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Late-Breaking Clinical Trials: American College of Cardiology Scientific Sessions—March 1999

CONFERENCE COVERAGE

Note: *The following reports are summaries and comments on some of the more interesting late-breaking clinical trials presented at the American College of Cardiology Annual Scientific Sessions, March 8-10, 1999, in New Orleans, LA. The reports are based upon handwritten notes taken during the presentation of data and the comments are by the notetakers. No abstracts or written reports were available for these sessions and some of the data presented were preliminary.*

SHOCK

The shock trial, an international multicenter study (30 hospitals) enrolling patients with acute myocardial infarction (AMI) and cardiogenic shock between 1993-1998, tested the hypothesis that immediate revascularization would reduce 30-day and 6-month mortality. There is suggestive evidence from observational studies that there may be up to a 30-40% benefit from early revascularization in such patients, although not all data are supportive. Eligible patients with AMI and cardiogenic shock within 36 hours were randomized to either emergency revascularization or supportive therapy with optional late revascularization after a minimum of 54 hours. The hypothesis was that the revascularization group (REV) would have a 20% decrease in mortality compared to the delayed cohort, who had initial medical stabilization (IMS). Patients had sustained hypotension with end-organ malperfusion and no mechanical cause of shock. Wedge pressure had to be more than 15 mmHg and cardiac index less than 2.2 L/min/m^2. The IMS group all received intra-aortic balloon (IABP) support and thrombolytic therapy; delayed revascularization was an option, and was carried out in approximately 25% of this cohort.

The overall SHOCK cohort was felt to be representative of an acute infarction-cardiogenic shock population. Fifty-five percent of the patients were transferred from an outlying hospital to one of the

participating centers. A total of 302 patients were randomized, representing approximately 25% of eligible candidates.

The primary end point of 30-day all-cause mortality was not achieved, but survival did favor the REV group. Thirty-day mortality was 48% vs. 56%, and six-month mortality was 54% vs. 66%, REV vs. IMS, respectively. Although 30-day mortality rates did not achieve statistical significance, there was a relative risk reduction of 17%, whereas the six-month survival was significantly increased (P = 0.04). There were an equivalent number of major adverse events in both groups, although acute renal failure was more common in the REV patients. A registry was kept of nonenrolled patients and survival results were roughly equivalent. A total of 87% of the REV group actually received angioplasty or bypass surgery (49% and 38%, respectively) after randomization. Of interest, when the cohorts were analyzed with respect to age, there was a favorable trend toward improved survival in those individuals younger than 75 years of age, whereas in patients older than 75 there was an increased risk ratio. Other parameters, such as infarct location, diabetes, or gender, did not affect the outcomes between the two groups.

An angiographic analysis was also reported; approximately 20% had left main disease, and two- or three-vessel disease was found in 80%. Half of the patients had a left anterior decending culprit lesion. TIMI-3 flow was achieved in approximately 60% of the angioplasty patients; there was increasing use of stents in the last years of the trial; stenting did not improve TIMI flow, but did result in increased procedural success rates. Patients who were sent for bypass surgery had more left main and three-vessel disease. In those who underwent a successful angioplasty, 30-day mortality was 38% vs. 79% in subjects with an unsuccessful procedure and 100% in those individuals who did not achieve TIMI-2 or TIMI-3 flow. A separate echocardiographic substudy was reported at another session. An initial echo was performed within 24 hours and a subsequent echo at two weeks or discharge. Many patients were on IABP. Approximately 90 patients in each group were included in this study. One-third did not have their initial echo until after revascularization. Severe mitral regurgitation was an exclusion to enter into the SHOCK study. Echos demonstrated 1-2+ mitral regurgitation in most patients and a tendency for left ventricular volumes to increase over time. The baseline ejection fraction was 33%. Sphericity was increased. Ventricular thrombus was noted in 25% of the IMS group vs. 9% in REV. Left ventricular ejection fraction (EF) did not change significantly over the first two weeks. Individuals with an EF of less than 25% had a 65% 30-day mortality compared to a 30-40% mortality in those with an EF of more than 25%. Left ventricular function tended to improve after revascularization. Mortality was correlated with low EF and mitral regurgitation severity.

