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INSIDE

Prophylactic Use of An ICD After Acute Myocardial Infarction

ABSTRACT & COMMENTARY

Source: Hohnloser SH, et al. Prophylactic Use of An Implantable Cardioverter-Defibrillator After Acute Myocardial Infarction. *N Engl J Med.* 2004;351:2481-2488.

THE DEFIBRILLATOR IN ACUTE MYOCARDIAL INFARCTION TRIAL (DINAMIT) examined the question whether prophylactic implantable cardioverter defibrillator (ICD) therapy begun soon after myocardial infarction would reduce long-term mortality. Patients were eligible for inclusion in the trial if they were younger than age 80 and had suffered a myocardial infarction within the previous 6 to 40 days. In addition, they were required to have a left ventricular ejection fraction of 0.35 or less, and either abnormal heart rate variability or an elevated baseline heart rate during 24-hour ambulatory ECG monitoring. Patients who had either undergone coronary artery bypass grafting or 3 vessel percutaneous coronary interventions after the infarction were excluded. In addition, patients who had sustained ventricular tachycardia or ventricular fibrillation more than 48 hours after the qualifying infarction were also excluded. Patients were randomized in a 1:1 ratio to receive either an ICD plus medical therapy or standard medical treatment only. The ICD chosen was a market-approved, single chamber ICD that was set with a tachycardia detection cut-off of 175 bpm. The bradycardia pacing setting was back-up VVI at 40 bpm. The primary end point was death from any cause. Death due to cardiac arrhythmia was a secondary end point.

The study group included 676 patients. About three quarters were men. The mean age was 62 ± 11 years. The index MI was anterior in 72%. The mean left ventricular ejection fraction was 0.28. During the index MI, 26% had received percutaneous coronary intervention only, 24% had received thrombolysis only, and 11% had received both percutaneous interventions and thrombolysis. At study entry, 87% of the patients were on beta adrenergic blockers, 94% were on angiotensin converting enzyme inhibitors, 92% were on antiplatelet agents, and 77% were on lipid lowering agents.

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Among the 332 patients randomized to the ICD group, 20 patients refused to have one implanted and 2 patients died while awaiting the procedure. These patients were included in the ICD group in the intention-to-treat analysis used for the study. The average time between randomization and ICD implantation was 6.3 days ± 7.3 days. During an average observation period of 30 ± 13 months, 62 patients in the ICD group and 58 patients in the control group died. Life-table analysis showed no significant difference between the survival curves. The annual mortality rates were 7.5% in the ICD group and 6.9% in the control group. ICD therapy did effect the mode of death, as determined by an events committee. Among the 62 deaths in the ICD group, 12 were classified as due to arrhythmias, 34 were classified as cardiac but nonarrhythmic, and 16 were noncardiac. In the control group, there were 58 deaths, with 29 were due to arrhythmia, 20 classified as cardiac but nonarrhythmic, and 9 thought to be noncardiac. In-hospital device related complications were noted in 25 patients. These included lead dislodgement, pneumothorax, and inappropriate shocks.

Hohnloser and colleagues concluded that ICD therapy did not improve survival in high risk patients with recent myocardial infarction. Although there was a decrease in arrhythmia-related deaths in the ICD group, this effect was offset by a significant increase of equivalent magnitude in the rate of death from nonarrhythmic causes. The reason for this is uncertain, but it should be noted that in another defibrillator trial (The Multicenter Automatic Defibrillation Implantation Trial II), no effect was also seen in patients with the most recent infarctions

COMMENT BY JOHN P. DiMARCO, MD, PhD

DINAMIT focused on a group of patients who have not been included in previous randomized trials of ICD therapy. There was clearly no benefit with ICD therapy in this trial, even though there was a marked reduction in the frequency of arrhythmic deaths. The reasons for this surprising observation are uncertain. In DINAMIT, patients were identified by both their low ejection fraction and either abnormal heart rate variability or an elevated baseline heart rate. The latter 2 are markers of persistent and ongoing heart failure, rather than solely risk for arrhythmia. It may be that in patients with this degree of heart failure, a treatment directed only at arrhythmias will have no or only minor effects on overall mortality. It should also be noted that the DINAMIT population was not particularly aggressively treated during the infarction that qualified them for the study. Only 35% of the patients enrolled received any mechanical revascularization. One-third received no acute revascularization, and an additional 25% received only thrombolysis. It is therefore possible that, in the absence of an aggressive revascularization strategy, recurrent ischemia and heart failure dominated the patients' outcomes and overwhelmed any benefit from defibrillator therapy. It remains to be seen whether or not defibrillators would be of benefit in patients who are aggressively revascularized. The CABG-Patch Trial failed to show benefit in patients undergoing surgical revascularization, but in that study, early surgical mortality accounted for a large portion of the deaths.

