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## CURRENT CONCEPTS IN Hypertension

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## Editor's Comments

### DIABETIC HYPERTENSIVES: MORE FROM CAPPP, UKPDS, FACET, HOT, SHEP AND SYST-EUR AND PREGNANCY-INDUCED HYPERTENSION

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In this final issue for the millennium of *Current Concepts in Hypertension* we have an excellent update on recent trials of blood pressure (BP) control in hypertensives with diabetes. Dr. James Sowers reviews the evidence for the striking increase in cardiovascular events resulting from the presence of even a mild increase in BP in individuals with diabetes mellitus as well as the marked decrease in risk when active BP reduction is achieved in this group. The results from several recent studies, using a variety of antihypertensive therapies, confirm the benefit of aggressively lowering BP in this subpopulation. Added to this benefit in the overtly diabetic population is the knowledge, reviewed in previous issues of *Current Concepts in Hypertension*, that frank diabetes mellitus represents only the tip of the iceberg, since as much as 50% of the hypertensive population manifests insulin resistance although not all fulfill the criteria for diabetes. Thus, the findings in the diabetics studied may have implications for a larger segment of the hypertensive population.

This issue also features a concise review, by Drs. Granger and Alexander, of the pathophysiology of pregnancy-induced hypertension incorporating evidence from both clinical and experimental observations. It is disappointing that we are little closer to understanding and preventing this not-uncommon complication of pregnancy than we have been for the past 20 years. Certainly the older axiom that careful medical evaluation and access to medical care are important preventive approaches bears reiterating. We also have a clearer insight into which current drugs available for treatment might best be used to diminish the once-devastating impact of hypertension in pregnancy.

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The goal of lowering blood pressure (BP) in persons with diabetes is to prevent hypertension-associated death and disability. Persons with diabetes mellitus, in part because of decreased baroreceptor sensitivity and autonomic nervous system dysfunction, often have more labile BPs, are more susceptible to postural hypotension, and often do not have a normal nocturnal “dip” of BPs. Thus, the level of BP and the diagnosis of hypertension should be based on multiple BP measurements obtained in a standardized fashion on at least 3 occasions. Because of the propensity to orthostatic hypotension, standing BPs should be measured at each office visit. Further, because of the increased BP variability in these patients, ambulatory BP measurements or home BP monitoring may be particularly valuable. The consensus BP goal in diabetic persons with hypertension is <130/80 mm Hg. Pharmacologic therapy should be initiated when lifestyle modifications do not lower BP to <130/85 in diabetic persons. Combination therapy is usually necessary for adequate BP control. Recent data from the United Kingdom Prospective Diabetes Study underscores the importance of rigorous BP control, requiring several antihypertensive medications. Indeed, outcome studies from a number of clinical trials indicate that combination therapy should include an angiotensin converting enzyme inhibitor (ACEI) for maximal benefits in protecting against cardiovascular disease (CVD) as well as renal disease.

Type II diabetes mellitus is becoming increasingly prevalent in westernized, industrialized societies as the populations become more obese, sedentary and older.<sup>1-5</sup> Four out of 5 persons with type II diabetes will die of CVD.<sup>1,2,5-7</sup> Many factors contribute to this high prevalence in CVD in persons with diabetes. These include hypertension, dyslipidemia, platelet coagulation and endothelial abnormalities, as well as hyperglycemia, microalbuminuria, and hyperinsulinemia.<sup>1-9</sup> Within the Multiple Risk Factor Intervention Trial (MRFIT), over 5,000 diabetic persons were followed for 12 years and compared to over 350,000 persons without diabetes.<sup>4</sup> The risk of cardiovascular death at the 12-year follow-up was approximately 3 times higher in diabetic males than in their nondiabetic controls, regardless of age, ethnic group, cholesterol, systolic blood pressure (SBP), or tobacco use. When patients had optimal control of SBP and were nonsmokers, the relative risk of CVD was still 2.5 times higher in the diabetic. The MRFIT study confirmed that diabetes is a strong independent risk factor for CVD mortality above the risk incurred from hypercholesterolemia, systolic hypertension, and cigarette use. It also confirmed that hypercholesterolemia, systolic hypertension, and cigarette smoking were significant independent predictors of mortality in men with and without diabetes. The presence of 1 or more of these risk factors had a greater impact on increasing CVD risk in diabetics than in nondiabetics.

