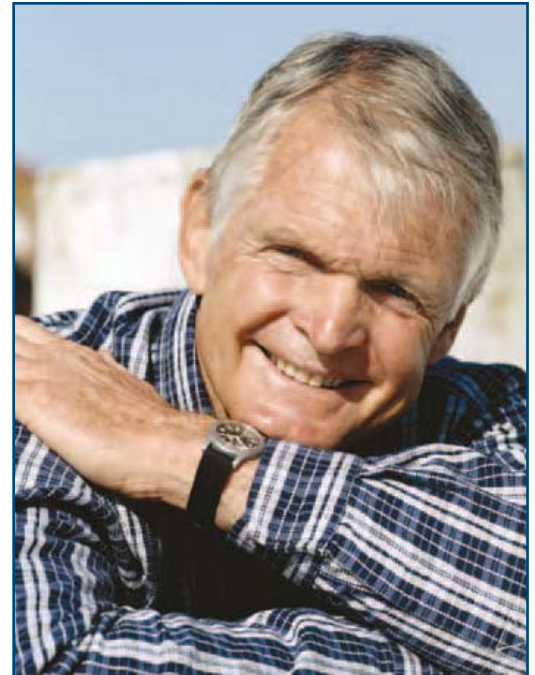


CardioCase

of the Month

Managing Hypertension Post-ALLHAT

By Norman R.C. Campbell, MD, FRCPC



CardioCase Presentation

Mr. J.H. is a 68-year-old patient who has seen you occasionally over the last 24 years. About six years ago, he had a small heart attack. His blood pressure (BP) has been high for several years, but he has never been interested in treatment and only comes to appointments when he is feeling ill. He is retired, a widower, and has financial troubles. He is a non-smoker, doesn't take any medication, and is sedentary without any interest in physical activity. He doesn't follow any particular diet and does not appear to want to change

that. He comes to you after having witnessed his brother suffer a disabling stroke. He was told the stroke could have been prevented if his brother was treated for his hypertension.

On examination, Mr. J.H.'s BP of 164/96 mmHg is similar to that obtained in the past. His pulse is 92 beats per minute and regular. His weight is 94 kg, and his body mass index is 33.4. The remainder of his examination is unremarkable. Laboratory tests are shown in Table 1.

What's Your CardioCase Diagnosis?

About the author ...

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Table 1

Laboratory tests

Test	Result
Complete blood count	Normal
Serum electrolysis and creatine	Normal
Urinalysis	Normal
Electrocardiogram	Old inferior MI/left ventricular hypertrophy
Fasting blood glucose	6.3 mmol/L borderline
Fasting total cholesterol	6.4 mmol/L
High-density lipoprotein cholesterol	0.95 mmol/L
Low-density lipoprotein cholesterol	4.62 mmol/L
Triglycerides	1.8 mmol/L

MI: myocardial infarction

What do the trials say?

The recent media results of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) suggested that diuretics were the best initial treatment for hypertension.¹ Unfortunately, there has never been a scientific meeting where one could learn the strengths and weaknesses of the study, and even local consultants seem unclear as to what the results of ALLHAT mean. Prior to ALLHAT, the Losartan Intervention for Endpoint reduction in hypertension (LIFE) study indicated that angiotensin receptor blockers were more effective than beta blockers for treatment of hypertension in the elderly with left ventricular (LV) hypertrophy.² Finally, the Canadian Hypertension Education Program (CHEP) has indicated that diuretics, angiotensin-converting enzyme (ACE) inhibitors, and long-acting calcium channel blockers are all reasonable first-line therapies in older patients, and beta blockers can be added to that list for younger patients.³ The CHEP recommendations are updated annually, but until the 2002 ver-

sion is released, they do not account for these newer clinical trials.

So the question remains, what are you going to do with Mr. J.H.?

What are the treatment options?

The management of hypertension advocated by CHEP is cost-effective, and in high-risk patients, combination antihypertensive therapy is not only cost-effective, but can also be cost-saving to the health-care system.⁴ Lost in the hype about the new clinical trials and the rhetoric about which drug is best, is the actual need to reduce morbidity and mortality through the treatment of hypertension. All the major classes of antihypertensive drugs are underutilised in clinical practice. Many

patients with hypertension are undiagnosed, and of those who are diagnosed, many are untreated or undertreated. A further concern is the changing social environment in Canada, which is predicted to result in increases in the incidence of hypertension and cardiovascular disease (CVD).