The DINAMIT results leave cardiologists without an answer to a common clinical situation. We often identify high risk patients during the in-hospital phase after acute infarcts. DINAMIT suggests that ICD therapy, the most effective treatment we have to prevent sudden death, is of little benefit. Exactly how to manage these patients in this early phase after acute myocardial infarction, therefore, remains uncertain. ■

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Antiplatelet or Anticoagulant Therapy in Atrial Fibrillation

ABSTRACT & COMMENTARY

Synopsis: *The addition of antiplatelet therapy to reduced intensity anticoagulation in atrial fibrillation patients reduces death and embolic events without increasing bleeding.*

Source: Perez-Gomez F, et al. Comparative Effects of Antiplatelet, Anticoagulant, Or Combined Therapy in Patients With Valvular and Non-Valvular Atrial Fibrillation. *J Am Coll Cardiol.* 2004;44:1557-1566.

In this study, Perez-Gomez and colleagues report the results of the National Study for Prevention of Embolism in Atrial Fibrillation (NASPEAF) trial. The hypothesis for this trial was that the addition of an antiplatelet agent to a moderate intensity anticoagulant regimen would improve mortality and embolic events in atrial fibrillation patients at intermediate or high risk for such events. Patients were eligible for the study if they had either intermittent or persistent atrial fibrillation and were either older than age 60 or had other risk factors for embolic events. The high-risk group consisted of 495 patients with a history of prior embolism and/or mitral stenosis. The intermediate group consisted of 714 patients without mitral stenosis or prior embolism. Patients with prosthetic valves, a stroke in the pervious 6 months, renal insufficiency, uncontrolled hypertension, or other indications for nonsteroidal, inflammatory, antiplatelet drugs or anticoagulants were excluded. The antiplatelet agent used in the study was triflusal, a drug structurally similar to acetylsalicylic acid. Triflusal was administered at a dose of 600 mg per day, the equivalent of 300 mg of aspirin per day. The anticoagulant used was acenocumarol, the coumarin derivative most commonly used in Spain. In the intermediate risk group, patients were randomized between antiplatelet therapy only, anticoagulant therapy with a target INR of 2-3, and combination therapy with triflusal and acenocumarol, with a target INR of 1.25-2. In the high-risk group, patients were randomized to either anticoagulant therapy with a target INR of 2-3 or combination therapy with triflusal and an INR range of 1.4-2.4.

The primary outcome was a composite of vascular death, transient ischemic attack, nonfatal stroke, and systemic embolism. Secondary end points were severe bleeding, myocardial infarction, nonvascular death, and minor bleeding.

In the intermediate risk group, the annual event rates for the combined primary end points were 3.82% in the triflusal group, 2.70% in the anticoagulant group, and 0.92% in the combined therapy group. In the high-risk group, the annual event rates for the composite end point were 4.76% in the anticoagulant only group and 2.44% in the combined triflusal-anticoagulant group. Among the intermediate risk patients, the annual rates for severe bleeding were 0.35% in the triflusal group, 1.8% in the anticoagulant group, and 0.9% in the combined therapy group. In the high-risk group, the annual rate for severe bleeding was 2.1% in the anticoagulant group and 2.1% in the combined therapy group. Actuarial analysis of the primary composite end point showed that combined therapy was superior to the other treatment modalities in both the intermediate and high-risk patients.

Perez-Gomez et al concluded that addition of antiplatelet therapy to reduced intensity anticoagulation in atrial fibrillation patients reduces death and embolic events without increasing bleeding.

