

Rationale and Design of the Avoiding Cardiovascular events through COMBination therapy in Patients LIving with Systolic Hypertension (ACCOMPLISH) Trial

The First Randomized Controlled Trial to Compare the Clinical Outcome Effects of First-Line Combination Therapies in Hypertension

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Reducing blood pressure (BP) to target levels is a major priority in preventing clinical events in hypertension. Typically this requires more than one drug, and recent guidelines on hypertension management therefore recommend starting with combination treatment in many patients. Diuretics have often been part of such therapy, usually paired with angiotensin converting enzyme (ACE) inhibitors or similar agents; but calcium channel blockers are also highly efficacious in reducing BP when combined with ACE inhibitors. In addition, these drug classes, separately and in combination, appear to have vasculoprotective properties. Because the primary goal of treating hypertension is to enhance survival and reduce cardiovascular outcomes, the Rationale and Design of Avoiding Cardiovascular events through COMBination therapy in Patients LIving with Systolic Hypertension (ACCOMPLISH) trial is designed as the first blinded and randomized study to prospectively compare the effects on these endpoints of two antihypertensive combinations, benazapril/hydrochlorothiazide (force titrated to 40/12.5 mg) and amlodipine besylate/benazapril (force titrated to 5/40 mg). The doses

can be further titrated to 40/25 mg or 10/40 mg, and other classes of drugs can be added as needed for optimal BP control. The primary study endpoint is a composite of cardiovascular mortality and morbidity. The study will be performed in hypertensive patients (systolic BP \geq 160 mm Hg or currently on antihypertensive therapy) with risk factors for cardiovascular events (prior events, target organ damage, kidney disease, or diabetes). A total of 6300 subjects will be randomized to each group with the expectation that a total of 1642 primary endpoints will occur during a 5-year period, providing 90% power to detect the 15% relative reduction in events ($\alpha = 0.05$) hypothesized to favor the amlodipine besylate/benazapril group. The ACCOMPLISH study will be performed in the United States and Europe. The first patient was randomized during 2003, and the trial should conclude in 2008. Am J Hypertens 2004;17:793-801 © 2004 American Journal of Hypertension, Ltd.

Key Words: Randomized controlled trial, hypertension, combination therapy.

There are two underlying principles in treating hypertension. The first is to reduce blood pressure (BP) to below the hypertensive range. The second is to choose antihypertensive drugs that, through

their effects on related concomitant risk factors, and perhaps by acting directly on vascular mechanisms intrinsic to hypertension, provide benefits that go beyond BP reduction.

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Considerations Regarding BP

There is strong evidence for a relationship between BP and the probability of cardiovascular events.^{1,2} Even differences in systolic BP as small as 2 mm Hg have meaningful effects on such outcomes as fatal strokes or coronary events.³ Recently cited data, however, indicate that only about one third of hypertensive individuals in the United States have their BP adequately controlled,⁴ despite evidence that aggressive BP treatment is associated with more effective prevention of major events.^{5–7}

Clinical trials have confirmed that successful treatment of hypertension will require combination therapy in a majority of patients.^{5–7} Clinicians have also come to recognize the benefits of combination treatment. Beyond producing greater efficacy, this approach allows adverse effects of drugs to be minimized by using relatively low doses of two agents in combination or by selecting drugs that can counteract each other's side effects.^{8,9} The use of fixed combinations may also be more convenient than taking two drugs separately, thus enhancing patient compliance with treatment and also providing more cost-effective treatment. Importantly, influential hypertension guidelines recently put out by such organizations as the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure,⁴ the International Society on Hypertension in Blacks,¹⁰ and the European Society of Hypertension¹¹ all recommend that combinations be used to initiate therapy in the large proportion of patients in whom single agents are unlikely to achieve needed BP targets.

Effects of Different Drug Types

Early clinical trials showed that active antihypertensive therapy was superior to placebo in reducing major clinical events. In general, more recent studies have shown similar outcomes when differing drug classes, both older and newer, are compared with each other.^{7,12–15} Meta-analysis of the large trials in general has not demonstrated major overall differences among the antihypertensive drug classes in their outcomes effects,¹⁶ although there might be differences when individual events such as stroke, renal endpoints, and heart failure are taken into account.^{7,12–19}

Experience With Combinations

Few if any of the major hypertension trials have depended on a single drug. Rather, to achieve adequate BP control in the treatment groups, additional drugs generally have been used, making it difficult to determine whether the original drugs being tested, as opposed to the regimens built around them, were responsible for the clinical effects. The most common combinations tested have used diuretics. Diuretics work well in com-

bination with such agents as angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, and β -blockers, because these drugs, as discussed elsewhere,²⁰ can prevent the countervailing effects of stimulation of the renin-angiotensin system that is commonly produced by diuretics. Because these types of combinations are effective in reducing BP they have become popular as fixed-dose products in clinical practice.

