Angiotensin Receptor Blocker Added to Previous Anti hypertensive Agents on Arteries of Diabetic Hypertensive Patients

Carmine Savoia, Rhian M. Touyz, Dierk H. Endemann, Qian Pu, Eun A. Ko, Carolina De Ciuceis, Ernesto L. Schiffrin

Abstract—Lowering elevated blood pressure (BP) in diabetic hypertensive individuals decreases cardiovascular events. We questioned whether remodeling of resistance arteries from hypertensive diabetic patients would improve after 1 year of tight BP control with addition of either the angiotensin receptor blocker (ARB) valsartan or the β-blocker (BB) atenolol to previous therapy, which included angiotensin-converting enzyme inhibitors (ACEIs) and/or calcium channel blockers. Twenty-eight hypertensive type 2 diabetic patients treated with oral hypoglycemic and antihypertensive agents (not receiving ARBs or BBs) were randomly assigned to double-blind treatment for 1 year with valsartan (80 to 160 mg) or atenolol (50 to 100 mg) daily, added to previous therapy. Resistance arteries dissected from subcutaneous tissues were assessed on a pressurized myograph. After 1 year of treatment, systolic and diastolic BP and glycemia were equally well controlled in the valsartan and atenolol groups. Endothelium-dependent and independent relaxation did not change in the treated groups. After 1 year of treatment, resistance artery media:lumen ratio decreased in the valsartan group (7.9±0.5% after versus 9.8±0.6% before; P<0.05) but not in the atenolol-treated group (9.9±0.9% versus 10.6±1%; P value not significant). Artery walls from atenolol-treated patients became stiffer, with no change in the valsartan-treated patients. In conclusion, similar intensive BP control for 1 year with valsartan was associated with improved structure of resistance arteries in diabetic hypertensive patients, whereas vessels from atenolol-treated patients exhibited unchanged remodeling and a stiffer wall. The addition of ARBs but not BBs to antihypertensive medications that may include angiotensin-converting enzyme inhibitors and/or calcium channel blockers results in an improvement in resistance artery remodeling in diabetic hypertensive patients. (Hypertension. 2006;48:271-277.)

Key Words: vascular diseases ■ antihypertensive agents ■ angiotensin antagonist ■ hypertrophy ■ remodeling ■ microcirculation

The frequency of diabetes mellitus is increasing rapidly worldwide.1 Diabetes mellitus doubles the risk of cardiovascular events.2-4 Eighty to 90% of patients with type 2 diabetes mellitus develop hypertension, and ≥20% of hypertensive patients develop diabetes. This combination of cardiovascular risk factors will account for a large proportion of cardiovascular morbidity and mortality. In the United Kingdom Prospective Diabetes Study (UKPDS), tight blood pressure (BP) control in hypertensive patients with type 2 diabetes reduced the risk of macrovascular disease, stroke, and deaths related to diabetes.5 Most clinical trials fail to show the beneficial effects on cardiac ischemia expected from population studies, which may imply that BP lowering alone does not normalize altered vessels. In hypertensive patients, the extent and consequences of tissue ischemia (in the heart, kidney, or brain) are influenced by small vessel disease.6,7 In the coronary circulation, for example, in the presence of intermediate coronary lesions, small arteries compromise coronary blood flow.8,9 Accordingly, structural alterations in small arteries of a high-risk population are associated with the occurrence of future cardiovascular events.10 In diabetic patients, vascular remodeling and endothelial dysfunction in small (resistance) arteries are similar to those found in hypertensive patients.11 BP control with angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), or calcium channel blockers (CCBs) has corrected small artery structure and/or endothelial dysfunction in hypertensive patients.12-19 Treatment of patients with hypertension and diabetes with ACEIs20 and ARBs21 improved both macrovascular and microvascular alterations. However, despite achieving BPs similar to those reached at the end of UKPDS with ACEIs and/or CCBs, hypertensive diabetic patients with well-controlled blood glucose and lipid levels showed persistent remodeling of resistance arteries.22 We, therefore, questioned whether remodeling of

Received January 26, 2006; first decision February 12, 2006; revision accepted May 23, 2006.
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Hypertension is available at http://www.hypertensionaha.org

DOI: 10.1161/01.HYP.0000230234.84356.36

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resistance vessels from hypertensive diabetic patients would improve after 1 year of tight BP control with either the ARB valsartan or the β-blocker (BB) atenolol added to previous therapy that included ACEIs and/or CCBs.

