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INSIDE

A Bad Month for Beta-Blockers

After years of kowtowing to the beta-blocker police, it is interesting to see the pendulum start to swing back. What follows is a discussion of 3 new studies that challenge the conventional wisdom on beta-blocker use for heart failure, hypertension, and acute myocardial infarction.

Beta-Blockers for Heart Failure

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

Source: Willenheimer R, et al. Effect on Survival and Hospitalization of Initiating Treatment for Chronic Heart Failure with Bisoprolol Followed By Enalapril, As Compared with the Opposite Sequence: Results of the Randomized Cardiac Insufficiency Bisoprolol Study (CIBIS) III. *Circulation*. 2005;112:2426-2435.

GIVEN THE IMPRESSIVE RESULTS OF BETA-BLOCKERS ADDED TO angiotensin-converting-enzyme (ACE) inhibitors in heart failure patients, many have suggested that had beta-blockers been studied first for heart failure, they would have been so impressive that we would start them before ACE inhibitors. Accordingly, the group from the Randomized Cardiac Insufficiency Bisoprolol Study (CIBIS III) studied the effect of the order of initiating beta--blockers or ACE inhibitors for initial monotherapy of congestive heart failure (CHF). They randomized 1010 patients age > 65 with mild to moderate CHF and left ventricular ejection fraction < 35% who were not on beta-blockers, ACE inhibitors, or angiotensin-receptor blocking therapy to open-label monotherapy with bisoprolol (10 mg a day) or enalapril (10 mg twice a day) for 6 months, then the combination for 6 to 24 months. The primary end point was time to first event of mortality or hospitalization for any cause. The major exclusion criterion was prior study drug use. Two groups were analyzed, the intention-to-treat sample and the per protocol sample. The latter patients were those who actually completed the study protocol.

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Results: In the intention to treat group, the primary end point was reached in 35% of the bisoprolol-first patients and 37% of the enalapril-first patients (noninferiority for bisoprolol first, P = .02). In the per-protocol group, 32% bisoprolol first reached the primary end point vs 33% for enalapril first (noninferiority for bisoprolol first, P = .05). Deaths and hospitalizations analyzed separately were not different between the 2 treatments. During monotherapy, 65% of the bisoprolol group reached the target dose of 10 mg daily vs 82% of the enalapril group. Bisoprolol was not tolerated by 7%, enalapril by 10%. Willenheimer and colleagues concluded that bisoprolol-first treatment for patients with CHF was not noninferior to enalapril-first treatment on a per-protocol analysis.

COMMENTARY

Many beta-blocker proponents were disappointed by these results, since not only was beta-blocker first not superior to ACE inhibitors first, it was not noninferior in the per protocol analysis, which is generally considered more robust for this purpose than the intention-to- treat approach. Also, there was a trend toward more hospitalizations for worsening heart failure in the beta-blocker-first group. This would argue that it is safer to start beta-blockers after ACE inhibitors are onboard.

Another consideration was that patients are often on lower than recommended doses of one drug when they are on both, or end up on only one because of concerns about blood pressure. Thus, order of administration would be important if one drug was clearly superior. These results suggest that ACE inhibitors first is still the preferred policy. There may be selected individuals in whom starting with a beta-blocker first makes sense, (eg, patients with supraventricular arrhythmias, but there are no specific data on this). ■

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Questions & Comments

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Beta-Blockers for Hypertension

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

Source: Lindholm LH, Carlberg B, Samuelsson O. Should Beta Blockers Remain First Choice in the Treatment of Primary Hypertension? A Meta-Analysis. *Lancet*. 2005;366: 1545-1553.

For the past 3 decades, beta-blockers have been first-line therapy for hypertension. However, recently the efficacy of beta-blockers for treating primary hypertension has been challenged. Thus, Lindholm and colleagues from Sweden conducted a meta-analysis of 13 randomized, controlled trials for the treatment of primary hypertension where a beta-blocker was used in at least 50% of the patients. Both placebo-controlled and drug comparison studies were considered. End points were stroke, death, and myocardial infarction (MI). In comparison to other drugs, the risk of stroke was 16% higher with beta-blockers (P < .01). All-cause mortality and MI were not different. The main difference in stroke rates was observed in the trials involving atenolol. In the non-atenolol trials there were too few strokes to analyze. Compared to placebo, beta-blockers reduced the risk of stroke by 19%, which is half the magnitude of reduction seen in other studies. Lindholm et al concluded that in comparison to other therapy in patients with hypertension, beta-blockers are less efficacious and increase the risk of stroke.

