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## CURRENT CONCEPTS IN Hypertension

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## Editor's Comments

### MORE ALPHABET SOUP: HOT, CAPP, UKPDS AND ESRD

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This issue of Current Concepts continues the discussion of some of the clinical outcome trials in hypertension. The results of 3 newly completed and long-term studies have recently been reported. Professor Lennart Hansson provides a summary of the most important findings of the HOT trial, the largest antihypertensive study conducted to date. The clinical implication of the primary results as well as a tantalizing suggestion of further findings yet to be reported are summarized in this succinct article. Dr. Norman Kaplan contributes a critical assessment of HOT trial results as well as incisive comments about the recently completed UKPDS and CAPP studies in hypertensives with and without diabetes mellitus. These findings provide new information about the relative antihypertensive efficacy and cardiovascular disease benefits of angiotensin converting enzyme inhibitors and beta adrenergic blocking agents.

In addition to these discussions of recently completed studies, Drs. Wen-Ting Ouyang and Christopher Wilcox discuss the increasing problem of hypertension and end-stage renal disease. They provide information regarding our current understanding of the pathophysiology of this relationship as well as evidence in support of aggressive blood pressure reduction in such subjects.

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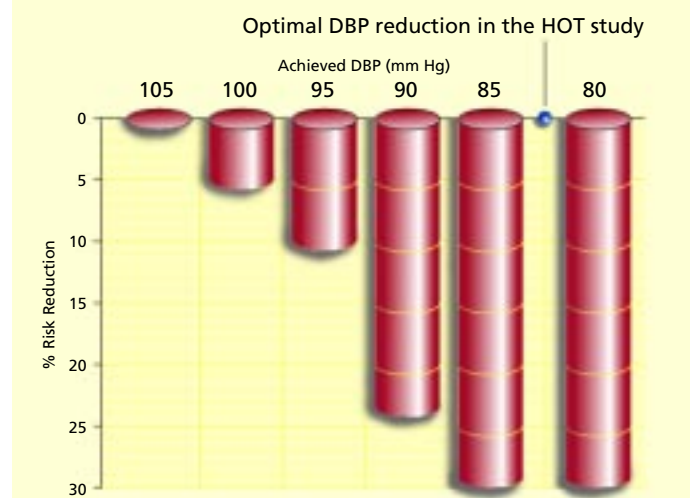
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The Hypertension Optimal Treatment (HOT) Study is the largest completed intervention trial in hypertension. Several lessons can be learned from the HOT Study, such as the optimal target blood pressure (BP) when treating hypertensive patients, the effect of treatment on risk reduction in hypertensive patients with diabetes, and the effects of intensive therapy on quality of life.

In the HOT Study 18,790 hypertensive patients aged 50 to 80, average 61.5 years, with a mean diastolic blood pressure (DBP) of 105 mm Hg were randomized to 1 of 3 target DBP groups:  $\leq 90$  mm Hg,  $\leq 85$  mm Hg, or  $\leq 80$  mm Hg. All were given felodipine as basic therapy with other agents according to a 5-step regimen. In addition, patients were randomized to receive aspirin (75 mg daily) or placebo.<sup>1</sup>

Major cardiovascular (CV) events (fatal and nonfatal stroke, myocardial infarction, and other CV mortality) declined in relation to the randomized target BP (272, 268, and 258 in the 3 groups, respectively). In relation to the achieved DBP the lowest incidence of all major CV events combined was found at 82.6 mm Hg (Fig. 1).

**Figure 1 Reduction of Major Cardiovascular Events in Relation to the Achieved Diastolic Blood Pressure**  
Fatal and nonfatal stroke and myocardial infarction plus other cardiovascular deaths



The optimal reduction in this risk was found at 82.6 mm Hg. Below this level no further significant benefit was observed. However, equally important, neither was there a significant increase in risk at least down to 70 mm Hg, an observation of obvious importance for the so called J-curve discussion.

In 1501 patients with noninsulin dependent diabetes (type 2) at baseline the benefits of effectively lowering BP were especially clear. This subgroup had an increased risk of major CV events of 2.5 times baseline, over and above the risk seen in patients with hypertension alone, which was attributable to diabetes. In patients randomized to the target of  $\leq 80$  mm Hg DBP the increased risk of having diabetes was reduced to 0.2 (essentially nullified).