Methods
Patients
The study protocol was approved by the Ethics Committee of the Clinical Research Institute of Montreal. Normotensive nondiabetic subjects and hypertensive patients with type 2 diabetes (aged 30 to 70 years) provided written informed consent to participate in the study. Clinic sitting BP was measured after 15 minutes of rest; diastolic BP was read as phase V Korotkoff sounds. The BP was measured in the morning before antihypertensive drugs were taken. Control subjects had systolic and diastolic BP <130 and <85 mm Hg, respectively. Recumbent systolic and diastolic BPs of hypertensive type 2 diabetic patients were >130 and/or >85 mm Hg, respectively, on ≥3 occasions. None of the patients received ARBs or BBs. Sixty-eight percent of patients were receiving an ACEI (average equivalent to 22.2 mg of lisinopril per day) and 46% a CCB (average equivalent to 7.7 mg per day of amlodipine), which were not stopped. All of the patients had a history of diabetes for ≥6 months, well controlled with oral hypoglycemic agents or insulin (only 4 patients had glycohemoglobin >8%). The absence of secondary forms of hypertension was confirmed by usual diagnostic techniques. Left ventricular mass was evaluated from 12-lead electrocardiograms with the product of QRS duration and Cornell voltage criteria23 and with Sokolow-Lyon criteria.24 Exclusion criteria included smoking >10 cigarettes per day, serum creatinine concentration >200 μmol/L, asymptomatic ischemic heart disease or myocardial infarction within the previous 6 months, congestive heart failure, or systemic diseases.

Trial Design
Gluteal subcutaneous biopsies were obtained under local anesthesia during a run-in period of 4 weeks on placebo, and a second biopsy was obtained after 1 year of treatment, and these were performed as in previous studies.14,17,22 Biopsies were performed only once on normotensive subjects. Patients were randomly double-blindly assigned to treatment with 80 mg of valsartan or 50 mg of atenolol. If systolic and diastolic BP were >130 and/or >80 mm Hg, respectively, after 2 weeks, the dosage of valsartan was raised to 160 mg and atenolol to 100 mg. Four weeks later, open-label hydrochlorothiazide (12.5, raised later to 25 mg if needed) was added to achieve goal BP.

Vascular Studies
The study of resistance arteries was performed by individuals unaware of the groups to which samples belonged. Small arteries (lumen diameter 150 to 300 μm) were isolated from subcutaneous tissue immediately after the biopsy and mounted on a pressurized myograph, and experiments were carried out as described previously.22 Calculation of vascular morphology and mechanics, and indexes thereof, was carried out as described previously.14,25

Data Analysis
Results are presented as mean±SEM. Comparisons were performed by 2-tailed Student t test, 1-way ANOVA followed by the Newman-Keuls test, or 2-way or repeated-measures ANOVA, as appropriate. Regression analysis was done by the least-squares method. P<0.05 was considered statistically significant.

Results
Dyslipidemia was the history of diabetes tended to be longer (Table). Diabetic hypertensive patients randomly assigned to atenolol were slightly but significantly older than control subjects. There was a nonsignificant trend of body weight and body mass index to be higher in patients than controls. Body weight and body mass index of patients were unchanged at the end of the study. Systolic and diastolic BP at the beginning of the study (under their previous antihypertensive therapy, including an ACEI in 68%, receiving a mean dose of different ACEI equivalent to 22.2 mg of lisinopril per day and/or a CCB in 46% of the patients, equivalent to a mean dose of 7.7 mg per day of amlodipine, similarly distributed in both groups) were significantly higher (P<0.05) than in normotensive subjects. During the study, systolic and diastolic BP were equally well controlled by atenolol at a final dose of 64±6 mg per day in one group and by valsartan at a final dose of 114±11 mg per day in the other group (Figure 1a and 1b). Hydrochlorothiazide was added to 3 patients on valsartan and 4 patients on atenolol to achieve goal BP. Mean arterial pressure was similar in both treatment groups (Table). There was no correlation between mean arterial pressure, duration of diabetes, or hypertension in either group. Pulse pressure (PP) was significantly (P<0.01) higher in patients than in normotensive subjects before random assignment and significantly (P<0.02) reduced only by valsartan (Table). PP correlated with age (P<0.05) and duration of diabetes (P<0.05) and hypertension (P<0.05).

