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CLINICAL CARDIOLOGY ALERT

A monthly update of developments in cardiovascular disease

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Late-Breaking Trials: American Heart Association

CONFERENCE COVERAGE

Source: American Heart Association Annual Scientific Sessions, November 7-10, 1999, Atlanta, GA.

THE HOPE STUDY

The heart outcomes prevention evaluation (hope) trial randomized 9541 high-risk patients to the angiotensin-converting enzyme (ACE) inhibitor ramipril (10 mg/d) or placebo and vitamin E (400 IU/d) or placebo for a mean follow-up period of 4.5 years. This international study was carried out in 267 hospitals and 19 countries, with the majority of patients coming from the United States. The ramipril arm was stopped in early 1999 because of a favorable outcome for the ACE inhibitor; the vitamin E arm has continued. The study population consisted of individuals with documented coronary artery disease (CAD), cerebrovascular, or peripheral vascular disease. In addition, diabetics without vascular disease with at least one additional CAD risk factor were enrolled. All individuals were older than 55 years of age. Patients had no history of heart failure; hypertensives could be enrolled if blood pressure was controlled (46% had hypertension). Thirty-eight percent had diabetes, 11% had a previous stroke, 43% had peripheral vascular disease, and two-thirds had an elevated cholesterol level. Eighty-one percent of all patients had CAD, half with a prior myocardial infarction (MI). The results were striking, with a robust 20-25% reduction in relative risk favoring ramipril for all vascular end points. (*See Table.*) There was a 22% reduction in the primary end point of cardiac death, stroke, or nonfatal MI (17.7% vs 14.1%). There was a major decrease in stroke and in new heart failure as well as for revascularization. Of interest, new onset diabetes was decreased by 32% (P = 0.002). New renal dysfunction/dialysis or microalbuminuria was also decreased by ramipril. An echo substudy of approximately half the entire cohort (mean ejection fraction of 60%) demonstrated comparable risk reductions for all end points as the entire cohort. Higher risk patients had a greater reduction in events than those at lower risk. It was concluded that lowering of blood pressure only accounted for a small proportion of the decrease of MI and other end points; indi-

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viduals in the highest quartile of baseline systolic blood pressure had the greatest risk reduction. The hypertensive and nonhypertensive patients had no difference in benefit from ramipril. Vitamin E had no effect on total mortality, cardiovascular deaths, or other end points.

COMMENT BY JONATHAN ABRAMS, MD

These data have already achieved considerable attention and were formally announced at the European Cardiac Society Meeting at the end of August. The benefits of the ACE inhibitor in individuals who ordinarily would not be treated with such a drug are impressive and concordant with a large amount of vascular biology research, endothelial function studies, and mechanistic hypotheses regarding prevention or slowing progression of vascular disease. These data raise the question as to whether *all* individuals who meet the HOPE criteria should be treated with an ACE inhibitor. Given that the entire cohort had an event rate of cardiac death, stroke, or MI of greater than 3% per year, it seems reasonable that for patients with documented vascular disease, representing the majority of the HOPE cohort, or individuals at high risk for future events (e.g., diabetics with risk factors or those with multiple CAD risk factors), ACE inhibitor therapy should be considered. There is considerable disappointment regarding the antioxidant hypothesis because of the null effects of vitamin E. Earlier data this year from the GISSI-3 trial were also negative in a large population given vitamin E. Some believe that the combination of vitamin E and vitamin C, or the use of different antioxidants, will be necessary to really test the oxidation hypothesis. Certainly, HOPE and GISSI-3 deflate the present enthusiasm for routine use of antioxidant vitamins.

Table

HOPE	End Points (Ramipril vs Placebo)			
	RAM (%)	PLAC (%)	P Value	RR
CV death, MI, or stroke	14.1	17.7	0.001	0.78
All MI	9.8	12.0	0.0005	0.80
CV death	6.0	8.0	0.0002	0.75
NMFI	5.9	7.5	0.0002	0.78
Revascularization	16.0	18.6	0.001	0.85
All death	10.3	12.2	0.003	0.83
Stroke	3.4	4.9	0.0002	0.68
Nondiabetes	3.7	5.3	0.002	0.68
CHF	9.2	11.7	0.002	0.77

Note: The *New England Journal of Medicine* has taken the unusual step of premature electronic publication of this trial on its electronic website: (http://www.nejm.org/content/yusuf/1.asp).