COMMENTARY

Propelled by its benefits in post MI patients and low costs, beta-blockers have become first-line therapy for hypertension. Proponents have impugned the motives of anyone who thought that newer and more expensive drugs were better (eg, calcium blockers,

ACE inhibitors, ARBs). Since beta-blockers lowered blood pressure as much as newer agents, they must be as effective. Large trials published since 2002 have shown otherwise, and these trials dominate this meta-analysis. Also, many older studies combined diuretics with beta-blockers, which obscure the effect of beta-blockers alone. In this meta-analysis beta-blockers had no affect on MI or death, and lowered stroke 19%. A similar meta-analysis of newer antihypertensives showed stroke reduced by 38%. Lindholm et al estimated based on this difference that if newer drugs were used instead of beta-blockers in the European Union, 125,000 stokes would be prevented in 5 years.

Given identical lowered blood pressure reduction, why would beta-blockers be less effective? Some have suggested the deleterious metabolic effects on lipids and glucose, which would be exacerbated by thiazides, is the reason. Others believe beta-blockers lower peripheral blood pressure more than central, hence they observed lesser effects on left ventricular hypertrophy regression. Whatever the reason, the proponents of using newer drugs rather than beta-blockers seem vindicated, rather than being pharmaceutical company shills. ■

Beta-Blockers for Acute Myocardial Infarction

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

Source: Chen ZM, et al. COMMIT Collaborative Group. Early Intravenous Then Oral Metoprolol in 45,852 Patients with Acute Myocardial Infarction: Randomised Placebo-Controlled Trial. *Lancet*. 2005;366:1622-1632.

THE EMERGENCY TREATMENT OF PATIENTS WITH acute myocardial infarction (MI) with intravenous then oral beta-blockers has become the standard of care based upon randomized trials of over 27,000 patients. However, most of these trials were done before the advent of reperfusion therapy and aggressive platelet antagonists. Thus, the Clopidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT) studied the balance of risks vs the benefits of this aggressive beta-blocker strategy in acute MI treated by current methods. In over 45,000 patients admitted to 1250 hospitals within 24 hours of suspected acute MI, a 2 × 2 factorial trial of early beta-blockers or clopidogrel vs placebo plus aspirin was conducted. In 93%, ECG ST-elevation or new left bundle-branch block was present. The metoprolol protocol was up to 15 mg IV then 200 mg po daily until discharge or 4 weeks in the hospital. The primary outcome end points were: 1) death, reinfarction or cardiac arrest; 2) all-cause mortality, at first discharge or 28 days. No long-term therapy or follow-up was attempted, possibly because the study was done in China.

Results: Metoprolol did not reduce either primary end point (9.4% metoprolol, 9.9% placebo, and 7.7% metoprolol vs 7.8% placebo for death alone). However, metoprolol did decrease reinfarction (2% vs 2.5%; $P = .001$) and ventricular fibrillation (2.5% vs 3.0%; $P = .001$), but these positive effects were counterbalanced by an increase in cardiogenic shock (5% vs 4%; $P < .001$) during the first day after admission. Consequently, overall effects were adverse during the first day and then improved. Also, metoprolol increased the number of patients developing heart failure (14% vs 13%; $P < .001$) or non-shock hypotension (6% vs 3%; $P < .001$). Although bradycardia was more common with metoprolol, atrioventricular block was not. Not unexpectedly, metoprolol produced worse outcomes in hemodynamically unstable patients and no benefit in stable patients. Chen and colleagues concluded that beta-blockers should not be started until hemodynamic stability can be assured in acute MI patients.

■ COMMENTARY

Despite several trials touting the benefits of early IV beta-blockers for acute MI there has been physician ambivalence about its use. Reportedly, use in the United Kingdom is less than 1%, and in Sweden, 54%. Many physicians have observed marked bradycardia and hypotension, and the appearance of signs of left heart failure after IV beta-blockers for acute MI. Also, during the era of widespread use of indwelling right heart catheters to manage acute MI (before revascularization); many were concerned about the almost universally observed increase in pulmonary capillary wedge capillary wedge pressures after IV beta-blockers. Such observations understandably lead to a more cautious approach to IV beta-blocker use among many physicians. In addition, many of us were puzzled by the push for IV beta-blocker use when earlier studies that started beta-blockers after 30 days post MI showed a strong benefit. The small gain of early administration seemed to be balanced by greater risks in the pre-reperfusion era, but the beta-blocker police persisted, as the acute MI care guidelines for several organizations can attest.