COMMENT BY JONATHAN ABRAMS, MD

The investigators in the SHOCK Trial are to be congratulated on carrying out a difficult protocol in extremely ill individuals. While a 20% mortality reduction was not achieved in individuals revascularized within six hours, this may be in part because the intensive medically treated patients received superb care, including IABP and thrombolysis. In addition, approximately 25% of the IMS group underwent revascularization after 54 hours. Thus, the SHOCK Trial actually investigated urgent revascularization vs. optimal medical therapy with IABP. The latter group achieved a high level of care in the study centers, as attested by the relatively good mortality at 12 months. The observation that individuals younger than 75 appear to have a survival benefit is considered to be preliminary until the data are further analyzed; however, a six-month mortality of 48% in the younger cohort is impressive. Furthermore, successful angioplasty was associated with a 38% 30-day mortality; for REV patients who underwent either angioplasty or CABG, the 30-day mortality rate was 42% vs. 53% in those who did not undergo revascularization.

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Recent data from the National Registry of Myocardial Infarction-2 (NRMI-2) shock cohort, reflecting 23,000 patients with cardiogenic shock post-AMI, documents an overall mortality of 70%, with or without receiving thrombolysis (Barron HV, personal communication; Barron HV, et al. *J Am Coll Cardiol*, 1998;31:135A). In patients who received thrombolytic therapy and IABP, mortality was 49%; the investigators concluded that the use of balloon pumping and thrombolytic therapy decreased the odds of death by 18%. In the entire NRMI-2 shock registry, 24% received thrombolytic therapy, 15% underwent early revascularization, and 60% received no immediate reperfusion treatment. IABP was performed in 32%. Those individuals who received IABP tended to be younger, were more likely to be male, and had lower comorbidity than those individuals who did not receive IABP. The hospital mortality rate for patients treated with primary angioplasty with or without IABP was approximately 45% in the NRMI-2 registry, compared to 49% in those individuals who received thrombolytic therapy and IABP. These results are comparable to the 30-day mortality in the SHOCK Trial REV patient.

What conclusion can be drawn from the SHOCK Trial? It seems clear that contemporary therapy of cardiogenic shock complicating AMI demands immediate exclusion of a significant mechanical defect, such as acute severe mitral regurgitation or ventricular septal defect, with initiation of IABP and thrombolytic therapy or direct angioplasty as soon as possible. The SHOCK Trial did not directly test thrombolytic therapy vs. direct angioplasty, but rather an early revascularization strategy vs. stabilization with intra-aortic balloon pumping and thrombolysis with optional revascularization after two or more days. Cardiogenic shock mortality in the SHOCK Trial and the NRMI-2 registry is lower than in previous decades, and convincingly supports a survival improvement in this devastating complication of AMI. One can cautiously conclude that for patients younger than the age of 75, a direct catherization approach followed by angioplasty or bypass surgery is the therapy of choice in suitable patients when treated by highly experienced cardiologists and surgeons. (***Editor's note:*** *More information was recently published in the following article: Goldberg RJ, et al. N Engl J Med 340:1162-1168.*) ❖

The SHOCK trial demonstrated that the best treatment for cardiogenic shock is:

a. thrombolysis.
b. intra-aortic balloon pumping.
c. intravenous milrinone.
d. early revascularization.

FRISC II

FRISC II comprises two multicentered trials conducted in Scandinavia: FRagmin during InStability in Coronary artery disease (FRISC) and Fast Revascularization during InStability in Coronary artery disease (FRISC). The first hypothesis tested was that low molecular weight heparin (Fragmin) given bid for three months would reduce death and myocardial infarction rates (primary endpoint). Secondary end points included the need for revascularization and bleeding complications in patients with unstable angina or non-Q-wave myocardial infarction. The second hypothesis tested was the strategy of a noninvasive evaluation vs. an early invasive strategy with revascularization of appropriate patients. Criteria for enrollment in the study were two of the following three: characteristic chest pain (present in 82%), ST-T wave changes (50%), or elevated CK-MB or troponin (60%). Since cardiac catheterization and revascularization was not feasible in all 58 Scandinavian centers in the trial, 2457 patients were in the Fast Revascularization subgroup. During the first five to seven days, all eligible patients were treated with aspirin, beta blockers, nitrates, and Fragmin and those in the strategy subgroup were randomized within 48 hours to either the noninvasive or the invasive arm. The subsequent double-blind phase randomized patients to Fragmin for another three months or placebo. In the strategy subgroup, those in the invasive arm underwent revascularization within the first seven days. Those in the noninvasive arm only underwent revascularization if clinically indicated.