BEST

Many knew something was amiss when the BEST report was canceled at the March 1999 American College of Cardiology meeting. When finally reported at the American Heart Association meeting, the problem was clear—the results were strikingly negative. BEST is a heart failure survival trial using the beta-blocker bucindolol. The study randomized 2708 mainly class III (92%) and class IV (8%) heart failure patients on standard therapy including ACE inhibitors to the nonselective beta-blocker or placebo and followed the patients for a mean of two years. Although bucindolol reduced deaths by 10% overall, this was not statistically significant and those with more advanced disease in particular did not benefit. Also, subgroup analyses showed that African-American patients did not benefit from bucindolol therapy (23% of the study population).

Carvedilol and metoprolol studies have been clearly positive. What went wrong with BEST? Discussion at the meeting focused on several issues. First, most of the other beta-blocker trials focused on class II patients, with some class IIIs and a few class IVs. In fact, carvedilol is not recommended in class IV or unstable patients even with lesser symptoms. Thus, beta-blocker therapy should perhaps be applied early rather than later in the course of heart failure. Second, bucindolol is nonselective like carvedilol, but bucindolol does not have much alpha-blocking properties like carvedilol does. Thus, perhaps the wrong beta-blocker was chosen for the trial. Third, the relative lack of effect in

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the African-American patients who comprised about a quarter of the patients may have reduced the results of an otherwise positive trial. Clearly, the Scandinavian metoprolol trials and the carvedilol studies done in southeastern Asia included few black patients. **—mhc**

ELITE II

ELITE I was a study of the effect of the angiotensin receptor blocker (ARB) losartan on renal function in elderly patients with heart failure, which surprisingly showed reduced mortality in the losartan group. Accordingly, an international, multicentered, randomized trial of losartan vs. captopril therapy in 3152 severe heart failure patients was undertaken (ELITE II). The results presented at the AHA meeting showed no difference in all-cause mortality between the two groups. Since these two therapies seem roughly equivalent, losartan could be used if the patient was intolerant to ACE inhibitor therapy, but ACE inhibitors remain the treatment of choice. Trials with other ARBs are under way, so we should have more data soon.

Clearly, this is a disappointment for the proponents of ARB therapy, which now has no primary indications. Their sole role seems to be a substitute for ACE inhibition when adverse effects preclude its use. Despite the theoretic advantage of blocking more of angiotensin's effects on the body, in practice it seems to make little difference. Of interest were some early reports at this meeting of a new class of drugs called vasopeptidase inhibitors, which block ACE, bradykinin degradation, and atrial naturetic factor (ANF) metabolism, thus decreasing angiotensin II and increasing bradykinin and ANF. These drugs have a solid theoretic basis and look promising in initial studies, but again large clinical trials will be needed to establish their role, if any, in the treatment of hypertension, heart failure, and other circulatory diseases. **—mhc**

Tilt Table Training for Recurrent Syncope

ABSTRACT & COMMENTARY

Synopsis: *Orthostatic training improved symptoms in adolescents with neurocardiogenic syncope unresponsive or intolerant to traditional pharmacologic therapy.*

Source: Di Girolamo E, et al. *Circulation* 1999;100: 1798-1801.

Young adults with neurocardiogenic syncope often do not get relief or cannot tolerate traditional pharmacologic therapy. Thus, Di Girolamo and colleagues evaluated the use of a tilt table training program in a controlled trial of 47 adolescents (18 men, 29 women; mean age, 16 years) with recurrent head-up tilt test positive syncope refractory to traditional pharmacologic therapies. In 24 patients, orthostatic training was started in the hospital (5 sessions) and continued at home for one month. Hospital training consisted of daily tilt table sessions (60°) of incremental duration (10 minutes added each day) and home sessions consisted of standing against a wall twice a day for up to 40 minutes. Retesting at one month showed that 96% of the training patients were tilt negative as compared to 26% of the controls ($P < 0.001$). Di Girolamo et al concluded that orthostatic training improved symptoms in adolescents with neurocardiogenic syncope unresponsive or intolerant to traditional pharmacologic therapy.

COMMENT BY MICHAEL H. CRAWFORD, MD

Recurrent syncope in a young adult is rarely life threatening, but it can significantly reduce quality of life. In my experience, it can limit job and school opportunities and cause serious psychological consequences, such as fostering dependency on parents or others. Although traditional pharmacologic therapy often works in my experience, the few refractory cases can be vexing. This report gives some hope for such patients.

