

Working Group Report: Expert Panel on a Hypertension Treatment Trial Initiative
Meeting Summary
January 16, 2007

EXECUTIVE SUMMARY

A special ad hoc panel of scientific leaders in clinical hypertension research and clinical trials in cardiovascular diseases (CVD) was convened in Bethesda, Maryland, on January 16, 2007. The Institute asked the expert panel to:

- Critically examine relevant research developments since 2003;
- Decide whether they agree with the 2003 NHLBI Workshop recommendation¹ that the most important trial question is whether treating to a systolic blood pressure goal lower than the currently recommended goal will reduce cardiovascular (CVD) mortality and morbidity (“lower-goal trial”);
- If they agree, consider critical design features for such a trial;
- If they do not agree, decide on the highest priority alternative.

There was a strong consensus among the panel that the most important trial question is still whether treating to a systolic blood pressure lower than the currently recommended goal will reduce CVD mortality and morbidity. The design would involve 7,500 non-diabetic patients age 55 or older with systolic blood pressure (SBP) of 130-180 mmHg at baseline, and at least one other CVD risk factor, randomized to goals of <140 mmHg (“standard”) versus <120 mmHg (“lower”) SBP goals, and followed for a mean of 5 years. The CVD risk factors would include, but not be limited to, clinical coronary artery disease, peripheral arterial disease, and stage 3 chronic kidney disease. Alternative or complementary trial objectives were discussed and all had merit. The major alternative focused primarily on isolated systolic hypertension (ISH) below 160 mmHg (Stage 1 ISH). One of the attractions of this trial was the relative paucity of trial evidence on the effectiveness of treating ISH below 160 mmHg. Neither the proposed lower-goal trial nor the ongoing NHLBI Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial will answer completely the ISH question. One difficulty in conducting an ISH trial is that many patients with ISH are already on antihypertensive therapy, and withdrawal of treatment to confirm that they have ISH would be difficult and would likely make recruitment challenging. The lower-goal trial was given the highest priority.

Several complementary objectives were considered as possibly being incorporated into a factorial design or added as a third arm to the lower-goal trial. One factorial question discussed was what is the best combination of drugs to use in treating hypertension to either the current standard goal or a new lower goal. This factorial design was one of the recommendations of the 2003 workshop. While this remains an important question, there was an overall conclusion that trials completed since 2003 and those currently underway may provide additional useful information about the best combination of drugs for treating hypertension (the “second drug” question). The group concurred with the view that a factorial design with several different required drug combinations and with a lower-goal objective might make answering the primary goals question more difficult. The protocol-specified need in such a factorial trial to use specific drug combinations might reduce the likelihood of attaining an adequate difference in mean blood pressure between the lower-goal and standard-goal groups.

¹ The National Heart, Lung, and Blood Institute Working Group on Future Directions in Hypertension Treatment Trials. Major Clinical Trials of Hypertension What Should be Done Next? Hypertension. 2005;46:1-6.

Another complementary objective discussed was a test of the efficacy of isosorbide dinitrate/hydralazine (IDH) as antihypertensive therapy. The rationale for the IDH approach was the additional benefit observed when IDH was added to guideline therapy for heart failure and the possibility that IDH might work by a different pathway (increased nitric oxide or reduced oxidative stress) than most other hypertensive agents. During the discussion it was noted that there is little to no experience with IDH therapy in hypertension trials, and its use may reduce the likelihood of attaining an adequate difference between the lower-goal and standard-goal groups. This issue may be addressed by raising the lower limit of the SBP inclusion criteria by 5-10 mmHg. There was some enthusiasm for exploring whether a lower-goal trial could incorporate drugs that work by less well-understood mechanisms, e.g. reduction of oxidative stress, with the caveat that only agents that had been used in hypertension trials and that would not jeopardize achieving the blood pressure goals would be considered for inclusion.

