

Diabetes and Hypertension

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This article covers presentations and symposia dealing with the relation between diabetes and hypertension that were given at the 16th Scientific Meeting of the American Society of Hypertension, San Francisco, CA, 15–19 May 2001.

At a symposium at the 16th Scientific Meeting of the American Society of Hypertension (ASH), San Francisco, CA, 15–19 May 2001, Willa Hsueh, Los Angeles, CA, discussed clinical trials in hypertension. The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC-VI, 1997, available at <http://www.nhlbi.nih.gov/guidelines/hypertension/jnc6.pdf>) defined essential hypertension as a blood pressure (BP) >140/90 mmHg, but Hsueh noted that only 25% of patients with hypertension have no complications such as renal disease, cardiac disease, obesity, diabetes, and hyperlipidemia. BP goals are lower for patients with such complications. In the JNC-VI, patients with diabetes were noted to be at high risk and were given a BP goal of <130/85 mmHg, whereas for individuals with >1 g proteinuria, the goal to lessen target organ damage was set at 125/75 mmHg. In the U.K. Prospective Diabetes Study (UKPDS) patients were treated with either an ACE inhibitor (ACEI) or β -blocker (BB) and achieved levels of 144/82 vs. 154/87 mmHg over 8 years. However, at a question-and-answer session after the lecture, it was noted that captopril was given only once or twice daily and therefore may not have had optimal benefit. Both treatments reduced microvascular end points of re-

nal and eye disease, macrovascular end points, and congestive heart failure (CHF), which may in part reflect diabetic cardiomyopathy. The Hypertension Optimal Therapy (HOT) trial of 18,790 patients, of whom 8% had diabetes and were treated with felodipine followed by ACEI and then followed by additional agents, showed a clear relation of BP to cardiovascular disease (CVD) events in the diabetes subgroup when comparing patients titrated to diastolic BP <90, <85, and <80 mmHg, with lowest risk at BP <138/83 mmHg (1). This was less evident without diabetes. At enrollment, most patients were treated with a single drug, but by the time the study was over, two-thirds required multiple drug treatment. Whether the post hoc diabetic subgroup analysis was positive because of the increased event rate among individuals with diabetes, leading to greater statistical power, or because of a real difference between patients with and without diabetes is not known. In the Systolic Hypertension in Europe Trial (Syst-Eur), even more impact was seen in diabetic versus nondiabetic patients, again suggesting the need to aggressively treat BP in patients with diabetes (2).

Which class of BP treatment should be used? The Captopril Prevention Project (CAPPP) trial showed that patients with diabetes had decreased cardiovascular events, stroke, and other end points with captopril, and again the nondiabetic group showed a less definitive difference (3.) In the Appropriate Blood Pressure Control in Diabetes (ABCD) trial, which compared nisoldipine with enalapril and 75 mmHg with <90 mmHg

diastolic BP goals at 5 years in 235 patients in each group, there were 25 myocardial infarctions with nisoldipine patients vs. 5 with enalapril patients; stroke occurred in 11 vs. 7 patients, and CVD death occurred in 10 vs. 5 patients, respectively, suggesting an increase in risk with the calcium channel blocker (CCB) (4). In the Fosinopril vs. Amlodipine Cardiovascular Events Trial (FACET) of 380 patients, 38% of the patients were treated with amlodipine, 34% were treated with fosinopril, and 28% were treated with combination. "The bottom line of that trial" was that myocardial infarction, stroke, and hospitalization angina occurred more frequently with the CCB alone, with rates of stroke, myocardial infarction, or hospitalized angina occurring 5.0, 2.6, and 1.1 times per 100 person-years in the respective groups, suggesting "that the combination fared better" (5). In the Heart Outcomes Prevention Evaluation (HOPE) trial of patients at high risk for CVD treated with ramipril vs. placebo, 38% had diabetes, with myocardial infarction, stroke, CVD death, and total mortality all significantly reduced with ramipril administration (6). Furthermore, there was less need for revascularization, less hospitalization for heart failure, and a 32% decrease in new-onset diabetes among those not known to have diabetes at onset. Although BP was 3 mmHg lower in the ramipril group, these data offer the "tantalizing suggestion" that angiotensin 2 (A2) is a "real culprit" in diabetes and that treatment directed at A2 is particularly beneficial. George Bakris, Chicago, IL, who spoke later, noted that more than half of patients with diabetes in the HOPE trial were hypertensive according to the 130/85 mmHg definition, so that, in a sense, the study shows the usefulness of the stricter JNC-VI BP goals.