More recently, however, the combination of a calcium channel blocker and an ACE inhibitor has also become widely used. This type of combination is efficacious in reducing BP and is well tolerated.²⁰ Of equal importance, there is strong evidence both from clinical investigation and studies in animal models that ACE inhibitors^{21–23} and dihydropyridine calcium channel blockers^{24–26} each exhibit vasculoprotective effects. These findings may be partly explained by data showing that each of these drug classes has apparently beneficial actions on endothelial function.²⁷ Diuretics, on the other hand, despite their BP lowering properties, have not demonstrated similar vascular effects when given alone or in combination with an ACE inhibitor.^{28–30} Thus, the hypothesis that, for the same BP effects, an ACE inhibitor/calcium channel blocker combination might have cardiovascular advantages over an ACE inhibitor/diuretic combination, clearly has a credible basis.

In addition, observations in the canine coronary have shown that an ACE inhibitor and amlodipine each stimulate nitric oxide production; their combination, however, actually appears to produce a synergistic effect on this index of endothelial function, suggesting that this therapy could be beneficial in preventing or stabilizing atherosclerosis.³¹ In a recent clinical trial, single agent therapy with full doses of the ACE inhibitor benazepril and the calcium channel blocker amlodipine besylate each significantly reduced left ventricular muscle mass and increased arterial compliance; yet, when the two drugs were given in combination, at half doses, the effects on the heart and the vessels were significantly greater than with the monotherapies.³² This finding that the nonhemodynamic cardiovascular actions of these drugs might be additive suggests that this type of combination might be particularly beneficial in preventing major clinical events in hypertensive patients.

First Combination Comparison

For these reasons, there is considerable interest in comparing the clinical endpoint effects of this ACE inhibitor/calcium channel blocker combination (benazepril/amlodipine) with an ACE inhibitor/diuretic combination. If the newer combination produces greater cardiovascular benefits, it would obviously become a powerful tool for improving clinical outcomes in patients with hypertension.

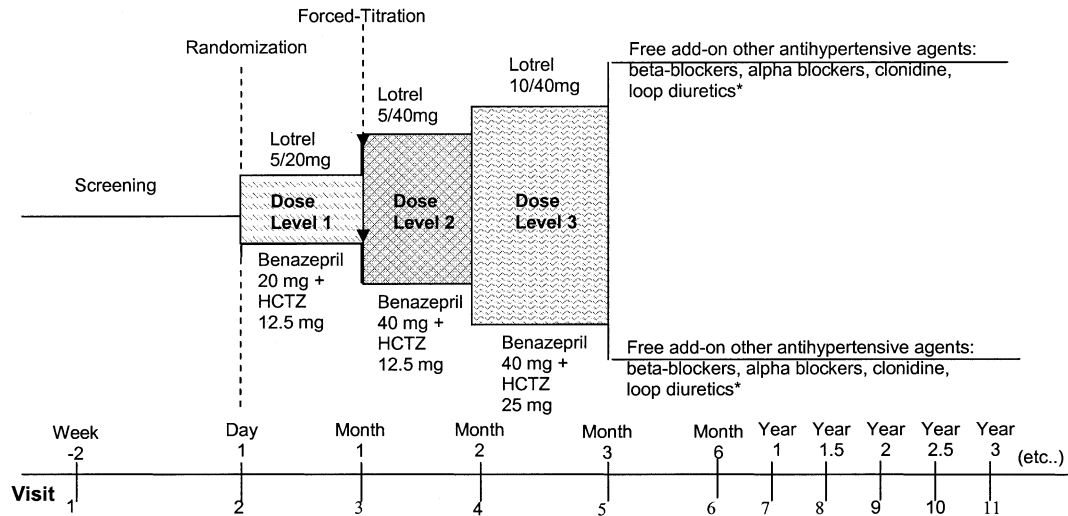


FIG. 1. Study design for the Avoiding Cardiovascular events through COMBination therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial. *Medication from study drug classes (including angiotensin-converting enzyme inhibitors, calcium channel blockers, thiazide, or thiazide-like diuretics) and specific inhibitors of the renin-angiotensin-aldosterone system (RAAS) (ie, angiotensin receptor blockers, aldosterone receptor blockers) are not allowed as add-on therapy.