In the reperfusion era, it is perfectly reasonable to restudy this issue. This is the era of bringing blood to ischemic myocardium, not drugs after all. Low and behold, our old fears are justified; in this trial early IV beta-blockers caused net harm that was never overcome despite later benefits over one month of therapy. You could almost make the argument that they should be withheld for the first month, but Chen and colleagues concluded that they should be avoided in patients who showed early high-risk signs for developing cardiogenic shock such as, tachycardia, hypotension, or heart failure. Interestingly, there was no specific subgroup that always benefited from early beta-blocker use.

This study is larger than all previous trials by 2-fold, and has 3 times the number of deaths. Thus, it is a robust study of a wide spectrum of patients. The major limitation of the study is that it was done in China, and only thrombolytic reperfusion was used in a little over half the patients. Regardless, this study should temper the early aggressive beta-blocker proponents and support a more clinical judgment-based approach. Unfortunately, the latter is difficult to get into algorithms and guidelines, and doesn't lend itself well to quality improvement data gathering. ■

Risk of Myocardial Ischemia in ICD Patients

ABSTRACT & COMMENTARY

By John P. DiMarco, MD, PhD

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: *Ischemia during stress echocardiography is an independent predictor of death and ICD therapy in patients with coronary heart disease at high risk of arrhythmic death.*

Source: Elhendy A, et al. Association of Myocardial Ischemia with Mortality and Implantable Cardioverter-Defibrillator Therapy in Patients with Coronary Artery Disease At Risk of Arrhythmic Death. *J Am Coll Cardiol*. 2005; 46:1721-1726.

In this paper, Elhendy and colleagues look at the value of inducible ischemia during stress echocardiography for predicting mortality and major ischemic events in ICD patients. Elhendy et al studied 90 consecutive patients with coronary artery disease who had received an ICD and underwent a stress echo exam. The stress echo was performed 3 ± 2 years after ICD implantation. The indications for stress testing were for the evaluation of chest pain in 50 patients, for a functional assessment after revascularization in 26 patients, and for investigation of reversible causes of heart failure in 14 patients. Most patients in the group had received an ICD for secondary prevention after an episode of aborted sudden cardiac death or sustained ventricular tachycardia (VT). Stress echocardiography was performed after beta blockers had been discontinued. ICDs were inactivated before the stress test in order to minimize the potential for shocks. Patients underwent either a symptom-limited exercise treadmill test or a graduated-dose dobutamine infusion. Images were acquired at rest, immediately after exercise/dobutamine stress, and in recovery. A 16-segment model was used for analysis of regional ventricular function, and an ejection fraction was calculated at each point. Ischemia was defined as new or worsened wall motion abnormalities during stress, associated with an increase in wall motion score > one grade in > one segment. Follow-up was obtained during scheduled visits to the ICD clinic. Patients who underwent surgical or percutaneous myocardial revascularization were censored at the time of recurrence. The end points of the trial were death or appropriate ICD therapy, which could include either antitachycardia pacing or shock for either ventricular tachycardia or ventricular fibrillation.

The study group included 90 patients, of whom 70% were men. The mean age was 65 ± 13 years. Most had a history of either cardiac arrest, syncope with inducible ventricular tachycardia, or sustained ventricular tachycardia. During the stress test, the target heart rate was reached in 81 of 90 patients. There were no episodes of death, myocardial infarction, ventricular fibrillation, or sustained VT during or shortly after the test. Ischemia was detected during the stress test in 44 of 90 patients.

During a mean follow-up of 2.8 ± 1.5 years, 5 patients died and 19 patients had appropriate ICD therapy. Thirteen patients underwent revascularization and were censored at that point. All of the 5 patients who died during follow-up had inducible ischemia, and 3 of these 5 deaths were classified as cardiac. Patients with events more often had a history of spontaneous sustained VT, inducible VT at

electrophysiologic study, and inducible ischemia on stress echocardiograms. A Cox multivariate analysis model was used to assess independent predictors of events. Independent predictors of events in the Cox model included a history of spontaneous sustained VT (hazard ratio, 1.9), inducible VT in response to programmed stimulation (hazard ratio 1.7), and myocardial ischemia during stress echocardiography (hazard ratio, 2.1). Kaplan-Meier event-free survival curves in patients with or without ischemia showed a 3-year event-free survival above 90% in those without ischemia vs approximately 45% in those with ischemia.