Why does A2 have such a strong effect on CVD? A2 is both a direct vasoconstrictor and stimulates endothelin-1 (ET-1), another potent vasoconstrictor. A2 is proinflammatory, stimulates adhesion molecule expression by the endothelial surface, stimulates the prothrombotic substance plasminogen-activator inhibitor-1 (PAI-1), decreases nitric oxide (NO) activity and has pro-oxidant action in converting NO to superoxide radical, and

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Abbreviations: A2, angiotensin 2; ABCD, Appropriate Blood Pressure Control in Diabetes; ACEI, ACE inhibitor; ANP, atrial natriuretic peptide; ARB, angiotensin receptor blocker; ASH, American Society of Hypertension; AT-1, A2 type 1; BB, β -blocker; BP, blood pressure; CCB, calcium channel blocker; CHD, coronary heart disease; CHF, congestive heart failure; CVD, cardiovascular disease; ESRD, end-stage renal disease; ET-1, endothelin-1; GFR, glomerular filtration rate; HCTZ, hydrochlorothiazide; HOPE, Heart Outcomes Prevention Evaluation; HOT, Hypertension Optimal Therapy; JNC-VI, Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure; NO, nitric oxide; PAI-1, plasminogen-activator inhibitor-1; RAS, renin-angiotensin system; RBF, renal blood flow; TGF- β , transforming growth factor- β ; TNF, tumor necrosis factor; UKPDS, U.K. Prospective Diabetes Study; VA, Veterans Administration.

acts as a growth factor that leads to tissue remodeling, which may be enhanced in diabetes. Hsueh noted that PAI-1 also inhibits tissue matrix metalloproteinases, with less degradation of interstitial matrix increasing fibrosis. In the kidney, nephropathy is controlled by hyperglycemia, hyperinsulinemia, A2, and stretch, all of which affect transforming growth factor- β (TGF- β), which stimulates extracellular matrix and thereby promotes the sclerotic changes in the kidney. As seen in a mouse failing to express the LDL receptor and atherosclerosis evident at age 2 months, BP is increased with A2 infusion, with further "dramatic changes" involving fibrosis, inflammation, and atherosclerosis. A2 binds to receptors in cardiac fibroblasts of mice, rats, and humans, promoting growth and stimulating TGF- β , increasing extracellular matrix with increased fibronectin and collagen I and III in the heart, affecting local PAI-1, and stimulating adhesion receptors, thereby increasing "the ability of these fibroblasts to stick to their extracellular matrix" via mediators such as osteopontin. There is prominent cardiac interstitial fibrosis with A2 infusion in animal models of diabetic cardiomyopathy.

Bakris stressed that diabetes is now the main cause of end-stage renal disease (ESRD) in both the U.S. and Europe. He noted that in the third National Health and Nutrition Examination Survey, only 11% of patients with diabetes had BP <130/85 mmHg, and stated, "If you're not at goal, [the treatment is] not sufficient." More recently than JNC-VI, lowering the diastolic goal to 80 mmHg, with ACEI as initial treatment, has been suggested. By comparing a variety of trials of BP treatment of patients with renal disease and with and without diabetes, it has been shown that systolic BP between 130 and 140 mmHg, compared with levels between 140 and 150 mmHg, leads to patients "do[ing] a lot better." Indeed, Bakris noted, a patient with a creatinine level of 2 mg/dl whose systolic BP decreases from 160 to 130 will "save 5 years" of ESRD, with the degree of decrease in proteinuria being an important marker of future benefit. Bakris pointed out, "The sicker you are, the more impact you're going to have." In addition, lowering BP will "save the taxpayer \$250,000."