This is the critical question that underlies the rationale and design of the Avoiding Cardiovascular events through COMBination therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial, which will be conducted primarily in the United States (9000 patients at 500 sites) as well as in Sweden (2400 patients at 120 sites) and other Nordic countries (1540 patients at 52 sites).

Objectives and Study Endpoints

Hypothesis Based on the clinical and preclinical evidence already discussed, the principal hypothesis of ACCOMPLISH is that therapy with a high-dose fixed combination of benazepril and amlodipine will be more efficacious than the combination of benazepril and hydrochlorothiazide in reducing cardiovascular morbidity and mortality in patients with high risk hypertension.

Objectives

To test the hypothesis, the primary objective of ACCOMPLISH is to measure the time to first event of a composite of cardiovascular morbidity and mortality during treatment with a fixed combination of benazepril and amlodipine as compared with the combination of benazepril and hydrochlorothiazide in hypertensive patients at high risk. The secondary objectives of the study are to compare the effects of the two combination therapies on composite cardiovascular morbidity, new onset diabetes, progression of renal disease, and hospitalization for congestive heart failure.

Specific Endpoints

The events comprising the outcomes listed in the objective are described below.

Primary Endpoint The primary endpoint is the time to first event of composite cardiovascular morbidity and mortality. Cardiovascular morbidity is defined as non-fatal, clinically evident acute myocardial infarction; nonfatal stroke; hospitalization for unstable angina; resuscitated sudden cardiac death; and coronary revascularization procedures. Cardiovascular mortality is defined as death due to sudden cardiac death, fatal myocardial infarction, fatal stroke, death due to coronary intervention, or death due to congestive heart failure or other cardiovascular causes.

Secondary Endpoints Secondary endpoints include composite cardiovascular morbidity (defined as for the primary endpoint), new onset diabetes, evidence of renal disease (doubling of serum creatinine or progression to end-stage renal disease as defined by a glomerular filtration rate of <15 mL or renal replacement therapy), and hospitalization for heart failure.

Other Endpoints Other endpoints include all-cause mortality, all hospitalizations, change in microalbuminuria or proteinuria, change in renal function (measured by glomerular filtration rate), presence of left ventricular hypertrophy (by electrocardiography), peripheral arterial revascularization procedure or nontraumatic amputation, and transient ischemic attacks.

Study Design

The ACCOMPLISH trial is a randomized, double blind trial that will compare the efficacy of the amlodipine besylate/benazepril combination with that of a benazepril/hydrochlorothiazide combination in preventing fatal and nonfatal cardiovascular outcomes. The study design is

Table 1. Cardiovascular Disease/Target Organ Damage

- One of the following three coronary artery disease events:¹
 - Prior myocardial infarction.
 - Hospitalization for unstable angina.
 - Coronary revascularization (coronary artery bypass graft or percutaneous coronary intervention). The above events should be appropriately documented by hospital records, angiographic reports, electrocardiogram (ECG), or other diagnostic tests.
- History of stroke, verified by persistent hemiparesis, magnetic resonance imaging, computed tomography, angiography, or appropriate hospital records.¹
- Peripheral arterial occlusive disease defined as: 1) previous non-traumatic leg amputation, limb bypass surgery, or percutaneous revascularization; 2) history of intermittent claudication with ankle:arm blood pressure ratio of ≤ 0.80 in at least one side; or 3) previous carotid endarterectomy.
- Diabetes defined as: 1) overnight fasting blood glucose concentration ≥ 7.0 mmol/L (≥ 126 mg/dL) (ADA criteria, 2 confirmatory values); 2) long-term treatment with oral hypoglycemic agent and/or insulin; or 3) a documented history of 2 h post-challenge glucose of ≥ 11.1 mmol/L (≥ 200 mg/dL) after oral glucose tolerance test (75 g glucose load).²
- Left ventricular hypertrophy (LVH) confirmed by central ECG laboratory reading (Sokolow and Lyon criteria or Cornell criteria).²
- One of the following renal events:²
 - Serum creatinine defined as >1.5 mg/dL or $133 \mu\text{mol/L}$ (women) and >1.7 mg/dL or $150 \mu\text{mol/L}$ (men).
 - Macroalbuminuria defined as albumin/creatinine ratio of >300 mg/g or >200 mg/g if patient is receiving an ACE inhibitor or aldosterone receptor blocker, on a spot urine collection, confirmed on 2 separate occasions at least 48 h apart.

