Premature Termination of Clinical Trials—Lessons Learned

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Controlled clinical trials in cardiovascular disease are the cornerstone for therapeutic advances in this field of medicine. Since the introduction of the concept of controlled clinical trials there has been substantial progress in the design, conduct, and analysis of such studies. A growing awareness of ethical issues emerging from such trials has heightened public awareness, increased investigator scrutiny, and reinforced the need for interim data analysis. A benefit of such interim analyses is that either an entire clinical trial or a specific treatment limb can be stopped if the observed findings argue for premature termination. For example, highly positive findings, as were noted in the HOPE Study (Heart Outcomes Prevention Evaluation), led to its being stopped after 4.5 years of treatment, which was 1 year early. Alternatively, the doxazosin treatment limb of the ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) and the amlodipine treatment limb of AASK (African American Study of Kidney Disease and Hypertension) were stopped early because of negative findings with each respectively. Finally, economic considerations can enter into the decision to close a study early as was the case in the CONVINCE (Controlled Onset Verapamil Investigation of Cardiovascular End Points) trial. Most such decisions rely heavily on information obtained from independent data and safety monitoring boards. Such boards ensure patient safety by providing an unbiased ongoing review of data, which would otherwise be unavailable until a study's completion. Early termination of a clinical trial can have important clinical implications and, in particular, can redirect patterns of clinical practice. (J Clin Hypertens. 2002;4:219–225) ©2002 *Le Jacq Communications, Inc.*

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Several factors can influence the decision to terminate an ongoing clinical trial including ethical concerns, alterations in accepted clinical practice that make the continuation of a clinical trial unwise, and/or reaching a positive or negative statistical end point earlier than anticipated (Table). The discontinuation of a clinical trial can be prompted by either the investigator(s), the study sponsor, or by mutual agreement. This decision can be reached with or without the input of a properly constituted independent Data and Safety Monitoring Board.[1] Investigator-specific considerations are generally more relevant for single-center trials (Table) but may also influence multicenter trials, particularly if the investigative site in question has been a heavy enroller in the clinical trial.[2]

There are a number of "positive" findings that can correctly prompt the early termination of a study. For example, the unexpected benefit on cardiovascular disease (CVD) event rate in the Heart Outcomes Prevention Evaluation (HOPE) trial, 4.5-years into a planned 5–6-year trial, led to its early closure so that the benefit of these observations could be quickly disseminated.[3] Although not specifically stated as such, it can be inferred that it would have been unethical to withhold the findings of the HOPE study any longer than was done. Another example of early trial discontinuation for proper reasons was the collaborative β Blocker Heart Attack Trial (β Blocker Heart Attack Study Group).[4,5] The β Blocker Heart Attack Trial was a randomized, double-blind, controlled trial com-

Table. Selected Negative Reasons for Discontinuing a Clinical Trial
Serious adverse reactions, including abnormalities in laboratory analytes, vital signs, or outcomes
Inability to recruit or adequately enroll an adequate number of patients
Financial considerations
Protocol found to be impractical or unworkable
Investigator(s) loses interest
Problems arise in the medicine's stability or manufacture
New toxicological findings affect the benefit-to-risk ratio
Failure of the investigator and/or staff to follow either good clinical practice standards or to adhere to protocol requirements
Termination of the test medicine's development by the sponsor
Unacceptable change in personnel or facilities at the investigator's site
Determination that no statistically significant result can be obtained

paring propranolol with placebo in 3837 patients with a recent myocardial infarction (MI). The trial was terminated 9-months before the scheduled closing date on recommendation of the Policy and Data Monitoring Board. At the time of the decision the propranolol treatment group had a strikingly lower mortality (↓26%). Several issues were considered in this decision including the magnitude and consistency of the overall results across all subgroups, clinical centers, and cause of death, as well as the completeness of follow-up obtained.