The United Kingdom Prospective Diabetes Study (UKPDS) similarly showed, in 1148 hypertensive diabetic patients, that intensive

(“tight”) BP control reduced CV risk markedly compared to traditional BP control.<sup>2</sup>

Thus, both HOT and UKPDS strongly support the notion that intensive BP control is highly beneficial in hypertensive patients with type 2 diabetes. This view is reflected in the 1999 Hypertension Guidelines from the World Health Organization (WHO) and the International Society of Hypertension (ISH), which advocate a target BP  $<130$  mm Hg systolic and 85 mm Hg diastolic for type 2 diabetes.<sup>3</sup>

Another important clinical finding was observed in a substudy of HOT conducted in 610 patients in Canada, the United States, and the Scandinavian countries. In this substudy quality of life was shown to be significantly related to the achieved BP level, with the greatest improvement in well-being found in patients who reached a DBP  $<80$  mm Hg. This prompted the authors of this substudy to conclude “the lower the better”.<sup>4</sup>

A wealth of data remains to be analyzed from the HOT Study and its many substudies (e.g., the effects of intensive antihypertensive treatment on renal function, left ventricular hypertrophy, and 24-hour ambulatory BP levels). Results of such further analyses should be available soon. However, the implications are already clear. First, a target DBP of 80 to 85 mm Hg appears to best reduce the risk of major CV events. For systolic BP a target of 130 to 140 mm Hg was linked to optimal risk reduction. Second, in diabetic patients a target DBP of  $<80$  mm Hg virtually abolished the risk of having diabetes. Third, quality of life improved significantly in relationship to the level of achieved BP.

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Now that enough trials have been done to document the value of antihypertensive therapy in all save the very mild and very old, a plethora of trials are in progress and a few have been completed that examine the relative benefits of 1 drug against another. Thirty-six trials, mostly comparative, have been reviewed and will provide almost 1 million patient years of observation.<sup>1</sup> Two of these<sup>2,3</sup> have recently been published along with another, the United Kingdom Prospective Diabetes Study (UKPDS),<sup>4</sup> that did not make the list. To get ready for the deluge will take much attention to a lot of detail so a few thoughts about the 3 recently published trials may be helpful.

### The HOT Trial

As reviewed in this issue of *Current Concepts in Hypertension* by Lennart Hansson, the principal investigator for both the HOT and Captopril Prevention Project (CAPP) trials, the HOT trial was not a comparative trial but rather a massive attempt to determine the appropriate goal of therapy in almost 19,000 patients with fairly severe hypertension, all of whom were given a felodipine-based regimen. The best BP turned out to be 139/86 for mortality and 139/83 for overall morbidity. As he notes, the 1501 diabetics did even better the lower their BP and we want additional details about these impressive results.

Despite Dr. Hansson's disclaimer, the absence of a J-curve was really not totally proved, at least not by this observer's view of the data (in particular the bottom left curve of CV mortality at various levels of DBP). The HOT observations may not prove that a J-curve exists but it surely does not disprove it.

Be that as it may, the overall HOT data confirm two vital points. First, even fairly severe hypertension can be effectively treated if enough potent medications are given in a progressive manner. Second, the effort is clearly worthwhile. Mortality rates in HOT are well below those achieved in previous trials where lesser reductions of BP were achieved.

### The UKPDS Study

The value of more intensive treatment of the highly vulnerable diabetic hypertensive population, shown in HOT, was confirmed in the UKPDS trial with a different mix of medications. Diabetics given more intensive therapy and, thereby, lowering BP 10/5 mm Hg more, had a 36% reduction in major CV and diabetic complications.

The UKPDS study was begun in the late 1970s when, at least in the UK, the goal of more intensive therapy was to bring BP below 150/85 mm Hg. Today, even in the UK, a lower goal would certainly be sought but the investigators should not be faulted for not predicting the future when they devised their trial.

