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UNIVERSITY OF TORONTO
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Scientific Update™

Simplifying the Management of Patients with Hypertension

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"There is overwhelming evidence that the vast majority of hypertensive patients around the world are not adequately controlled, employing even the loosest definition of adequate control."
John D. Swales, MD

Complexities in the management of patients with hypertension

In the United States, only 65% of hypertensive patients are aware of their condition, 49% are treated, and 21% have adequate blood pressure (BP) control.

High systolic and diastolic BPs predict cardiovascular (CV)-related deaths in every age group. Systolic BP increases with age, whereas diastolic BP increases until the fifth or sixth decade of life, then declines. In young hypertensive patients, diastolic BP tends to be disproportionately high, whereas, in the elderly, systolic BP is disproportionately high.

Isolated systolic hypertension doubles the risk of coronary artery disease (CAD). The SHEP study followed 4,700 patients with isolated systolic BPs ranging from 160-220 mm Hg for 4.5 years.[1] In this study, chlorthalidone reduced isolated systolic BP by a mean of 12 mm Hg. CV disease endpoints were reduced by 32%; stroke, by 36%.

From the 1960s to 1990s, the incidence of CV-related death and stroke has declined by 58% and 65%, respectively. Progress against CV disease was attributed to better recognition and management of hypertension. However, over the last decade, BP levels that define hypertension have been revised downwards and thresholds to treatment have been decreased. Target BP is lower than ever. There is now incontrovertible evidence that systolic BP is as important as diastolic BP and isolated systolic hypertension in the elderly is not a normal phenomenon.

Clinical challenges in the management of hypertension

Although awareness of hypertension in Europe has increased from 50% of patients in 1970 to 84% in 1990 and treatment has increased from 36-73% of patients, adequate BP control – defined as BP≤160/95 mm Hg – has only increased from 16-55%. Even more importantly, good BP control, defined as a treated BP of ≤140/90 mm Hg, is present in only 21% of all hypertensive patients in Europe. Multiple European surveys have recently confirmed that a high proportion of patients have inadequate BP control. This lack of control is not only true for clinically measured BP but home BP measurement and ambulatory BP recordings.

Mortality is linearly associated with BP for all values, suggesting that the "J-shaped curve" of higher mortality with lower BPs probably does not exist. Patients with a BP≥150/90 mm Hg have an estimated 10-year risk of CHD of 20% and should be treated with antihypertensive drugs.

Reasons for incomplete and inadequate treatment worldwide include: incomplete understanding of the links between the risk of CHD and high BP, confusion about the balancing of cost vs. benefit, uncertainty about the goals of antihypertensive therapy (the lower BP, the better), an incomplete appreciation that hypertension is a chronic ailment requiring life-long therapy, and the presence of

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adverse drug effects, which limit compliance in about 50% of patients in clinical practice.

Management of hypertensive patients in the year 2000: a clinical view

Meta-analysis of all randomized trials of antihypertensive therapies published before 1995 reveals a 38% reduction in stroke deaths and a 16% reduction in coronary heart disease (CHD) deaths in treated patients. However, some data suggests that U.K. guidelines for antihypertension therapy are not reliably followed by family physicians and that patient understanding of hypertension is generally poor, leading to average compliance rates of ≤50%. Half of hypertensive patients discontinue therapy after 6 months, regardless of the type of antihypertensive agent, e.g., diuretic, beta-blocker, calcium antagonist, or angiotensin-converting enzyme (ACE) inhibitor.

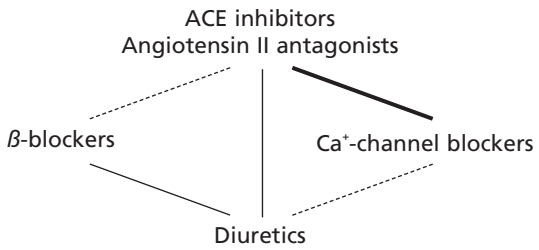
Despite relatively low rates of adverse effects in clinical trials, in clinical practice, most antihypertensive therapies are not well-tolerated by patients. For patients to take their antihypertensive medication, treatment regimens need to be simple, well-tolerated, effective, safe, and inexpensive (Figure 1). Angiotensin II (A-II) antagonists, which appear to be very well-tolerated, may improve compliance.

Angiotensin II antagonists: Impact on cardiac risk factors and outcomes

About 6% of all deaths worldwide are related to hypertension, whereas 12% are related to malnutrition, 6% to smoking, and a fraction of 1% to warfare.