The African American Study of Kidney Disease trial showed that the ACEI ramipril was quite effective in this ethnic

group, and, indeed, for patients with glomerular filtration rate (GFR) between 20 and 65 mg/day and with >300 mg/day proteinuria, use of ramipril as primary treatment led to a 36% lower rate of decline in GFR and to a 48% lesser chance of GFR <25 mg/day, ESRD, or death, as compared with amlodipine treatment, despite slightly better BP control in the latter group (systolic BP 132 vs. 133 mmHg with ramipril) (7). Bakris stated that to achieve this degree of benefit, "You need meaningful doses" (ramipril 10–20 mg, enalapril or lisinopril 40–80 mg, etc). It appeared likely that patients with lesser degrees of proteinuria also showed better outcome with the ACEI.

With microalbuminuria, Bakris emphasized the need to "forget the kidney, think heart, think vasculature." In large epidemiologic trials, microalbuminuria is a major risk factor for CVD, even in patients without hypertension, as defined by systolic BP >140 mmHg. In a recent Danish study, nondiabetic, nonobese, normotensive individuals with albuminuria had slightly higher systolic BP and showed a smaller vasodilatory response to nitroglycerin, suggesting that albuminuria itself may be an important treatment goal (8). He pointed out that the CCB group of the ABCD study, which had more CVD events, did not show the reduction in microalbuminuria seen with the ACEI. Although it is uncertain whether this is important at systolic BP <115–120 mmHg, at higher levels, inhibition of the renin-angiotensin system (RAS) is required. Also, referring to a study in which verapamil showed similar decrease in proteinuria to that seen with ACEI (9), Bakris pointed out that there are two classes of CCB and that nondihydropyridines may protect the kidney. He concluded that one should start with an ACEI, then use a thiazide or a nondihydropyridine CCB, with BB treatment for patients with rapid pulse or post-myocardial infarction. He noted that for patients under age 50 years, he used diastolic <80 mmHg, and for patients over age 50 years, he used systolic <130 mmHg as the main BP targets. When asked about the use of high-dose ACEI versus somewhat lower-dose ACEI in combination with other agents, Bakris replied that there are as yet no data; he also noted that combinations of ACEI with diuretics or CCB may be as useful as those with angiotensin receptor blockers

(ARBs). A requirement for more than one agent is almost invariable in patients with BP >15/10 mmHg above the goal of 130/85 mmHg. He stressed the need to reduce morbidity and mortality "by the least intrusive means possible."

Arya Sharma, Berlin, Germany, discussed the related topic of the choice of BP treatment in obese individuals. "Obesity," he said, "is not only the most important, but it is also the most widespread" risk factor. Thus, weight loss is crucial. Sodium retention accompanies weight gain, driven by both increased sympathetic activity and an increase in the activity of the RAS. Obesity is associated with increased cardiac output, increased plasma volume, and, initially, decreased peripheral resistance. In his studies of BMI-matched hypertensive and normotensive individuals, plasma norepinephrine levels were increased. Leptin may play a role in obesity-hypertension by driving sympathetic activity, increasing heart rate, and causing volume retention and ultimately leading to increased BP. Interestingly, there is a correlation between leptin and plasma angiotensinogen. All of the RAS is expressed by adipose tissue, including renin, angiotensinogen, ACE, and the A2 type 1 (AT-1) receptor. In hypertensive versus normotensive subjects, renin is increased and the AT-1 receptor downregulates. "One wonders what is happening," Sharma said, "to all the angiotensinogen that's coming out of the adipose tissue" in overweight individuals. Fasting is associated with diuresis, related to action of atrial natriuretic peptide (ANP). Obese patients have low ANP and show poor response to exogenous ANP. This is caused in part by the high adipocyte expression of the ANP "clearing receptor." Diet downregulates the clearing receptor, a major mechanism of the diuresis of fasting. Thus, adipose tissue as a paracrine organ mediates the relationship between BMI and BP. But "the story is far more exciting," with a variety of cardiovascular genes, including ET-1 and tumor necrosis factor (TNF)- α expressed by adipose tissue. "There is a lot of scope for research here," Sharma said, that will assist in our understanding of the relation between adipose tissue and BP.