Mr. J.H. is a very high-risk patient. His social circumstances—prior myocardial infarction (MI), hypertension, dyslipidemia, glucose intolerance, obesity, non-adherence to therapy, and sedentary lifestyle—are all substantial risks. Current CVD risk calculations would markedly underestimate the risk, as they do not account for prior CVD, social circumstances, or lack of adherence, and most do not account for glucose intolerance, an all-important risk factor.

Mr. J.H. would markedly benefit from lifestyle change involving modest physical activity, healthy eating, and weight reduction. Informing him about these changes and determining if he is willing to consider them can work, but is a lengthy process. He needs risk reduction quickly and this means pharmacotherapy. Acetylsalicylic acid (ASA) once a day

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Table 2

Drug combinations

Column 1	Column 2
low-dose thiazide diuretic	beta blocker
long-acting dihydropyridine calcium channel blocker	ACE inhibitor angiotensin receptor blocker

For additive hypotensive effect in dual therapy, combine a drug from Column 1 with any from Column 2.*

*Avoid combinations of two drugs within a column unless there is specific indication (e.g., ACE inhibitor and beta blocker in patients following MI). In uncomplicated hypertension, when using triple or quadruple therapy, all potential antihypertensive combinations of first-line drug classes are effective except combining an ACE inhibitor with an angiotensin receptor blocker. This is currently not recommended in usual clinical practice.

ACE: angiotensin-converting enzyme
MI: myocardial infarction

reduces his cardiac risk by about 25% and lipid-lowering therapy is clearly indicated with a low-density lipoprotein cholesterol target of <2.5 mmol/L. Teaching about adherence is required and social work referral may be helpful.

In hypertension, notwithstanding results from the most recent trials, the message is clear that thiazides, like diuretics, ACE inhibitors, long-acting dihydropyridine calcium channel blockers, and angiotensin receptor blockers,



For a good move
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are very effective at reducing the cardiovascular complications associated with hypertension. Beta blockers are effective in those under age 60 and a large unpublished trial indicates that a non-dihydropyridine calcium channel blocker (chronovera) is effective in this population as well. The major issue with regard to optimally reducing CVD is to start with a proven initial drug and in many, if not in most patients, to proceed to rational drug combinations (Table 2) that are tolerated to achieve BP targets (Table 3).

A closer look at ALLHAT

ALLHAT was a very large trial that examined coronary event rates (fatal and nonfatal) in high-risk older hypertensive patients. Patients were randomised to receive a thiazide-like diuretic (chlorthalidone), an ACE inhibitor (lisinopril), a long-acting dihydropyridine calcium channel blocker (amlodipine), or a long-acting alpha blocker (doxazosin).⁵ All drugs were equivalent on the primary end point of the study and on total mortality, but there were substantial differences in outcomes on the secondary

Table 3

Blood pressure targets

Clinical settings	Blood pressure targets	
	Systolic BP (mmHg)	Diastolic BP (mmHg)
Hypertension (most cases)	< 140	< 90
Diabetes	< 130	< 80
Renal disease	< 130	< 80
Renal disease with proteinuria (> 1g/24 hours)	< 125	< 75

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end points. The doxazosin aspect of the trial was stopped early because of a high total CVD, congestive heart failure, and stroke event rate.⁵ Similarly, at the end of the trial, patients randomised to the ACE inhibitor had a higher total CVD, stroke, and congestive heart failure (CHF) event rate.¹ The long-acting dihydropyridine calcium channel blocker had a higher rate of CHF.¹ In interpreting the trial, it is important that these findings are understood relative to treatment with the diuretic, as all the drugs, with the exception of doxazosin, are proven to substantially prevent these events relative to no treatment.

There were other findings as well, such as a higher rate of diabetes in those treated with the diuretic, and a slower rate of decline in renal function in those treated with the calcium channel blocker.

The clear conclusion provided to the media is that the diuretic, chlorthalidone, is as good or better than the other treatments and it is conveniently very inexpensive. Unfortunately, there has been no opportunity for the strengths and weaknesses of ALLHAT to be discussed by clinical scientists and clinicians prior to the release of the results. The trial's strengths are its overwhelming size and the impartial conduct by academics and a branch of the American government (the National Heart, Lung, and Blood Institute).