COMMENT BY JOHN P. DiMARCO, MD, PhD

Numerous studies have established the value of warfarin anticoagulation in patients with valvular and nonvalvular atrial fibrillation. When warfarin is used alone, the optimal target INR appears to be 2-3. Attempts to use warfarin at a dose that would produce only minimal or no changes in the INR in combination with antiplatelet therapy have been unsuccessful. In this paper, Perez-Gomez et al attempted to use a moderate reduction in target INR in association with antiplatelet therapy in both a very high risk group and an intermediate risk group. Although the study group is relatively small, the data do suggest that this approach may be effective. The key difference between this and prior studies is that the reduction in anticoagulation target intensity was only moderate. In the intermediate group, the median INR was 1.93 vs 2.47 in the anticoagulant group. Adherence to this target was quite good. Two-thirds of the INR values were within the prescribed range in both groups. In the high-risk group, the median INR in the combined therapy group was 2.17 and in the anticoagulant group it was 2.50. By lowering the target INR, Perez-Gomez et al were able to add an antiplatelet agent without increasing bleeding or losing the benefits of anticoagulation.

These data suggest that very careful monitoring of INR during warfarin therapy, plus the addition of an antiplatelet agent, can allow lower targets to be used without detrimental effects. This approach may be of benefit for patients who have a perceived increased risk for bleeding, in whom physicians might otherwise be reluctant to use standard anticoagulant therapy, despite the presence of atrial fibrillation. ■

Coronary Revascularization Before Vascular Surgery

ABSTRACT & COMMENTARY

Synopsis: *The substantial differences in opinion concerning the need for revascularization prior to elective vascular surgery are present among cardiologists.*

Source: PierpontGL, et al. Disparate Opinions Regarding Indications For Coronary Artery Revascularization Before Elective Vascular Surgery. *Am J Cardiol.* 2004; 94:1124-1128.

THE INCREASING USE OF DRUG ELUTING STENTS HAS created a dilemma regarding the necessity for coronary revascularization prior to vascular surgery, since the intensive, uninterrupted antiplatelet therapy delays surgery 3-6 months. Thus, Pierpont and colleagues selected 12 cases from the Coronary Artery Revascularization Prophylaxis (CARP) VA study of the long-term benefit of preoperative coronary artery revascularization in high-risk patients undergoing elective vascular surgery. Three cases were randomly selected from each of the 4 study groups: percutaneous coronary intervention (PCI); coronary artery bypass surgery (CABG); PCI candidate randomized to medical therapy; and CABG candidates randomized to medical therapy. Summaries of these cases, including nuclear perfusion studies and coronary angiograms, were reviewed by 31 board certified cardiologists evenly recruited from California, New York, and the upper Midwest. Each reviewer gave an opinion as to whether preoperative revascularization was needed, using a 7-point scale ranging from 1 = no revascularization to 7 = revascularization strongly recommended. Also, preference for PCI or CABG was noted. In addition, the opinions of the 21 interventionalists were compared to the 10 noninterventionalists.

Results: Scores of 1 or 2 and 6 or 7 predominated, with few scores in the middle. So, to simplify, revascularization was recommended 40% of the time (6 or 7), no intervention 43% of the time (1 or 2), and equivocal recommendations (3, 4, 5) 15% of the time. To view the data another way, there was only a 46% chance that 2 cardiologists would agree on their recommendation. There was no difference in the recommendations of the interventionalists vs the noninterventionalists. Choice of procedure varied considerably with only 1 case showing 100% agreement. Pierpont et el concluded that substantial differences in opinion concerning the need for revascularization prior to elective vascular surgery are present among cardiologists.

■ COMMENT BY MICHAEL H. CRAWFORD, MD

This small opinion survey is not the type of paper we usually cover, but I thought it highlighted some important issues in contemporary cardiology practice. First, the decision to recommend revascularization, whether by PCI or CABG, will now delay vascular surgery by 3-6 months. Thus, in urgent or emergent cases, this consideration is almost moot. In elective cases, this decision for revascularization effectively transfers the patient to the cardiologist's care until vascular surgery can safely be performed. In this study, 40% of the opinions were for revascularization, even though none of the patients met traditional criteria for revascularization, such as left main disease or severe angina, by study design.

The CARP patients all had high-risk features for coronary artery disease, and underwent coronary angiography by protocol because it was hypothesized that they may benefit from preoperative revascularization. Currently, no other randomized, controlled study has addressed this issue. So, cardiologists had no strong evidence to base their decision upon. Also, they did not follow ACC/AHA Guidelines, which state that revascularization should only be done in patients who would benefit from it independent of their vascular surgery. In the absence of data, some believe in revascularization and others do not, and this often drives their decision rather than guidelines.