If ethical considerations exist at the outset of a clinical trial then carefully defined end points should be established, which, if reached, would prompt discontinuation of the trial. It should also be appreciated that discontinuation of a trial because the results are either strongly positive or negative generally makes it difficult, if not impossible, to conduct a similar trial in the future. If the trial is to be terminated early as per pre-established criteria, the confirming data must be adequate to convince the overwhelming majority of statisticians and clinicians of the validity of the conclusion; otherwise, positive findings of a trial may not be accepted or negative findings dismissed. For example, in the β Blocker Heart Attack Trial two different statistical methods were used in declaring the overall mortality results significant.[4,5] The premature termination of a trial can sometimes be fiscally prudent if valuable resources can then be reallocated. When an investigator terminates a clinical trial careful consideration must also be given as to how patients might best return to their pretrial treatment regimen.[6] In many instances this is an easy issue to address. In other cases, when patients have benefited both medically and psychologically from being in a trial, the transition from frequent contact with the investigator and staff, plus the benefits of treatment, may prove challenging.

ABCD STUDY

The Appropriate Blood Pressure Control in Diabetes (ABCD) trial was a prospective, randomized study in patients with type 2 diabetes. It was designed to test the primary hypothesis that two modes of treatment—intensive vs. moderate blood pressure (BP) reduction—would either prevent CVD-related events or slow the progression of nephropathy, neuropathy, and retinopathy. A secondary hypothesis of this study was that a long-acting dihydropyridine calcium channel blocker (CCB), nisoldipine, and an angiotensin-converting enzyme (ACE) inhibitor, enalapril, would have equivalent effects on the rate at which diabetic complications progressed.[7]

A total of 950 subjects with diabetes, both normotensive (n=480) and hypertensive (n=470), were randomly assigned to moderate (target diastolic BP, 80–89 mm Hg) or intensive (target diastolic BP, 75 mm Hg) antihypertensive treatment, administered in a double-blind fashion. In the hypertensive cohort, patients were randomly assigned to either nisoldipine or enalapril as a primary antihypertensive medication. Nisoldipine was started at 10 mg with titration to 20, 40, or 60 mg/day as necessary, whereas enalapril treatment began at 5 mg/day with increases to 10, 20, or 40 mg/day, as needed. If study medication did not bring BP to goal, add-on therapy with open-label metoprolol or hydrochlorothiazide was permissible.

After 67 months, the Data and Safety Monitoring Committee observed a significantly higher CVD event rate in the hypertensive cohort being treated with nisoldipine; therein nisoldipine therapy was

terminated in the hypertensive cohort on July 14, 1997. The normotensive cohort still continued to receive treatment with nisoldipine, which in retrospect has proven important in understanding nisoldipine effects in diabetic patients since both treatments—enalapril and nisoldipine—were equally effective in reducing CVD events.[8] The enalapril treatment group had fewer CVD events than did the nisoldipine treatment cohort in both the intensive and moderate BP treatment groups (*25* fatal/nonfatal MIs for nisoldipine vs. *5* for enalapril). These data led to a computed unadjusted-risk ratio of 5.5 (95% confidence interval [CI], 2.1–14.6) and an adjusted risk ratio of 7.0 (95% CI, 2.3–21.4) for the combined end point of fatal and nonfatal MIs (nisoldipine:enalapril).

Because more than 50% of the subjects were not taking the original study medication by the end of the study, an additional analysis, according to actual drug exposure, was performed. This yielded a continued significant difference in the rate of MIs between nisoldipine- and enalapril-treated patients. These findings suggest that patients taking nisoldipine were more apt to experience an MI and to do so earlier than enalapril-treated patients. Because of the gravity of these findings at the time, those patients in the hypertensive cohort randomized to nisoldipine were reassigned to treatment with enalapril.

Lesson

Do not prematurely report study results, particularly if the result is not prespecified* a priori *as an end point. The results of the ABCD trial require careful interpretation. The decisions to prematurely stop the study and to report a *secondary end point* only in the hypertensive subgroup are open to criticism. At the time of this study report the treatment environment for the hypertensive diabetic was highly charged, which could have influenced the Data and Safety Monitoring Committee to act on an extreme result. This result was not prespecified *a priori* as an end point. Also, it was not subject to monitoring boundaries, which may have inflated the risk of a false-positive finding. Other confounding variables of this interim analysis included the fact that diuretic and β blocker add-on therapy were more common in the enalapril treatment group and study medication was discontinued more often in the nisoldipine treatment group. Because of these differences, overall CVD protection may have been tipped in favor of the enalapril-treated group.