Hypertension in persons with diabetes manifests certain unique and challenging characteristics. For example, many diabetic patients lose their normal nocturnal drop in BP<sup>3,10,11</sup> which may reflect both autonomic dysfunction and/or abnormal renal-neural sensing of volume and pressure status.<sup>11,12</sup> There are several important practical caveats of these observations. First, any BP reading in the healthcare provider's office, often in the morning hours, is likely an underestimation of the 24-hour integrated pressure load on the cardiovascular system and

the kidney. Secondly, disproportionate elevations of nocturnal blood pressures, especially systolic pressures, may enhance CVD risk as well as progression of renal disease in these patients.<sup>13</sup> Hypertension in persons with diabetes mellitus is usually characterized by sodium and fluid retention and increased peripheral vascular resistance.<sup>13,14</sup> Isolated systolic hypertension is more common in diabetic persons even at a relatively young age.<sup>13,14</sup> Supine hypertension with orthostatic hypotension is not uncommon in diabetic patients with autonomic neuropathy.<sup>3,13</sup> BPs tend to be more labile in persons with diabetes, necessitating more measurements to get a handle on mean BPs.<sup>3,13</sup> Finally, diabetic nephropathy, which occurs in approximately 20% of those with type II diabetes and one third of those with type I diabetes, is an important risk factor for development and progression of hypertension in these patients.<sup>3</sup>

### Hypertension Therapy in Diabetic Persons

The goal of lowering BP in persons with diabetes and hypertension is to prevent the inordinate hypertension-associated death and disability in this population.<sup>3,11</sup> Because of increased BP variability in these patients, more BP measurements over a longer period of time are needed to establish the “representative” BP. Because of the greater propensity to orthostatic hypotension, standing BP should be obtained on each office visit.<sup>3</sup> Therapy should begin with lifestyle modifications (Table 1) involving weight reduction, increased physical activity, and moderation of dietary salt and alcohol intake.<sup>10</sup> If goal BP of 130/85 mm Hg is not achieved, then pharmacological intervention is indicated.

**Table 1 Lifestyle Modifications for Hypertension Prevention and Management**

- Lose Weight if overweight
- Limit alcohol intake to no more than 1 oz (30 mL) of ethanol (eg, 24 oz of beer, 10 oz of wine, or 2 oz of 100 proof whiskey) per day or 0.5 oz of ethanol per day for women and lighter-weight people
- Increase aerobic physical activity (30 to 45 minutes most days of the week)
- Reduce sodium intake to no more than 100 mmol/d (2.4 g of sodium or 6 g of sodium chloride)
- Maintain adequate intake of dietary potassium (approximately 90 mmol/d)
- Maintain adequate intake of dietary calcium and magnesium for general health
- Stop smoking and reduce intake of dietary saturated fat and cholesterol for overall cardiovascular health

