Nephrol Dial Transplant (2008) 1–3
doi: 10.1093/ndt/gfn455

NDT
Nephrology Dialysis Transplantation

Editorial Comment

The choice of antihypertensive therapy in patients with the metabolic syndrome—time to change recommendations?*

Karl F. Hilgers[1] and Johannes F. E. Mann[2]

[1]Department of Nephrology and Hypertension, University of Erlangen-Nürnberg and [2]Department of Medicine VI, Schwabing General Hospital, Ludwig-Maximilians-University of Munich, Germany

Keywords: ACE inhibitors; diabetes; hypertension; thiazides

Patients with hypertension and the metabolic syndrome have high risk of suffering from future cardiovascular and kidney disease. There are no large-scale, randomized trials to establish the antihypertensive drug of choice for this important group of patients, but several authors consider angiotensin converting enzyme inhibitors (ACEI) as preferable, calcium channel blockers as intermediate, and beta-blockers as well as thiazide diuretics as less well suited (see for example the latest guidelines of the European Society of Hypertension [1]). This notion is primarily based on the metabolic side effects of thiazides and beta-blockers that may increase blood lipids and glucose, relative to ACEI and CCB [2]. Beta-blockers also promote weight gain, and both thiazides and beta-blockers are associated with an increased incidence of diabetes, compared to CCB and ACEI [3].

Wright *et al*. [4] have recently published a subgroup analysis of the ALLHAT study that appears to challenge the notion that thiazides and/or beta-blockers are second-line antihypertensive therapy in people with the metabolic syndrome. These authors state that their 'findings fail to support the preference for calcium channel blockers, alpha-blockers, or angiotensin-converting enzyme inhibitors compared with thiazide-type diuretics in patients with the metabolic syndrome, despite their more favorable metabolic profiles' [4]. We will discuss this report in the context of the ongoing controversy over the interpretation of the results of ALLHAT [5,6,7].

The ALLHAT study [8] needs little introduction today: it was the largest trial ever performed in the field of hypertension to compare the cardiovascular outcomes of different antihypertensive medications, recruiting >40 000 patients. Four different regimens were compared: the thiazide diuretic chlorthalidone, the CCB amlodipine, the ACEI lisinopril and the alpha-adrenoceptor antagonist doxazosin were used as first-line antihypertensives. A beta-blocker or a sympatholytic agent could be added as second-line therapy if needed, and hydralazine as third-line therapy. The doxazosin arm was terminated early because of an excess of congestive heart failure. The primary endpoint, a composite of fatal coronary heart disease or nonfatal myocardial infarction, did not differ between chlorthalidone, lisinopril and amlodipine, respectively. However, several secondary endpoints (notably, congestive heart failure as defined in ALLHAT study) were better prevented by chlorthalidone than by the CCB or the ACEI. The analysis of secondary endpoints when there is no difference of the primary endpoint is questionable.

The interpretation of ALLHAT's findings was hampered by the fact that the chlorthalidone-based regimen lowered systolic blood pressure more than either the CCB-based or the ACEI-based regimen [8]. In other words, despite a highly significant reduction in blood pressure, the expected difference in cardiovascular outcome of ∼20% was not observed. Several authors have criticized other aspects of the ALLHAT trial, including the choice of drug combinations (unfavourable particularly for the ACEI group) [5], the lack of a true baseline blood pressure [7], the extensive crossover between randomized treatment arms and the assessment of endpoints [6]. Nevertheless, the ALLHAT trial has strongly influenced prescription patterns [9] and several current guidelines for antihypertensive treatment, including the US JNC 7 guidelines [10] that recommend thiazide diuretics as the only first-line antihypertensive therapy (unless compelling indications for other drugs are present).

Wright *et al*. [4] analysed metabolic and cardiovascular outcomes of the ALLHAT trial in patients stratified according to race (black versus non-black), and the presence or absence of the metabolic syndrome (defined as the presence of hypertension and two of the following: a glycaemic disorder, a body-mass index >30, a fasting triglyceride level of 150 mg/dl or above and HDL cholesterol levels

Correspondence and offprint requests to: Karl F. Hilgers, Nephrology Research Laboratory, Loschgestrasse, 891054 Erlangen, Germany. Tel: +49-9131/853-6214; Fax: +49-9131/853-5821; E-mail: karl.hilgers@uk-erlagen.de

*Wright JT Jr, Harris-Haywood S, Pressel S *et al.* Clinical outcomes by race in hypertensive patients with and without the metabolic syndrome: Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *Arch Intern Med* 2008; 168: 207–217.