The second issue is that outside a protocol, some of these patients may not have had catheterization or stress testing. In the face of these 3-6 month

revascularization delays, should we even bother evaluating vascular surgery patients preoperatively, and just clear those who have no compelling clinical reason to undergo catheterization? Given the low incidence of death and myocardial infarction even in these high-risk patients with vascular disease (about 2% now), can any evaluation, revascularization strategy improve on these results? Clearly, the CARP data are anxiously awaited. ■

Statin Metabolism Interactions

ABSTRACT & COMMENTARY

Synopsis: *Pravastatin is the statin with the least interactions with cytochrome P450-(CYP) 3A4 inhibitors.*

Source: Jacobson TA. Comparative Pharmacokinetic Interaction Profiles of Pravastatin, Simvastatin, and Atorvastatin When Coadministered With Cytochrome P450 Inhibitors. *Am J Cardiol.* 2004;94:1140-1146.

STATINS HAVE BECOME THE MAINSTAY OF PREVENTIVE cardiology. However, concern continues regarding the potential for rhabdomyolysis, especially at higher doses of these agents. Thus, Jacobson studied 4 groups of healthy subjects to assess the pharmacokinetics of: 1) 40 mg pravastatin or 40 mg simvastatin coadministered with 480 mg verapamil; 2) 40 mg pravastatin or 80 mg of atorvastatin plus 100 mg mibefradil; 3) 40 mg pravastatin or 80 mg atorvastatin plus 200 mg itraconazole; and 4) 40 mg pravastatin, 40 mg simvastatin, or 80 atorvastatin plus 500 mg clarithromycin.

Results: When compared to pravastatin alone, coadministration of verapamil, mibefradil, or itraconazole with pravastatin did not alter pravastatin pharmacokinetics. Clarithromycin did increase the area under the curve (AUC) of plasma pravastatin (100% $P < .001$), but increased the AUC of simvastatin 219% and atorvastatin 343%. Verapamil increased simvastatin AUC 4-fold. Mibefradil increased atorvastatin AUC > 4-fold, and itraconazole increased atorvastatin AUC 47%. Clarithromycin increased the AUC of all 3 statins; simvastatin 10 fold, atorvastatin > 4-fold, and pravastatin almost 2-fold. Jacobson concluded that pravastatin is the statin with the least interactions with cytochrome P450-(CYP) 3A4 inhibitors.

COMMENT BY MICHAEL H. CRAWFORD, MD

The withdrawal of cervastatin from the market, and the recent physician notification that the starting dose of rosuvastatin is 10 mg, underscores the concern about anything that may increase the incidence of the rare but serious adverse reaction of rhabdomyolysis, which is dose related. Coadministration of other agents that share the CYP receptor may lead to increased serum levels of certain statins for prolonged periods. These agents include gemfibrozil, calcium channel blockers, immunosuppressives, macrolide antibiotics, certain antifungal agents, protease inhibitors of HIV, amiodarone, and grapefruit juice.

Some have estimated that more than half the rhabdomyolysis cases reported to the FDA involved coadministration of other CYP inhibitors. In fact, the package insert for simvastatin recommends a daily dose no higher than 20 mg with the coadministration of verapamil or amiodarone. Simvastatin and atorvastatin are lipophilic statins which demonstrate profound increases in drug levels over time when given with CYP inhibitors. Pravastatin is hydrophilic and is not a CYP substrate. Mibefradil is a T-channel calcium blocker, which is a strong CYP inhibitor and was withdrawn from the US market because of numerous serious drug interactions. However, in this study, it did not interact with pravastatin. Other studies have shown an overall extremely low incidence of rhabdomyolysis with pravastatin, 0.04 per million prescriptions vs 0.12 for simvastatin, 0.10 for lovastatin and 3.2 for cerivastatin.

The down side of pravastatin is that it is not a particularly potent statin and may require concomitant lipid-lowering agents to get the desired effect. This may be the reason that Merck came out with Vytorin, which combines lower doses of simvastatin with ezetimibe. Thus, when using more potent statins, one must weigh the tiny risk of rhabdomyolysis against the major benefits of effective lipid-lowering in patients with vascular disease. However, care must be taken when the coadministration of CYP inhibitors is necessary. In these situations,

pravastatin may be an alternative if lipid targets can be met. ■

Nifedipine For Chronic Stable Angina

ABSTRACT & COMMENTARY

Synopsis: *The addition of nifedipine to conventional treatment in patients with chronic stable angina did not affect overall event-free survival, but was safe and reduced the need for coronary interventions.*

Source: Poole-Wilson PA, et al. Effect of Long-acting Nifedipine on Mortality and Cardiovascular Morbidity in Patients With Stable Angina Requiring Treatment (ACTION Trial): Randomized, Controlled Trial. *Lancet.* 2004;364:849-857.