Glycemia was identical and well controlled in both treatment groups. Sixty-four percent of patients received lipid-lowering therapy with fibrates or statins. Total and low-density lipoprotein cholesterol and triglycerides were well controlled in the whole cohort. Renal function was well preserved in patients before and after treatment. Two patients randomly assigned to atenolol and 6 randomly assigned to valsartan presented microalbuminuria (>2.5 mg albumin/mmol creatinine). Only 3 patients presented microalbuminuria after treatment with valsartan. None of the patients had ECG left ventricular hypertrophy before random assignment. At the end of the study, there was a trend toward reduction of left ventricular hypertrophy ECG criteria in the valsartan group (mean Cornell voltage-duration product, −10±5% and −2±4%; Sokolow-Lyon voltage, −5±3% and...
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Clinical Parameters of Subjects Studied

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control</th>
<th>Atenolol Before</th>
<th>Atenolol After 1 Year</th>
<th>Valsartan Before</th>
<th>Valsartan After 1 Year</th>
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<td>10</td>
<td>14</td>
<td>14</td>
<td>14</td>
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</tr>
<tr>
<td>Sex (M/F)</td>
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<td>9/5</td>
<td>9/5</td>
<td>8/6</td>
<td>8/6</td>
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<td>Age, y</td>
<td>51.2±1.7</td>
<td>59.9±1.2†</td>
<td>+1</td>
<td>55.4±2.2</td>
<td>+1</td>
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<td>Body weight, kg</td>
<td>75.1±4.3</td>
<td>80.9±3.3</td>
<td>81.5±4</td>
<td>88.9±4.9</td>
<td>89.6±4.7</td>
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<td>BMI, kg/m²</td>
<td>26.8±1</td>
<td>28.7±0.9</td>
<td>28.8±1</td>
<td>32.2±2</td>
<td>32.4±1</td>
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<td>Systolic BP, mm Hg</td>
<td>109.4±3.1</td>
<td>143.6±1.9†</td>
<td>127.9±2.6†</td>
<td>143.9±3†</td>
<td>123.1±2.5†</td>
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<tr>
<td>Diastolic BP, mm Hg</td>
<td>76.1±18</td>
<td>82.9±2.2†</td>
<td>75.2±2.1†</td>
<td>84.1±2.1†</td>
<td>74.1±2.1*</td>
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<td>PP, mm Hg</td>
<td>33.4±2.3</td>
<td>60.3±2.2†</td>
<td>52.3±2.6†</td>
<td>59.7±3.9†</td>
<td>48.9±2.8†</td>
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<td>Mean arterial pressure, mm Hg</td>
<td>87.1±2.0</td>
<td>103.4±2.0†</td>
<td>92.3±2.0*</td>
<td>104±1.6†</td>
<td>90.4±1.8*</td>
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<td>Heart rate, bpm</td>
<td>77.2±3.4</td>
<td>72.1±2.6</td>
<td>60.8±2.5†*</td>
<td>72.9±3</td>
<td>72.2±3</td>
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<td>16.2±2.2</td>
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<td>Duration of diabetes, y</td>
<td>NA</td>
<td>4.5±2.3</td>
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<td>No antihypertensive drugs‡</td>
<td>NA</td>
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</tr>
<tr>
<td>No patients on ACEIs</td>
<td>NA</td>
<td>9 (64%)</td>
<td>UN</td>
<td>10 (71%)</td>
<td>UN</td>
</tr>
<tr>
<td>No patients on CCBs</td>
<td>NA</td>
<td>6 (43%)</td>
<td>UN</td>
<td>7 (50%)</td>
<td>UN</td>
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<tr>
<td>Fasting glucose, mmol/L</td>
<td>4.7±0.1</td>
<td>7.1±0.4†</td>
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<td>8.6±0.5†</td>
<td>7.7±0.5†</td>
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<td>Glycated hemoglobin, %</td>
<td>ND</td>
<td>6.8±3.7</td>
<td>6.4±0.02</td>
<td>7.1±0.3</td>
<td>7.1±0.5</td>
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<td>Serum creatinine, μmol/L</td>
<td>81.6±5.6</td>
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<td>80.9±2.3</td>
<td>75.5±1</td>
<td>86.3±4.5</td>
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<td>Total cholesterol, mmol/L</td>
<td>5.0±0.2</td>
<td>4.6±0.2</td>
<td>4.8±0.2</td>
<td>4.8±0.2</td>
<td>4.4±0.3</td>
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<td>HDL cholesterol, mmol/L</td>
<td>1.4±0.1</td>
<td>1.4±0.1</td>
<td>1.3±0.1</td>
<td>1.4±0.1</td>
<td>1.2±0</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>3.1±0.2</td>
<td>2.6±0.2</td>
<td>2.8±0.2</td>
<td>2.5±0.2</td>
<td>2.6±0.3</td>
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<tr>
<td>Triglycerides, mmol/L</td>
<td>1.1±0.2</td>
<td>1.4±0.2</td>
<td>1.5±0.2</td>
<td>2.5±0.6</td>
<td>2.1±0.4</td>
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<tr>
<td>Microalbuminuria, mg/mmol cr</td>
<td>0.8±0.3</td>
<td>2.9±1.2</td>
<td>2.4±1</td>
<td>2±0.5</td>
<td>1.2±0.4</td>
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</tbody>
</table>