The ABCD trial served to galvanize opinions for those inclined to the belief that CCB use carried a substantial CVD risk. Its findings provided significant momentum to the drive to relegate CCBs to a secondary position in the treatment of hypertension. This was particularly true when these findings were combined with the presumably negative findings of the Fosinopril vs. Amlodipine Cardiovascular Events Randomized Trial (FACET).[9] Unfortunately, as presented originally, the ABCD data were inaccurate. During the remaining year of the study, a private detective identified six additional nonfatal MIs, which were confirmed by the blinded end point committee. Thus, since the publication of the original report, the number of patients in the nisoldipine group with fatal or nonfatal MIs has increased from 25 to 27 and the number in the enalapril group has increased from five to nine. Hence, the unadjusted risk ratio is now 3.3 (95% CI, 1.5–7.1; p=0.029) rather than 5.5, and the adjusted risk ratio is now 4.2 (95% CI, 1.8—10.1; p=0.001) rather than 7.0.[10]

One can only speculate on the magnitude of the adverse consequences on CCB prescription use of this reporting error. As the issue has unfolded over the past 3 years a series of studies now suggest that CCB therapy is not deleterious *per se*,[11,12] an observation also supported by a recent overview of antihypertensive therapy.[13] This overview provided strong support for the benefits of ACE inhibitor and CCB therapy and weaker evidence of differences between treatment regimens based on different drug classes.[13] These more recent data support the original belief that the ABCD study could not determine if the differences between the rates of MI were because of a beneficial effect of enalapril or because the CCB was specifically harmful.

CONVINCE TRIAL

The Controlled Onset Verapamil Investigation of Cardiovascular End Points (CONVINCE) trial was an international clinical trial that compared outcomes in hypertensive patients randomized to initial treatment with either controlled-onset extended-release verapamil or the investigator's choice of either atenolol or hydrochlorothiazide.[14] This study was uniquely successful in achieving goal systolic and diastolic BP. At randomization, BP was <140/90 mm Hg in only 20.3% of the 16,602 subjects. After medication titration, with a transtelephonic computer that recommended an increase in the dose or number of antihypertensive medications whenever the BP was ≥140/90 mm Hg, 84.8% of the subjects attained the goal BP. During the 2 years of treatment, BP control was maintained in ≈70% of the subjects for a systolic BP <140 mm Hg and in ≈90% of the subjects for a diastolic BP <90 mm Hg.[15] These data, like those of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)[16] and Losartan Intervention For End Points (LIFE)[17] studies, suggest

that the control of systolic hypertension is more difficult than that of diastolic.

The CONVINCE trial was intended to provide insight into the influence of verapamil in a controlled-onset extended-release form on the incidence of fatal or nonfatal MIs, fatal or nonfatal stroke, or CVD-related death when compared to standard of care therapy employing either a diuretic or a β blocker. Since the verapamil form administered in this study was given at bedtime and had its major antihypertensive effect 6–12 hours after administration it was hoped that the question of how this particular form of verapamil influenced the time-wise pattern of end events might be answered.[18]

Lesson

It is imprudent, if not unethical, to prematurely terminate a clinical trial poised to answer an important clinical question, particularly if it is near completion.

There was considerable disappointment when the CONVINCE study was prematurely closed. This trial was completely enrolled and approximately 4 years into follow-up. Only a year of additional follow-up was necessary to collect the prespecified number of events required to reach statistically sound conclusions. A loss of power typically results from stopping a study short of its planned date of completion. It is poorly appreciated that the power of a study increases dramatically the longer the follow-up. Moreover, verapamil use will be adversely impacted by the decision to close this study prematurely. Verapamil use in hypertension has been held back for some time by a lack of outcome data, despite the favorable experience with its use in coronary heart disease. The absence of such data is the basis for its exclusion from the hypertension guidelines in most countries. This study was poised to answer the aforementioned question with some finality, which unfortunately will not come to pass.