ALTHOUGH EFFECTIVE FOR PREVENTING SYMPTOMS, long-acting dihydroperidine calcium antagonists are still controversial with regard to long-term safety. Hence, Poole-Wilson and colleagues designed the A Coronary Disease Trial Investigating Outcome with Nifedipine GITS (ACTION) to study clinical outcomes in patients with stable symptomatic coronary artery disease. This multicenter, placebo-controlled, double-blind trial randomized 3825 patients to long-acting nifedipine vs 3840 to placebo. The primary end point was a combination of death, acute myocardial infarction, refractory angina, new heart failure, stoke, or peripheral revascularization. The patients were followed for a mean of 5 years, and an intention-to-treat analysis was used.

The patients all had angina, requiring medical therapy and either: were post myocardial infarction; had angiographically proven coronary artery disease; or had a positive exercise or perfusion study. Those undergoing a coronary intervention were excluded, as were those intolerant to nifedipine or had other confounders that could affect outcome (eg, left ventricular dysfunction). Nifedipine was started at 30 mg per day, and increased to 60 mg if tolerated. All other cardiovascular drugs were permitted except other calcium blockers, digoxin, class I antiarrhymics, and certain other noncardiac drugs which might interfere with nifedipine (eg, cimetidine). About 80% of both groups were on beta-blockers, and 99% were on either nitrates, beta-blockers, or both.

Results: In the nifedipine group, 310 patients died vs 291 in the placebo group (HR, 1.07; CI, .91-1.25; P = .41). The composite primary end point was not different between the groups (HR, 0.97; CI, .88-1.07; P = .54). However, death or any cardiovascular procedure was reduced in the nifedipine group (HR, 0.89; CI, .83-.95; P = .0012) because of reduced rates of coronary interventions. The rate of myocardial infarction and stroke were not affected by nifedipine, but new heart failure was reduced (HR, 0.71; CI, .54-.94; P = .015). Nifedipine significantly reduced blood pressure, and the hypertensive subgroup was the only one in which nifedipine clearly showed improvement vs placebo (P = .015). Nifedipine safety was excellent and comparable to placebo (HR, 1.01; CI, .9-1.14; P = .86). Poole-Wilson and colleagues concluded that the addition of nifedipine to conventional treatment in patients with chronic stable angina did not affect overall event-free survival, but was safe and reduced the need for coronary interventions.

■ COMMENT BY MICHAEL H. CRAWFORD, MD

Recently, I asked a resident what she would do for a patient on beta-blockers and nitrates with persistent angina who was not a candidate for revascularization. Her first response was disbelief that we could not revascularize the patient, and when I was persistent, she said ACE inhibitors. I understand the disbelief that we could not revascularize the patient since this seems true for very few patients today. It makes you wonder how Poole-Wilson et al in this long-term study found more than 7000 patients in this category. Since all 291 centers were either in Europe, Canada, or Israel, it may be that different criteria for whom to revascularize were used than those in the United States. Regardless, this is a large trial definitively showing that a long-acting dihydroperidine calcium blocker was safe and reduced symptoms and the need for coronary interventions in patients with chronic stable angina. Not surprisingly, based upon previous studies, there was no beneficial effect on mortality or myocardial infarction.

Given the mortality reducing effects of beta-blockers, they should be first-line therapy, but clearly calcium blockers are a legitimate second-line therapy, as nitrates have no proven benefit on cardiovascular outcomes either. Also, the safety of nifedipine GITS was impressive. New heart failure rates were reduced on nifedipine. Adverse effects were minor: edema in 139 vs 20 on placebo and

headache in 43 vs 20. Study drugs were continued in 79% on nifedipine and 82% on placebo. Dose reductions to one-half (30 mg nifedipine) were done in 16% on nifedipine and 6% on placebo. The major mechanistic difference shown was a significant reduction in blood pressure on nifedipine.