The comparison of low molecular weight heparin vs. placebo showed a small but significant reduction in the primary end point of death or Q-wave myocardial infarction at 45 days (3.7% vs 6.5%; $P < 0.003$), but at 90 days, this difference was no longer statistically significant (6.7% vs 8.0%). In the strategies evaluation, 98% of the patients randomized to the invasive group underwent angiography and 71% underwent revascularization within 10 days and 78% underwent revascularization by six months. In the noninvasive group, only 9% were revascularized by 10 days and 38% by 6 months. Of note, the mortality in the patients undergoing coronary artery bypass graph surgery was 1.2%.

The primary end point was significantly reduced in the early revascularization group compared to the conservative strategy at six months (9.5% vs 12%; $P = 0.045$), which represents a 21% reduction in risk. Mortality alone was not significantly different in the total cohort, but it was in the male subjects (1.5% vs 3.2%; $P = 0.03$). One reason women may not have demonstrated the mortality benefit was that 30% of them had normal coronary arteries on angiography. Bleeding complications on low molecular weight heparin were higher; especially severe bleeding (4.1% vs 1.7%) and cerebral hemorrhage (5 vs

0). No significant change in platelet count was detected on low molecular weight heparin. The authors concluded that low molecular weight heparin produced a modest decrease in the primary end point at 45 days, which was offset by higher bleeding complications and the effect was not present at three months. Thus, they could not strongly recommend prolonged low molecular weight heparin treatment. On the other hand, an early invasive strategy significantly reduced the primary end point at six months, suggesting that for unstable coronary artery syndromes, early invasive management should be recommended with individualization of low molecular weight heparin treatment as clinically indicated. Since the primary end point was reduced at 45 days on low molecular weight heparin, it could be used to help tide patients over until the revascularization strategy could be applied to them.

COMMENT BY MICHAEL H. CRAWFORD, MD

This trial was heartening to the interventional cardiologists who were depressed after the VANQWISH trial showed that the invasive strategy in unstable coronary syndrome patients resulted in higher mortality rates and was not recommended as an initial strategy. The TIMI III trial also showed no advantage to an early invasive strategy. Thus, this is the first trial to show an advantage for the invasive strategy. During the discussion, Lars Wallentin, MD, who presented the data, commented that there were three potential explanations for the differences in these three trials. First, in the FRISC II trial, almost 80% of the patients underwent revascularization in the invasive arm. This was not the case in the two U.S. trials, where it was 44% in the VA trial and about 60% in the TIMI trial. The fact that there were patients in the U.S. trials referred to the invasive arm who did not undergo revascularization suggests that these are different patients than those seen in the FRISC II trial. It is unlikely that they had minimum or no disease since the VANQWISH trial was done in a VA population. Thus, it is more likely that the U.S. patients had more severe three-vessel disease that was not amenable to angioplasty and may not have been particularly attractive for bypass surgery. This impression is supported by Dr. Wallentin's second point, which was that the U.S. trials' patients had more comorbidities, such as diabetes. Third, Dr. Wallentin noted that they had a low surgical mortality compared to the U.S. trials, especially the VANQWISH trial. This further supported the contention that the Scandinavian patients were a less sick group in general, and with less extensive coronary artery disease. In support of this was the interesting results in the women patients in the invasive arm, 30% of them had normal coronary arteries.

In the VANQWISH trial, it was not just the higher surgical mortality that contributed to the increased mortality in the invasive arm, since many of the patients died before revascularization could be accomplished. Just performing a cardiac catheterization was associated with a higher mortality in the VANQWISH trial. Also, when the surgical mortality in the VANQWISH trial was adjusted for comorbidities, it was not appreciably more than expected. All these data point to the fact that the U.S. trials dealt with a less favorable patient population. In the United States, we have seen an explosion in the number of patients with non-Q-wave myocardial infarction because of treatment with thrombolytics and more patients who have already been revascularized coming in with ischemic events. Perhaps the de novo unstable angina or non-Q infarction patients, especially if they are younger and less likely to have severe three-vessel disease, should undergo an early invasive strategy and revascularization if feasible. Patients with prior revascularization or known multivessel coronary artery disease should perhaps be treated more conservatively unless they do not do well. In some patients, this treatment might include low molecular weight heparin if catheterization and revascularization decisions are being delayed beyond the first week. In other patients, it may be appropriate to treat with platelet glycoprotein 2B/3A inhibitors. It is of interest that in the FRISC II trial, only 10% of patients receive such agents and this number was equal in all groups. Until the FRISC II study is published and we can carefully look at subgroups, we are going to have to use our best clinical judgment, since the evidence-based medicine approach conflicts with these disparate trials. ❖