How then should we manage our obese hypertensive patients? Before addressing pharmacologic treatment, weight loss—the highest priority—must

be achieved. Although weight loss can decrease hypertension, after several years “these patients are back where they started,” so this clearly is not a clinically effective approach. Sharma noted that the guidelines “tell us nothing” in terms of pharmacology. We have much information pertaining to hypertension treatment in minorities and for patients with diabetes or dyslipidemia. Obesity starts with a BMI of 30 kg/m², but in most recent studies, with the exception of the UPKDS and the ABCD trial, these patients were excluded; consequently, data are limited. As far as pharmacokinetics, it is uncertain what happens to lipophilic drugs with this “enormous reservoir.” Body fat predicts response to vasodilators, while there is an inverse relationship between body fat and the BP response to nifedipine. A study comparing efficacy in obese and lean patients with hypertension suggests that CCBs are more effective than BBs for lean subjects, whereas the BB response is better in obese subjects. In the Treatment in Obese Patients With Hypertension (TROPHY) study, 232 obese patients were treated with lisinopril or hydrochlorothiazide (HCTZ). Of these patients, 60% responded to lisinopril 40 mg, but only 43% responded to HCTZ, only at an excessive dose of 50 mg daily (10). However, Sharma noted that BBs promote weight gain, as seen in the UKPDS, in which the degree of weight gain was twice as great with atenolol than with captopril. Weight gain from BBs is seen within 6 months, in association with decreased metabolic rate, with decreased postprandial thermogenesis, and with increased lipogenesis. This may explain several metabolic side effects, such as the 30% increased risk of type 2 diabetes with BBs. In contrast, the HOPE and CAPPP studies show decreased risk of type 2 diabetes with ACEI treatment. Thus, the treatment of hypertension in obese individuals is preferentially an ACEI or perhaps an ARB, in combination with a diuretic, or perhaps with a nondihydropyridine CCB. He noted that an additional pharmacologic approach is that of treatment of obesity per se, as with orlistat, which can cause and maintain weight loss; hypertensive patients on this agent showed the expected fall in BP proportional to the degree of weight loss.

In conclusion, Sharma mentioned that “there are currently no hard endpoint studies in obese hypertensive [pa-

tients],” suggesting that investigators should perform such post hoc analyses of existing trials and should pay more attention to the pharmacologic treatment of obesity. When asked whether tying “the leptin theory with angiotensinogen would support the argument for using an ACE inhibitor,” Sharma answered in the affirmative, pointing out that, in addition to ethnic differences in response to drugs, there may be equally important differences based on body weight. Another audience member asked about clonidine, which Sharma suggested has good blood pressure-lowering effects but “practically abolishes postprandial thermogenesis,” which may explain the frequency of weight gain. In addition, Sharma encouraged frequent measurement of BP and the use of large cuff size, noting that one can also use a wrist BP measurement. Obese patients, he stated, often require a greater number of medicines, and “obese patients are usually managed very poorly. Doctors often have a very negativistic approach to these patients.” In regard to central versus peripheral obesity, the relation of the RAS and of 11- β hydroxysteroid dehydrogenase to central versus peripheral fat, and the potential impact of drugs on fat distribution, Sharma agreed that hypertension risk is related more to fat distribution. Moreover, study of gene expression by Peter Arner showed that β -adrenergic expression differed in subcutaneous and visceral fat (11). Drug studies of antihypertensive agents may show that BBs promote development of visceral adipose tissue, which might be significant.

