al. *Am J Cardiol*. 2005;96:1699-1704). Atorvastatin may also have anti-thrombotic effects in patients with unstable angina according to a study from Greece. Forty-five patients with normal cholesterol levels and unstable angina were randomized to 10 mg of atorvastatin or placebo, starting right after hospital admission and continuing for 6 weeks. After one week of treatment circulating levels of anti-thrombin III, factor V, and von Willebrand factor were all significantly reduced in the atorvastatin group (Tousoulis D, et al. *Int J Cardiol*. 2006;106:333-337).

FDA Actions

The FDA has approved the first inhaled insulin for the treatment of adults with type I and type 2 diabetes. Inhaled insulin, a powder form of recombinant human insulin, has been in development for over 10 years, and has been the subject of intense scrutiny by the FDA. Concerns over long-term safety, particularly in people with underlying lung disease, has delayed approval, and safety in children and teenagers is still under investigation. Inhaled insulin is delivered through a device that is significantly larger than an asthma inhaler and, even folded, is the size of a flashlight. A blister pack of insulin powder is inserted into the device, which is then triggered. It is not to be used by smokers or people who quit smoking within last 6 months, and is not recommended for people with asthma, bronchitis, or emphysema. The FDA also recommends pulmonary function testing prior to starting inhalation therapy, and every 6 to 12 months thereafter. Although the product is approved for treatment of both type I and type 2 diabetes, fewer than 30% of type I diabetics achieve adequate control with inhaled insulin alone. Inhaled insulin is a joint effort by Pfizer, Sanofi-Aventis, and Nektar Therapeutics. It will be marketed under the trade name Exubera.

The FDA has approved an intravenous form of Ibandronate that can be administered every 3 months for the treatment of postmenopausal osteoporosis. The 3 mg dose is injected intravenously over 15 to 30 seconds by a healthcare professional. The drug is an option for women who cannot take pills or are unable to sit upright for 30 to 60 minutes after taking an oral bisphosphonate. Efficacy with the injectable form of ibandronate was better than once-a-day oral dosing of Ibandronate 2.5 mg in a study of over 1300 women with osteoporosis. Intravenous and oral forms of the drug were equally well tolerated. The FDA is recommending measurement of serum creatinines prior to administration each dose. Ibandronate is also approved is a 2.5 mg once a day oral dose and a 150 mg monthly oral dose. All 3 formulations are marketed as Boniva.

Berlex's combination estradiol-levonorgestrel patch (Climara Pro) has been approved for the indication for prevention of postmenopausal osteoporosis in women with an intact uterus. The patch was previously approved for the indication of moderate to severe vasomotor symptoms associated with menopause. The osteoporosis indication was based on a 2-year, double-blind, randomized trial that showed that the estradiol-levonorgestrel patch was associated with significant maintenance of bone density compared to placebo. ■