Another complementary objective discussed was the opportunity to test an intervention using omega-3 fatty acids – eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) – to reduce CVD event rates. Fish oil supplements contain EPA and DHA. The NHLBI and the NIH Office of Dietary Supplements Working Group Report (2004) on *Future Clinical Research Directions on Omega-3 Fatty Acids and Cardiovascular Disease* concluded that a definitive CVD events trial is needed. The recommended trial included both primary and secondary prevention populations. A trial of an omega-3 fatty acids (O3FA) intervention could be added as a factorial question to the lower-goal trial because the lower-goal trial would include both primary and secondary prevention populations, and the O3FA intervention would not have much effect on achieving the blood pressure goals. There was support for identifying for consideration other major questions similar to the proposed O3FA intervention that are ripe for a CVD events trial and could be factored into a lower-goal trial, as long as such a question would not greatly increase the cost of the trial and the intervention would not impact blood pressure.

There was extensive discussion of the lower-goal trial with regard to which patient populations and what secondary outcomes should be included. One important scientific gap that the lower-goal trial should address is the lack of current scientific information on whether a lower SBP goal would reduce cardiovascular events and slow the progression of kidney disease patients with stage 3 chronic kidney disease and less than moderate proteinuria (< 300 mg albumin/d). (There is strong evidence that targeting SPB in patients with higher levels of proteinuria, equivalent to spot urine albumin greater than 300 mg/g, should be lower than the usual goal of <140 mmHg, and that such treatment should include an ACE inhibitor). Although extra recruitment efforts would be needed to achieve the proposed goal of including 3500 patients with stage 3 non-diabetic chronic kidney disease (CKD), the group felt that it was feasible and desirable to include a CKD subgroup with estimated glomerular filtration rate (eGFR) between 30 and 59 ml/min, with subgroup analyses planned in advance for the CKD subgroup as a whole and separately for those with spot urine with an albumin-to-creatinine ratio less than or greater than 30 mg/g. A factorial design in the CKD subgroup to examine the benefits of initial therapy using an ACE inhibitor versus a diuretic would be of interest, but would likely complicate the study design for the main question. The group concluded that there should be further discussion between NHLBI and NIDDK about the possibility of including an adequate number of CKD patients. There was support for incorporating into the lower-goal trial as study endpoints both kidney events and measures of decline in renal function. Moderate or high-risk cardiovascular patients should be a requirement for the study, but a balance should be found between ensuring that patients have an elevated cardiovascular risk and avoiding too restrictive eligibility criteria, which would limit recruitment or reduce generalizability of trial results. Patients with treated and untreated ISH would comprise a large component of the patients in the lower-goal trial, and it was recommended that a pre-specified analysis of this group be conducted.

For the lower-goal trial, a number of different drug regimens were discussed, including the therapeutic strategy used in the ACCORD trial, an IDH strategy, and a strategy for using angiotensin converting enzyme inhibitors in all patients with stage 3 CKD. No specific drug regimen was recommended for use in the trial, although there was support for the ACCORD approach because it is consistent with JNC 7 recommendations and because this approach allows the withdrawal of medications in the standard goal group if the SBP becomes too low. Because of the epidemiological evidence and the magnitude of the problem of cognitive decline and dementia in the elderly population, there was substantial support for including quality measures of cognitive function. The hypothesis that the lower SBP goal would reduce the rate of cognitive impairment and new onset of structural white matter abnormalities could also be evaluated in the study.

In conclusion, there was a clear consensus that a hypertension trial comparing a lower SBP goal with a standard goal in patients without diabetes was the top priority. The lower-goal trial should include a substantial subgroup of CKD patients and appropriate kidney disease outcome measures. The panel also recommended that the eligibility criteria be broad, including patients with isolated systolic hypertension. Consideration should also be given to evaluating the effect of nitric oxide enhancing therapy if there is a feasible intervention that would not threaten the goal of achieving a substantial SBP delta between the two randomized groups. The panel also encouraged inclusion of measures of cognitive impairment and, if feasible, structural abnormalities of the central nervous system white matter. If the addition of an O3FA intervention as a factorial in a hypertension goals trial would not increase the cost of the trial substantially, then it deserves consideration because the O3FA intervention should not have a large effect on blood pressure, and the O3FA question has substantial public health and scientific importance.