This training program was simple and straightforward, but 40 minutes twice a day for an active teenager is a big commitment (remember trying to get the kids to practice piano?). Also, this study was done in Italy; five days of hospitalization to do daily tilt tests will not be feasible in the United States, but five sequential outpatient visits with tilt training would be. The exact training method may not be important and something adaptable to U.S. medicine could surely be devised.

Traditional pharmacologic therapy has included a wide variety of peripheral and centrally acting agents that affect the antonomic nervous system. Most popular have been beta blockers, alpha adrenergic vasoconstrictors, minerolocorticoids, and seratonin reuptake inhibitors. The patients in this study were refractory or intolerant to all four of these agents. Other approaches, such as disopyramide, theophylline, support hose, and cardiac pacing, are generally less successful and were not used in this study.

There are several limitations to this study. First, the patients were not randomized, training was offered to all, and only half consented. This tells you something about the popularity of such a time commitment despite the serious nature of the symptoms. The most enthusiastic and motivated were in the training group, which may explain the spectacular results. Thus, this approach, while effective, may not be widely applicable. Second,

the mechanism of the training effect is unknown. The most likely explanation is desensitization of antonomic receptors, but other factors may also be important. In my experience, adolescents often "outgrow" neurocardiogenic syncope. The 18-month clinical follow-up in this study may have allowed this phenomenon to occur, since almost half the control group were asymptomatic during follow-up. Also, patients may change their lifestyle to avoid situations that cause syncope, and this was not controlled in the study. Finally, considerable variability in head-up tilt table testing has been observed in young adults including false-positive results in asymptomatic individuals. Despite these deficiencies in our knowledge about neurocardiogenic syncope, this report suggests that a noninvasive, nonpharmacologic approach may be effective therapy in selected patients. ❖

Stroke Prevention in Patients with Atrial Fibrillation

ABSTRACT & COMMENTARY

Synopsis: *Antithrombotic agents reduce the risk of stroke in nonvalvular atrial fibrillation.*

Source: Hart RG, et al. *Ann Intern Med* 1999;131: 492-501.

In this paper, hart and associates performed a meta-analysis of data from 16 randomized clinical trials of antithrombotic therapy for patients with nonvalvular atrial fibrillation. The 16 trials included a total of 9874 participants, including 2239 patients who were assigned to placebo.

Six trials involving 2900 patients compared adjusted-dose warfarin with placebo or control. The mean age of participants at study entry was 69 years, with 29% of the patients being women. The control stroke rate was 4.6% and 12.3% per year for primary and secondary prevention trials, respectively. Meta-analysis showed that therapy with adjusted-dose warfarin reduced the relative risk of stroke by 62%. The absolute risk reduction for all strokes was 2.7% per year in primary prevention and 8.4% per year in secondary prevention. All-cause mortality was decreased by 26% in patients who received warfarin.

Six trials compared antiplatelet therapy vs. placebo. Approximately 90% of total follow-up exposure during antiplatelet therapy was with aspirin alone. The aspirin dosage ranged from 25 mg twice daily to 1300 mg daily. The mean age of participants was 70 years, with 38% women. The average rate of stroke among participants assigned to placebo was 5.2% per year for primary prevention and 12.9% per year for secondary prevention.

Meta-analysis of all six trials showed that aspirin reduced the incidence of stroke by 22%. The absolute risk reduction was 1.5% per year for primary prevention and 2.5% per year for secondary prevention.

Adjusted-dose warfarin was compared to aspirin in five trials involving 2837 patients. The mean age of participants was 71 years and 38% were women. The results of these comparisons were variable but meta-analysis showed that adjusted-dose warfarin reduced overall relative risk for stroke by 36%. The paper also lists data from trials that compared adjusted-dose warfarin with fixed doses of warfarin and aspirin and a number of other antithrombotic regimens. However, these trials were sufficiently different to prevent meaningful use of meta-analysis to combine results. Hart et al then present a table giving the estimated size of treatment effects according to risk status. The greatest benefit is seen with warfarin compared to aspirin in high-risk patient groups, with a 48% reduction with warfarin seen for secondary prevention and a 24% reduction for primary prevention in these subgroups.