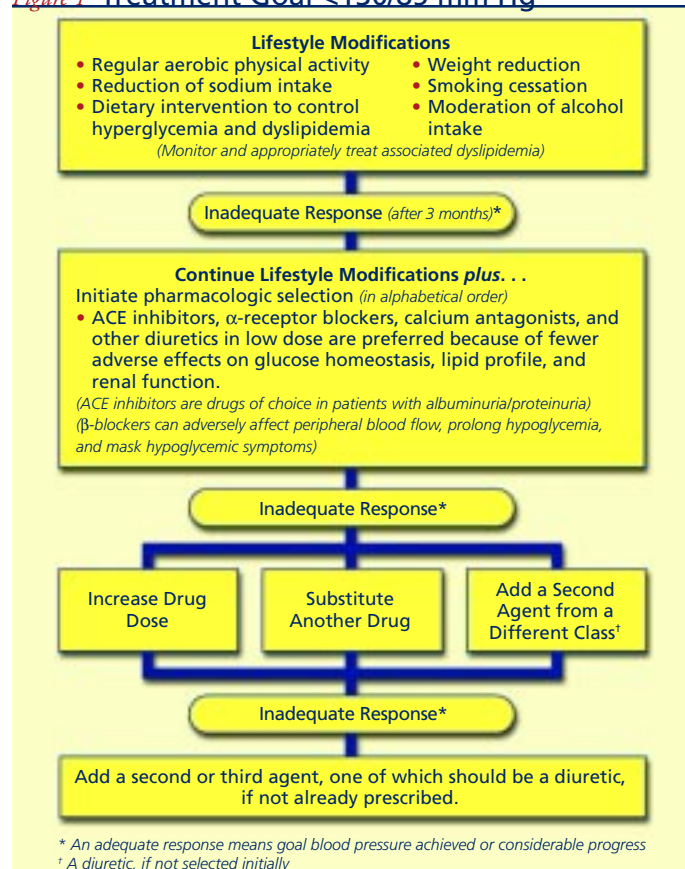
### Pharmacologic Therapy

Drug therapy should be initiated when lifestyle modifications do not lower BP to <130/85 in diabetic persons.<sup>3,10,15</sup> The National Institutes of Health Consensus Panel recommended 4 classes of drugs as effective first-line therapy in these patients.<sup>15</sup> Each drug class has potential

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advantages and disadvantages. Furthermore, most diabetic patients will need several different agents to adequately lower BP (Fig 1).

**Figure 1 Treatment Goal <130/85 mm Hg**



ACEIs have been recognized as the first-line antihypertensive therapy in diabetic patients with proteinuria.<sup>10,15</sup> Since proteinuria is a harbinger for CVD as well as renal disease, these agents may offer some unique benefits in preventing CVD as well as diabetic nephropathy. However, in the recent United Kingdom Prospective Diabetes Study Group report, BP lowering with atenolol was as effective as captopril in reducing the incidence of diabetic complications (both macrovascular and microvascular).<sup>16,17</sup> Nevertheless, it should be emphasized that many of these patients required both drugs for “tight control” of 144/82 mm Hg. In patients assigned to less tight control (154/87 mm Hg), there was less use of more than 1 antihypertensive agent. Reductions in risk in the group assigned to tight BP control were 24% in diabetes-related end points, 32% in deaths related to diabetes, 44% in strokes, and 37% in microvascular end points, predominantly related to a reduced risk of retinal photocoagulation. In essence, these results could be interpreted as evidence that combination therapy with an ACEI and a  $\beta$ -blocker is very effective in lowering macrovascular and microvascular events as long as BP was adequately lowered.

That a combination of an ACEI and a calcium antagonist may be beneficial in reducing CVD in diabetic persons was suggested by the results of the Fosinopril versus Amlodipine Cardiovascular Events Trial (FACET).<sup>18,19</sup> This open-label, single-center study was designed to compare the effects of fosinopril and amlodipine on serum lipid levels and

diabetic control in patients with type II diabetes mellitus and associated hypertension. Prospectively defined CVD events were accessed as secondary outcomes. Subjects were randomly assigned to treatment with fosinopril or amlodipine. If BP was not controlled, the other study drug was added. The incidence of major cardiovascular problems was lowest in the patients treated with both fosinopril and amlodipine. Since the combination therapy resulted in a lower incidence of cardiovascular events than treatment with either agent alone suggests combination therapy with an ACEI and a calcium antagonist is very good for treating hypertension in patients with type II diabetes. In a diabetic cohort in the Systolic Hypertension in Europe (Syst-Eur) study use of the calcium antagonist nitrendipine, often in combination with another antihypertensive agent, significantly decreased CVD.<sup>20</sup> These results underscore the utility of calcium antagonists in combination with other antihypertensive agents in treating this high risk population.