INTRODUCTION

A special ad hoc panel of scientific leaders in the field of hypertension convened in Bethesda, Maryland, on January 16, 2007. The Institute asked the expert panel to:

- Critically examine relevant research developments since 2003;
- Decide whether they agree with the 2003 NHLBI Workshop recommendation that the most important trial question is whether treating to a systolic blood pressure (SBP) goal lower than the currently recommended will reduce cardiovascular (CVD) mortality and morbidity;
- If they agree, consider critical design features for such a trial; and
- If they do not agree, decide on the highest priority alternative.

Co-Chair Dr. Jackson Wright summarized the charge, which was to recommend a single hypertension trial that the NHLBI should initiate, based on the following four evaluation criteria:

1. Scientific importance of the research question
2. Potential impact on clinical practice and public health
3. Low likelihood of being addressed by industry without NIH involvement
4. Feasibility and timeliness of a clinical events trial

In a pre-meeting process, the co-chairs of the panel (Drs. Califf and Wright) with input from the other participants, developed an agenda of possible trial designs that should be considered and assigned presenters for the discussions. The agenda included the following:

- An overview by Dr. Fine of ongoing blood pressure clinical events trials
- A presentation by Dr. Cutler on a proposed lower versus standard SBP goal trial - Systolic PReSSure IIntervention Trial (SPRINT)
- A presentation by Dr. Levy on a proposed placebo-controlled trial in older patients with stage 1 hypertension
- Presentations addressing design issues for a SBP goals trial
 - Factorial designs comparing 2nd drugs in multi-drug regimens, by Drs. Cushman and Probstfield
 - Subtrial in chronic kidney disease (patient characteristics and trial outcomes), by Drs. Levey, Bakris and Toto
 - Factorial design: comparing isosorbide dinitrate/hydralazine to a dihydropyridine calcium channel blocker for prevention of CVD and heart failure, by Dr. Taylor
 - Factorial design: An omega-3 fatty acid intervention, by Dr. Appel
- Brief presentations by Drs. Oparil and Appel on other potential hypertension research topics

A number of scientific publications were provided to participants, including the 2003 NHLBI working group report, reviews providing summaries of completed trials, treatment of hypertension in chronic kidney disease, and the relationship of SBP to cognitive decline.

PRESENTATIONS

Overview of Recent and Ongoing Hypertension Trials

Dr. Fine briefly reviewed recently completed and ongoing hypertension trials that have CVD events as primary outcomes. Adequately powered clinical events trials will need to include at least several thousand patients and at least a few years of follow-up. Using clinicaltrials.gov, we identified over two hundred phase 3 clinical trials involving pre-hypertensive or hypertensive patients. The abstracts of these trials, and if necessary their websites or scientific publications, were reviewed in order to determine the principal scientific hypothesis, primary outcome measure, number and clinical characteristics of patients, and likely completion date of the study. The principal scientific hypotheses were compared to the goals of the proposed trials that were to be discussed during the meeting to determine if recently completed or ongoing studies had goals similar to the proposed trials. For the standard versus lower blood pressure goal trial, only one study with a similar goal was identified. This trial is the NHLBI Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, which involves three major hypotheses, one of which compares treatment to a SBP goal of 120 mmHg versus a goal of 140 mmHg, but the patient population is restricted to patients with type 2 diabetes. The trial results should be available in 2010. During the discussion of the ongoing trials, no goals trial was identified other than ACCORD.

Systolic Blood Pressure Intervention Trial (SPRINT): Lower vs. Standard SBP goal

Dr. Cutler reviewed the SPRINT initiative. This trial had been developed by NIH staff based on the recommendations of the 2003 workshop. A minimally modified version of the 3-page write-up previously presented to the NHLBI Board of Extramural Advisors and Advisory Council had been circulated to the expert panel. The presentation covered the background and rationale, objectives, proposed design, and how this proposal aligned with the evaluation criteria. Briefly,

the concept is driven by very consistent and massive data from observational epidemiology suggesting that a SBP below 115 mmHg is optimal, juxtaposed with limited, mostly positive randomized trial data that are, however, not conclusive as to benefit, especially in non-diabetic patients. It is further motivated by the incomplete evidence for the current SBP goal of <140 mmHg in most patient groups, and the slow progress in moving clinical practice to achieve that goal.