The FRISC II study showed that which of the following is the best approach to unstable coronary syndromes?

a. Low molecular weight heparin
b. An early invasive strategy
c. Medical therapy with noninvasive risk stratification
d. Platelet glycoprotein IIb/IIIa inhibitors

OPUS

The multicenter optimal angioplasty vs. primary stenting study was presented by W. Douglas Weaver, MD. This trial is the first to compare primary stenting with stenting only if plain old balloon angioplasty (POBA) is unsuccessful. The hypothesis tested was that primary stenting would reduce the incidence of death, myocardial infarction (MI), or re-revascularization of the target vessel within six months. OPUS randomized 479 patients with stable or unstable angina, or recent MI. Results showed that significantly fewer patients in the

primary stent group reached the primary end point compared to the POBA plus stent if necessary group (6.1% vs 14.9%). Also, a cost analysis was done that showed that the POBA plus or minus stent group cost less initially vs. primary stenting, but when the added cost of readmission for MI or need for re-revascularization was factored in, the overall costs were less in the primary stenting group. Thus, the authors concluded that primary stenting resulted in better clinical outcomes and lower costs than POBA plus stenting if necessary.

COMMENT BY MICHAEL H. CRAWFORD, MD

Previous studies have shown that stents are associated with lower rates of restenosis than POBA, but these differences were not large and primary stenting is a more expensive approach. Several editorials have been written on this topic in major journals, with some discussants decrying "stent-o-mania" over the more reasoned approach of POBA with stenting only if necessary. Others have touted the lower restenosis rate of stent use and, therefore, the potential for lower long-term costs. Another issue in this debate has been the high cost of stents in the United States compared to other countries. Stents and platelet glycoprotein 2B/3A inhibitor drugs have broken the bank at some hospitals and have contributed to increased tensions between hospital administrators and cardiologists. In this milieu, a well-done clinical trial with definitive results in favor of primary stenting is certainly welcome and supports the usual practice of the majority of cardiologists in the United States. ❖

The OPUS trial showed that in patients with symptomatic ischemic heart disease, recurrent events were prevented best by which of the following?

a. Medical therapy
b. Balloon angioplasty alone
c. Primary stenting
d. Selective stenting

CLASICS

The CLopridigel Aspirin Stent Intervention Cooperative Study (CLASICS) was conducted in 48 European centers and tested the hypothesis that clopridigel plus aspirin would be superior to ticlopidine plus aspirin in patients undergoing coronary artery stenting. Previous studies have shown that ticlopidine plus aspirin reduced in-stent thrombosis, but was associated with significant side effects. Thus, this trial comparing clopridigel to ticlopidine had the primary end point of 28-day safety. Secondary end points were death, myocardial infarction, or need for re-revascularization. This was a randomized double-blind study looking at two doses of clopridigel with standard aspirin therapy vs. aspirin plus ticlopidine. In the high-dose clopridigel group, an intravenous clopridigel load was given first followed by oral therapy. In 90% of the patients, only one stent was placed. The results showed that the primary end point was lower in all clopridigel patients vs. the ticlopidine-treated patients (4.6% vs 9.1%; $P < 0.005$) with a relative risk reduction of 50%. Patients treated with low-dose clopridigel had a higher event rate than those treated with the intravenous load followed by oral therapy (6.3% vs 2.9%). Bleeding complications occurred in less than 1% of patients and were not statistically different between the groups. Clopridigel did not affect white blood cell counts and there was a minimal decrease of platelets that was of no clinical significance. Also, fewer patients discontinued clopridigel for side effects. The secondary end point of death, infarction, or re-revascularization was not statistically different between the groups. The authors concluded that clopridigel plus aspirin was safer than ticlopidine plus aspirin in patients treated with coronary stenting, a clopridigel intravenous load in the cath lab was well tolerated without increased bleeding risks.