William Cushman, Memphis, TN, reported analysis of data from the Veterans Administration (VA) Cooperative Study Group on Antihypertensive Agents, who assessed whether obesity influences the response to antihypertensive agents and examined the effects of BP drugs on weight over time. He noted that some drugs, particularly BBs, may promote weight gain and that in the UKPDS, there was a 3.4-kg weight gain in the group treated with atenolol compared with the group treated with captopril, although it was uncertain whether this was a beneficial effect of captopril or an adverse effect of atenolol. A total of 1,292 men from 15 U.S. VA centers with untreated diastolic hypertension (95–109 mmHg), excluding patients with diabetes on treatment or with recent cardiac events, were randomized to HCTZ 12.5–50 mg daily, atenolol

25–100 mg daily, captopril 12.5–50 mg twice daily, clonidine 0.1–0.3 mg twice daily, diltiazem SR 60–180 mg twice daily, or prazosin 2–10 mg twice daily, titrated to a diastolic BP goal of <90 mmHg, and then placed on a 1-year maintenance phase. Clonidine and prazosin were associated with more side effects and drug withdrawals.

Age and race were the major variables explaining differences in response to the various agents. Obese patients were younger, with lower systolic and similar diastolic BP. Only the 1-year success with atenolol was affected by obesity, with patients whose BMI exceeded 30 kg/m² being 2.5 times more likely to have BP successfully controlled than those with BMI <27 kg/m². For hypertensive men with similar levels of untreated BP, there was no other difference in response to the antihypertensive medications based on presence or absence of obesity. Pulse pressure showed the greatest response to the diuretic and α -blocker; there was no significant difference between the weight groups. Weight increased 1.7 lb with prazosin, with evidence of fluid retention rather than increased adipose mass, and decreased 2.1 lb with HCTZ and captopril. Patients treated with atenolol showed a nonsignificant “upward trend” in weight.

Naftali Stern, Tel Aviv, Israel, noted that “the large trials have achieved systolic levels significantly higher than the current targets. The feasibility of achieving systolic [BP] <130 and the implication of such treatment for the diastolic BP are unknown.” He studied “the practicality of intensive blood pressure lowering to <130/85” in 257 type 2 diabetic hypertensive patients over a 22-month period. Treatment was individualized, with ACEI whenever possible, and with BB for patients with a history of prior coronary heart disease (CHD). The final BP was defined by either a stable level of <130/85 mmHg, a diastolic BP <50 mmHg, or “a stable BP that the treating physician thought was not amenable to further intervention.” The diastolic target was achieved in >90% of the patients, but the systolic goal was achieved in only 32% of the patients, with an achieved mean systolic BP of 133 mmHg. Upon entry, patients used a mean of 1.2 antihypertensive agents, and at study end, close to three drugs were used per patient. The final diastolic BP was \leq 70 mmHg in 57% of the patients, with levels <70 mmHg occur-

ring particularly in older patients, whose prevalence of CHD was 52%. Those with higher final diastolic levels, however, had a 28% prevalence of CHD. Stern stated, "Once the diastolic reaches 50, I tend not to push the systolic further, particularly in light of the high prevalence of coronary disease." He concluded, "Attempting to lower the systolic to <130 leads to excessive diastolic lowering in a significant fraction," and wondered "whether or not the benefits of attempted tight lowering of systolic pressure in type 2 diabetes outweigh the risk of excessive reduction of diastolic pressure," although there was no definite evidence of adverse effect in his study.