Physician's Point-of-View

In my opinion, there is an unfortunate design weakness in ALLHAT that precludes the conclusion that diuretics are preferred initial therapy as compared to ACE inhibitors. The second-line therapy in ALLHAT was a beta blocker (clonidine or reserpine). The beta blocker can be combined with a diuretic, but is less

effective with an ACE inhibitor (Table 2). Because many patients required combination therapy in ALLHAT, the proper conclusion is that a diuretic/beta blocker antihypertensive regimen is better than an ACE inhibitor/beta blocker regimen. Those who use the CHEP summaries would have predicted that an ACE inhibitor/beta blocker regimen would have less antihypertensive effectiveness, result in higher drug doses, more side effects and more dropouts than a diuretic/beta blocker antihypertensive regimen—exactly what was seen in ALLHAT. It is not surprising that the combination of an ACE inhibitor and a beta blocker is less effective at preventing cardiovascular complications. In fact, such treatment has not been recommended for use by CHEP for several years.

A key message for clinicians is to use a rational antihypertensive regimen (Table 2) and one that is tolerable and achieves BP targets (Table 3).

A comparative study

An Australian trial also compared ACE inhibitor-based therapy to a diuretic-based therapy (ANBP2).⁶ The study found a reduction in the primary end point of cardiovascular events using the ACE inhibitor-based therapy.⁷ In a subgroup analysis, the benefits were restricted to males. The study allowed more rational second-line therapies following the initial randomisation.

So, which drug is best?

Whether a diuretic or an ACE inhibitor is superior at preventing cardiovascular events is still unanswered. Both are highly effective therapies, but the diuretic is

Combining an ACE inhibitor/beta blocker would have less antihypertensive effectiveness, result in higher drug doses, more side effects, and more dropouts than combining a diuretic/beta blocker.

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substantially less expensive. In any case, many patients require both and/or other antihypertensive therapies.

More recent trials have broadened our therapeutic arsenal. The Controlled Onset Verapamil Investigation of Cardiovascular Endpoints (CONVINCE) trial used a non-dihydropyridine calcium channel blocker-based therapy. The trial was stopped early for administrative reasons, but results showed similar outcomes to those with beta blocker/diuretic therapy. The LIFE trial showed angiotensin receptor blocker-based therapy was superior to a beta blocker-based treatment in older hypertensive patients with LV hypertrophy. The conclusions of both industry-sponsored and conducted trials were significantly weakened by designs that included beta blockers in the initial treatment of the older participants.

Back to the case...

Regarding Mr. J.H., what are you going to do? Post-ALLHAT, why not use the inexpensive, highly effective, low-dose thiazide diuretic?

I would start with hydrochlorothiazide, 12.5 mg, or a similar dose of hydrochlorothiazide in a potassium sparing combination. Realise that similar good (but higher patient costs) could be achieved with other drugs, as mentioned above. Monitor blood glucose and potassium. Hypokalemia reduces the protec-

tion provided by diuretic therapy and diabetes is a potential risk.

As expected, the BP-lowering effect of your first drug did not achieve target. If the BP were close to target, I would increase to hydrochlorothiazide, 25 mg. However, Mr. J.H. has a BP of 152/92 mmHg and, therefore, I would change to a combination tablet with an ACE inhibitor. I selected the ACE inhibitor based on the glucose intolerance, but a beta block-

Table 4

Frequent causes of drug resistant therapy


1. Non-adherence to therapy.
2. White-coat hypertension/white-coat effect.
3. Secondary hypertension.
4. Interfering drugs or lifestyle habits.
5. Inappropriate drug combinations/doses.

Can the ratio change the future?

The TC/HDL-C ratio is a **comprehensive lipid assessment** that encompasses the risk associated with both elevated LDL-C **and** reduced HDL-C.¹ It is a key treatment goal in current Canadian Cholesterol Treatment Guidelines.²


Are you treating to ratio? 

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er combination would be effective as well (Table 2).

Are three or four drugs necessary? You can add in a beta blocker and/or long-acting dihydropyridine calcium channel blocker, but remember to check factors that cause resistant hypertension (Table 4). Keep to once-a-day, long-acting medications. 

The opinions expressed in this case are those of the author and do not represent those of CHEP. The CHEP process incorporates the opinions of over thirty leading Canadian hypertension experts in a structured, evidence-based system and represents the most advanced disease management recommendations process. CHEP has considered the LIFE trial results and is postponing the 2002 hypertension recommendations to consider the ALLHAT trial results. As per CHEP policy, trials that are not yet published (*i.e.* ANBP2, ACCESS, SCOPE, and CONVINCED) are not considered. The author suggests you refer to the authoritative CHEP recommendations when they are released.

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