The design would involve 7,500 non-diabetic patients age 55+ with SBP of 130-180 mmHg at baseline and at least one other CVD risk factor, randomized to goals of <140 ("standard") versus <120 mmHg ("lower") SBP, and followed for a mean of 5 years. The trial would use drugs from a formulary added to first-step choices, generally a thiazide and/or angiotensin converting enzyme inhibitor (ACEI). This is the strategy used in the ACCORD trial. Either chlorthalidone or hydrochlorothiazide could be the initial thiazide used. The trial evidence is stronger for chlorthalidone but more physicians currently use hydrochlorothiazide. The primary endpoint would be a composite of non-fatal MI, non-fatal stroke, heart failure hospitalization, and CVD mortality. Overall, the sample size would provide 90% power to detect a 20% effect on this outcome based on a 2-sided alpha of 0.05, using ALLHAT as the primary source of event rates but making a 25% adjustment for downward secular trends. With a somewhat expanded primary endpoint, an over-sampled subgroup with stage 3 chronic kidney disease (CKD) (N=3,500) would provide 90% power for a 25% effect. The delta in SBP is assumed to be at least 10 mmHg between the lower-goal and standard-goal groups.

Discussion centered on issues of feasibility, the possibility of addressing the ISH question, the CKD subgroup, and the criteria for patient eligibility. The African American Study of Kidney Disease and Hypertension (AASK) provides evidence that a delta of at least 10 mmHg can be achieved between the standard goal and the lower-goal group. SPRINT would involve a substantial number of patients with treated ISH and some additional patients with untreated ISH because ISH is very common in the adult population over the age of 55. There was support for a recommendation for a pre-specified analysis of patients who meet the criteria for isolated systolic hypertension at the onset of the trial or prior to the start of hypertension therapy before the trial. While there was agreement that the CKD subgroup is an important aspect of SPRINT, there was a concern that the chronic kidney disease subgroup might not be large enough to have adequate power. A few study options were discussed to enhance the power of the CKD subgroup analyses. Since current guidelines for CKD patients recommend a systolic blood pressure goal of 130 mmHg, there was a discussion of whether institutional review boards would be concerned about the standard treatment goal of less than 140 mmHg for patients with stage 3 CKD and less than moderate proteinuria. There was agreement that it should be possible to convince institutional review boards that it is appropriate in the standard goal arm to have a treatment goal of less than 140 mmHg for all patients because of the limited available trial data in patients with and without stage 3 CKD.

Discussion also centered on criteria for patient eligibility. There was agreement that patients for the proposed trial should have moderate or high cardiovascular risk based on the traditional cardiovascular risk factors. There was a recommendation that patient eligibility criteria should be balanced between ensuring that patients have at least a moderate risk of cardiovascular disease, but not be too restrictive so that patient recruitment is difficult or that trial results would have limited generalizability. There was a recommendation, however, that there should not be a preference for patients with metabolic syndrome over patients with other cardiovascular risk factors, in part because the outcome of the ACCORD trial may alter the treatment of diabetes patients. Although SPRINT would not recruit patients with diabetes, it was noted that patients

with metabolic syndrome would be more likely than others to develop diabetes than other patients during the course of the trial.

ACCORD is expected to report results in 2010, about the time that SPRINT would be beginning to recruit patients. There was a discussion of whether the SPRINT trial should proceed if the results from the ACCORD trial found that the lower blood pressure goal was not superior to the standard goal in type 2 diabetes mellitus patients. The ACCORD trial excluded most patients with stage 3 chronic kidney disease. Regardless of the results of the ACCORD trial, there are reasons to proceed with the lower-goal trial in the patient population without diabetes, especially if a factorial design with omega-3 fatty acids or IDH/hydralazine were incorporated. The relationship between cognitive function, or other endpoints, and blood pressure might be different in the two patient groups.

