EDITORIAL

Lessons from the ACCOMPLISH trial

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Clinical trials in cardiovascular medicine have become major foci for "evidence-based medicine". Yet it is not always clear that the results of the trials, which are often subject to bias introduced by restrictive selection criteria from heterogenous clinical populations, co-mingling of poorly documented mortalities with endpoints representing diverse disease mechanism and subjective interpretation, should be applied uniformly to clinical practice. The ACCOMPLISH (Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension) trial is instructive in this regard.

Study summary ACCOMPLISH was a parallel-arm, randomized, double-blinded study in 11,506 high-risk subjects (treated or stage 2 hypertension with other cardiovascular disease [CVD] risk factors, vascular disease or diabetes) to determine whether amlodipine was superior to a thiazide diuretic in reducing CVD events when either drug was combined with an angiotensin converting enzyme (ACE) inhibitor.[1] Both study arms achieved identical excellent treatment blood pressures (BPs) in the clinics (about 132/74 mmHg) and during 24-hour ambulatory BP monitoring (Jamerson, unpublished data). The study was terminated prematurely at 36 months because the global CVD event rate (myocardial infarction, stroke, coronary intervention, heart failure, and other fatal or non-fatal cardiovascular disease) diverged early and linearly throughout the trial and was about 20% lower (9.6% vs. 11.8%) in those who received amlodipine/benazapril compared to those who received hydrochlorothiazide/benazapril. The investigators concluded that combined ACE inhibitor-amlodipine therapy is superior to ACE inhibitor-thiazide therapy.

Unresolved background issues **Blood pressure thresholds** BP treatment thresholds have been decreasing for several decades.[2] Worldwide guidelines now recognize 140/90 mmHg as the standard threshold for treatment of "uncomplicated" hypertension but lower treatment thresholds are now recommended for people with other high-risk CVD conditions. JNC 7 (The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure) (2003) and current British-European guidelines (2007) both identify 130/80 mmHg as the treatment threshold for BP in the presence of high risk conditions such as diabetes and chronic kidney disease[2,3], with lower BPs for proteinuric renal disease (<125/75 mmHg)[2]. A recent scientific statement from the American Heart Association extended the 130/80 mmHg threshold to all forms of ischemic heart disease and recommended a lower threshold for heart failure (<120 systolic).[4] Nevertheless, whether the precept that "lower is better" applies in all clinical situations continues to be hotly debated. Epidemiological data demonstrate unequivocally that those with lower BPs live longer, healthier lives[5] but treatment benefits are not quite as clear. In "intention-to-treat" analyses such as those in the Hypertension Optimum Treatment Trial[6] or the African American Study of Kidney Disease (AASK)[7], subjects treated to thresholds below 130/80 mmHg did not fare much better in CVD or renal endpoints than those with BP at about 140/90 mmHg. In contrast, "per protocol" subgroup analyses have demonstrated that individuals who achieve and maintain the lowest BPs (<120/80 mmHg) have the greatest regression of coronary atheroma volume[8] and the lowest stroke recurrence rates.[9] At the extreme, some investigators believe that a "J-curve" exists, where excessive BP lowering actually increases CVD risk[10], although for all practical purposes, the J-curve phenomenon exists for diastolic, not systolic BP.

Response heterogeneity There is little published information regarding the wide diversity in the individual responses to antihypertensive drugs in clinical trials, a phenomenon that may affect outcomes as well. It seems likely that individuals who experience a vigorous BP response to a given drug are biologically different from

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those who respond sluggishly; these response patterns may be phenotypes or prognostic markers. Given the heterogeneity of participants in all trials, the principal "ITT" result is almost certainly shared unequally in different subgroups. Population heterogeneity has also necessitated the use of very large sample sizes to ensure statistical proof of concepts that are often empirically or mechanistically obvious and it is questionable whether current clinical trial methodology is sufficiently robust to yield important clinical information in a cost-effective manner. It also seems highly unlikely that current methods of genotyping will be helpful because most of the critical characteristics associated with hypertension (obesity, etc.) are acquired and modifiable, not predestined fixed traits. This is likely the reason why a durable, relevant "genetic footprint" of hypertension has not been found in animals or man.