Risk factors for cardiac death, such as hypertension, diabetes, and smoking, are multiplicative; therefore, the management of hypertension is even more crucial in the company of other risk factors. The presence of LVH, either on ECG or echocardiogram, doubles the risk of an adverse cardiac outcome in hypertensive patients.

Figure 1: Drug combinations in the treatment of hypertension.



Dashed lines indicate less useful combinations
Heavy line indicates very useful combinations

Adapted from Swales J

Even apparently minor reductions of 5-6 mm Hg in diastolic BP can reduce stroke deaths by 40%. Even greater reductions in morbidity and mortality may be achieved by larger overall reductions in BP with longer duration of therapy, especially in patients with evidence of end-organ damage, LVH, microalbuminuria, proven CAD, or elevated creatinine.

Angiotensin II is a potent functional and structural mediator of CV disease. The effects of angiotensin II can be blocked by renin inhibitors, ACE inhibitors, or the emerging class of A-II antagonists, which block the AT_1 receptor. Aldosterone antagonists block a small portion of the effector system.

AT_1 receptor activation mediates an increase in BP and proliferative response, whereas activating the AT_2 receptor, a less-understood process, mediates an antiproliferative effect.

Six different A-II antagonists or "sartans" are now available or under investigation. All act by blocking the AT_1 receptor, eliminating the effects of angiotensin II at the arterial wall. In humans, these agents have been shown to lower BP and are well-tolerated, although long-term morbidity and mortality data are not yet available.

In animal studies, A-II antagonists cause regression of left ventricular hypertrophy (LVH), prevent reinfarction in appropriate animal models, reduce mortality and heart failure, and slow diabetic nephropathy.

Only one large randomized study has reported morbidity and mortality data for A-II antagonists. The ELITE study randomized a large cohort of elderly patients with hypertension to Iosartan or captopril.[2] The primary endpoint was the time to increase in creatinine. This study found no difference between the two drugs on this primary endpoint, but side effects were less frequent with the A-II antagonist (12.2%) than the ACE inhibitor (20.8%). Death or hospitalization for heart failure occurred significantly less often in patients receiving the A-II antagonist than in the control group (9.4% vs. 13.2%, respectively). Overall mortality was reduced by 46%. Since death was not a prespecified endpoint for the study, this intriguing observation requires confirmation and will be subject to an even larger clinical trial called ELITE-II.

A novel angiotensin II antagonist simplifies antihypertensive therapy

Emerging data on a new A-II antagonist, eprosartan, indicate that this drug controls BP in once-daily dosing. In

double-blinded trials, adverse-effect rates were the same as placebo.

A-II antagonists are lipid-neutral, do not lead to insulin resistance, and are not associated with cough. In contrast, ACE inhibitors cause cough in 1-4.5% of patients and may lead to angioedema or bronchospasm, each of which are occasionally fatal, in about 1 in 6,000 patients.

In a recent comparative trial, the A-II antagonist eprosartan (up to 400 mg daily) and the ACE inhibitor enalapril (up to 20 mg daily) reduced BP to a similar extent. Both drugs had about a 60% efficacy.

In another study, patients who had complained of ACE inhibitor-related cough were washed out and randomized to receive eprosartan 600 mg daily, enalapril 20 mg daily, or placebo. Cough developed in about 20% of enalapril-treated patients, 4.4% of placebo-treated patients, but only 2.2% of eprosartan-treated patients.

In a third study, eprosartan (up to 600 mg daily) was compared to enalapril (up to 20 mg daily) in patients with diastolic BPs of 90-115 mm Hg. Blood pressure response was similar in both groups, however, at study endpoint, the response rate was significantly greater with eprosartan at 81.7%, compared with enalapril at 73.4% (p=.018). Cough was reported significantly more often with enalapril (5.4%) than with eprosartan (1.5%). A beneficial BP response lasted for all 26 weeks of study. In a subgroup analysis, eprosartan was equally effective in young vs. old patients, men vs. women, and African Americans vs. Caucasians.

The dose response curve for eprosartan tended to be linear between 50 mg daily, the minimum dosage associated with beneficial effects, and 800 mg daily.

The kidney as a window on the vasculature

Microalbuminuria is a precursor of overt renal disease in patients with diabetes or hypertension and a potent, independent risk factor for the development of CAD. In a sense, microalbuminuria reflects renal, endothelial, and vascular dysfunction. In both hypertensive and diabetic patients, microalbuminuria indicates the presence of vascular disease elsewhere in the body and powerfully predicts CAD death. In a study from Hammersmith Hospital, now in press, the odds ratio for CHD death when microalbuminuria was present was 7.7, compared to an odds ratio of 2.9 for hypercholesterolemia, 2.4 for hypertension, and 2.0 for smoking.