Hart et al conclude that there is conclusive evidence from a large number of randomized trials that antithrombotic agents reduce the risk of stroke in nonvalvular atrial fibrillation.

COMMENT BY JOHN P. DiMARCO, MD, PhD

This paper summarizes two decades of clinical trials in the field of stroke prevention among patients with atrial fibrillation. By combining data from these trials in a meta-analysis, Hart et al give physicians a better estimate of the magnitude of treatment effect of such therapy.

The most valuable parts of this meta-analysis are the comparisons of warfarin vs. placebo, aspirin vs. placebo, and warfarin vs. aspirin. It is clear that warfarin is superior to aspirin or aspirin plus low, fixed-dose adjusted warfarin in high-risk populations. Here, the magnitude of treatment effect is substantial and the risk of excess bleeding relatively modest. Controversy about the role of warfarin still exists, however, for relatively low-risk patients. Here, there is only a modest benefit achieved with warfarin over aspirin or even over placebo, but the excess risk of hemorrhage is still present. A possible conclusion from these data is that physicians should still exercise judgment when considering warfarin for patients at low risk for stroke. A conservative approach may be appropriate for patients at low risk but physicians should be aggressive in the use of warfarin in patients at high risk. High-risk factors include: older women, patients with prior stroke or transient ischemic attack (TIA), and those with hypertension and diabetes.

Table

ACCP Recommendations

Age	High Risk	Antithrombic
< 65 yrs.	No	Aspirin
	Yes	Warfarin
65-75 yrs.	No	Aspirin or Warfarin
	Yes	Warfarin
> 75 yrs.	All	Warfarin

It is disappointing that this meta-analysis does not allow us to show any regimen superior to adjusted-dose warfarin. Although a large number of alternative antithrombotic strategies have been tested, none has proved to be superior to warfarin. Anticoagulation with warfarin is still difficult and one hopes that in the future some effective alternative strategy may be identified. Until then, the recommendations of the American College of Chest Physicians (*Chest* 1998) (*see Table*) are worth considering. ❖

PTCA vs. Thrombolytic Therapy for Acute MI

ABSTRACT & COMMENTARY

Synopsis: *Higher early patency rates in PTCA subjects resulted in better LV systolic function, less reinfarction, and improved survival.*

Source: Zijlstra F, et al. *N Engl J Med* 1999;341: 1413-1419.

Prompt revascularization of the infarct-related artery (IRA) in acute myocardial infarction (MI) by thrombolytic therapy or direct angioplasty is proven to decrease mortality and morbidity. In 1993, two small, randomized trials of thrombolytic therapy vs. percutaneous transluminal coronary angioplasty (PTCA) suggested a benefit for PTCA, but other data were conflicting. This important report represents a five-year follow-up of the original Netherlands trial,[1] and confirms a robust advantage of PTCA over streptokinase (SK). The PTCA group manifest increased survival, had fewer hospitalizations and invasive procedures, better LV function, less heart failure, and a lower clinical angina class compared to the SK cohort over a mean of 5 ± 2 years. Of the original 395 randomized subjects (194 PTCA, 201 SK), 16 of the angioplasty group received no procedure or coronary artery bypass graft (CABG). TIMI-3 flow was confirmed in 90% of the PTCA group vs. 65% of the SK cohort. This translated into better LV function at discharge in the PTCA patients (only 14% with LVEF < 40% vs 26% of the SK cohort). Late (5 ± 2 years) follow-up demonstrated a persistent advantage for primary angioplasty: total long-term mortality was 13% vs. 24%; nonfatal MI occurred in 6% vs. 22% (RR = 0.27). All recurrent infarcts were documented to occur in the IRA. The primary end point of death and nonfatal MI was markedly reduced during long-term follow-up; reinfarctions were considerably higher in the SK patients, as were readmissions for ischemia or heart failure. Interestingly, total medical charges per patient were comparable, and actually lower in alive PTCA subjects at the end of follow-up.

Zijlstra and colleagues conclude that the major factor explaining the results is the higher early patency rates in PTCA subjects, resulting in better LV systolic function, less reinfarction, and improved survival. Reinfarction rates in the IRA were high in the lytic therapy subjects.