In retrospect, the UKPDS investigators also made a rather peculiar choice of drugs to compare (an angiotensin-converting enzyme inhibitor [ACEI] against a  $\beta$ -blocker). Although all subsequently recognized values of ACEIs in diabetics were not known in the late 1970s, many warned that  $\beta$ -blockers would likely not be an appropriate choice. As their data shows, however, their choices were correct. The patients treated with a beta-blocker had fewer events than did those started on an ACEI, although the difference was not statistically significant.

One more important point came from UKPDS. It takes a lot of antihypertensive therapy to effectively lower BP in diabetic hypertensives, even when the goal of therapy was, by today's standard, not very low. More than a third of the patients needed 3 or more drugs to achieve the average of 144/86 mm Hg. If, as both the Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of Hypertension (JNC VI)<sup>5</sup> and WHO/ISH<sup>6</sup> guidelines call for, the goal should be below 130/85 mm Hg, many drugs may be needed.

### The CAPP Trial

In this trial, half of the 10,985 hypertensives received captopril-based therapy; the other half were treated with a  $\beta$ -blocker. Unfortunately, those on captopril started (and maintained) a BP 2 mm Hg higher than those on the  $\beta$ -blocker. Moreover, captopril was given only once a day to about half of those assigned to the ACEI—a mistake that should have been obvious even 10 years ago when the study was started. Perhaps as a consequence of the higher starting BP and once-a-day regimen, the captopril half ended up having more strokes than those on  $\beta$ -blocker. Nonetheless, the 2 groups had an equal number of primary endpoints including myocardial infarction, stroke, and fewer of those on captopril developed diabetes. Moreover, among the 572 with pre-existing diabetes, the half on captopril generally did better than those on conventional therapy. CAPP, but not UKPDS, supports use of ACEIs as the best drug type for treating diabetic hypertensives. Perhaps the major message from all 3 trials in regard to diabetes is in line with the JNC VI and WHO/ISH recommendation of lowering BP more than the usual goal of 140/90. How low to lower BP remains uncertain. However, 130/80 seems appropriate until more data become available.

One additional issue deserves comment, at least in the mind of one of the JNC VI committee. In the introduction of the CAPP paper, the authors raised a straw man in an unnecessary attempt to justify their trial. JNC VI, it was said, did not recommend ACEIs as first-line treatment and no data have shown ACEI treatment protects against CV morbidity and mortality. As JNC VI clearly indicates, first-line treatment for many patients (except for the relatively small portion with uncomplicated hypertension) may include an ACEI. Three of the 4 compelling indications call for ACEIs as do many of the comorbid conditions. To justify the need for a trial such as CAPP, the investigators need not misrepresent the JNC VI recommendations.

### Conclusion

Despite these criticisms, all 3 of these trials provide important new information that should be incorporated into clinical practice. More such data from over 30 other trials now in progress will be forthcoming. Careful attention must be given to them all so we can best protect our hypertensive patients.

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The last few years have seen major advances in the understanding of the pathophysiology of hypertension in chronic renal insufficiency, the role of hypertension and other risk factors in the progression of chronic renal failure, and the definition of treatment strategies that limit the adverse consequences of hypertension in this patient population. These will be the focus of this review.

### Pathophysiology and Rational Basis for Therapy

As renal function declines, the incidence of hypertension rises. It exceeds 90% at the time of end stage renal disease (ESRD). The incidence rate for hypertension is higher in those with primary glomerular than tubulointerstitial diseases. A consequence of nephron loss is an impaired ability to excrete salt and water rapidly and efficiently during periods of increased intake. This underlies the finding that the degree of salt sensitivity in hypertensive patients with renal disease increases in direct proportion to the reduction in creatinine clearance. Consequently, measures to limit body salt by reducing dietary salt intake and increasing salt elimination by escalating dosages of diuretic therapy are necessary components of most treatment regimens.

Impaired regulation of peripheral blood vessels contributes to hypertension in chronic renal failure. Direct recording of peripheral sympathetic nerve activity in ESRD patients shows enhanced rates of neuron firing that are restored to normal in subjects with bilateral nephrectomy. This intriguing finding raises the possibility that the damaged kidney is the afferent site for a reflex drive to sympathetic tone in patients with ESRD.