In these patients, AT_1-receptor activation of angiotensin II leads to renal hypertrophy and hyperplasia. Not all AT_1 receptor activation occurs via angiotensin I degradation to angiotensin II – a process blocked by ACE inhibition – but also by direct synthesis of angiotensin II from angiotensinogen or angiotensin I conversion to angiotensin II via non-ACE-mediated mechanisms.

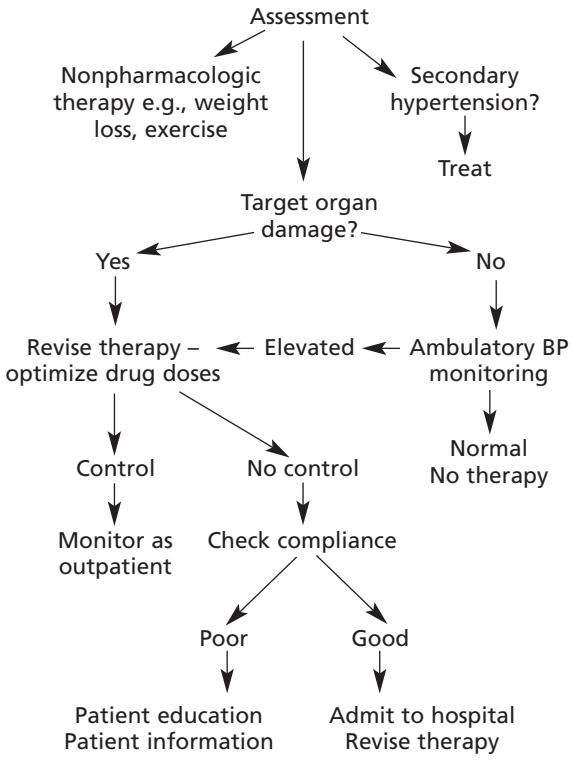
Direct AT_1 receptor antagonism would be expected to block the effects of angiotensin II more completely than ACE inhibition. In preliminary studies, eprosartan led to a 32% fall in albumin excretion as well as marked increases in renal blood flow, suggesting beneficial renal effects in hypertensive patients.

The role of angiotensin II antagonists in managing hypertension

Several factors are responsible for unsuccessful antihypertensive therapy. About 10-15% of patients have severe hypertension, due to secondary causes or difficult-to-treat hypertension. Figure 2 illustrates an approach to the management of these patients.

Drug interactions often curtail patient compliance, particularly the hypertensive effect of nonsteroidal anti-

Figure 2: Optimizing management of difficult-to-control hypertension



inflammatory drugs. In the U.K., 27% of elderly patients, on admission to hospital emergency rooms, are taking non-steroidal anti-inflammatory agents.

The inadequate or incomplete compliance of both medical professionals and patients limits attempts to reach target BPs. In multiple surveys, the threshold at which physicians begin to treat hypertension climbs as patients age, although the risk of CHD increases with age and mounting clinical evidence suggests that these thresholds ought to fall. Physicians need to treat elderly patients as aggressively as younger ones.

Physicians need to increase their awareness of patients' difficulties with compliance. In a small but interesting study from England, the vast majority of physicians were satisfied with antihypertensive therapy in a hypertension clinic, but only half of patients perceived themselves to be better and almost all of the patients' relatives perceived them to be worse. These results highlight another important aspect of compliance: the physician-patient relationship. Compliance could be improved by informing patients about hypertension, helping them better understand their illness and the need for treatment, and increasing patient satisfaction by close follow-up.

Conclusion

Despite decreases in mortality from cardiovascular diseases over the past 30 years, cardiac death continues to be the most common mode of death in western society. Likewise, progress in the understanding of the morbidity and mortality associated with hypertension and improvements in therapy have obscured the past performance of the medical community with respect to *managing* (as opposed to really *treating*) hypertension.

Reductions in mortality and morbidity (manifest as patient suffering) are possible with:

1) Careful assessment of blood pressure especially in patients at risk for coronary artery disease.
2) Recognition of the increased risk both of mild or only systolic BP elevation.
3) The crucial importance of patient education and monitoring of compliance with therapy.
4) Adequate doses of drugs with a clear-cut prior definition of goals of therapy.
5) Consideration of newer therapies which offer greater simplicity, fewer adverse effects, and possibly greater efficacy.

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2. Pitt B, Segal R, Martinez FA et al. Randomized trial of losartan versus captopril in patients over 65 with heart failure. *Lancet* 1994; 349(9054):747-52.