HDL indicates high-density lipoprotein; LDL, low-density lipoprotein; BMI, body mass index; cr, creatinine; NA, not applicable; UN, unchanged; NA, not done.  
*P<0.05 post-treatment vs pretreatment.  
†P<0.05 vs control.  
‡No. of antihypertensive drugs patients were taking before addition of atenolol or valsartan.

0±5% in the valsartan and atenolol group respectively; P value not significant).

Resistance vessels of hypertensive diabetic patients exhibited significantly greater media thickness (+24%; P<0.05) and media:lumen ratio (M/L; +19%, P<0.05) than normotensive subjects. Media cross-sectional area tended to be increased in the hypertensive diabetic patients compared with control subjects without achieving significance (16±1×10³ versus 14±1.7×10³ μm², respectively; +12%). However the remodeling and growth indexes were ~80% and ~10%, respectively, suggesting that vessels in these subjects with relatively well-controlled BP, with many taking ACEIs and/or CCBs, exhibited eutrophic remodeling. After 1 year of treatment, media thickness was unchanged in both groups (~9% and ~14%, respectively, versus before treatment; P value not significant). There was a trend toward an increase of the lumen after valsartan treatment (+10% versus before treatment; P value not significant) and a decrease in the atenolol group (~9% versus before treatment; P value not significant). M/L was significantly reduced at the end of the study only in valsartan-treated patients (P<0.05; Figure 2), independent of the lumen diameter achieved in vitro at each pressure level (Figure 3). Cross-sectional area was unchanged in the valsartan group (16±1.6×10³ μm²) and tended to be slightly reduced in atenolol group (13±1×10³ μm², −19%; P value not significant). Thus, eutrophic outward remodeling occurred in valsartan-treated patients, whereas inward remodeling occurred in atenolol-treated patients. There was no correlation between M/L and age, duration of diabetes, or hypertension in either group.

Stress-strain curves of vessels from the hypertensive diabetic patients were shifted to the left (increased stiffness) compared with controls (Figure 4). A further leftward shift occurred under atenolol, whereas the stress-strain curve of vessels from valsartan-treated patients remained unchanged.

Endothelium-dependent and independent relaxation of vessels was similar in patients before randomization and the control group and did not change significantly under treatment (Figure 5a). N⁶-nitro-L-arginine methyl ester (L-NAME) significantly reduced acetylcholine-induced dilation equally in all of the groups (Figure 5b).