With regard to other evaluation rating criteria, it was agreed that the pharmaceutical industry has not and would not be expected to undertake a BP goals trial using a formulary approach. The industry is likely to be more interested only if their patented agent was featured, as was done in the HOT trial, which failed to achieve the target BP deltas between arms. The public health impact of a positive trial would be expected to be very large, and the formulary approach would likely facilitate translation to practice. Finally, the reversibility of BP-related cardiovascular and renal damage in this range will remain unknown unless a trial of this kind is completed.

A Placebo-Control Trial in Older Patients with Stage 1 Hypertension

Dr. Levy presented a study directed at answering the question of whether treating stage 1 isolated systolic hypertension (ISH; SBP of 140 to 159 mmHg with diastolic pressure less than 90 mmHg) reduces CVD morbidity and mortality in patients over the age of 55. The patients in the trial would be at intermediate CVD risk based on multivariable risk assessment. This would be a primary prevention trial since patients with cardiovascular disease, including heart failure, would be excluded. Patients with diabetes or chronic kidney disease would be excluded. The blood pressure treatment goal in the lower-goal arm would be less than 130/90 mmHg. The initial treatment would be either chlorthalidone or a calcium channel blocker (CCB). The combined endpoint would be nonfatal myocardial infarction, hospitalization for heart failure, stroke or CVD death. The rationale for the trial is the high prevalence of ISH among adults over the age of 55 and the limited trial data for treating stage 1 ISH, although treatment has been widely recommended in guidelines, including the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC 7).

This trial concept was discussed. There was agreement that there are few trial data for this patient group, but that recruitment might be difficult because many patients who would be eligible for such a trial would already be treated for hypertension, and drug washout in order to accurately characterize baseline SBP is complex and presents feasibility issues. The sample size for the ISH trial might need to be larger than SPRINT because patients with stage 3 CKD or with cardiovascular disease would not be eligible for the ISH trial. There was greater support for the standard-goal versus the lower-goal trial than for the trial of stage 1 ISH, although an ISH trial was also seen as having merit. The difference between the primary focus of these two trials could be summarized as the question of where to start treatment compared to the question of what is the SBP goal of treatment.

Factorial Designs for 2nd Drugs

Dr. Cushman presented a possible two-by-two factorial design to address both the question of the lower versus standard goal and that of whether a CCB such as amlodipine or an angiotensin converting enzyme inhibitor (ACEI), such as ramipril or benazepril, is a better second drug. Two possible study designs were reviewed for the second drug. In the first design, the initial drug was chlorthalidone and the second drug was amlodipine or ramipril. The second alternative design would have a different class of drug as the initial drug. The initial drug could be either an ACEI or an angiotensin receptor blocker (ARB), and the second drug choice would be chlorthalidone compared to amlodipine.

There was a discussion whether the results from the ACCOMPLISH study, which is testing the amlodipine/benazepril combination (Lotrel®) compared to a combination of benazepril and hydrochlorothiazide, would reduce the importance of the second drug. During this discussion, it was noted that by the time a new lower-goal study was completed there would be a wider variety of generic antihypertensive medications. Whatever first drug and whatever two second drugs were chosen, one limitation of a factorial design that includes both a BP goal question and a second drug comparison is the problem of possible over-treatment of the standard BP goal group. The limitation results from the likely possibility that some patients – particularly in the standard goal group – will need only one drug to reach the BP goal. If the protocol mandated or too strongly encouraged the use of at least two drugs in the standard goal group, there may be an inadequate BP delta between the standard and lower-goal groups. In the ACCORD trial, which has lower and standard SBP goal groups similar to the SPRINT proposal, the protocol requires that if a standard goal patient has a SBP below 130-135 mmHg, the dose or number of medications could be reduced. Another limitation is that at least one major drug class would not be available for the intensive BP goal group, possibly impeding the ability to reach the lower goal in some participants. Overall, the panel concluded that although the second drug question was important, it was not as important as the goals question, and that the best second factorial intervention was one that would not compromise the objectives of the goals trial.