Thiazide diuretics in relatively low dosages (i.e., 25 mg or less of hydrochlorothiazide or chlorthalidone daily) are effective and safe antihypertensive agents in patients with diabetes. In the Systolic Hypertension in the Elderly (SHEP) study, elderly men with type II diabetes derived as much benefit, in terms of stroke and ischemic heart disease reduction, as those without diabetes.<sup>21</sup> Diuretics in low dosages are not generally associated with significant metabolic abnormalities.<sup>15</sup> Prescribing diuretics in conjunction with ACEIs often produces synergistic effects and, together, they minimize potential metabolic problems associated with diuretic usage. Diuretics are often necessary as part of the antihypertensive regimen in diabetics because of the salt sensitivity and expanded plasma volume that is often present in these patients.<sup>1</sup> This is especially relevant since multiple drugs are often thought to control BP levels to <130/85 in these patients. An analysis of clinical trials suggested that, on average, diabetic patients require 3 to 5 different classes of antihypertensive medications to achieve BP levels <130/85 mm Hg.<sup>22</sup>

Thus, persons with diabetes and coexistent hypertension should have their BPs lowered to a goal of <130 mm Hg systolic and <85 mm Hg diastolic in order to reduce both macrovascular and microvascular disease. Results of the Hypertension Optimal Therapy (HOT) study suggest that further reduction in diastolic BP, <80 mm Hg, is likely beneficial.<sup>23</sup> Adequately lowering BP in this high risk group often requires a minimum of 3 drugs, at least 1 of which should be an ACEI, if tolerated. Indeed, we now have at least 6 clinical trials that unequivocally demonstrate the substantial benefits of aggressive BP lowering in diabetic patients.

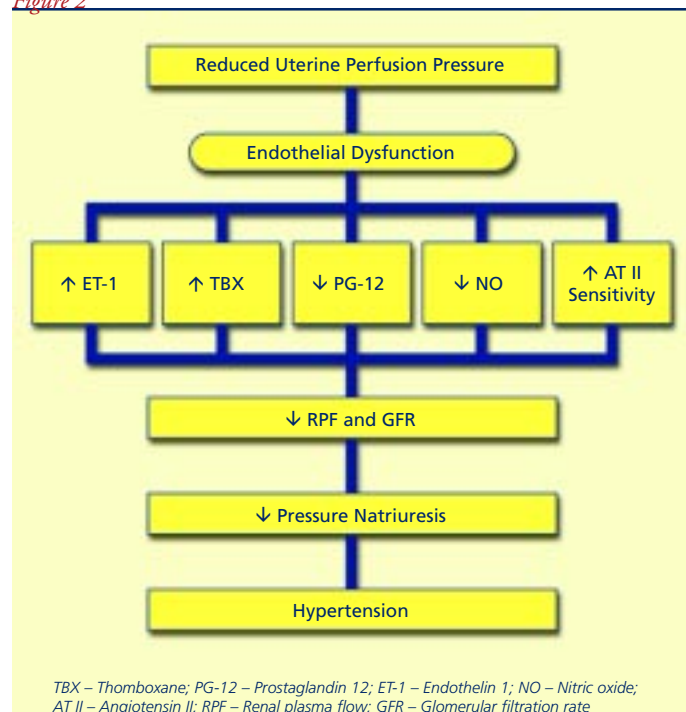
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Pregnancy-induced hypertension (PIH) is estimated to affect 7% to 10% of all pregnancies in the United States. Despite being the leading cause of maternal death and a major contributor to maternal and perinatal morbidity, the mechanisms responsible for the pathogenesis of PIH have not yet been fully elucidated. Hypertension associated with preeclampsia develops during pregnancy and remits after delivery, implicating the placenta as a central culprit in the disease. An initiating event in PIH has been postulated to be reduced placental perfusion which leads to widespread dysfunction of the maternal vascular endothelium by mechanisms that remain to be defined. The mechanisms leading to reduced placental perfusion in PIH may be multiple but most studies in humans suggest abnormal cytotrophoblast invasion of spiral arterioles as an important factor.