Co-mingling of endpoints In order to increase event rates, it has become standard practice to mix endpoints representing different disease mechanisms in clinical trials. Total and CVD mortality are usually included, even in trial in which the death rate is low or not likely to add useful insight to trial interpretation. The most common practice is to include endpoints related to both hypertension and atheromatosis, most notably ischemic heart disease (IHD) rates, on the grounds that the issue is relevant to everyday medical decision-making. While this may indeed be so, it is also likely that additional confounding can occur in the attribution of trial results such that an erroneous impression of benefits of more stringent BP control can be confused with an effect "beyond BP."

Specific benefits of drug therapy Meta-analyses show quite clearly that the degree of BP lowering is more important than the type of drug for the prevention of premature mortality in hypertension.[11] Such a statement cannot be made for all people with hypertension, however, due to the presence of specific co-morbidities that necessitate the use of specific agents for "compelling indications"[2] For better or worse, the question of superior benefits of specific monotherapies continues to be investigated, in general a relatively meaningless question because combination therapy is needed for BP control. For that matter, all clinical trials have been multi-drug regimens chosen for commercial or socio-economic reasons, sometimes using treatment algorithms that are not considered to be best clinical practice.

Critique of ACCOMPLISH In light of the foregoing discussion, where does ACCOMPLISH fit in? First, it asked a clinically relevant question that yielded a conclusion that was surprising to some: that a calcium channel blocker could be superior to a diuretic in CVD outcome reduction. These results should cause appropriate consternation for the ALLHAT (Anti-hypertensive and Lipid-Lowering Heart Attack Trial) investigators, who concluded that thiazide diuretics should be used as first-line therapy in anyone with hypertension because of their "superiority" to amlodipine.[12] Such a disparity is not so surprising because ACCOMPLISH and ALLHAT differ in many important ways. Most obviously, the design and execution of ACCOMPLISH were superior. Instead of unwisely focusing on the choice of initial drug, the more sophisticated question of optimizing combination therapy was investigated. Despite clear evidence of the need for combination therapy well before the study was designed, ALLHAT paid virtually no attention to mechanisms of actions of the study drugs and the wisdom of the combinations that arose, especially inability to combine ACE inhibitor with diuretic as was already common practice. In ACCOMPLISH, it was possible to combine drugs with probable beneficial effects on cardiac, renal, and stroke outcomes. Why then was there a specific benefit of amlodipine? Most likely because of the specific characteristics of the population studied, the use of a co-mingled endpoint, and the interaction of the primary drugs with background therapy.

In all clinical trials, inclusion/exclusion criteria play a major role in determining the pattern of outcomes. The composite clinical endpoint of ACCOMPLISH, as is the case in most United States trials, was heavily weighted toward IHD and therefore to events co-dependent on hypertension and atherosclerosis. Rational combinations employed in the right doses yielded BPs well below those achieved in most trials (about 132/74 mmHg in the clinic in both groups, confirmed by 24-hour ambulatory monitoring). Central BPs (noninvasive assessment is possible by applanation tonometry – editorial note) were not measured in this study but it is highly unlikely that there were major differences between the two groups.

If each of the treatment arms was affected equally by the substantial BP reductions that occurred, it is logical to conclude that any additional benefit of amlodipine ("beyond BP") is most likely due to its well-known direct anti-ischemic actions in a population enriched by selection bias for coronary artery disease. Favorable interactions with background therapy likely played an additional role in the outcomes. The omnipresence of the ACE inhibitor would be expected to help preserve cardiac and renal function and the ability to add loop diuretics further lessened the chance for the development of overt heart failure. Of note, the incidence of heart failure hospitalizations was low in both groups; if ACCOMPLISH had been performed in a population enriched for heart failure risk or if the background drugs had been different, a different overall outcome may have been seen.

Future implications The ACCOMPLISH study may well have a significant effect on future

hypertension trials because it signals that hypertension treatment using an ACE inhibitor combined with a thiazide or a dihydropyridine can achieve a dramatic degree of BP lowering and a high control rate. The low CVD event rates in this study was a mild surprise in light of the risk profiles of the study subjects, so future trials may need to be larger and more expensive, raising serious questions about their potential value and affordability. The continued practice of co-mingling endpoints related to hypertension and atherogenesis must also be re-evaluated because both type 1 and type 2 error rates in future trials may be unacceptably high. It could also be argued that the standard is set and that for ethical and practical reasons, future hypertension trials should be performed against the ACE inhibitor-calcium channel blocker combination.