COMMENT BY MICHAEL H. CRAWFORD, MD

Ticlopidine was a significant advance over coumadin treatment to prevent early thrombosis of stented coronary arteries and ticlopidine plus aspirin has been shown to be superior to aspirin alone in preventing in-stent thrombosis. However, ticlopidine is expensive and associated with considerable side effects. Thus, when clopridigel came on the market, there was considerable enthusiasm for its use because of its lower cost and better side effect profile. Thus, many interventional cardiologists have already switched to clopridigel plus aspirin in patients receiving stents. The CLASIC Study supports this choice and also suggests that an intravenous load of clopridigel in the cardiac catheterization laboratory may be the best approach, since there was no increase in bleeding and the primary end point was lowest with this approach. Thus, for reasons of cost and side effects, clopridigel would seem to be the drug of choice in the poststent patient.

Unfortunately, the secondary end point of death, MI, and re-revascularization was not influenced by the various therapies tested. One reason for this is that the event rate was low and the study was underpowered to detect differences in clinical outcome. Thus, we will need to await the results of other trials to determine whether clinical outcomes are better in patients treated with intravenous clopridigel in the catheterization laboratory vs. those just started on oral therapy afterward. ❖

The CLASICS trial showed that the safest and most effective post-stenting regimen combined with aspirin was:

a. intravenous clopridigel followed by oral therapy.
b. low-dose oral clopridigel therapy.
c. oral ticlopidine therapy.

d. ticlopidine and clopridigel.

Antiarrhythmics vs. Implantable Defibrillators (AVID) Registry

ABSTRACT & COMMENTARY

Synopsis: *An analysis of patients who were identified as having significant ventricular arrhythmias but were not randomized in the study showed that the prognosis of patients with all the types of arrhythmias is poor.*

Source: Anderson JL, et al. *Circulation* 1999;99: 1692-1699.

The antiarrhythmics vs. implantable defibrillators (AVID) trial tested the hypothesis that ICD implantation was better than antiarrhythmic drug therapy in selected survivors of sustained ventricular tachyarrhythmias. The main data from this trial have been previously reported (*N Engl J Med* 1997;337:1576-1583). The study showed that there was a significant reduction in total mortality with ICD therapy. This paper also includes an analysis of patients who were identified as having significant ventricular arrhythmias but were not randomized in the study.

During AVID, seven groups of patients were identified as candidates for a registry. The first three groups included patients with primary cardiac arrests due to ventricular fibrillation (VF), documented sustained primary ventricular tachycardia (VT) with syncope, and documented sustained primary VT with hypotension and a low ejection fraction. Only these three groups of patients were eligible for randomization in the main trial. The other groups that could be included in the registry but were not eligible for randomization consisted of patients with the following characteristics: 1) sustained VT with hypotension but an ejection fraction greater than 0.40; 2) hemodynamically stable VT; 3) sustained VT or cardiac arrest due to what was thought to be a transient or correctable cause; and 4) syncope with structural heart disease and VT or VF inducible at electrophysiologic study.

During the AVID trial, 4595 patients were placed in the AVID registry and 1016 were randomized. The patients in the registry averaged 64 years of age and 77% were male. The mean left ventricular ejection fraction in the registry was 35% and 77% of these patients had evidence of coronary artery disease. Among the patients with arrhythmias who were eligible for randomization, the reasons for not participating in the trial included patient or family refusal (45%), treatment predetermined by referring physician (28%), physician refusal (11.5%), prior amiodarone use (2%), and miscellaneous reasons (13%). There were only minor differences between randomized and nonrandomized patients among the patients eligible for the trial. Mortality in the registry patients was sought through the national death index service. When survival was analyzed by arrhythmia type, it was noted that there was a relatively high rate of mortality for all arrhythmia groupings. Two-year survival rates ranged from 76% in patients with syncopal VT to 84% in patients with unexplained syncope and inducible VT. Survival was also associated with ejection fraction. This was particularly noticeable for patients with asymptomatic VT and transient or correctable causes of VT/VF. For these two diagnoses, two-year survival rates for patients with ejection fractions greater than or equal to 35% and less than 35% were 85.3% vs. 67.7% and 86.1% vs. 70.8%. Anderson and associates conclude that the patients entered into the randomized portion of the trial were representative of all patients with serious ventricular arrhythmias. They also note that the prognosis of patients with all the types of arrhythmias included in the registry is poor.