Subtrial in Chronic Kidney Disease (patient characteristics and trial outcomes)

Patients with estimated glomerular filtration rate (eGFR) of 30-59 ml/min per 1.73 m² have stage 3 CKD. Approximately four to five percent of the adult population has stage 3 CKD. These patients are at increased risk for developing kidney failure, and eGFR in this range is an independent risk factor for CVD. JNC 7 recommended a BP target of less than 130/80 mmHg in patients with CKD. This recommendation is primarily based on observational data from the long term follow-up of patients from the Modification of Diet in Renal Disease (MDRD) study (a study of non-diabetic CKD stage 3-4, measured GFR of 13-55 ml/min/1.73 m²). The results of the study suggested that the decline in kidney function in CKD and progression to kidney failure was slowed in the lower blood pressure group (target MAP <107 mmHg, equivalent to average blood pressure 125/75 mmHg). The benefit of therapy appeared greater in patients with higher levels of proteinuria. The AASK trial did not show an added benefit of a mean blood pressure of 128/78 versus a mean BP of 141/85 mmHg in African Americans with stage 3 CKD due to hypertension. AASK participants had lower average proteinuria than MDRD study participants. The 130 mmHg goal in patients with CKD was not based on trial data showing a reduction in CVD events, since the completed kidney trials were not large enough to examine cardiovascular events with substantial power.

The discussion of past studies concluded that there was a definite gap in the current scientific information on whether a lower BP goal would reduce both CVD events and slow the progression of kidney disease in patients with stage 3 CKD who had lower levels of proteinuria. Because of this gap, there was strong support for inclusion of a CKD subgroup with estimated GFR between 30 ml/min/1.73 m² and 59 ml/min/1.73 m² and spot albumin-to-creatinine ratio of 30 to 300 mg/g. Outcome measures for the CKD subgroup would include 1) progression of CKD, based on worsening of eGFR or albuminuria (criteria to be defined); and/or 2) onset of kidney failure. In addition, there was a suggestion that for all patients in the lower-goal trial, kidney disease outcome measures should be included: new onset CKD (estimated GFR less than 60 ml/min/1.73 m² or spot albumin-to-creatinine ratio greater than 30 mg/g). The CKD subgroup should be large enough so that there would be adequate power for the combination of kidney and CVD outcomes. The panelists had enthusiasm for including a substantial group of patients with CKD as a study subgroup in a lower-goal trial.

Possible Factorial Design: Isosorbide dinitrate/hydralazine

Dr. Taylor presented the concept of adding a test of the efficacy of isosorbide dinitrate/hydralazine (IDH) compared to a dihydropyridine CCB in a two-by-two factorial design to the lower-goal trial. The primary outcomes would be similar to the SPRINT proposal. An attraction of testing IDH therapy in hypertension is the possibility that IDH may reduce CVD morbidity by alternative or additional mechanisms that are not activated by most classes of antihypertensive drugs. Some of the support for this concept is based on the results of the African American Heart Failure Trial (A-HeFT), which added IDH therapy to current guideline therapy for stage III heart failure with systolic dysfunction. The large reduction of CVD adverse outcomes in this trial raises the possibility that IDH therapy was effective because of alternative mechanisms, i.e., nitric oxide enhancement or reduced oxidative stress. Ninety percent of the patients in the A-HeFT trial had a history of hypertension. The IDH factorial trial would test whether this therapy was more effective than a traditional antihypertensive regimen in patients without heart failure and in a multi-ethnic high-risk population. Potential substudies could include NO metabolism, oxidative stress, endothelial function, inflammatory markers, and genetic studies. Surrogate markers related to the proposed alternative mechanism, such as left ventricular mass, vascular reactivity and other biomarkers, might be included in the proposed study. Despite industry sponsorship of the A-HeFT study, it is very unlikely that industry will conduct this type of study. A factorial study would not only answer the BP goals question but would also allow assessment of another potentially effective therapy in hypertension and provide insights into therapeutic pathways that may prevent CVD or its progression.