Elhendy et al conclude that myocardial ischemia on stress echocardiography is associated with an increased risk of death and need for therapy in ICD patients. These data suggest, but do not prove, that aggressive treatment of ischemia can reduce the incidence of events in ICD patients.

COMMENTARY

This paper highlights the important role of ischemia in the pathogenesis of sudden death in patients with coronary artery disease. When electrophysiologic studies were first introduced for the evaluation of patients with ventricular arrhythmias, much of the initial focus was on sustained monomorphic ventricular tachycardia in patients with large, fixed scars or aneurysms. In these patients, sustained VT could be easily reproduced with stimulation. However, a different pattern of electrophysiologic responses was seen in cardiac arrest survivors. Although some had inducible, sustained monomorphic VT, many had either no inducible arrhythmia or only polymorphic VT or ventricular fibrillation. Since those early studies used more aggressive treatment in patients with myocardial infarction and myocardial ischemia, it has decreased the numbers of patients with the large, dense scars likely to produce monomorphic ventricular tachycardia at random intervals. This has increased the importance of transient phenomena such as heart failure or ischemia as primary or contributing factors in sudden death.

A number of other observations support this concept. Among cardiac arrest victims in the community, ventricular tachycardia is now rarely documented by first responders, and either ventricular fibrillation or bradycardic rhythms are more commonly seen. In autopsy studies of cardiac arrest survivors, active coronary lesions are frequently seen, even in the absence of preceding chest pain. For example, in the ATLAS trial (*Circulation*. 2000;102:611-616), acute coronary findings were present in 54% of the patients with coronary artery disease who died suddenly. It has also been observed in the Coronary Artery Bypass Graft ICD Patch Trial that recently revascularized patients did not benefit from ICD therapy. Similar results were seen in the Multicenter Unsustained Tachycardia Trial in which patients who had their devices implanted shortly after surgical revascularization received no benefit from the ICD.

The data presented here emphasize that we need to provide comprehensive care to prevent sudden death. Although an ICD can reverse acute episodes, aggressive treatment to prevent both ischemia and heart failure is necessary for optimal patient outcomes. ■

Role of Adrenaline and Procainamide Infusion in the Evaluation of Unexplained Cardiac Arrest

ABSTRACT & COMMENTARY

By John P. DiMarco, MD, PhD

Synopsis: *Provocative testing with adrenaline and procainamide infusions is useful in unmasking the etiology of apparent unexplained cardiac arrest.*

Source: Krahn AD, et al. Diagnosis of Unexplained Cardiac Arrest: Role of Adrenaline and Procainamide Infusion. *Circulation*. 2005;112:2228-2234.

KRAHN AND COLLEAGUES FROM LONDON, ONTARIO, Canada performed a long-term study on the value of provocative drug infusions in selected survivors of unexplained cardiac arrest and their family members. Survivors of a cardiac arrest were eligible for the study if they had experienced a cardiac arrest or syncope with documented ventricular tachycardia or ventricular fibrillation. Patients who had any evidence of left ventricular dysfunction, coronary artery disease, or anomalies, manifest long QT syndrome or reversible cardiac causes of cardiac death were excluded. First degree relatives of unexplained cardiac arrest were recruited and offered a similar testing protocol.

The testing protocol included a clinical assessment, an electrocardiogram, a treadmill exercise

test, an echocardiogram, a cardiac MRI, and coronary angiography. If the cardiac arrest remained unexplained after these studies, the patients then underwent provocative adrenaline (epinephrine) and procainamide infusions. The adrenaline test was performed using escalating doses from 0.05 mcg per kg per minute to 0.40 mcg per kg per minute. Twelve lead electrocardiograms were monitored. The infusion was discontinued for either severe systolic hypotension (< 80 mmHg) or hypertension (> 200 mmHg), or when ventricular arrhythmias were noted. The following ventricular arrhythmias during the adrenaline infusion were considered significant: nonsustained ventricular tachycardia, greater than 10 premature beats per minute, or previously absent T wave alternans. QTc prolongation was considered significant if the QTc interval prolonged by greater than or equal to 65 msec above control levels.