COMMENT BY JOHN P. DiMARCO, MD, PhD

It is always important to know whether the population enrolled into a randomized clinical trial is representative of patients with a similar condition encountered in the community. These data from the AVID trial support our ability to apply the findings of the trial to the general population. It is particularly interesting, however, to note that there was still a high mortality among patients who were not eligible for registry. In particular, patients who have what are usually thought to be transient or correctable causes had a higher mortality than the patients who were eligible for entry into the trial. Too frequently, physicians will ascribe the occurrence of a serious ventricular arrhythmia to some transient complicating factor. However, it may well be that the substrate for the arrhythmia is always there. Multiple triggers may precipitate life-threatening episodes or the same trigger may occur in the future. The advantage of ICD therapy for such patients would be that it will always be there but will remain inactive unless an arrhythmia develops. However, unless there is some irreversible condition, device therapy should still be effective if an episode of VT or VF occurs.

The major limitation with this paper is some degree of uncertainty about the completeness of the registry. Patients with ventricular arrhythmias can present in a number of ways. Also, it is possible that the registry doesn't reflect the population of patients in the more general medical community. However, the data present-

ed in this paper represent the largest survey of patients with sustained ventricular arrhythmias yet available and should form the basis for estimates made for planning future trials. ❖

The AVID registry showed that which of the following patients were at high risk for sudden death?

a. Sustained VT, but ejection fraction greater than 0.40
b. Sustained VT/VF with a correctable cause
c. Inducible VT in patients with heart disease and syncope
d. All of the above

Mechanisms of Death in the CABG Patch Trial

ABSTRACT & COMMENTARY

Synopsis: *In this trial, ICD therapy did reduce arrhythmic death but had no significant effect on nonarrhythmic deaths. Total mortality was not significantly reduced.*

Source: Bigger JT, et al. *Circulation* 1999;99: 1416-1421.

The cabg patch trial was a randomized, controlled clinical trial evaluating the efficacy of implantable cardioverter defibrillator (ICD) implantation at the time of coronary artery bypass surgery in patients with low ejection fractions and a positive signal averaged ECG. In the CABG Patch trial, all patients undergoing coronary revascularization surgery without concomitant valve surgery or aneurysm resection were screened for participation in the trial. Patients who had an ejection fraction less than 36% had a signal averaged ECG performed. If the signal averaged ECG was positive and no other exclusions were present, they were invited to participate in the trial. Patients with a previous history of sustained ventricular tachycardia or fibrillation were excluded. A high proportion (approximately 70%) of eligible patients participated. Although patients gave consent before their operation, the actual randomization occurred as the patient was coming off cardiopulmonary bypass. This randomization timing was chosen to allow the surgeon to only randomize patients in whom no early major complication had occurred and in whom they felt implantation of an epicardial ICD and its testing would be safe. The results of the trial have been previously reported (Bigger JT Jr. *N Engl J Med* 1997;337:1569-1575). No difference in survival was noted between the ICD and control groups.

During the study, there were 198 deaths among the 900 patients randomized in the trial. This paper describes the mechanisms of death and the significance of the observed pattern.

Data concerning each death were reviewed by an independent events committee. Deaths were classified as either arrhythmic or nonarrhythmic cardiac deaths or noncardiac deaths. A primary arrhythmic death was defined as sudden and unexpected death within five minutes of acute cardiac symptoms in patients without preceding active symptoms and/or signs of cardiac failure or prior NYHA functional class IV. Deaths in patients who were previously well and died during sleep were classified as primary arrhythmic deaths. Secondary arrhythmic/mechanical deaths were those where preceding acute symptoms and/or signs of heart failure were present but there was no evidence of myocardial pump failure before death. Nonarrhythmic cardiac deaths included deaths due to myocardial pump failure with circulatory collapse, despite a maintained rhythm, and deaths due to cardiac procedures. The location of death was also determined.