The placebo mortality rate was 1.5 per 100 patient-years vs 1.6 for nifedipine (NS), and other cardiovascular events were also infrequent. Thus, in patients treated with beta-blockers (80%) and lipid-lowering drugs (68%) with these low event rates, it may be unrealistic to expect further reductions by another drug. With regard to the resident's answer of ACE inhibitors for my patient, there have been trials of patients with risk factors for coronary disease or some manifestation of it that showed benefits in mortality (HOPE, EUROPA), but studies in patients with angina have failed to show improvement in symptoms with ACE inhibitors. Also, in HOPE and EUROPA, fewer patients were on beta-blockers (39% and 62%, respectively) and lipid-lowering drugs (28% and 57%). Hence, an ACE inhibitor may be beneficial to my patient for longevity, but would not address his persistent angina on beta-blockers and nitrates. This study shows that long-acting dihydroperidine calcium blockers are safe and effective treatment for the relief of angina. ■

Atenolol For Hypertension

ABSTRACT & COMMENTARY

Synopsis: *Atenolol is unsuitable as a first-line drug in hypertension.*

Source: Carlberg B, et al. Atenolol in Hypertension: Is It a Wise Choice? *Lancet.* 2004;364:1684-1689.

ATENOLOL IS WIDELY USED AS A FIRST-LINE THERAPY for hypertension because it is beta 1 selective and it has low lipophilicity, which should result in fewer central nervous system side effects. However, recent studies have questioned its effectiveness. Thus, Carlberg and colleagues reviewed available randomized, controlled trials of atenolol in hypertension that evaluated morbidity and mortality. They identified 4 studies that compared atenolol to placebo or no treatment, and 5 that compared it to other drugs. The 4 placebo controlled trials encompassing 6825 patients followed for a mean of 4.6 years showed major differences in blood pressure, as expected by no difference in outcome vs placebo: all cause mortality RR = 1.01; cardiovascular mortality .99; and myocardial infarction .99. The risk of stroke showed a trend downward on atenolol (RR, 0.85; CI, .72-1.01). In the 5 drug comparison trials encompassing 17,671 patients followed for 4.6 years on average, atenolol was equally effective at lowering blood pressure, but demonstrated a higher mortality (RR, 1.3; CI, 1.02-1.25) and more strokes (RR, 1.3; CI, 1.12-1.50), as compared to other non-beta blocker drugs. Carlberg et al concluded that atenolol is unsuitable as a first-line drug in hypertension.

COMMENT BY MICHAEL H. CRAWFORD, MD

These provocative results cast doubt on the use of atenolol as a first-line antihypertensive agent. What could explain these findings? Atenolol is less lipophilic. Animal studies have shown that the amount of beta-blocker in the central nervous system correlates with anti-ventricular fibrillation effects. Studies of metoprolol, propranolol, and timolol, which are more lipophilic, have shown reductions in mortality. Also, atenolol is beta 1 selective, but so is metropolol and others. In addition, the effects of atenolol on left ventricular hypertrophy have not been characterized. Finally, atenolol does not improve endothelial function in hypertensives.

There are some issues with this analysis. First, few trials have compared different beta blockers in hypertension. Those that used different beta blockers considered them as a group and did not break down the results with regards to the different beta blockers. So, this analysis compares results from studies using various beta blockers alone or versus other classes of antihypertensive agents, as well as studies where not all the patients were hypertensive, such as post myocardial infarction trials. Second, Carlberg et al are from Sweden, as is metoprolol. Perhaps there is some nationalistic bias here, since metoprolol is the only other beta 1 selective agent readily available in the United States. Third, atenolol is usually given once a day to be competitive with other agents, but its half life doesn't really support this dosing frequency. It should probably be given twice a day. Metoprolol, on the other hand, now comes in a sustained release form (Toprol XL), which permits once a day dosing despite its relatively short half life. Many comparison drug trials suffer from not using comparative doses or dosing strategies; comparing different studies compounds this problem even more.

Regardless of these concerns, the data are provocative. The fact that placebo controlled trials of atenolol for hypertension showed no mortality benefit is disturbing, since we have several other agents that have been shown to reduce mortality (eg, ACE inhibitors and angiotensin receptor blockers). Thus, Carlberg et al make a cogent point that perhaps atenolol should not be considered first line monotherapy for hypertension. ■

CME Questions

1. **Recent studies show that ICDs are indicated for which patients?**
   a. CAD, normal EF
   b. Acute MI with LV dysfunction
   c. Heart failure and EF <35%
   d. Heart failure due to diastolic dysfunction

2. **Appropriate therapy for atrial fibrillation includes all but:**
   a. warfarin to an INR of 2-3 (all).
   b. warfarin INR 1.4-2.4 plus ASA 325mg/day (high risk).
   c. warfarin INR 1.25-2.0 plus ASA 325 (int. risk).
   d. warfarin INR 1.0-1.5 plus ASA 81mg (low risk).