At a symposium on the role of ARBs in the management of hypertension in patients with type 2 diabetes, Norman Hollenberg, Boston, MA, noted that clinical trials have shown the greater importance of systolic BP over diastolic BP, with progressive downward recommendations for BP goals and the benefit of blocking the RAS in preventing adverse outcome. Many years ago, data from the Joslin Clinic showed the prevalence of diabetic retinopathy to increase over time, with almost all patients eventually showing evidence of disease, whereas nephropathy showed a delay in onset, reflecting the insensitivity of the early measurements of proteinuria and a subsequent plateau in frequency, suggesting that some patients are and others are not at risk. This discrepancy, presumably, is not only related to glycemia, but is also related to hereditary factors. The first report of the latter showed that indeed a polymorphism of the ACE gene predisposes to nephropathy. The patient with type 2 diabetes shows low renin, as compared with the normal to high renin state found in type 1 diabetes. In studies with the ARB irbesartan, patients with type 2 diabetes and nephropathy showed greater activation of the RAS than nondiabetic subjects, despite their suppression of renin. Hollenberg pointed out that the low basal renin activity with paradoxically enhanced response to irbesartan suggests increased tissue renin response. Indeed, analysis of the response of renin activity to progressively higher doses of irbesartan shows that the low plasma renin in type 2 diabetes "masks a highly active system." There is a marked increase in renal blood flow (RBF) with hyperglycemia, which can be shown with glucose infusion in normal

individuals to raise glucose to 8–9 mmol/l. When captopril is administered, RBF increases further. Lansang et al. (12) reported a similar finding of glucose-induced RAS activation in a rat model, with glucose infusion increasing the RBF response to the ARB candesartan. Obesity further activates the system, perhaps because of either increased hepatic or increased adipocyte production of angiotensinogen.

Hollenberg discussed the question of non-ACE pathways to A2 generation. If ACE is the only pathway, "it shouldn't matter whether you block" at the level of renin, at ACE, or with an angiotensin antagonist. However, renin inhibitors have greater effects than ACEI, suggesting that there may be non-ACE pathways of A2 generation. Similarly, A2 antagonists appear to have greater effects than captopril, suggesting that ARB may have greater clinical efficacy than ACEI. Hollenberg concluded with a reference to Albert Einstein, who said, "Everything should be made as simple as possible but not simpler," stressing that blocking the renin system is particularly effective in patients with diabetes because of their multiple renin-related abnormalities, including genetic factors, obesity, ethnicity, and hyperglycemia, converging at the AT-1 receptor.

Joel M. Neutel, Orange, CA, discussed the role of combination therapy in the management of high-risk hypertensive patients, pointing out that the 10/5-mmHg systolic/diastolic BP difference in the UKPDS led to improvement in CVD, as did the 4-mmHg diastolic BP difference between the high and low BP arms of the HOT study. "This," he said, "is where we have the great disconnect," as data from many studies show "that we are not getting even close." Only ~25% of patients in the U.S. have BP <140/90 mmHg, and in Canada this figure is 16%, in the U.K. it is 6%, and in the developing world it is zero. "If we really want to get CVD down, we have to get back to the basics." In the U.S., \$12 billion per year is spent on BP treatment. A problem is that compliance is important, influenced by the side effects of the drugs and their convenience of dosing; a drug that must be taken twice daily will show lower compliance than a daily treatment agent. Another barrier to BP control is the clinical practice of doctors to not titrate drugs because of concern about side effects or because of

patient reluctance. The final problem is that hypertension is complex, and in many patients it cannot be controlled with a single drug. In the 1980s, a diastolic BP of 95 mmHg was shown to be achieved with monotherapy only in approximately half of patients; with more aggressive goals, this figure is less likely to be reached. Physicians favor monotherapy because of cost, although Neutel pointed out that combination drugs are often available. Another reason often given is the difficulty in distinguishing the cause of side effects with multiple agents (although this appears to be an incorrect objection as it is usually clear which agent is causing which side effects). He suggested that giving a maximal dosage of any agent may increase side effects, again suggesting the benefit of low-dose fixed combination treatments, such as those with low-dose thiazides, which may particularly improve the benefit of ARBs. An addendum mentioned after a subsequent talk is that loop diuretics do not reduce BP other than with volume overload, while thiazides have vasodilatory actions and may play a role even with serum creatinine as high as 2 mg/dl.