Discussion

This randomized, double-blind, parallel-design, 1-year trial demonstrates that tight BP control (BPs <130/80 mm Hg) with the angiotensin type I (AT₁) receptor antagonist valsartan added to previous antihypertensives, including ACEIs and CCBs, improved structural changes in resistance vessels of hypertensive
diabetic patients. Equally effective BP control with the BB atenolol failed to influence remodeling of resistance arteries and resulted in increased wall stiffness.

Structural remodeling of resistance arteries in high-risk populations predicts a worse cardiovascular outcome. It is, therefore, likely that small artery remodeling predicts increased cardiovascular risk in diabetic hypertensive subjects. Intervention to improve remodeling of resistance vessels in these high-risk subjects may, thus, improve outcome, although this remains to be demonstrated.

Drugs that interfere with the renin-angiotensin system (ACEIs and ARBs) and calcium movements (CCBs) seem to be more effective than some BBs, such as atenolol, to improve vascular structure. Patients in our study presented persistent vascular remodeling before randomization (Figure 2) despite the fact that ≈68% were treated with ACEIs and/or ≈46% with CCBs, drugs that may correct small artery remodeling, and BP was reduced to the level achieved at the end of UKPDS (Table). This suggests that more selective or intensive treatment must be undertaken to improve vascular structure and cardiovascular risk in patients with hypertension and type 2 diabetes mellitus.

Regression of small artery M/L in the valsartan but not the atenolol group (Figure 2), together with the leftward shift of the stress-strain curve (increased wall stiffness) in vessels from the atenolol but not the valsartan group (Figure 4), suggests that blockade of AT₁ receptors in addition to ACEIs and/or CCBs (most patients were already receiving these agents) provides added value in the treatment of hypertensive vascular remodeling.

Figure 2. M/L of resistance arteries (measured at 60 mm Hg intraluminal pressure). Top, results from control subjects and hypertensive diabetic subjects before the study and after 1 year of treatment with atenolol or valsartan. Bottom, individual results for the atenolol and valsartan groups. *P<0.05 vs all groups; ††P<0.05 valsartan after 1 year vs valsartan before.

Figure 3. Mean M/L of resistance arteries measured at increasing intraluminal pressures.

Figure 4. Stress/strain relationship of resistance arteries from normotensive individuals and patients in the study. ΔD is the increase in internal diameter at each level of increasing intraluminal pressure over D₀, which is the original diameter at 3 mm Hg.

Figure 5. a, Endothelium-dependent (acetylcholine, Ach) and -independent (sodium nitroprusside, SNP) relaxation of resistance arteries from normotensive individuals and patients in the study. Vessels were preconstricted with norepinephrine 1 μmol/L. b, Effect of L-NAME, NO synthase inhibitor, on acetylcholine-induced relaxation. *P<0.05 Ach+L-NAME vs Ach in all groups.
diabetic patients. AT₁ receptor blockade may be particularly effective in light of reports that dual pathways for angiotensin II generation by angiotensin-converting enzyme and a chymostatin-sensitive enzyme, presumably chymase, exist in human resistance arteries. In hypertensive diabetic patients, selective AT₁ blockade with candesartan was more effective than enalapril in reducing collagen content in the vasculature, although both drugs corrected small artery remodeling. Hemodynamic actions could contribute to the disparate impact of these drugs on small artery structure. Vasoconstriction may represent one of the mechanisms leading to eutrophic remodeling as the vasoconstricted state becomes embedded in the newly secreted extracellular matrix. Accordingly, vasodilation rather than specific actions of the antihypertensive agents used could play a role in the correction of remodeling. Indeed, valsartan acts as a vasodilator thanks to its AT₁ antagonistic properties, whereas atenolol may induce vasoconstriction and reduced blood flow. In the present study, inward remodeling occurred after atenolol treatment as reported by others in small vessels after blood flow reduction. Furthermore, the “downstream” increase in impedance at the level of the remodeled arteries may cause early reflected waves and an “upstream” increase in transmural pressure at the level of central elastic arteries that leads to increased systolic BP and arterial stiffness. BP was equally tightly controlled by valsartan and atenolol, without improved vascular structure with the latter, suggesting that intensive BP control alone did not play a role in our findings. However, and although during the study BP was equally well controlled in both groups (Figure 1), at the end of the study, systolic BP was 5 mm Hg (although not significantly) higher in the atenolol than in the valsartan group. Valsartan but not atenolol reduced PP, a marker of arterial stiffness. Stiffness of small arteries was, in fact, enhanced in patients treated with atenolol, which may have also occurred in large arteries. This may explain differences in systolic BP at the end of the study. Although the patients randomly assigned to atenolol were slightly older, and duration of diabetes was slightly shorter, neither the latter nor age correlated with M/L. Duration of hypertension, similar in both groups, did not correlate with M/L, suggesting that none of these parameters influenced findings.