3. **Opinion regarding coronary revascularization before vascular surgery is:**
   a. diverse.
   b. accurately reflected by the ACC guidelines.
   c. identical by 2 cardiologists 80% of the time.
   d. more aggressive with interventional cardiologists.

4. **Which statin has the least interactions with cytochrome P450-3A4 inhibitors?**
   a. Atorvastatin
   b. Pravastatin
   c. Simvastatin
   d. Cerivastatin

5. **Symptom relief in chronic stable angina on beta blockers and nitrates is most likely with:**
   a. ACE inhibitors.
   b. angiotensin receptor blockers.
   c. dihydroperidine calcium blockers.
   d. statins.

6. **All but which drug has been shown to reduce mortality in hypertensive patients?**
   a. Ramapril
   b. Hydrochlorthiazide
   c. Losartan
   d. Atenolol

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

PHARMACOLOGY WATCH

Hypertension: Therapy vs Calcium Channel Antagonists

Pharmacotherapy of hypertension has been much in the news in the last 2 months. Standard therapies such as atenolol have been challenged, while calcium channel antagonists may be making a comeback.

Researchers from Sweden performed a meta-analysis of 9 randomized, controlled trials that looked at the effectiveness of atenolol on cardiovascular morbidity and mortality in patients with hypertension. Four of the studies compared atenolol with placebo or no treatment, and 5 studies compared atenolol with other antihypertensive drugs. Although atenolol was effective at lowering blood pressure, there were no outcome differences with regard to all cause mortality (RR 1.01; 95% CI, 0.89-1.15), cardiovascular mortality (RR 0.99; 95% CI, 0.83-1.18), or myocardial infarction (RR 0.99; 95% CI, 0.83-1.19), compared to placebo. The risk for stroke was lower with atenolol, compared to placebo (RR 0.85; 95% CI, 0.72-1.01). When compared with other antihypertensives, no difference in blood pressure lowering was noted between treatment groups, but the meta-analysis revealed a higher mortality with atenolol, compared with other treatments (RR 1.13; 95% CI, 1.02-1.25). This included a higher risk of cardiovascular mortality and stroke. The authors suggest that the results "cast doubts on atenolol as a suitable drug for hypertensive patients." They further postulate that atenolol's low lipophilic profile, which theoretically may reduce its ability to prevent cardiac arrhythmias, could be responsible for these findings (*Lancet.* 2004; 364: 1684-1689). Some have criticized the study because it did not include newer well-designed trials in which atenolol was used in combination with other drugs including diuretics. In these studies, including ALLHAT and SHEP, the addition of atenolol resulted in overwhelming benefit. In the meantime, use of atenolol as monotherapy needs to be reevaluated, however, addition of atenolol to an existing regimen will probably remain a part of most clinical guidelines.

GEMINI Trial

Speaking of beta-blockers, a new study suggests that carvedilol may be a better choice for diabetic patients than metoprolol. The Glycemic Effects in Diabetes Mellitus: Carvedilol-Metoprolol Comparison in Hypertensives (GEMINI) trial was designed to compare the effects of beta-blockers with different pharmacological profiles on glycemic and metabolic control in diabetic patients who were already receiving renin-angiotensin system (RAS) blockade with either a ACEI or ARB. Over 1200 patients with diabetes and hypertension were randomized in GEMINI. The main outcome was change in baseline HbA1c after 5 months of therapy. A difference was noted in mean change of HbA1c for baseline between the drugs (0.13%;95%CI -0.22%-0.4%. *P*=.004) The mean HbA1c increased with metoprolol (0.15% [0.04%]; *P* < .001), but not for carvedilol (0.02% [0 .04%]; *P* =

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.65). Insulin sensitivity also improved with carvedilol but not with metoprolol, and progression to microalbuminuria was less frequent carvedilol than with metoprolol (6.4% vs 10.3%; *P* = .04). The drugs were used in equipotent doses to achieve similar blood pressure lowering effects. The authors conclude that the carvedilol, used in the presence of RAS blockade, does not effect glycemic control, and improves some components of metabolic syndrome relative to metoprolol in patients with diabetes and hypertension (*JAMA.* 2004;292:2227-2236). The study points out again that beta-blockers, with variable pharmacologic effects, may result in different clinical outcomes. Carvedilol is a nonselective beta antagonist, but has alpha 1 antagonist properties and mild vasodilatory properties.