<40 mg/dl in men or 50 mg/dl in women, respectively). Of note, patients with pre-existing type 2 diabetes were included in this analysis, in contrast to a recently published, related ALLHAT substudy [11].

Throughout the groups, chlorthalidone had the least favourable effects on blood glucose and cholesterol levels that were lower in the lisinopril, amlodipine and doxazosin than in the chlorthalidone arms [4]. These differences of metabolic effects were small but consistent. Similar to other subgroup analyses of the ALLHAT study [12], the large size of that trial may have impaired the collection of sufficient information: no data were included on waist circumference, HbA1c levels or LDL and HDL levels during the follow-up [4]. Even the meagre information used to define the metabolic syndrome at baseline was not available for an astounding 12% of the patients. These patients were thus excluded from the analysis. The most important metabolic outcome, the new occurrence of type 2 diabetes, is not mentioned in the report by Wright *et al*. [4]. However, these data can be derived from the recent publication by Black and coworkers [11]: if the ALLHAT patients with the metabolic syndrome but without diabetes at baseline were analysed, type 2 diabetes developed in 17.1% on chlorthalidone, 16.0% on amlodipine and 12.6% on lisinopril ($P < 0.05$, lisinopril versus chlorthalidone). In patients without the metabolic syndrome, both the ACEI and the CCB lowered the incidence of type 2 diabetes significantly, compared to the thiazide [11].

Wright *et al*. [4] make very little of the metabolic derangements, but the ALLHAT trial indeed confirmed that the thiazide affected lipids and glycaemic control in an unfavourable manner, compared with the CCB and—particularly—the ACEI. The authors argue that the metabolic profile of the different drugs is largely irrelevant because the main cardiovascular outcomes were no better with CCB or ACEI, compared with the diuretic. In fact, some outcome measures (heart failure in particular) were better with chlorthalidone in all subgroups. In addition, patients in the non-thiazide arms of the study could not be treated with a diuretic; no wonder that fluid retention necessitating hospital admission occurred more frequently than in the chlorthalidone group. Black patients with the metabolic syndrome had an especially poor outcome with lisinopril, compared to chlorthalidone, with regard to almost every outcome measure. However, when these patients were randomized to lisinopril they also had a 3–5 mmHg higher systolic blood pressure throughout the trial, compared to the respective participants on chlorthalidone. Such a difference of blood pressure control will affect cardiovascular endpoints. Those differences in efficacy of antihypertensive monotherapies in Afro-Americans had to be expected, given previous trials [13].

One may accept the conclusion by Wright *et al*. [4] that ACEI should not be the first-line monotherapy for black patients with the metabolic syndrome, if only for the lack of a sufficient blood pressure lowering effect. Of note, this consideration does not apply to combinations of ACEI and diuretics that were not permitted in ALLHAT. However, should we accept their conclusion that the metabolic effects of the different drugs are irrelevant because they do not transmit to an effect on cardiovascular outcomes within the time frame of this study? This question is the crucial point in the interpretation of the data. We will focus on glycaemic control because the relatively small drug effects on total cholesterol cannot amount to much in the context of a trial in which even a 'professional' cholesterol-lowering agent, pravastatin, did not affect cardiovascular outcomes [14] (a 'knock-out' argument for small cholesterol changes; discussing the reasons for this surprising finding is beyond the scope of this editorial).

The ALLHAT trial had an average follow-up of 4.9 years. The idea that type 2 diabetes that occurs during the trial phase should transmit to cardiovascular endpoints within this time frame seems counterintuitive to clinicians. Wright *et al*. [4], anticipating this argument, cite a long-term follow-up study of the SHEP trial. In this study, Kostis *et al*. [15] reported that participants of the SHEP study who had developed diabetes while on treatment with chlorthalidone during the trial did not suffer from significantly increased cardiovascular death rates or total mortality during a mean follow-up of 14.3 years. At first glance, the latter results appear reassuring.

However, the report by Kostis *et al*. [15] does also provide some information on the time frame of cardiovascular death following a new diagnosis of type 2 diabetes, and these data do not support the argument of Wright *et al*. In the placebo cohort of the SHEP study, a new diagnosis of diabetes during the controlled trial did transmit to a higher rate of cardiovascular death. However, it took about 9 years of follow-up for this effect to become apparent [15]. In the active treatment, only a nonsignificant trend towards higher cardiovascular death rates was observed in patients who developed diabetes during the active trial phase. The fact that patients from the placebo group had substantially higher rates of cardiovascular death during the long-term follow-up, compared with active treatment, may explain the lack of significance. Moreover, one should be aware that the design of this retrospective follow-up study, based on death certificates of relatively few participants, has obvious limitations.