Among other explanations, the site investigators were left with the impression by the study sponsor that the study was being closed for "business reasons." The Data and Safety Monitoring Board for this trial has not provided any reason for premature closure of the entire study. The early termination of the trial wasted valuable resources that had been allocated to this study. Patients were willing to assume risks in this study, no matter how trivial, and cancellation of a trial requires explanation for the patients as well as the treating physician. Patients as well as physicians must have been confused, based on the turn of events. Moreover, early cancellation of this trial should refocus thinking on how to best balance the risk-benefit ratio of patient participation in a clinical trial. The manner in which the investigator-patient relationship was terminated in this study will, no doubt, have implications for future randomized clinical trials. Future trials will require different assurances that funding will be available to complete a trial irrespective of shifts in business philosophy. Interestingly, some in industry, though not all, have suggested that the investigators in this study were being paid for their time, therefore, there would be little harm in closing the study early. The import of such a view, if it were to become more pervasive, should be obvious and could seriously jeopardize what in many cases are already fragile academic-industry relationships.

ALLHAT STUDY

ALLHAT studied high-risk hypertensive patients aged 55 years or older. ALLHAT was a large, simple trial, designed in a fashion to closely mimic clinical practice as it occurs in high-risk patients. Its goals were to determine whether the incidence of the *primary outcome*, a composite of fatal coronary heart disease and nonfatal MI, differed between treatment with a diuretic (chlorthalidone) (12.5–25.0 mg/day) and treatment with each of three other antihypertensive drugs—the CCB amlodipine, the ACE inhibitor lisinopril, and the α-adrenergic blocker doxazosin. *Secondary outcomes* included all-cause mortality, stroke, and all major CVD events. If patients did not meet the BP goal with the maximum tolerated dose of the initial medication, an open-label step 2 agent (atenolol, 25–100 mg/day; reserpine, 0.05–0.2 mg/day; or clonidine, 0.1–0.3 mg twice daily) or an open-label step 3 agent (hydralazine, 25–100 mg twice daily) could be added. In addition, a number of ALLHAT participants (n=10,337) participated in a randomized, open-label trial designed to determine whether lowering low-density lipoprotein cholesterol with pravastatin reduced all-cause mortality compared to a control group receiving usual care. Patient enrollment in ALLHAT began in February, 1994 and active follow-up concluded in March, 2002[19] with final study results to be released in December, 2002.

These data from the ALLHAT trial would have allowed doxazosin to have been directly compared, for the first time, to the gold standard for hypertensive therapy from an evidence-based medicine perspective[19]—that is, the thiazide-type diuretic.[20,21] There was considerable rationale for the inclusion of a peripheral α-adrenergic antagonist—such as doxazosin—as one of the treatment limbs of the ALLHAT study. Doxazosin, as well as other α-adrenergic antagonists, had previously been demonstrated to effectively reduce BP and to do so comparably to the BP reduction observed with hydrochlorothiazide.[22–24] In addition, these drugs had been well documented to favorably modify the insulin resistance and hyperlipidemia features of the hypertensive metabolic syndrome.[25–27] A number of these findings became apparent even as

the ALLHAT trial was in progress and simply supported the prior suppositions. Thus, it was anticipated that beyond its ability to reduce BP, doxazosin would confer additional CVD benefit as a consequence of its favorably effecting metabolic risk factors known to increase the risk of coronary artery disease.[28]

Thus, there was considerable surprise and maybe more so, disappointment, when the National Heart, Lung, and Blood Institute (NHLBI) announced that doxazosin was being withdrawn from the trial after an interim analysis of ALLHAT showed a 25% greater rate of a secondary end point, combined CVD in patients on doxazosin than in those on chlorthalidone, largely driven by congestive heart failure (CHF).[16] Also, there was no difference in the primary end point, fatal coronary heart disease or nonfatal MI, and calculations indicated that this was unlikely to change by the end of the trial. Following independent data reviews on January 6 and 21, 2000, the director of the NHLBI accepted a recommendation to discontinue the doxazosin treatment arm in the BP component of the trial. It was determined that participants assigned to the doxazosin group should be informed of their BP treatment assignment and that the major clinical findings regarding this treatment and its comparison agent, chlorthalidone, should be reported as soon as possible. The ALLHAT Data and Safety Monitoring Board specifically stressed the importance of continuing the rest of the BP and lipid-lowering trial.