ACCOMPLISH may also have an effect on future medical practice and practice guideline development. One cannot easily dismiss the superior outcome with dihydropyridine/ACE inhibitor in the high-risk, obese, IHD-prone, sedentary US population tested. At the very least, dihydropyridine/ACE inhibitor should be considered to be an appropriate first-line therapy for anyone whose BP is >150/90 mmHg (>20/10 mmHg above the IHD target) who also has elevated cholesterol, diabetes, or a prior CVD event. But is it also true that the dihydropyridine/ACE inhibitor combination would be superior in a population at lesser risk for IHD, where stroke, heart failure, or chronic kidney disease are relatively more prevalent (e.g. the very elderly or Orientals)? Both dihydropyridines[13] and thiazide-type diuretics[14] are extremely effective in reducing the incidence of first cerebrovascular events and thiazide-type diuretics help reduce stroke recurrence[9]. Potential benefits of amlodipine in chronic kidney disease are less clear. In AASK[7], there are lingering questions of whether dihydropyridine monotherapy accelerates renal deterioration, although excellent systemic BP control and combination with an ACE inhibitor may negate any negative effects. Precisely the same argument can be made for heart failure, where it is clear that amlodipine-based therapy is inferior to thiazide-based therapy in preventing recurring heart failure events.[12]

Despite the apparent clarity of the ACCOMPLISH results in an "IHD population", each physician must assess the risk of other comorbidities in each patient before prescribing therapy. Hopefully, guideline committees will remember that application of the results of any trial to the broader population is subject to many limitations, especially the biases created by population selection and trial design. It will never be appropriate to extrapolate confounded results of any single trial to the treatment of diverse populations in whom other therapies may be more beneficial.

REFERENCES

1 Jamerson K, Weber MA, Bakris GL, et al. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. N Engl J Med. 2008; 359: 2417-2428.

2 Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. JAMA. 2003; 289: 2560-2572.

3 Cifkova R, Erdine S, Fagard R, et al. Practice guidelines for primary care physicians: 2003 ESH/ESC hypertension guidelines. [See comment]. J Hypertens. 2003; 21: 1779-1786.

4 Rosendorff C, Black HR, Cannon CP, et al. Treatment of hypertension in the prevention and management of ischemic heart disease: a scientific statement from the American Heart Association Council for High Blood Pressure Research and the Councils on Clinical Cardiology and Epidemiology and Prevention. Circulation. 2007; 115: 2761-2788.

5 Lewington S, Clarke R, Qizilbash N, et al. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet. 2002; 360: 1903-1913.

6 Hansson L, Zanchetti A, Carruthers SG, et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomized trial. Lancet. 1998; 351: 1755-1762.

7 Wright JT, Jr., Bakris G, Greene T, et al. Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: results from the AASK trial. JAMA. 2002; 288: 2421-2431.

8 Nissen SE, Tuzcu EM, Libby P, et al. Effect of antihypertensive agents on cardiovascular events in patients with coronary disease and normal blood pressure: the CAMELOT study: a randomized controlled trial. JAMA. 2004; 292: 2217-2225.

9 Arima H, Chalmers J, Woodward M, et al. Lower target blood pressures are safe and effective for the prevention of recurrent stroke: the PROGRESS trial. J Hypertens. 2006; 24: 1201-1208.

10 Cruickshank J, Cruickshank J. The J-curve in hypertension. Curr Cardiol Rep. 2003; 5: 441-452.

11 Turnbull F, Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomised trials. Lancet. 2003; 362: 1527-1535.

12 ALLHAT Officers, Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). JAMA. 2002; 288: 2981-2997.

13 Staessen JA, Fagard R, Thijs L, et al. Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. The Systolic Hypertension in Europe (Syst-Eur) Trial Investigators. Lancet. 1997; 350: 757-764.

14 SHEP-Cooperative-Research-Group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension: final results of the systolic hypertension in the elderly program (SHEP). JAMA. 1991; 265: 3255-3264.