In summary, the ALLHAT trial confirmed the adverse metabolic effects of a thiazide diuretic, compared with CCB, ACEI and alpha-antagonists. The trial reminds us not to forget that lowering blood pressure to target levels is among the most important goals of antihypertensive therapy. Further, the results of Wright *et al*. urge caution for the use of ACEI as antihypertensive monotherapy in black patients with the metabolic syndrome. Unfortunately, the design of ALLHAT precludes any information on the potential of a thiazide/ACEI combination, a logical choice for these patients. The risk to develop type 2 diabetes was substantial in black as well as in non-black patients with the metabolic syndrome on chlorthalidone, and clearly lowered by lisinopril. We do not share the interpretation of Wright *et al*. that these metabolic effects can be dismissed as irrelevant because they did not affect cardiovascular outcomes during 5 years or less of follow-up. Rather, we hold that the financial savings associated with thiazides over ACEI—that are minimal in our country—would be bought dearly by an increased incidence of type 2 diabetes. Would it not be a joke of nature if long-term drug-induced type 2 diabetes would have no cardiovascular consequences? At least in non-black

patients, the recommendation to prefer ACEI over thiazide diuretics appears justified by the data and should not be changed.

Conflict of interest statement. HM and KFH have received grant support, advisory board and speakers fees from several pharmaceutical companies which market a wide range of antihypertensive drugs, including ACE inhibitors, ATI receptor antagonists, calcium channel blockers, and diuretics.

References

1. Mancia G, De Backer G, Dominiczak A *et al*. 2007 Guidelines for the Management of Arterial Hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens* 2007; 25: 1105–1187
2. Elliott WJ, Meyer PM. Incident diabetes in clinical trials of antihypertensive drugs: a network meta-analysis. *Lancet* 2007; 369: 201–207
3. Messerli FH, Grossman E, Leonetti G. Antihypertensive therapy and new onset diabetes. *J Hypertens* 2004; 22: 1845–1847
4. Wright JT Jr, Harris-Haywood S, Pressel S *et al*. Clinical outcomes by race in hypertensive patients with and without the metabolic syndrome: Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *Arch Intern Med* 2008; 168: 207–217
5. Hebert LA, Rovin BH, Hebert CJ. The design of ALLHAT may have biased the study's outcome in favor of the diuretic cohort. *Nat Clin Pract Nephrol* 2007; 3: 60–61
6. Messerli FH. ALLHAT, or the soft science of the secondary end point. *Ann Intern Med* 2003; 139: 777–780
7. Sleight P, Yusuf S. New evidence on the importance of the renin-angiotensin system in the treatment of higher-risk patients with hypertension. *J Hypertens* 2003; 21: 1599–1608
8. 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
9. Austin PC, Mamdani MM, Tu K *et al*. Changes in prescribing patterns following publication of the ALLHAT trial. *JAMA* 2004; 291: 44–45
10. 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
11. Black HR, Davis B, Barzilay J *et al*. Metabolic and clinical outcomes in nondiabetic individuals with the metabolic syndrome assigned to chlorthalidone, amlodipine, or lisinopril as initial treatment for hypertension: a report from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *Diabetes Care* 2008; 31: 353–360
12. Rahman M, Pressel S, Davis BR *et al*. Renal outcomes in high-risk hypertensive patients treated with an angiotensin-converting enzyme inhibitor or a calcium channel blocker vs a diuretic: a report from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *Arch Intern Med* 2005; 165: 936–946
13. Materson BJ, Reda DJ, Cushman WC *et al*. The Department of Veterans Affairs Cooperative Study Group on Antihypertensive Agents. Single-drug therapy for hypertension in men. A comparison of six antihypertensive agents with placebo. *N Engl J Med* 1993; 328: 914–921
14. Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin vs usual care: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT). *JAMA* 2002; 288: 2998–3007
15. Kostis JB, Wilson AC, Freudenberger RS *et al*. Long-term effect of diuretic-based therapy on fatal outcomes in subjects with isolated systolic hypertension with and without diabetes. *Am J Cardiol* 2005; 95: 29–35

Received for publication: 19.6.08
Accepted in revised form: 15.7.08