Although plasma renin activity is usually within the normal range, it is typically inappropriately elevated for the state of extracellular fluid volume (ECFV) excess in most patients. It thereby contributes to the hypertensive syndrome. Circulating levels of endothelin increase in proportion to the severity of chronic renal failure. It is unclear whether this is an important determinant of peripheral vascular resistance.

The endothelium-derived relaxing factor (EDRF) or nitric oxide (NO) is released by the endothelium of healthy blood vessels in response to increased flow or agonist stimulation. NO not only combats vasoconstriction but also prevents hypertrophic, sclerotic, or thrombotic processes at the vessel wall. Therefore, it is a major defense mechanism against hypertension and its complications. The EDRF-NO pathway is defective in animals with hypertension and renal failure, and in the peripheral blood vessels of humans with hypertension and chronic renal insufficiency. This defect may be associated with generation of an endothelium-derived contracting factor. This factor likely represents the net effect of a group of mediators that include oxygen radicals and vasoconstrictor prostaglandins that combine to prevent the beneficial effects of NO on blood vessel physiology.

NO is generated from L-arginine by a family of enzymes termed nitric oxide synthases (NOSs). NOS is inhibited competitively by asymmetric dimethylarginine (ADMA). Both ADMA and its stereoisomer, symmetric dimethyl arginine (SDMA) inhibit L-arginine

uptake into target cells. Therefore, ADMA and SDMA may endogenously inhibit NOSs' activity. They are formed in normal subjects but their concentrations increase in the plasma of uremic subjects to a level that may be sufficient to impair L-arginine transport or NOSs' activity. Dimethylarginines' accumulation provides a direct link between renal insufficiency, endothelial dysfunction, vessel wall pathology, and hypertension. However, their clinical importance and effective means of combating accumulation in patients with chronic renal insufficiency await resolution.

Currently, rational strategies for treating hypertension in chronic renal insufficiency include measures to combat ECFV expansion (diuretics and salt-restricted diet), to counteract inappropriate renin-angiotensin-aldosterone system stimulation (ACEIs and angiotensin receptor blockers [ARBs]), methods to reduce sympathetic tone (central sympatholytic agents or peripheral adrenergic blocking drugs), or means to diminish calcium-activated vascular contraction (calcium antagonist [CAs]). All of these drugs effectively lower BP in selected patients with chronic renal insufficiency.

### Hypertension as a Risk Factor for Progression of Chronic Renal Failure

A special feature of chronic renal failure is its propensity for progression, even after the inciting cause has been corrected. Recent studies have defined two clinical parameters that are of major importance in defining the rate of progression of chronic renal insufficiency. First, proteinuria of greater than 1 to 3 gm/24 hr is associated with much higher rates of progression than less severe levels of proteinuric renal failure. Second, a mean arterial pressure of >90 mm Hg (corresponding to a BP of approximately 120/75 mm Hg) in a proteinuric patient is a predictor of rapid loss of renal function. Some forms of renal disease, such as diabetic nephropathy, predict a greater loss of renal function than others, such as those primarily affecting the tubulointerstitium. This may reflect, at least in part, the influences of heavy proteinuria and hypertension on renal failure progression characteristic of diabetic nephropathy. The rate of protein filtration and reabsorption by the tubules appears to be directly pathogenic for the kidney. Therefore, goals of therapy are to limit proteinuria to as close to the normal range as is possible and reduce BP, especially in proteinuric individuals, to a goal of 125/75 mm Hg.

### Practical Prescribing

First, use a combination of agents to lower BP in patients with proteinuria of >1 gm/24 hr. Most patients with hypertension and chronic renal insufficiency require more than 1 agent to control hypertension adequately, especially if a lower BP goal is to be achieved. Large population studies show that achieving this lower

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**Figure 2. Some Pathophysiologic Mechanisms That May Contribute to Hypertension in Patients With Renal Disease**