¹ If appropriate documentation is unavailable, coronary artery disease events and stroke must be confirmed by the physician through a detailed patient interview and documented in the source documents.

² Diabetes (with exception of treated diabetes or documented history of elevated glucose on OGTT), LVH, and renal events must be documented with central laboratory reading/value during the screening phase.

shown in Fig. 1. After an initial screening visit, eligible patients will return 2 weeks later for randomization to their blinded treatment assignments. Patients who are not receiving treatment at the time of screening will remain without treatment until they commence their blinded medications immediately after randomization; those patients already receiving antihypertensive therapy will remain on their previous therapy until immediately switching to randomized study drugs at the time of randomization. Patients taking appropriate medications for concomitant conditions will continue those treatments throughout the study.

Patients eligible to enter the study will have their drug doses force titrated during the first 2 months of the trial to maximal ACE inhibitor levels: amlodipine besylate/benazapril 5/40 mg, and benazapril/hydrochlorothiazide 40/12.5 mg. Within the first 3 months, the doses can be increased to 10/40 mg or 40/25 mg, respectively, and other antihypertensive agents (excluding the drug classes involved in the primary treatments but including β -blockers, α -blockers, clonidine and, if needed, loop diuretics) may be added to reach BP targets ($<140/90$ mm Hg for most patients, and $<130/80$ mm Hg for patients with diabetes or renal insufficiency). Achieving BP parity between the two groups is desirable in this trial, and investigators will be strongly encouraged to reach target BP in all patients. After the initial 3-month period, patients will be seen again at 6 months after the start of study and thereafter at 6-month intervals until the end of the 3- to 5-year trial. Although most of the antihypertensive treatment adjustments will be made in the early part of the study, approved

additional drugs should be added if there is evidence at any time that BP remain above target levels.

Study Population

The patients to be enrolled in this study are hypertensive individuals at high risk. The broad definition of such patients is that they are ≥ 60 years of age, with a systolic BP ≥ 160 mm Hg or currently on antihypertensive therapy, and in addition have evidence of cardiovascular or renal disease or target organ damage. Men or women of any ethnic background are eligible to be enrolled.

Inclusion Criteria

Beyond the age and BP criteria already defined, patients must have evidence of at least one of the items listed in Table 1. In addition, patients aged 55 to 59 years are eligible if they have evidence of two or more of the cardiovascular diseases or target organ damage listed in Table 1.

Exclusion Criteria

Cardiovascular conditions that would prevent recruitment of a patient to the study include current evidence for angina pectoris (specifically, any symptom within 3 months before evaluation for study entry); a history of symptomatic heart failure or evidence of left ventricular ejection fraction $<40\%$; myocardial infarction, other acute coronary syndromes, or coronary revascularizations within 1 month of the first visit; stroke or other

ischemic cerebrovascular episodes within 3 months preceding study evaluation; or hypertension that is excessively severe, known to be refractory to treatment, or known to have a secondary cause. In addition, any other concomitant illness, physical impairment, or mental condition that could interfere with the effective conduct of the study during its likely duration would also serve as an exclusion criterion.

Statistical Considerations and Study Size

Power of the Study

Sample size is calculated with 90% power to detect a treatment difference of 15% risk reduction for the primary efficacy endpoint for the benazepril/amlodipine combination group compared with the benazepril/hydrochlorothiazide combination group at a two-sided overall significance level of 5%. An annual event rate of 3.5% for the primary efficacy endpoint is assumed for patients in the benazepril/hydrochlorothiazide combination group. Considerations for the performance of four equally spaced interim analyses and one final analysis using O'Brien-Fleming group-sequential methods are also made. To fulfill these assumptions, 1642 patients with primary efficacy endpoint are required for both treatment groups combined. To achieve this number of events and to allow for a lost-to-follow-up rate of less than 5%, a total of 12,600 patients (6300 in each treatment arm) are required to be enrolled during an 18-month recruitment period.

Statistical Analysis

For the primary efficacy endpoint, the primary analysis will be carried out using a log-rank test for the intent-to-treat population, which consists of all randomized patients. Cumulative event rates will be calculated using the Kaplan-Meier method. In addition, the point estimate and confidence interval for the risk ratio between the two treatment groups will be obtained from a univariate Cox regression analysis, which will include only treatment in the model. Similar to the primary efficacy endpoint, all secondary endpoints will be analyzed using log-rank test and the univariate Cox regression analysis. However, to preserve an overall type I error rate of 0.05% in the multiple test for the secondary endpoints, the significance testing will be carried out using Hochberg procedure.