Neutel presented an analysis of 50 patients treated with a combination of ACEI and ARB. Administering irbesartan 150 mg, lisinopril 10 mg, or the combination and then a doubled dose showed significant improvement in BP with both the low- and high-dose combinations over the medicines given individually. Thus, these agents are complementary in BP effect, and other data show complementary renal effect, although we do not have data on cardiovascular end points. Combinations of CCB and ACEI show benefit, as compared with single agents, probably because of the lower BPs achieved. An important lesson shown in the HOT study is that the reduction of BP in the lowest goal group could only be achieved with monotherapy in 25% of patients. Neutel suggested that physicians should begin to use combination therapy as a first-line approach, particularly with initial BP >160/100 mmHg.

Thomas Giles, New Orleans, LA, discussed the relation between endothelial function and the RAS. The normal endothelium resists thrombi and allows penetration of complexes such as the LDL particle. The endothelium plays a role in the regulation of vascular tone and smooth muscle function. Endothelial dys-

function may be considered a difference in response to agonists from that seen with normal endothelium. In states of hypertension, the effect of A2 on vascular hypertrophy and remodeling shows this dysfunctional quality. Individuals with hypertension and those with a family history of hypertension whose blood pressure is in the normal range show increased vasoconstriction with a lesser fall in vascular resistance and increase in forearm blood flow in response to a variety of mediators. Hypertension is associated with endothelial thickening, with alteration in cell size and shape and increased expression of leukocyte adhesion molecules, thereby increasing atherosclerosis. The blood vessel undergoes pathologic changes that may be related to differences in endothelial function, with concentric remodeling, leading to increased vascular smooth muscle and wall thickening without change in the lumen. In atherosclerosis, the wall remodels outward until injury with infection, such as chlamydia, or until glucotoxicity supervenes, leading to fracture of the cap, which caused thrombosis if sudden or ischemia if gradual.

ACE is an endothelial cell protein that only enters the circulation after specific enzymatic cleavage, but its most important activity occurs in the tissues. Thus, Giles stated, all effective ACEIs are "tissue ACEIs." He noted that the preferred substrate of ACE is bradykinin, and there are many other substrates of ACE. Thus, ACEIs have a variety of effects, including decreased action of A2 at the AT-1 receptor, causing suppression of renin and increased thirst, and blockage of local effects of A2, including inotropy, arrhythmogenicity, thrombogenicity via PAI-1 stimulation, neuroexcitation (both peripherally and centrally), and, finally, stimulation of ET-1 production. A2, if dysregulated, particularly with decreased NO, can stimulate an NADH-NADPH oxidase, leading to oxidant effects and to up-regulation of converting enzyme, a potential vicious cycle. ACEI and AT-1 receptor blockers, separately and together, are then rational treatment approaches. Other vasodilatory natriuretic hormones may be important future therapeutic targets.

David Gomolin, Boston, MA, discussing ARB in clinical practice, described the molecular structure of the AT-1 receptor, which has seven cell membrane-based

domains, creating a specific binding pocket. The activated AT-1 receptor couples with members of a G-protein nucleotide family and triggers phospholipase C and subsequently diacylglycerol, with vasoconstrictor and mitogenic effects. The "sartan" ARBs neutralize these effects, with differences in affinity and duration of effect between various agents. A2 triggers vascular oxidases that increase oxidative stress. These overpower the antioxidant systems, activating chemokines and cytokines, leading monocytes to penetrate the vascular endothelium and form foam cells. In a study of a nonhuman primate model of atherosclerosis, losartan in a dose insufficient to lower blood pressure and without difference in lipids showed profound deactivation of monocytes and an anti-atherosclerotic effect.