During the discussion it was noted that trial data on BP-lowering efficacy and side effects of the IDH combination in hypertensive patients are limited, so a preliminary (phase 2) trial may be needed. There was concern that a mandated IDH therapy in the standard group may reduce the BP delta between the standard and the lower-goal groups unless individuals with SBP in the 130-135 mmHg range were excluded. Another possibility that was discussed was adding a third arm to the SPRINT study design, which would allow the comparison of the IDH combination to other drug combinations in achieving the lower blood pressure goal, although this would substantially increase the cost of a SPRINT-like trial. It was noted that some beta blockers probably enhance NO production. Overall, the group found merit in the IDH combination hypothesis, but gave the two-arm lower versus standard BP goals trial a higher priority.

Possible Factorial Design: Omega-3 Fatty Acids

Dr. Appel presented a proposal for adding an omega-3 fatty acid (O3FA) intervention to a BP goals trial. O3FAs are found in fish oils (eicosapentaenoic acid, EPA, and docosahexaenoic acid, DHA) and plant sources such as canola oil, walnuts, soybeans, and flaxseeds (alpha-linolenic acid, ALA). In 2004, the National Institutes of Health Office of Dietary Supplements and NHLBI sponsored a meeting leading to a *Working Group Report on Future Clinical Research Directions on Omega-3 Fatty Acids and Cardiovascular Disease*. The omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are contained in fish oil supplements. The previous Working Group recommended that a large simple trial of combined primary and secondary prevention of cardiovascular disease with three arms (fish oil, ALA, and placebo) be undertaken. The public health impact of the determination that fish oil supplements reduce cardiovascular events could be substantial. There is limited trial evidence and substantial epidemiological evidence supporting the hypothesis that O3FAs may reduce cardiovascular disease.

The discussion focused on the possibility of an O3FA intervention and not on the suggestion from the 2004 workshop that in addition to fish oil there should also be consideration given to an ALA intervention. There are more epidemiological studies of the relationship between fish consumption and cardiovascular disease than dietary ALA and cardiovascular disease. During the discussion, it was noted that a number of large phase 3 clinical trials of O3FAs in patients with moderate to high risk of cardiovascular diseases are currently underway. These include the ORIGIN trial (Outcome Reduction with Initial Glargine Intervention), AREDS2 (The Age-Related Eye Disease Study 2), and Alpha Omega Trial in the Netherlands. The latter two studies are funded in part by NHLBI. The consensus of the discussion was that inclusion of a O3FA intervention as a factorial in a hypertension goals trial deserved serious consideration because 1) the O3FA intervention should have either no effect or modest effects of approximately 2 mmHg on SBP; 2) the O3FA question has substantial public health and scientific importance; and 3) an O3FA intervention should not increase the cost of the trial substantially unless the addition of an O3FA factorial required an increase in sample size.

Cognitive Decline as a Secondary Outcome

Dr. Appel presented a brief synopsis of the scientific evidence on the relationship between BP level and cognitive decline. Several epidemiological studies have found a progressive relationship between BP and both greater levels of cognitive impairment and more white matter abnormalities. The latter are associated with dementia. There are a few hypertension intervention trials with cognitive impairment or white matter abnormalities as a secondary outcome measure. The results of these completed trials are not definitive. However, the importance of the question is extremely high in terms of the potential public health impact because the prevalence of cognitive impairment is high among the elderly population, and nearly all of the elderly population has a SBP above 120 mmHg. The panel strongly supported the inclusion of accurate measurements of cognitive impairment in either a large subgroup or in all trial participants and, if possible, a structural secondary outcome of white matter abnormalities in a subgroup. Several issues to be considered in protocol development include lag period between onset of treatment and possible change in cognitive or structural outcomes, possible effect modifiers such as age and baseline level of cognitive function, and selection of methods to measure cognitive function and structural abnormalities. The inclusion of these endpoints is feasible based on experiences in the ACCORD trial and in NHLBI-funded epidemiological studies.