Analysis of Subgroups

It is often of interest to learn whether potential differences in outcomes between treatments apply to all patient subgroups within the whole population studied, or whether such features as demographic differences, the presence or absence of concomitant conditions, the severity of prior

target organ damage, or the prestudy duration of antihypertensive therapy might be determinants of treatment results. For ACCOMPLISH, the predefined subgroups that will be considered include: age (<70 or \geq 70 years), gender, ethnicity, whether there was previous hypertension treatment, whether there was a previous diagnosis of diabetes mellitus, the presence or absence of a previous coronary event, or the presence or absence of target organ damage (including left ventricular hypertrophy and renal insufficiency or proteinuria). These subgroup divisions will be applied to the comparisons of the two treatment arms for the primary, secondary, and other study endpoints.

Additional Observations

Blood samples will be obtained for possible pharmacogenetic research protocols that could be done as a substudy to this trial. The details of such an observation, if it is to be performed, have not yet been established. In addition, biomarkers such as high sensitivity C-reactive protein and other measurements that might have predictive value for cardiovascular disease will be measured at baseline and during the study. Additional substudies and observations will include analysis of changes in electrocardiograms, ambulatory BP monitoring (ABPM), and proteinuria. The ABPM substudy will include 280 patients in each treatment group, providing sufficient power to detect BP differences if they exist and excluding them if they do not. Other prespecified BP analyses will include questions about 1) time to control and 2) 24-hour BP profile.

A total of 1200 patients will be included in the quality of life study, which will use two self-administered questionnaires: the Psychological Well-Being Index, and the Physical Symptoms Distress Scale. The substudy is sized to allow the detection of clinically significant differences in quality of life scores.

Determination of Endpoints

All primary endpoints in ACCOMPLISH will be adjudicated by an Endpoint Committee. The members of that committee will not be active investigators, nor will they be on the staff of the sponsor, Novartis Pharmaceuticals. The committee will be charged with establishing classifications and definitions of the endpoints that will be used in the adjudication, and they will provide an independent and blinded assessment of the efficacy endpoints as judged by the criteria that they have established. The decisions of the committee will be considered final and will become the basis for statistical analysis, publication, regulatory filings, and any other dissemination of study results.

Ethical Principles

The ACCOMPLISH trial will be carried out in accordance with the Declaration of Helsinki. All participat-

ing investigators will be required to obtain approval to conduct the trial from their local institutional review boards, and to carry out the research in accordance with good clinical practice as defined by the United States Food and Drug Administration. All patients will sign an approved informed consent. The safety and confidentiality of subjects participating in this trial will be paramount; and investigators, as well as individuals having responsibility for oversight of the study, will have full discretion to remove patients from the protocol if at any time such an action appears to be in the best clinical interest of such patients.

Responsibility for the scientific integrity of the study resides with the trial's Executive Committee (excluding those members employed by the sponsoring company). The database will be monitored by an external statistician who will have unrestricted access to the data and will report to the Executive Committee. In addition, the Executive Committee has resolved that the results of the Trial will be published regardless of what they might show.

Management of the Study

The overall responsibility for conducting the trial is vested in the Executive Committee, which is comprised of experts in the design, conduct, and analysis of large clinical trials with cardiovascular and renal endpoints. The Committee will be blinded to treatment assignments. Additionally, this committee will be responsible for selecting and administering substudies and ancillary studies, and will also take responsibility for publications arising from the trial.

A critical committee is the Data and Safety Monitoring Committee, which will be made up of experienced clinical trialists who are neither investigators in the study nor employees of the sponsor, Novartis Pharmaceuticals. This committee, which will not be blinded, will be responsible for monitoring the safety of patients in the study and for monitoring the relative efficacies of the two treatment groups in terms of the numbers of cardiovascular events and mortality. This committee will establish its own so-called "stopping rules" that govern whether it might recommend to the Executive Committee and the sponsor that the trial be discontinued prematurely because of a sharp therapeutic advantage to one treatment or the other. However, because each of the two treatment regimens planned for this trial are well established in terms of their safety and cardiovascular effects, it is considered to be unlikely that a difference in efficacy endpoints of sufficient magnitude to compel discontinuation of the trial will occur. In the event of a major safety or efficacy issue, the Chair of the Data and Safety Monitoring Committee will inform the Chairman of the Executive Committee, who in turn will assume responsibility for appropriate action.