During average follow-up of 32 ± 16 months, 198 (22%) of the 900 randomized patients died. For both groups combined, 130 deaths occurred in-hospital, 25 occurred in a nonhospital medical setting, and 29 occurred outside a medical facility. Thirteen deaths occurred in a hospital emergency room department and the location of one death was unknown. Of these deaths, 73% were witnessed. Most of the deaths in both the control group (82%) and the ICD group (75%) were due to cardiac causes. ICD therapy decreased the proportion of arrhythmic deaths in comparison to that in controls (15% vs 29%; P = 0.24). However, there was a slight excess of nonarrhythmic cardiac mortality in the ICD group, particularly during the first two years of follow-up. In this trial, relatively few of the devices implanted had the ability to store electrograms. A change in symptom status during the last seven days of life was noted in a large proportion of deaths. Angina was noted in 10% of patients who died, myocardial infarction occurred in 13%, and 68% had overt heart failure.

Bigger and colleagues conclude that in the CABG Patch trial, ICD therapy did reduce arrhythmic death but had no significant effect on nonarrhythmic deaths. However, since the majority (71% of the deaths) were nonarrhythmic, total mortality was not significantly reduced.

COMMENT BY JOHN P. DiMARCO, MD, PhD

Three reasonably large randomized, controlled trials on the efficacy of ICD implantation for primary prophylaxis of sudden death have been published. The Multi-Center Automatic Defibrillator Implantation Trial (MADIT) performed electrophysiologic studies in coro-

nary artery disease patients with low ejection fractions and nonsustained VT. Patients with inducible ventricular tachycardia were randomized to either ICD implantation or "conventional therapy." MADIT reported a large and highly significant reduction in total mortality and across-the-board mortality reductions were seen in arrhythmic, nonarrhythmic, cardiac, and noncardiac mortality. The CABG Patch trial found no difference in total mortality since, as shown in this paper, a slight advantage in arrhythmic mortality was offset by a slight disadvantage in nonarrhythmic mortality. The latter category constituted the largest proportion of deaths. Preliminary data from the Multi-Center Unsustained Tachycardia Trial (MUSTT) have shown no difference in mortality with electrophysiologically guided drug therapy but a major advantage with ICD therapy in low-ejection-fraction patients with inducible ventricular tachycardia. We should ask ourselves why the results of CABG Patch are different from those of MUSTT and MADIT. This paper goes a long way to explain that.

In the CABG Patch trial, about 25% of the deaths occurred during the in-hospital period after the coronary revascularization procedure. It would not be expected that the ICD would make a major impact on deaths in that period since the patient would be monitored and resuscitation facilities would be immediately available. In addition, the stress of cardiac surgery may have precipitated ventricular arrhythmias, which, if successfully terminated, would have led to the institution of appropriate additional therapy in both ICD and control group patients. Even after the early post-CABG period, many of the deaths in CABG Patch occurred in the setting of progressive heart failure. Once again, one would not expect ICD implantation to affect these deaths favorably.

These data pose a problem for electrophysiologists interested in the primary prevention of sudden death. The highest risk groups are almost always defined by severe depression of left ventricular function. However, these groups also have high mortality rates that are not directly due to a primary arrhythmia. In lower risk groups, a greater proportion of deaths may be due to arrhythmia without preceding progressive heart failure, but the overall incidence of sudden arrhythmic death would be too low to make ICD implantation an economically attractive option. It is also possible that by performing revascularization, the CABG Patch trial changed the mechanism of death. ICD implantation should favorably influence ischemic sudden deaths as well as nonischemic sudden deaths. Revascularization itself may have reduced the incidence of ischemically mediated arrhythmias and therefore caused the CABG Patch population to differ in a critical way from the populations in both MUSTT and MADIT.

Finally, we should also note that the data presented here are relevant toward the potential benefits of individual use of automatic external defibrillators (AEDs). These devices are now available by prescription for individual patient use. However, as seen in this study, relatively few of the deaths in high-risk populations occur outside the hospital in a witnessed setting. Thus, it would be anticipated that an AED prescription would have relatively little impact on overall mortality in these groups. ❖

In the CABG Patch trial, ICD placement:

a. reduced arrhythmic deaths.
b. reduced nonarrhythmic deaths.
c. reduced all-cause mortality.
d. increased mortality.

Readers are Invited . . .

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