Lesson

The discontinuation of the doxazosin treatment limb left open to speculation the role of doxazosin in the management of hypertension, either as first-step therapy or as add-on therapy and confused physicians as to the safety of its use in the treatment of symptoms of benign prostatic hyperplasia. The issue of what represents an adequate demonstration of safety of a compound has been raised by the ALLHAT study. In the future, hard end point studies may become an important, if not mandatory, requirement for a new compound to reach market. ALLHAT was not a placebo-controlled trial, but rather an active-controlled one, thus the study did not permit an assessment of whether doxazosin is better than placebo. ALLHAT was not exactly a simple drug-to-drug comparison of doxazosin to chlorthalidone since additional drugs were permitted *per protocol* as necessary to achieve goal BP. In this regard, 4 years into the study, 40% and 47% of the chlorthalidone and the doxazosin treatment groups were receiving step 2 and/or 3 medications, respectively. Furthermore, the use of doxazosin as part of a multidrug regimen for treating hypertension or benign prostatic hypertrophy was not *per se* tested in this trial and doxazosin should not be discontinued from such regimens based solely on the ALLHAT study results. Despite this, an admonition is necessary. Patients with recognizable CVD risk factors who happen to be treated with doxazosin should be carefully observed for any evidence of extra-cellular volume expansion and/or sympathetic activation as might be presumed by a persistent tachycardia. If either is observed, appropriate management steps should be taken, to include lowering/discontinuing the doxazosin dose, and/or correcting the volume-overload state with diuretics. Opinion is now fairly polarized relative to doxazosin. There is no good way to reconcile the differences of opinion concerning doxazosin use in the treatment of hypertension. A more complete understanding of the characteristics of those ALLHAT participants who developed CHF should assist in its ultimate therapeutic positioning.

Currently, the Joint National Committee recommendations include doxazosin as appropriate first-step therapy in certain patients when β blockers or diuretics are not advisable, in particular, for patients with dyslipidemia and with benign prostatic hypertrophy.[29] These recommendations, as well as those of The World Health Organization, the British Hypertension Society, the Canadian Medical Association, and the French Groupe de Travail may need to be revised to the effect that doxazosin, or for that matter all peripheral α-adrenergic antagonists, should no longer be considered for first-line antihypertensive therapy.[30] The final approach of the Food and Drug Administration (FDA) to these data will ultimately prove more problematic. Although labeling changes have been considered for doxazosin, no substantive change has occurred in the labeled recommendations for its use.[30] Moreover, this regulatory body has routinely accepted equivalent BP reduction as a suitable surrogate marker for comparability of different antihypertensive classes.[31] This position may need to be rethought when the final analyses of these interim ALLHAT findings become available. Equivalent BP reduction by different antihypertensive medication classes seemed an economically prudent way to bring new drug classes to market quickly and thereby expand treatment options for physicians. The ALLHAT data set would argue that hard end point trials—albeit more costly and time-consuming undertakings—may be required at an earlier stage of a compounds development, if not prior to regulatory approval.

HOPE STUDY

The HOPE study was a large, simple, factorial design, double-blind, placebo-controlled trial, which determined the risk of CVD events in more than 9500 patients.[32] The patients were studied in 267 centers in

19 countries. These patients were considered at high risk of future vascular death or morbidity by way of age, in that they were required to be older than 55 years of age or because they had either diabetes or evidence of a prior vascular event or existing vascular disease. Diabetics were required to have either known vascular disease or one other risk factor for CVD, such as cigarette smoking, a BP greater than 140/90 mm Hg, or elevated cholesterol (>5.2 mmol/L). Diabetics were included in this study because even without recognizable coronary artery disease they have about the same risk for coronary events as nondiabetic patients with established coronary disease.[33] Subjects also could not have CHF or an ejection fraction known to be below 40%.