If the response during the adrenaline test was negative, patients received a procainamide infusion after a 30 minute recovery period. This protocol involved a 30 minute infusion of 15 mg per kg (maximum 1000 mg) over 30 minutes. Electrocardiograms were monitored for ST segment elevation in the precordial leads, and changes were characterized as either saddleback or coved and considered positive for the Brugada syndrome according to established criteria. In patients with a positive ST segment response, isoproterenol was infused at a dose of 2 mcg per minute to see if the ST segment changes were reversible.

During follow-up, all the unexplained cardiac arrest survivors received an ICD. Patients with a clinical phenotype suggestive of catecholaminergic polymorphic ventricular tachycardia (CPVT) also received beta adrenergic blockers. Asymptomatic family members with positive test results suggestive of CPVT were also offered beta blockers.

The proband study group included 18 survivors of unexplained cardiac arrest or syncope with documented polymorphic ventricular tachycardia. Fifty-five family members of these patients also underwent the noninvasive testing protocol outlined above. These fifty-five family members included 8 patients (7 from a single CVPT family) with symptoms of either syncope or palpitations. The remaining 47 patients were had no symptoms of arrhythmia.

During exercise testing, 7 patients with unexplained cardiac arrest developed ventricular arrhythmias. Adrenaline infusion elicited a positive response in 9 patients. Procainamide infusion unmasked latent Brugada syndrome in 2 patients. Although the QTc interval was increased by both adrenaline and procainamide infusions, no patient had a QTc prolongation greater than 65 m/sec.

Based on exercise testing and drug infusions, the final diagnosis among the 18 unexplained cardiac arrest survivors was CPVT in 10 patients (56%), Brugada syndrome in 2 (11%), and idiopathic ventricular fibrillation in 6 (33%). Testing results in family members were less frequently positive. Among the 8 symptomatic patients, symptomatic polymorphic ventricular ectopy was observed during exercise testing in 7 patients from a single family and in one additional patient. One of 47 asymptomatic family members had similar findings. Two patients who had negative tests initially were retested subsequently after they developed symptoms. Both patients manifest previously absent polymorphic ventricular ectopy, similar to that observed in their proband mother, during repeat testing.

During follow-up, beta adrenergic blockade was not completely effective in CPVT patients. Four of 10 cardiac arrest survivors with CPVT and one previously symptomatic CPVT patient without cardiac arrest received appropriate ICD shocks despite antiadrenergic therapy.

Krahn et al conclude that provocative testing with adrenaline and procainamide is useful for unmasking the etiology of previously unexplained cardiac arrest. Following the same provocative but noninvasive testing protocol in symptomatic and asymptomatic family members provides an opportunity for identifying those at highest risk.

COMMENTARY

Inherited and previously undiagnosed electrophysiologic disorders are a common underlying cause of unexplained cardiac arrest in patients without known structural heart disease. In some patients, these electrophysiologic abnormalities are readily detected on the baseline electrocardiogram. Patients with the Wolff-Parkinson-White syndrome and many patients with either a congenital long QT syndrome or the Brugada syndrome can often be identified based on their resting electrocardiogram. In other patients, however, and in many family members of individuals known to be affected, diagnostic electrocardiographic findings are either not visible at baseline or are present only intermittently. In symptomatic relatives without documented arrhythmias and in asymptomatic family members, testing would be helpful to identify those who are at risk and would be likely to benefit from therapy.

For some patients, genetic testing may be helpful in identifying latent disease in asymptomatic individuals. A commercial test for the recognized long QT syndrome mutations is available but expensive and may not be covered by payors. In addition, all the genes responsible for inherited arrhythmias have not been identified. Therefore,

methods to detect the disorder in asymptomatic family members should be of clinical value.

In this paper, Krahn et al report on the yield of adrenaline and procainamide infusions. Adrenaline was shown to be useful in making the presumptive diagnosis of catecholaminergic polymorphic ventricular tachycardia. This is a relatively rare condition but one that is not associated with ECG findings at rest yet can be devastating. CPVT has been associated with mutations in the ryanodine type II receptor and in calsequestrin but other mechanisms may also be involved. Although the numbers are small, the paper confirms the usefulness of procainamide infusions in the Brugada syndrome. This syndrome has been associated with a mutation in the sodium channel gene SCN5A but many patients with this ECG pattern do not have any of the previously described genotypes.

In summary, the approach outlined in this paper seems a reasonable one for evaluating patients with cardiac arrest that remain unexplained after the initial evaluation. In particular, the test may be useful for identifying potentially life-threatening mutations in asymptomatic family members in whom early intervention can be justified. ■

Metabolic Syndrome: A Warning of Cardiovascular Disease and Type 2 Diabetes Mellitus?