A further committee is the Endpoint Committee, whose

function has already been defined and need not be discussed further here. Finally, there will be regular meetings of a Steering Committee, which will consist of representatives of each country participating in the trial and will be led by the Chairman of the Executive Committee. This Committee, like the Executive Committee, will be blinded to the study data but will provide advice concerning amendments to the protocol or other practical issues during the trial. It will also review the progress of recruitment; supervise and provide support and encouragement to individual investigators; and provide a further resource for reviewing possible substudies, publications, and other outside communications.

Discussion

The ACCOMPLISH trial is unique in being the first clinical outcomes trial in hypertension to compare two established forms of fixed-dosed combination therapy. This study is particularly timely, as the most recent clinical guidelines by the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7),⁴ International Society on Hypertension in Blacks (ISHIB),¹⁰ and the European Society of Hypertension¹¹ all now recommend starting treatment with drug combinations in patients whose hypertension is unlikely to be controlled by single agent therapy. In fact, the criterion for combination therapy recommended by JNC 7: in particular, a systolic BP of ≥ 160 mm Hg corresponds exactly to the BP entry criterion for ACCOMPLISH (other than for those patients already on therapy who will be switched immediately to study drugs).

There is one interesting difference among the recent guidelines regarding their recommendations for combination treatment. The JNC 7 guidelines suggests that a diuretic be part of the combination selected to start therapy, whereas the other guidelines are less prescriptive and encourage the selection of any logical two-drug combination for this purpose. In reality, though, there is currently no credible comparative outcomes evidence to support selecting one type of combination over another. Diuretics, used as first-line, full dose single agents, clearly have benefits in reducing endpoints in hypertension;^{7,16,35} but so also do calcium channel blockers.^{7,12–14,16} What is not known is whether diuretics and calcium channel blockers, when given in combination with ACE inhibitors, simply provide additive BP lowering properties or can add further protection against major clinical events. As discussed before, there may be some potentially beneficial interactions between ACE inhibitors and calcium channel blockers in their cardiovascular effects, but whether this translates into a measurable outcomes advantages will be known only at the conclusion of ACCOMPLISH.

The inclusion of an ACE inhibitor in each of the combinations being compared is risk hypertension. Many of the individuals satisfying the entry criteria for this trial will have conditions like diabetes mellitus or nephropathy; and many will have prior histories of cardiac events and strokes. For all such high risk patients, the published guidelines very properly give strong recommendations for the use of either ACE inhibitors or angiotensin receptor blockers.^{4,10,11} By including an ACE inhibitor in both arms of the study, ACCOMPLISH can enroll such individuals with the confidence that they are being cared for in a clinically proper and ethical fashion.

The two combination therapies will be force titrated to relatively high doses during the early part of the study, so it is expected that a large proportion of patients will have their BP reduced below the targets of 140/90 mm Hg (or 130/80 mm Hg for patients with diabetes or renal insufficiency) by the basic study therapies. If necessary, antihypertensive medications that are in different drug classes than those in the initial combinations can be added. For resistant hypertension, a loop diuretic will be permitted as a final step for volume control particularly in subjects with impaired renal function. Both treatment arms should have equal opportunities to have logical regimens that reduce BP similarly, thereby avoiding the inequalities in BP responses that can cause problems in interpreting outcomes in clinical trials.

Another strength of ACCOMPLISH is that all endpoints in the trial will be rigorously adjudicated by an Endpoints Committee of experienced trialists. Moreover, the end point data files will reside at Duke Clinical Research Institute and not with the trial sponsor. This should help avoid the types of controversies that can emerge when such careful steps are not taken³⁶ and give ACCOMPLISH data that are sufficiently robust to allow its scientifically and clinically important hypothesis to be carefully examined.

In conclusion, recent guidelines have strongly supported the use of combination treatment as first step therapy in stage 2 hypertension as a means to most effectively achieve BP control.⁴ However, there is currently no information on the relative effects on clinical outcomes of different types of drug combinations when used as first step therapies. The importance of ACCOMPLISH is that it will be the first study to compare the effects on cardiovascular morbidity and mortality of two ACE inhibitor-based antihypertensive drug combinations. This randomized controlled trial will test the hypothesis that the cardiovascular benefits of a dihydropyridine/ACE inhibitor combination (amlodipine besylate/benazapril) are greater than those of an ACE inhibitor/diuretic combination (benazapril/hydrochlorothiazide) in hypertensive patients at high risk. The study should be completed in 2008.

Appendix

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