COMMENT BY JONATHAN ABRAMS, MD

These data are impressive and confirm the findings of a (short-term) meta-analysis of 10 trials assessing early morbidity and mortality,[2] and a new long-term meta-analysis.[3] Moreover, the long-term results are reassuring, indicating that the PTCA patients do not develop an increased late hazard. The Kaplan-Meier survival curves are relatively parallel for mortality and nonfatal reinfarction after the first 30 days. While not discussed by Zijlstra et al, anterior infarction was an independent risk factor for death or MI; although data are not provided, it is possible that the benefits of PTCA are somewhat less in inferior infarcts. Other analyses have not been consistent regarding outcomes in anterior vs. inferior MI.

There are several caveats. Streptokinase does not result in TIMI-3 flow at 90 minutes in the majority of patients. Front-loaded t-PA vs. angioplasty would be likely to produce a smaller difference in outcomes. On the other hand, the use of stents during primary angioplasty, as well as therapy with platelet IIb-IIIa inhibitors, might result in even better PTCA outcomes.

Nevertheless, long-term cardiac mortality was threefold greater in the SK patients vs PTCA (2% vs 7%; P < 0.001); this outcome is impressive. Of the subjects initially randomized to PTCA, nine were treated conservatively and seven underwent urgent CABG. The intention to treat analysis does not allow one to know the possible influence of these 16 subjects who did not receive a PTCA on short- and long-term events.

It now seems clear that, in experienced hands, within an appropriate time window, direct or primary angioplasty is preferred in most patients. One recent report suggests that time to intervention may be more critical to outcome in lytic patients than direct PTCA. New thrombolytic agents and lytic combinations with IIb-IIIa inhibitors, as well as the increasing use of stents, will keep this subject on the front burner for years to come. ❖

References

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2. Weaver WD, et al. *JAMA* 1997;273:2093-2098.
3. Grines C, et al. *Circulation* 1999;100:I-499.

Incidence of Myopathy with Combined Statin Calcium Blockers Use

ABSTRACT & COMMENTARY

Synopsis: *The overall incidence of myopathy with HMG-CoA reductase inhibitor use is low and augmented by the use of potent P450 system inhibitors but not by calcium blockers.*

Source: Gruer PJ, et al. *Am J Cardiol* 1999;84: 811-815.

Although simvastatin is a well-tolerated effective therapy for preventing coronary events due to the consequences of hyperlipidemia, a generalized myopathy is a rare but well-recognized adverse effect of simvastatin and other hydroxymethylglutarate coenzyme A (HMG-CoA) reductase inhibitors. Since most HMG-CoA reductase inhibitors (simvastatin, lovastatin, atorvastatin, and cerivastatin) are metabolized by the cytochrome P450 system, the incidence of myopathy may be higher with the concomitant use of drugs that inhibit the P450 system. Of most concern is the use of calcium blockers, which are weak inhibitors of P450. Thus, Gruer and colleagues analyzed safety data from two large simvastatin trials (Scandinavian Survival Study and the Heart Protection Study) and post-marketing adverse experience data reported to the U.S. Food and Drug Administration (FDA). Myopathy was defined as unexplained muscle pain or weakness and creatine kinase elevations more than 10 times the upper limit of normal. Rhabdomyolysis cases were included in the term myopathy. Concomitant drugs surveyed included calcium blockers and known potent inhibitors of P450, such as cyclosporine, erythromycin, and ketoconazole. In both of the simvastatin trials, about 30% of the patients were on calcium blockers and there were three cases of myopathy in more than 12,000 patients (0.025%, or 1 case per 10,000 patient years); one of the three was on calcium blockers. The post-marketing FDA data confirmed the hypothesis that myopathy was more common with concomitant use of the potent P450 inhibitors, but not with calcium blockers. Gruer et al conclude that the overall incidence of myopathy with HMG-CoA reductase inhibitor use is low and augmented by the concomitant use of potent P450 system inhibitors, but not by calcium blockers.

COMMENT BY MICHAEL H. CRAWFORD, MD

Ever since the Seldane fiasco, physicians have been alert to drug interactions with the potent P450 inhibitors, but less is known about the weaker inhibitors such as calcium blockers. Thus, this report on the popular HMG-CoA reductase inhibitor simvastatin and calcium blockers is of interest. Although no interaction was seen, it reminds us that simvastatin use with potent P450 inhibitors is a potential problem. Patients on cyclosporine have had no problems reported with low-dose simvastatin (10 mg qd) but higher doses are problematic. If a short course of macrolide antibiotics is necessary, discontinuation of simvastatin or other HMG-CoA reductase inhibitors would be prudent.