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: *Metabolic syndrome is common and is associated with an increased risk for CVD and T2DM in both sexes.*

Sources: Wilson PW, et al. Metabolic Syndrome As a Precursor of Cardiovascular Disease and Type 2 Diabetes Mellitus. *Circulation*. 2005;112:3066-3072; Reaven G. Insulin Resistance, Type 2 Diabetes Mellitus, and Cardiovascular Disease: The End of the Beginning. *Circulation*. 2005;112: 3030-3032.

THE METABOLIC SYNDROME (MS) HAS BECOME A household phrase, and a subject of enormous interest. In simple terms, MS represents a cluster or grouping of specific clinical abnormalities that appear to be linked together. Most of these features have a common denominator of insulin resistance, which appears to be a causal factor for the varied clinical manifestations. Wilson and colleagues analyzed the Framingham Heart Study Offspring Study over a period of 8 years to assess the hazard of MS and its individual components for the subsequent development of cardiovascular disease (CVD) and type 2 diabetes mellitus (DM).

In this analysis, approximately 3300 non-diabetic individuals, free from clinical heart disease, but with MS (defined by 3 or more criteria, including fasting plasma glucose of 100-125mg/dL; blood pressure >130/85; low HDL cholesterol; high triglycerides; and an increased waist circumference per the NCEP/ATP III definition of MS) were followed from 1989 to 1993; at the time of the fourth examination of Framingham Offspring Study. Interim follow-up examinations took place at 4 and 8 years. Mean baseline age for men and women was 50 years. The baseline prevalence of MS was 21% in men and 12.5% in women. By 8 years, the proportion of men with MS rose to 39%, and in women, from 12.5% to 30.6% (an increase of 47%). The relative risk of new CVD in males was 2.9, and for all coronary heart disease (CHD) was 2.5. The population attributable risk (PAR) was 30% for both CHD and CVD, indicating the fraction of vascular events that could be attributed to MS at baseline. An analysis of the specific number of MS traits per person demonstrated an additive effect for CVD and DM, although with a much steeper gradient for the development of DM. The most powerful metabolic syndrome traits related to CVD outcomes were blood pressure and HDL cholesterol; hypertension was present in half of all participants at baseline and imparted a risk of 49% for CVD. Furthermore, impaired fasting glucose (IFG) predicted a 12 fold increase in the risk for DM. Wilson et al point out a 50% increase in the prevalence in MS over an 8-year period.

Overall, CHD and CVD risk for MS doubled in men, less so for women. More MS traits increased the rate of CVD events, although 2 vs 3 risk factors for MS did not increase CVD risk substantially. Traditional CVD risk factors do increase the risk of developing CVD in MS subjects.

These data are "concordant with the NHANES 1988-1994 survey results that reported that approximately 23% of United States adults had the metabolic syndrome." Other data in the literature are supportive of these finding; baseline MS imparts much greater risk for the development of DM than CVD, approximately 4-fold. MS traits, other than a high IFG, were related to new DM, consistent with the importance of insulin resistance. Wilson et al noted "a large fraction of persons who developed diabetes

had MS during the observation period, with a significantly greater relative risk for the development of diabetes than overt CVD." Wilson et al conclude, "Amelioration of MS traits through lifestyle interventions or medications in patients with impaired glucose tolerance "may retard or prevent new DM." These findings have important implications for prevention. There may be value in diagnosing MS to identify "an extremely adverse metabolic state that warrants aggressive interventions for specific traits." In a companion editorial, Gerald Reaven reviews the data supporting insulin resistance and/or compensatory hyperinsulinemia as a predictor of DM and CVD. He downplays the usefulness of counting risk factors, noting that 2 traits seemed as predictive as 3 for the development of CVD or DM in the Framingham cohort. He calls for vigorous treatment of each risk factor individually, and emphasizes the role of insulin resistance and the need to treat all of its manifestations. He downgrades the importance of abdominal girth, stating that obesity is more a result of metabolic risk factors, rather than being causal.

COMMENTARY

This article from the Framingham Offspring Study clearly demonstrates that MS is highly predictive for the development of subsequent DM type 2, more so than for clinical CVD events. The data support treatment of each individual MS trait, including vigorous use of lifestyle behavior (diet, physical activity, etc). While the Framingham cohort reflect an all white, middle class population, it is likely that other ethnic groups will be similar in demonstrating increased risk of DM and CVD associated with IFG, low HDL, high triglycerides, and hypertension. The role of adiposity as a player or camp follower remains unclear. Other data sets are comparable, to this report, supporting a greater risk for DM than clinical cardiovascular events in subjects with MS. While not studied here, the combination of DM and MS is particularly lethal.