Patients with hypertension and type 2 diabetes have impaired subcutaneous small artery endothelial function. ACEIs and ARBs improve endothelial dysfunction of resistance arteries from patients with hypertension and/or diabetes mellitus related either to hemodynamic actions or reduction of oxidative stress. In this study, patients exhibited preserved endothelial function (Figure 5a) and inhibitory L-NAME effects (reflecting NO availability; Figure 5b) already at the time of random assignment. This may result from BP control and that ∼68% of patients were already on ACEIs and ∼46% were on CCBs, both of which improve endothelial function. The blood lipid profile of the patients was good before the randomization, and many were already treated with statins or fibrates, which may further improve endothelial function, because a substantial proportion of endothelial dysfunction in diabetes is attributable to abnormal lipid profile. Previous therapy with ACEIs, CCBs, statins, and fibrates may, thus, explain the absence of significant endothelial dysfunction at randomization in this cohort of patients as a whole and accordingly lack of further correction after treatment.

Perspectives

The benefit of treating hypertension in terms of reduction of morbidity and mortality is well established, mainly in high-risk patients. However, there is controversy on whether this benefit is derived exclusively from effects of BP reduction, which seems to be supported by recent multicenter clinical trials and meta-analyses, or whether the antihypertensive agents exert effects beyond BP reduction. Reduction of vascular remodeling may be an important goal to decrease cardiovascular risk, particularly in high-risk patients, such as those with the metabolic syndrome and a cluster of cardiovascular risk factors, as found in patients with hypertension and diabetes. In large studies, selective antagonism of the renin–angiotensin system with losartan was more effective than atenolol to improve cardiovascular outcomes in high-risk patients despite a similar level of BP control. Treatment with ARBs prevents progression of diabetic nephropathy, retinopathy, and neuropathy. Our results suggest that it may be preferable to achieve tight BP control by using ARBs in addition to other antihypertensive agents to improve vascular structure and reduce cardiovascular risk in diabetic hypertensive patients. A limitation to our conclusion is that because patients were already receiving ACEIs at a dose equivalent to 22.2 mg of daily lisinopril, and the maximum dose of the latter is 40 mg per day, it is possible that comparable effects might perhaps have been achieved by raising the dose of ACEIs to this maximum dose. Subcutaneous small arteries behave structurally and functionally like small arteries from the coronary, renal cortical, and mesenteric vascular beds in animal models of hypertension. Thus, vascular protection of subcutaneous resistance arteries under ARB treatment may reflect improvement in the remodeling of coronary, renal, and cerebral vessels, which could lead to improved outcome for these patients.

Acknowledgment

We thank Mireille Kirouac for devoted follow-up of patients and blood sampling.

Sources of Funding

This study was supported by grant 13570 (to E.L.S.) and a group grant to the Multidisciplinary Research Group on Hypertension, both from the Canadian Institutes for Health Research, and by a grant from Novartis Pharmaceuticals Canada. R.M.T. was supported by a scholarship from the Fonds de recherches en santé du Québec. C.S. and C.D.C. were supported in part by fellowships from the Italian Society of Hypertension. D.H.E. was supported by a grant from the Deutsche Forschungsgemeinschaft. E.L.S. received a research grant from Novartis Pharmaceuticals Canada.

Disclosures

None.

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Hypertension. 2006;48:271-277; originally published online June 19, 2006;
doi: 10.1161/01.HYP.0000230234.84356.36

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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