Patients already receiving vitamin E or for whom an ACE inhibitor was indicated, such as those with left ventricular dysfunction, were specifically excluded from the study. The HOPE protocol included a run-in period for tolerance. During this period, all 10,576 initially eligible patients received a 2.5 mg dose of ramipril for 7–10 days; thereafter they received a matching placebo for 10–14 days. This approach was taken to identify those prone to early side effects and/or to identify those who experienced an exclusionary change in serum electrolytes or creatinine. Approximately 10% of the population, or 1035 patients, were excluded for these reasons. The remaining 9541 subjects were randomized to ramipril or placebo, beginning with a titration phase of 2.5 mg/day for 1 week, followed by 5 mg/day for 3 weeks, and thereafter patients received 10 mg/day until study completion. Follow-up was at 1 month and thereafter every 6 months. All patients received either vitamin E (400 IU) or matching placebo (40 IU)

The primary end point was defined as a combination of CVD death, nonfatal MI, and nonfatal stroke. The trial was stopped about 1-year early, after 4.5 years of treatment, on the advice of the Data and Safety Monitoring Committee, since the weight of the available evidence strongly supported a more favorable outcome in the ramipril-treated group. During the study period 17.8% of subjects in the placebo group reached the primary combined end point compared with 14% in the ramipril-treated group. This difference represented a 22% reduction in relative risk. The individual components of the composite end point were also significantly reduced by 32% for stroke, 26% for CVD death, and 20% for MI. Ramipril also reduced the risk of several other clinical end points, including CHF by 23% and revascularization procedures by 15%.

Lesson.

Early discontinuation of a study is critical if the findings can be applied to the benefit of a broad-base of patients who are similarly at risk. These HOPE study results show substantial benefits in mortality and morbidity from the use of ramipril in a large group of subjects at high risk of future CVD events. The results of the HOPE study were of sufficient significance to prompt the American Heart Association to include this study in its top-ten list of research advances for the year 1999. In addition, the FDA has allowed a labeling change for ramipril to incorporate the findings of the HOPE study. Thus, if the sentiments of either the FDA or the American Heart Association are reflective of the significance of the HOPE study then it seems prudent to have stopped this study early.

The results of the HOPE study were achieved on top of current conventional treatment and therefore broadly applicable to clinical practice. The implications for diabetic patients are particularly striking from this study. These results should extend the use of ACE inhibitors to a wider group of patients. ACE inhibitor therapy has previously been shown to be of proven benefit to those with left ventricular dysfunction, hypertension, or diabetes with proteinuria. ACE inhibitor use can now be extended to a different patient group, including those at risk for vascular events but without substantive evidence for left ventricular dysfunction many of whom are receiving aspirin prophylaxis. Finally, the HOPE study findings provide the factual underpinnings for conducting additional studies, employing differing pharmacologic approaches to interruption of the renin-aldosterone system in at-risk patients. Alternatively, the HOPE study was not designed to either determine whether ACE inhibitors are the optimal agents for preventing cardiovascular events in high-risk hypertensive patients or to determine whether these findings were a class effect for ACE inhibitors.[34]

CONCLUSION

Guidelines for early termination of a clinical trial should be established before any data review is undertaken. Interim data analyses in conjunction with the totality of available evidence provides the necessary framework from which Data and Safety Monitoring Boards can make informed and prudent recommendations. Controlled clinical trials should not be prematurely terminated for trivial reasons. Controlled clinical trials should not be terminated prematurely on economic grounds, particularly if the information to be gained adds substantially to the knowledge base on the therapy of disease states. Such, for example, is the case with the early stoppage of the CONVINCE trial, where the motives for its discontinuation were a presumed fiduciary responsibility to the stockholders since it was believed that its findings might not fall into the "blockbuster" category. Finally, continuation of a trial deemed to be futile is wasteful of resources and

potentially unethical. This is the case in the ALLHAT study, wherein there was early termination of the doxazosin treatment limb because of an unacceptably high rate of CHF when doxazosin-treated patients were compared to those receiving chlorthalidone. Similarly, there was an early termination of the amlodipine treatment limb of the AASK trial. When amlodipine treated patients were compared to those receiving the ACE inhibitor ramipril there was a sufficient difference in rate of decline of renal function in proteinuric subjects that the Data and Safety Monitoring Board felt that discontinuation of the amlodipine treatment limb to be warranted.

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