CAMELOT Trial

The calcium channel antagonist amlodipine has beneficial cardiovascular effects in heart patients even if they have normal blood pressure according to new study. The Comparison of Amlodipine vs Enalapril to Limit Occurrences of Thrombosis (CAMELOT) study compared amlodipine 10 mg, enalapril 20 mg or placebo in patients with documented CAD and diatolic blood pressures < 100 mm Hg. The outcome measures were incidence of cardiovascular events and a second outcome was the use of intravascular ultrasound to measure atheroma volume. Nearly 2000 patients were followed over 24 months. New cardiovascular events (cardiovascular deaths, non-fatal myocardial infarction, resuscitated cardiac arrest, coronary revascularization, hospitalization for angina actors, hospitalization for congestive heart failure, fatal or non-fatal stroke or transient ischemic attack, or new diagnoses of peripheral vascular disease) occurred in 23.1% of placebo treated patients, 16.6% of amlodipine treated patients (HR 0.69; 95% CI, 0.54-0.88 [*P* = .003]) and 20.2% of enalapril treated patients (HR, 0.85; 95% CI, 0.67-1.07 [*P* = .16]). Plaque volume by ultrasound showed a trend towards less progression of atherosclerosis in the amlodipine group vs placebo (*P* = .12), with significantly less progression in the subgroup of patients with higher systolic blood pressures (*P* = .02). Compared with baseline atheroma volume progression in the placebo group (*P* < .001), the study showed a trend towards progression in the enalapril group, and no progression in the amlodipine group. The authors conclude that amlodipine reduced cardiovascular events and slowed progression of atherosclerosis in patients with CAD and normal blood pressure (*JAMA.* 2004;292:2217-2225). An accompanying editorial reviews the data and suggests mechanisms for the findings. More than any other factor, the editorialists suggest that lowering blood pressure to a systolic in the 120 mm Hg range may be the most important factor of all in patients with CAD (*JAMA.* 2004;292:2271-2273).

INVEST Trial

The INVEST study suggests that verapamil is as effective as atenolol with regard to benefit and side effects in diabetic patients with hypertension (*Hypertension* 2004;44:614-615). The PEACE trial looked at patients with coronary disease and normal or slightly reduced left ventricular function to assess whether addition of an ACE inhibitor would convey benefit, and found no benefit for these patients (*N Engl J Med.* 2004; 351:2058-2068).

The Dangers of Vitamin E

And vitamin E? Don't expect it to prevent cardiovascular disease or cancer for that matter. As vitamin E doses increase, so does all cause mortality, according to a large meta-analysis. Nineteen trials, which included nearly 136,000 participants, were evaluated in the analysis, of which 11 tested high dose vitamin E (400 IU/d). The pooled all-cause mortality risk difference for the high-dosage vitamin E was 39 per 10,000 (95% CI, 3-74 per 10,000; *P* = .035). For doses less than 400 IU/d, the mortality risk difference was 16 per 10,000 (CI, -41 to 10 per 10,000; *P* > .2). A dose-response analysis revealed an increase in all cause mortality with vitamin E dosages > 150 IU/d. The authors suggest that an increased mortality with higher doses of vitamin E is biologically plausible. Low doses of vitamin E may have some antioxidant effects, but higher doses may be pro-oxidant, particularly to LDL cholesterol. High doses of vitamin E may also displace other fats soluble antioxidants, disrupting the natural balance of antioxidant systems. Vitamin E may also be a mild anticoagulant, which may explain the increased hemorrhagic stroke seen in some vitamin E trials. This study was felt important enough to warrant early release online, since many people worldwide take vitamin E supplements on a daily basis far in excess of 400 IU/d. The full study will be published in the January 2005 *Annals of Internal Medicine*.

FDA Actions

The FDA has approved a new biologic for the treatment of relapsing forms of multiple sclerosis. Natalizumab is a monoclonal antibody that is given intravenously once a month. It will be marketed by Biogen as Tysabi.