There are a number of active controversies regarding MS, including a precise definition, the need (or not) for assessing insulin sensitivity, and the optimal treatment (eg, insulin sensitizers, inclusion of MS as a high risk factor for aggressive LDL lowering).

It behooves us all to acknowledge that both MS and DM are on the rise, and these conditions predict an increasing burden of CVD. It would seem that an army of preventionists will need to be rapidly trained and deployed for much important work. ■

Other Recent Readings

- Grundy S, et al. Diagnosis and Management of the Metabolic Syndrome: An American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. *Circulation*. 2005;112:2735-2752.
- Davidson MH. Management of Dyslipidemia in Patients with Complicated Metabolic Syndrome. *Am J Cardiol*. 2005;96:22E-25E.

CME Questions

1. **Mortality post ICD placement is increased with:**
   a. inappropriate shocks.
   b. myocardial ischemia.
   c. polymorphic VT pre device.
   d. All of the above

2. **Provocative drug testing of cardiac arrest survivors can identify:**
   a. catecholaminergic polymorphic VT.
   b. Brugada syndrome.
   c. idiopathic VT.
   d. All of the above

3. **Recent data on the order of drug therapy initiation in heart failure suggests:**
   a. ACEI first.
   b. beta blockers first.
   c. start both together.
   d. stagger starting either by one month.

4. **In hypertensive patients, beta blockers are most effective for reducing:**
   a. myocardial infarction.
   b. death.
   c. stroke.
   d. A and B

5. **Early IV beta blocker in acute MI reduces:**
   a. ventricular fibrillation.
   b. reinfarction.
   c. heart failure or shock.
   d. A and B

6. **Which of the following is the most common long term outcome of metabolic syndrome?**
   a. Cardiovascular events
   b. Hepatic failure
   c. Pancreatic tumors
   d. Diabetes mellitus type II

Answers: 1. (b); 2. (d); 3. (a); 4. (d); 5. (d); 6. (d)

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FDA Recommends Approval of Muraglitazar, But May Need To Reconsider

In September of 2005, an FDA advisory committee recommended approval of muraglitazar for the treatment of type 2 diabetes. However new review of the data presented to the FDA challenges the safety of the drug, and suggests that compared with placebo or standard treatment, muraglitazar is associated with excess mortality.

The drug is a peroxisome proliferator-activated receptor (PPAR) that has both alpha receptor activity (similar to fenofibrate and gemfibrozil) and gamma receptor activity (similar to pioglitazone and rosiglitazone). Muraglitazar has been widely anticipated because of its dual effect of improving lipid profiles and increasing insulin sensitivity in patients with type 2 diabetes.

In the new study, researchers from the Cleveland clinic reviewed the data submitted to the FDA from phase 2 and 3 clinical trials. The combined studies included 3725 patients who were randomized to receive differing doses of muraglitazar, pioglitazone, or placebo in combination with metformin or glyburide in trials ranging from 24 to 104 weeks. The primary end points were death, nonfatal MI, or nonfatal stroke and a more comprehensive composite outcome, which included those 3 outcomes plus incidence of CHF or TIA. The primary outcome (death, MI, or stroke) occurred in 35 of 2374 (1.47%) of muraglitazar treated patients and in 9 of 1351 (0.67%) of patients in the combined placebo and pioglitazone treatment groups (RR 2.23; 95% CI, 1.07-4.66; *P*. = .03). The more comprehensive outcome occurred in 2.11% of muraglitazar treated patients and 0.81% of control patients (RR, 2.62; 95%CI, 1.36-5.05; *P* = .004). Incidence of CHF was 0.55% muraglitazar and 0.07% controls (*P* = .053).

The authors conclude that compared with placebo or pioglitazone, muraglitazar was associated with increased risk of death, major adverse cardiovascular events, and CHF. They also recommend the FDA not approve the drug until safety can be documented (Nissen SE, et al. Effect of Muraglitazar on Death and Major Adverse Cardiovascular Events in Patients with Type 2 Diabetes Mellitus. *JAMA*. 2005;294: 2581-2586).