Figure 2



Several lines of experimental evidence support this hypothesis. For example, studies in various animal models, including sheep, dog, rabbit, and rat, have shown that reduction in uteroplacental blood flow leads to a hypertensive state that closely resembles PIH in women. Additional support for this concept derives from studies in humans that indicate increased circulating fibronectin and factor VIII antigen, both of which are markers of endothelial cell injury. Decreased production of endothelium derived relaxing factors, such as nitric oxide (NO) and prostacyclin, increased production of endothelin and thromboxane and enhanced vascular reactivity to angiotensin (AT) II in women with PIH also suggest abnormal endothelial function.

During normal pregnancy, significant changes in cardiovascular and renal function occur to meet the metabolic needs of the mother and the fetus. For example, maternal cardiac output and blood volume increase by approximately 40% to 50%, while total peripheral resistance and arterial blood pressure (BP) tend to decrease. In addition,

there are marked changes in renal function such as elevations in renal plasma flow (RPF) and glomerular filtration rate (GFR) of approximately 30% to 40%. Renin concentration, renin activity, and AT II levels are elevated. However, the vascular responsiveness to AT II appears to be reduced. The mechanisms involved in mediating these significant cardiovascular and renal changes during pregnancy have been studied extensively and it appears that endothelial factors such as NO play an important role.

The marked hemodynamic and renal changes that normally occur during pregnancy do not manifest themselves in women who develop PIH. PIH is associated with significant elevations in total peripheral resistance; enhanced responsiveness to AT II; and marked reductions in renal blood flow (RBF), glomerular filtration rate (GFR), and proteinuria. Although the physiological mechanisms that mediate the alterations in cardiovascular and renal function during normal pregnancy, information regarding the mediators of the reduction in renal and cardiovascular function during PIH has been limited because of the difficulty in performing mechanism studies in pregnant women. Although several animal models have been developed to study PIH, information on the mechanisms involved in mediating the long-term reduction in kidney function and increase in arterial pressure is lacking. Experimental induction of chronic uteroplacental ischemia appears to be the most promising animal model to study potential mechanisms of PIH since reduction in uteroplacental blood flow in a variety of animal models leads to an hypertensive state that closely resembles PIH in women.

Although the mechanisms leading to reduced placental perfusion in preeclampsia may involve various factors, most studies indicate that abnormal cytotrophoblast invasion of spiral arterioles appears to be one of the major factors. In normal human pregnancy, placental cytotrophoblasts that invade the uterus decrease the expression of adhesion receptors that are characteristic of their epithelial origin and enhance expression of adhesion receptors by vascular cells. This process is thought to play an important role in mediating the process whereby cytotrophoblasts invade and remodel the uterine spiral arteries to meet the metabolic needs of the uteroplacental unit. In preeclampsia, this process is abnormal. Therefore, invading cytotrophoblast fail to properly express adhesion molecules such as integrin, cadherin, and Immunoglobulin superfamily members. The failure of cytotrophoblasts to mimic a vascular adhesion phenotype is thought to reduce cytotrophoblast invasion and uterine arteriole remodeling, thereby producing placental hypoxia.