Despite these cautions, this report demonstrates that simvastatin-induced myopathy is rare (0.025% incidence). Even in the FDA database, there were only 25 reported cases and 14 were also taking cyclosporine. It has been estimated that more than 20 million people worldwide have been prescribed simvastatin.

The one patient with myopathy in the simvastatin mega-trials who was on a calcium blocker was on diltiazen, but the FDA database showed an even distribution of diltiazen and verapamil vs. the dihydroperidine calcium blockers. Thus, the lack of an association between calcium blockers and myopathy in patients on simvastatin cannot be explained by the type of calcium blockers being used.

There are some limitations to this study. First, the number of cases of myopathy is small, which reduces the power of these observations. However, it is unlikely that larger databases exist to address these issues. Second, the mega-trials used a maximum simvastatin dose of 40 mg qd and recently an 80 mg qd maximum dose was approved by the FDA. Third, FDA adverse drug reports probably underestimate the incidence of adverse events and are subject to physician reporting biases that have unpredictable effects. However, adverse event reports in clinical trials are highly accurate. Also, the finding that the potent P450 inhibitors increase the incidence of myopathy suggests that this analysis is robust. ❖

Causes of Death in the AVID Trial

ABSTRACT & COMMENTARY

Synopsis: *The ICD is more effective than an antiarrhythmic drug in reducing arrhythmic cardiac deaths while producing little or no effect on the frequency of nonarrhythmic cardiac deaths.*

Source: The AVID Investigators. *J Am Coll Cardiol* 1999;34:1552-1559.

The antiarrhythmics versus implantable defibrillators (AVID) Trial was a randomized comparison of antiarrhythmic drug therapy and implantable cardioverter defibrillator (ICD) therapy in patients who had survived cardiac arrest or sustained hypotensive ventricular tachycardia. Patients randomized to the antiarrhythmic drug arm could receive either amiodarone or sotalol but the majority received amiodarone. This study analyzes the causes of death among the 202 patients who died during the trial.

Death was defined as the time when respiration and blood circulation ceased without recovery. Information about each death event was collected from the principal investigator. The clinical information was then edited by the coordinating center to remove information on the type of antiarrhythmic therapy the patient was receiving. The edited information was then reviewed by an events committee and classified independently of the site principal investigator's decision. Deaths were classified as cardiac or noncardiac. Cardiac deaths were then subclassified as either arrhythmic or nonarrhythmic. The diagnosis of arrhythmic cardiac death required the absence of severe congestive heart failure or shock preceding a terminal arrhythmia. The location of death was also recorded and classified as either in-hospital (including in the emergency room) or out-of-hospital. Deaths due to pulmonary causes were reviewed after unblinding to see if amiodarone pulmonary toxicity might be responsible.

There were 122 deaths among patients assigned to an antiarrhythmic drug compared to 80 deaths among patients assigned to an ICD. A majority (78%) of these deaths were classified as cardiac. There were equal numbers of arrhythmic and nonarrhythmic cardiac deaths—79 vs. 78, respectively. The onset of terminal symptoms occurred nearly equally in-hospital vs. out-of-hospital (74 patients vs 83 patients). Most arrhythmic deaths occurred out-of-hospital vs. in-hospital (66 vs 13 patients). Most nonarrhythmic deaths occurred in-hospital vs. out-of-hospital (61 vs 17 patients). Enzymatic or electrocardiographic evidence of ischemia or myocardial infarction (MI) at the time of death was uncommon, with only 12 patients having such findings.

Arrhythmic deaths were more common in the antiarrhythmic drug therapy group. Nonarrhythmic cardiac deaths occurred with equal frequency in the ICD and drug therapy groups (39 vs 39). Noncardiac deaths were more common in the antiarrhythmic drug therapy group, with an excess of pulmonary and renal deaths accounting for most of the difference. There were 24 apparent arrhythmic deaths among patients with an ICD. Unfortunately, only seven of these patients had an ICD interrogation after death. In three of these seven, the ICD detected the arrhythmia and delivered shocks appropriately but could not terminate the arrhythmia. In four of the seven, no tachyarrhythmia was detected and either bradycardia or pulseless electrical activity was likely to have been the final rhythm. Autopsies were performed in only 14 patients and could not be used for classifying the cause of death.