A study of individuals in their 40s with coronary disease and with increased adhesion molecule release and oxidative stress showed that 75–150 mg irbesartan decreased inflammatory mediator release, adhesion molecule production, and superoxide anion production. In the Candesartan and Lisinopril Microalbuminuria (CALM) trial, 199 patients with type 2 diabetes, followed for 24 weeks, demonstrated a greater fall in BP and albuminuria with combination than with either agent alone (13). A number of clinical trials are in progress to further explore the efficacy of the combination.

Matthew Weir, Baltimore, MD, reviewed the processes of renal autoregulation designed to maintain pressure of 50 mmHg within the glomerulus by modulating the vasoconstrictive states of two arteriolar systems, the afferent and the efferent systems. In disease, there is damage to the afferent arteriole, leading to decreased autoregulation, with more pressure transmitted to the glomeruli, even at arterial normal BP. From the perspective of the glomerulus, then, the state we describe as "hypertension" has no meaning, as dysregulation of the afferent arteriole may damage the glomeruli at normal systemic BP. With diabetes, increasing mean BP within the normal range leads to loss of kidney function. In patients with poorly treated hypertension, the rate of loss of GFR is $12 \text{ ml} \cdot \text{min}^{-1} \cdot \text{year}^{-1}$, with a blood pressure of 140/90 mmHg, while the rate of loss is halved, and with lower blood pressures, one can further decrease the rate of loss in half again. How low is desirable? Weir suggested that, in diabetic

subjects, we should aim for "presyncope." There are, of course, both neuroendocrine benefits of RAS in providing BP regulation and injury and repair autocrine and paracrine effects of the RAS, which, "when they occur in a repetitive fashion lead to [. . .] maladaptive problems." Lowering BP with a RAS blocker can in concert lower systemic and glomerular pressures, reduce proteinuria, and provide nonhemodynamic benefits. The issue still to be addressed, Weir suggested, is what the difference between ACEI and ARB means clinically.

In a related report at the ASH meeting, Wheeldon et al. (14) discussed the results of the Micro-Albuminuria Reduction with Valsartan (MARVAL) trial, which compared 332 patients with type 2 diabetes treated with valsartan 80–160 mg or amlodipine 5–10 mg daily with addition of bendrofluazide and doxazosin and aimed for a target BP of 135/85 mmHg. Urine albumin decreased from 58 to 32 and from 55 to 51 mg/min in the two groups, with 30 vs. 15% becoming normoalbuminuric and BP decreasing 11.2/6.2 vs. 11.6/5.8 mmHg, respectively. Patel et al. (15) presented analysis of the relation between BP and progression from background retinopathy to maculopathy or proliferative retinopathy requiring photocoagulation. The retinal perfusion pressure, the difference between two-thirds of the mean arterial pressure and the intraocular pressure, and the pulse pressure, the difference between systolic and diastolic pressures, were more strongly associated with the need for photocoagulation than the systolic pressure alone. Patel et al. (15) suggested the use of these measures as specific goals of treatment. Swislocki et al. (16) reviewed outcome of BP treatment among the 5,225 patients with diabetes in the VA Northern California Health Care System. Systolic BP was <130 mmHg in 32% of the patients and >140 mmHg in 46% of the patients; diastolic BP was <85 mmHg in 83% of the patients and >90 mmHg in 9% of the patients, further suggesting the much greater ease of treating the latter.

Brook et al. (17), noting that earlier studies have shown abnormal endothelial function with obesity and that this predicts adverse prognosis, studied 32 adults with BMI 27–40 kg/m² and with normal levels of traditional CVD risk factors. Brachial artery flow-mediated dilatation

(FMD), which is NO-dependent, was not related to C-reactive protein, LDL particle size, postprandial hypertriglyceridemia, insulin, glucose, or free fatty acid levels. Those with waist-to-hip ratio >0.85 showed decreased FMD, while the BMI was not itself a risk factor.

In the next issue of *Diabetes Care*, reports dealing with hypertension and nephropathy from the 2001 American Diabetes Association Annual Meeting will be discussed.

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