Although reductions in blood flow to the uteroplacental unit are known to result in cardiovascular and renal abnormalities consistent

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with the pathophysiologic features of human PIH, the physiologic mechanisms linking placental ischemia with the abnormalities in maternal circulation are unclear. Several lines of evidence support the hypothesis that the ischemic placenta contributes to endothelial cell activation and dysfunction of the maternal circulation by enhancing the synthesis of cytokines such as tumor necrosis factor alpha (TNF $\alpha$ ) and interleukin 1 (IL-1). TNF $\alpha$  and IL-1 are inflammatory cytokines that have been shown to induce structural as well as functional alterations in endothelial cells. These inflammatory cytokines also enhance the formation of a number of endothelial cell substances such as endothelin and platelet-derived growth factor and reduce acetylcholine-induced vasodilatation. Also supporting a potential role of TNF $\alpha$  in preeclampsia are findings that plasma levels of TNF $\alpha$  are significantly elevated in women with preeclampsia by approximately 2 fold. Furthermore, IL-6 which is activated by TNF $\alpha$  has also been reported to be elevated in preeclamptic women. Although high levels of TNF $\alpha$ , as observed during septic shock or after lipopolysaccharide administration, activate gene expression of inducible nitric oxide synthase (iNOS), modest levels of TNF $\alpha$  have been shown to destabilize the mRNA of endothelial nitric oxide synthase (eNOS). Whether chronic and modest increases in plasma TNF $\alpha$  can activate the endothelium during pregnancy and lead to reduced kidney function, high BP, and other features of PIH is unknown. Consistent with a potential role of cytokine activation in PIH is the recent study by Faas and colleagues. They reported that an intravenous infusion of a high dose of lipopolysaccharide (LPS) decreased BP in pregnant rats while a very low dose infusion of the endotoxin resulted in significant and long-term increases in BP and urinary albumin excretion and significant platelet aggregation in conscious pregnant rats. Although LPS is known to activate TNF $\alpha$ , it is unclear whether the effects of low dose LPS on cardiovascular and kidney function were mediated via TNF $\alpha$  and/or IL-1 since these cytokines were not measured in that study.

Despite recent advances in our understanding of the pathophysiology of preeclampsia, progress in preventing and managing the disease has been limited. Results of clinical trials for the prevention of preeclampsia have been rather disappointing. Placebo-controlled trials evaluating calcium supplementation during pregnancy have shown that an increase in calcium intake does not reduce the incidence of preeclampsia in healthy nulliparous women. In addi-

tion, results of a recent multicenter trial involving over 23,000 women revealed minimal to no benefit of low dosage aspirin. The preferred pharmacologic therapy for the hypertension in the preeclamptic patient remains methyldopa since the drug it is known to reduce midtrimester abortions and perinatal deaths while causing no physical or mental deficits in the offspring. Other drugs such as labetalol,  $\alpha$ - and  $\beta$ -adrenergic blockers, clonidine and calcium channel blockers have also been used to treat hypertension in the preeclamptic patient. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are contraindicated in these patients because of their ability to induce neonatal renal failure and hypotension.

In summary, studies over the last decade have provided a better understanding of the potential mechanisms responsible for the pathogenesis of PIH. The initiating event in PIH has been postulated to be reduced uteroplacental perfusion as a result of abnormal cytotrophoblast invasion of spiral arterioles. Placental ischemia is thought to lead to widespread activation and dysfunction of the maternal vascular endothelium that results in enhanced formation of endothelin and thromboxane, increased vascular sensitivity to AT II, and decreased formation of vasodilators such as NO and prostacyclin. These endothelial abnormalities, in turn, cause chronic hypertension by impairing renal-pressure natriuresis and increasing total peripheral resistance. The quantitative importance of the various endothelial and humoral factors in mediating the reduction in renal hemodynamic and excretory function and elevation in arterial pressure during PIH is still unclear. Results from ongoing basic and clinical studies, however, should provide new and important information regarding the physiologic mechanisms responsible for the elevation in arterial pressure in women with preeclampsia. More effective strategies for the prevention of preeclampsia should be forthcoming once the underlying pathophysiologic mechanisms involved in PIH are completely understood.

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