Arrhythmic death was more common among patients whose index arrhythmia had been ventricular fibrillation (VF) than among patients who initially presented with ventricular tachycardia (VT). The ICD produced apparently greater benefit among the patients who presented with VF than it did among those who presented with VT.

Finally, the paper compares the classification by the principal investigators and the Events Committee. There was better than 90% agreement between the unblinded principal investigator and the blinded Events Committee for event classification.

The investigators conclude that the ICD is more effective than an antiarrhythmic drug in reducing arrhythmic cardiac deaths while producing little or no effect on the frequency of nonarrhythmic cardiac deaths.

COMMENT BY JOHN P. DiMARCO, MD, PhD

The AVID Trial was a large, multicenter, randomized trial that established the superiority of ICD therapy vs. antiarrhythmic drug therapy in patients who had survived an episode of a life-threatening ventricular arrhythmia. This paper confirms the hypothesis that the ICD produces its greatest benefit by affecting the frequency of arrhythmic death. Importantly, there was no excess in nonarrhythmic cardiac deaths, indicating that the ICD did not merely briefly postpone deaths among patients with an irreversible deterioration in cardiac function.

The classification process used in AVID has now become standard in large-scale arrhythmia mortality

trials. The most difficult decision is usually whether a terminal arrhythmia occurred in the setting of irreversible heart failure or shock. This requires extensive review of hospital records and requires a qualitative judgment by an experienced clinician. This paper is interesting since both the principal investigators and Events Committee agreed in a large majority of cases.

One disappointing feature in this report is the lack of information from ICD interrogation about the mechanism of deaths. During the period of AVID, event data storage was a relatively new feature of ICDs. Therefore, many clinicians, including many cardiologists, were not aware that important information about cause of death could be obtained by device interrogation. Programmers capable of interrogating the ICD at the time of death are still not universally available. As more and more physicians become knowledgeable about the capacity of current generation ICDs, we can hope that they will try to obtain interrogations even after out-of-hospital deaths so that we can learn more about the mechanism of death in these individuals.

In AVID, approximately 50% of the deaths occurred out-of-hospital. By contrast, another large trial that investigated the use of ICD therapy, the CABG Patch Trial, observed that 79% of their deaths occurred in-hospital. The CABG Patch Trial was unable to show a difference between the ICD and an untreated control group. This report from AVID demonstrates that the population selected for ICD therapy should have a high frequency of out-of-hospital arrhythmic events.

The slight increase in pulmonary deaths in the drug-treated group is of concern. There were nine pulmonary deaths among the antiarrhythmic drug-treated group vs. only two in the ICD group. Three of these nine deaths were classified as due to amiodarone toxicity. However, amiodarone does produce some slight progressive deterioration in pulmonary function, even in patients without full manifestations of amiodarone toxicity, and one must be concerned that there may be a subtle tendency toward pulmonary problems among amiodarone patients. ❖

CME Questions

29. Which is most correct concerning late-breaking trials at the AHA meeting?
a. ACE inhibitors are beneficial in a wide range of vascular disease patients.
b. Beta blockers continue to show benefit in heart failure patients.
c. Angiotensin receptor blockers reduce mortality in heart failure patients.
d. All of the above

30. Long-term follow-up of patients in a primary angioplasty vs. streptokinase for acute MI trial showed:
a. increased survival in the angioplasty group.
b. better LV function in the angioplasty group.
c. fewer recurrent MIs in the angioplasty group.
d. All of the above

31. A recent meta-analysis of 16 trials of antithrombic therapy for nonvalvular atrial fibrillation patients showed:
a. in clinically low-risk patients, warfarin is superior to aspirin.
b. in clinically low-risk patients, aspirin is superior to warfarin.
c. in high-risk patients, warfarin is superior to aspirin.
d. in high-risk patients, aspirin is superior to warfarin.

32. The antiarrhythmics vs. implantable defibrillators (AVID) trial showed that:
a. defibrillators reduced in-hospital deaths.
b. defibrillators reduced out-of-hospital deaths.
c. defibrillators reduced noncardiac deaths.
d. defibrillators reduced MI deaths.

33. Adolescents with neurocardiogenic syncope may benefit from:
a. psychological counseling.
b. job training.
c. orthostatic training.
d. physical conditioning.

34. The incidence of myopathy associated with statin therapy may be increased by:
a. cyclosporine.
b. diltiazem.
c. amlodipine.
d. verapamil.

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