In a related, provocative editorial, James Brophy MD from McGill University suggests tactics that pharmaceutical companies use to "foster an allusion of safety" when presenting data as part of a FDA application including selecting study populations unlikely to have adverse outcomes, conducting under powered studies that are unable to detect meaningful safety differences, reporting individual rather than composite safety outcomes, and others. He poses the question "which safety message will the FDA buy?" (Brophy JM. Selling Safety—Lessons From Muraglitazar. *JAMA*. 2005;294:2633-2635).

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Which Antipsychotics Are More Dangerous?

Newer atypical antipsychotic drugs have been associated with higher death rates in elderly patients. Now, a new study shows that conventional antipsychotics are at least as dangerous as the newer drugs. In a retrospective cohort study, nearly 23,000 patients age 65 and older who had received conventional or atypical antipsychotic medications between 1994 and 2003 were studied. Conventional antipsychotic medications were associated with a significantly higher adjusted death rate then atypical antipsychotic medications for all time intervals studied up to 180 days (relative risk 1.37; 95% CI, 1.27-1.49). The relative risk was also higher for less than 40 days (RR, 1.56), 40-79 days (RR, 1.37), and 80-180 days (RR, 1.27). The greatest risks were for death occurring within the first few weeks after initiation of medication especially higher doses of conventional antipsychotics drugs.

The authors conclude that conventional antipsychotic medications are least as likely as atypical agents to increase the risk of death among elderly patients, and that conventional drugs should not be used to replace atypical agents if they were discontinued because of recent FDA warnings (Wang PS, et al. Risk of Death in Elderly Users of Conventional Vs. Atypical Antipsychotic Medications. *N Engl J Med*. 2005;353:2335-2341).

Should CPOE Undergo Evaluation?

Physicians who use computerized physician order entry (CPOE) systems often report that it is not a panacea for saving time and preventing medication errors. A new study raises concerns about an increase in adverse outcomes associated with CPOE. Researchers from Children's Hospital of Pittsburgh reviewed demographic, clinical, and mortality data before and after implementation of a commercially sold CPOE. Mortality rates were significant higher after implementation (75 deaths among 1942 children, 3.86% after implementation vs 39 of 1394, 2.80% prior to implementation, odds ratio: 3.28; 95% CI; 1.94-5.55). The authors suggest that while CPOE may hold great promise, "Institutions should continue to evaluate mortality effects, in addition to medication air rates. . ." They also suggest that CPOE should undergo rigorous review and evaluation, similar to drugs, to assess safety prior to implementation (Han YY, et al. Unexpected Increased Mortality After Implementation of a Commercially Sold Computerized Physician Order Entry System. *Pediatrics*. 2005;116:1506-1512).

New Treatment for Tennis Elbow

Botulinum toxin may be effective for treating tennis elbow, according to new study. Sixty patients with lateral epicondylitis were randomized to injections of 6 units of botulinum toxin type A or normal saline placebo injections. Subjective pain was significantly reduced in the botulinum group at 4 weeks (visual analog scale 25.3 mm botulinum vs 50.5 mm placebo [$P < 0.001$]) and was sustained at 12 weeks. Grip strength was not statistically different between the 2 groups, although mild paresis of the fingers occurred in 4 patients in the botulinum group at 4 weeks, but none of the patients in the placebo group. In only one patient did the symptoms persist until week 12. More patients in the botulinum group experience weak finger extension at 4 weeks as well (10 patients botulinum vs 6 patients placebo).

The authors conclude that botulinum toxin may be effective in treating pain over 3-month periods in patients with lateral epicondylitis, but the injections may be assisted with digit paresis and weakness of finger extension (Wong SM, et al. Treatment of Lateral Epicondylitis with Botulinum Toxin: A Randomized, Double-Blind, Placebo-Controlled Trial. *Ann Int Med*. 2005;143: 793-797).

FDA Actions

Moxifloxacin (Avelox-Bayer) has been approved for the treatment of complicated intra-abdominal infections including polymicrobial infections. The approval was based on a study which showed that intravenous or oral moxifloxacin was as effective as IV therapies such as piperacillin/tazobactam (Zosyn) followed by oral amoxicillin/clavulanic acid (Augmentin). In a separate study, moxifloxacin was found to be equivalent to ceftriaxone plus metronidazole followed by oral amoxicillin/clavulanic acid for treating complicated intraabdominal infections. Moxifloxacin is also approved for treatment of acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis, community acquired pneumonia, and skin and skin structure infections caused by susceptible organisms. ■