Trial of Hypertension Prevention

Dr. Oparil briefly summarized the rationale for a trial of hypertension prevention with the goal of preventing disease with vascular remodeling, endothelial dysfunction, unfavorable metabolic parameters and/or other intermediate endpoints/surrogates for vascular disease as outcomes rather than morbidity and mortality outcomes. To address some of the deficiencies of the recently published TROPHY trial, participants should be younger (young adults or even children) and have fewer concomitant risk factors/comorbidities. Designs could compare lifestyle modification to pharmacologic antihypertensive treatment; pharmacologic treatments that differ in their mechanisms of action, e.g. RAAS blockade versus diuretic or beta-blocker treatment; or complex regimens that include interventions directed toward risk factors other than hypertension, e.g., glucose lowering agents or statins. Duration of treatment and post-treatment follow-up should be longer than in TROPHY; extended post-treatment follow-up would be a great strength. Although the topic of hypertension prevention, as well as prevention of subclinical disease, is very important, the group did not rate this area of research as high as a lower treatment goals trial.

RECOMMENDATIONS

There was a clear consensus that a hypertension trial comparing a lower blood pressure goal with a standard goal in patients without diabetes was the top priority. The lower-goal trial should include a substantial subgroup of chronic kidney disease patients and appropriate kidney disease outcome measures. The panel also recommended that the eligibility criteria be broad, including patients with isolated systolic hypertension. Consideration should also be given to evaluating the effect of nitric oxide enhancing therapy if there is a feasible intervention that would not threaten the goal of achieving a substantial delta between the two blood pressure groups. The panel also encouraged inclusion of measures of cognitive impairment and, if feasible, structural abnormalities of the central nervous system white matter. If the addition of an O3FA intervention as a factorial in a hypertension goals trial would not increase the cost of the trial substantially, then it deserves consideration because the O3FA intervention should not have a large effect on blood pressure, and the O3FA question has substantial public health and scientific importance.

NATIONAL HEART, LUNG, AND BLOOD INSTITUTE
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January 16, 2007

AGENDA

7:45 – 8:15 a.m. – Continental Breakfast

8:15 a.m. - Welcome, Introductions, Housekeeping – Dr. Cutler & Dr. Fine

8:25 a.m. - Introduction and Charge (evaluation criteria) – Dr. Wright

8:30 a.m. - Ongoing Trials – Dr. Fine, all participants

8:45 a.m. - Low vs. Standard SBP goal (SPRINT) – Dr. Cutler

9:15 A.M. - Systolic Hypertension in the Elderly – Dr. Levy

9:45 a.m. - Factorial Designs for 2nd Drug Combinations – Dr. Probstfield & Dr. Cushman

BREAK

10:30 a.m. - Subtrial: CKD (eligibility issues, etc) – Dr. Levey & Dr. Bakris & Dr. Toto

11:00 a.m. - Factorial Design: Isosorbide Dinitrate/hydralazine – Dr. Taylor

11:30 a.m. - Factorial Design: Fish Oil – Dr. Appel
Secondary Outcome: Cognitive Decline

LUNCH

1:00 p.m. - Discussion of Priorities – Dr. Califf & Dr. Wright

2:00 p.m. - Key Issues Related to the Top Priority Event Trial² – All

2:30 p.m. - Trials at Younger Ages (non-events) – Dr. Oparil and Dr. Appel

2:50 p.m. - Concluding remarks/Follow-up – Dr. Califf & Dr. Wright

3:00 a.m. - Adjourn

² Nature of intervention/control/background treatments, number of arms/factorial or not, eligibility criteria for study population, primary outcome, sample size considerations, esp. magnitude of effect and event rates, secondary outcomes and ancillary studies (renal and cognitive)

Expert Panel on a Hypertension Treatment Trial Initiative - Roster January 16, 2007

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Duke Translational Medicine Institute

Jackson Wright, Jr., M.D., Ph.D., FACP (Co-Chair)

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University Hospitals Case Medical Center
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Lawrence Appel, M.D., MPH

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George Bakris, M.D.

Professor of Medicine
University of Chicago School of Medicine
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William Cushman, M.D.

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