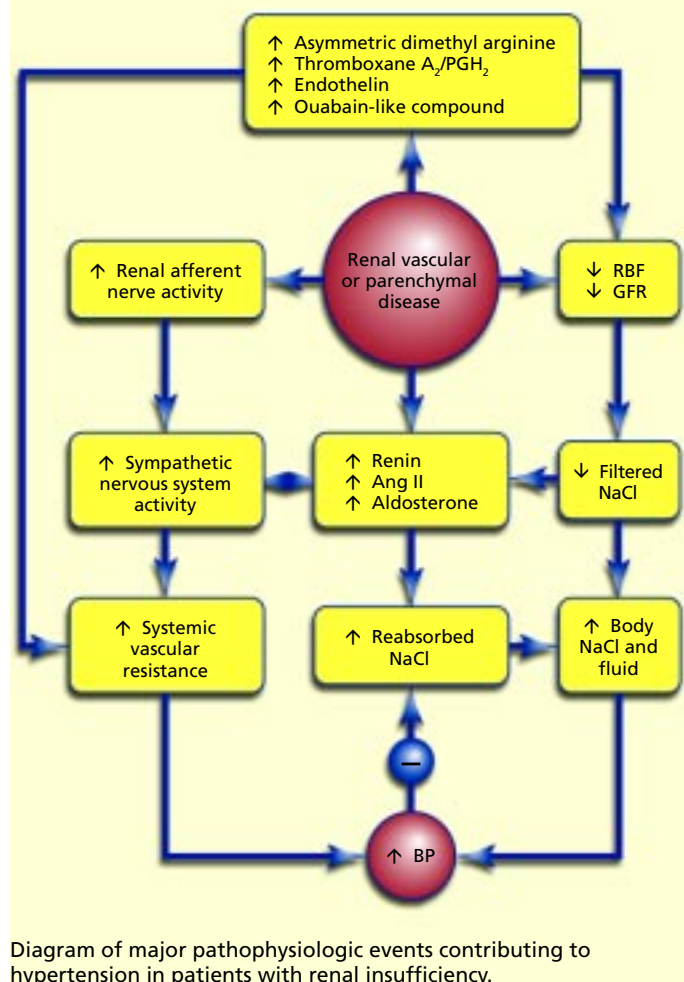


Diagram of major pathophysiologic events contributing to hypertension in patients with renal insufficiency.

BP goal does not lead to excess mortality or morbidity from adverse effects but rather reduces the decline in renal function.

Second, select drugs eliminated by metabolism rather than renal excretion. In practice, longer acting  $\beta$ -blockers such as atenolol or nadolol are predominantly water soluble and are eliminated in active form mainly by the kidney whereas shorter acting  $\beta$ -blockers such as propranolol or metoprolol are more lipid soluble and are eliminated predominantly by metabolism. The latter group is preferable in patients with renal insufficiency.

Third, select a treatment regimen that not only lowers BP but also combats proteinuria. It is clear that ACEIs and ARBs are the most predictable agents for reducing protein excretion, both in patients with microalbuminuria and in those with macroproteinuria. The nondihydropyridine CAs diltiazem and verapamil also reduce protein excretion, especially when used in conjunction with an ACEI or ARB. Recent preliminary reports suggest that a further fall in protein excretion can be anticipated in patients by adding an ARB to those receiving a full dose ACEI therapy. The clinical risks and benefits of this combined therapy remain to be explored. Protein

excretion should be monitored in the individual patient before therapy and again during steady state addition of each agent to determine the effectiveness of the regimen. Dihydropyridine CAs such as nifedipine are generally less effective in reducing protein excretion.

Fourth, select a therapy that targets associated CV risk appropriately. The mortality from CV disease in patients with chronic renal insufficiency or ESRD is increased strikingly. This cannot be explained adequately by hypertension, hypercholesterolemia, or smoking and awaits a precise definition. “Nontraditional” CV risk factors in this population include hyperhomocystinemia, elevated levels of lipoprotein a, and NO deficiency due to increased dimethylarginine and oxidative stress. New therapies targeting these specific potential risk factors are urgently required since traditional antihypertensive therapy is not designed to reverse these specific pathophysiologic events. Effective therapy for vascular disease and hypertension is critical for treating patients with chronic renal insufficiency and ESRD. These individuals have some of the highest rates of CV mortality from myocardial infarction, stroke, and peripheral vascular disease, and substantial morbidity associated with vascular access clotting during hemodialysis.

### Suggested Reading

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