Beneficial Effects of Valsartan in Asymptomatic Individuals With Vascular or Cardiac Abnormalities

The DETECTIV Pilot Study

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Objectives
We studied the efficacy of valsartan (Val) to slow cardiovascular disease progression in asymptomatic high-risk prehypertensive or hypertensive patients with blood pressure (BP) controlled to <140/90 mm Hg and with evidence for functional or structural alterations in the cardiovascular system.

Background
Identifying individuals with early markers for cardiovascular disease raises the possibility for pharmacotherapy to slow progression and delay or prevent future morbid events.

Methods
Seventy-six subjects with a Rasmussen Disease Score (RDS) of 6 or higher were randomized double-blind to receive placebo (Plac) or Val 160 mg once daily for 6 months followed by 6 months of single-blind Val in both groups. A panel of 10 tests, including large and small artery elasticity, resting and treadmill exercise BP, carotid intimal-media thickness, retinal vascular photography, microalbuminuria, electrocardiography, echocardiography, and plasma B-type natriuretic peptide, was performed at baseline and after 6 and 12 months of treatment. Each test result was scored as normal (0), borderline (1), or abnormal (2), and the total RDS was calculated by adding all the scores of the individual tests.

Results
Valsartan significantly reduced the RDS after 6 months versus Plac (p < 0.03) and at 12 months (either 12 or 6 months of Val, p < 0.0001). The major contribution in risk score reduction was due to an increase in small artery elasticity and a decrease in BP, and after 12 months there was a reduction in left ventricular mass index (p < 0.03).

Conclusions
Valsartan can slow progression and/or reverse early cardiovascular disease in asymptomatic high-risk patients with prehypertension or BP controlled to <140/90 mm Hg. (J Am Coll Cardiol 2007;50:836–9) © 2007 by the American College of Cardiology Foundation.

Most cardiovascular (CV) events are a consequence of a progressive atherosclerotic process that can be detected long before symptoms develop (1). Dysfunction of the vascular endothelium seems to be a key in the progression to atherosclerosis and CV events (2). Identifying individuals with early markers for this vascular disease process raises the possibility for pharmacotherapy to slow the progression and delay or prevent future morbid events (3,4).

Most attempts to identify individuals at risk for CV events have involved screening for risk factors that are statistically associated with future CV events (5). This approach does not provide any insight as to how the risk factors are impacting the biologic target organs, the vasculature, and the heart. Indeed, these traditional risk factors do not seem to be useful in stratifying the severity of disease in individual patients (6).

The role of angiotensin II, the key mediator of the renin-angiotensin–aldosterone system (RAAS), in the pathophysiology of CV disease is well known (7). Large-scale, well-controlled clinical trials in high-risk populations have demonstrated that angiotensin II receptor blockers (ARBs) reduce CV morbidity and mortality (8). As the underlying mechanisms of vascular disease and the effects of ARBs on these processes have been further defined, the therapeutic focus has begun to shift toward prevention of disease progression at earlier stages. Noninvasive diagnostic tests are now available to assess otherwise healthy individuals for subclinical CV disease (9). Our aim in this pilot trial was to examine whether the
CV benefit of the ARB valsartan (Val) extends to asymptomatic individuals with evidence of early CV disease in a randomized, double-blind, placebo-controlled study.

**Methods**

**Subjects.** Patients screened in the Rasmussen Center for CV Disease Prevention at the University of Minnesota were evaluated for participation in the DETECTIV (DEtection and Treatment of Early Cardiovascular disease Trial: Intervention with Valsartan) pilot study. Patients’ characteristics are described in the Results section. The study was approved by the local institutional review board.

**Measurements and study parameters.** The Rasmussen Center screening consists of assessment of vascular and cardiac function and structure on the basis of 8 noninvasive tests performed in 1 h by a single technologist and 1 blood and urine test analyzed in the laboratory (9). These tests include the following:

**SMALL AND LARGE ARTERY ELASTICITY.** Radial artery pulse waves are registered with the CV Profilor (Hypertension Diagnostics, Eagan, Minnesota). Small artery (C2) and large artery (C4) elasticity are derived from the pulse contour analysis.

**SITTING REST AND UPRIGHT EXERCISE BLOOD PRESSURE.** Sitting blood pressure (BP) is measured by standard sphygmomanometry at rest. The patient then stands on a treadmill, and BP is measured before and at the end of a 3-min workload at 5 METS on the basis of a treadmill speed of 2.3 mph at a slope of 7%.

**OPTIC FUNDUS DIGITAL PHOTOGRAPHY.** Optic fundus photos are taken with a digital camera (Canon, Greenville, South Carolina). Fundus photos are analyzed for the arteriole-to-venule (A/V) ratio and the presence of A/V crossing changes.

**CAROTID INTIMAL-MEDIA THICKNESS.** Ultrasound with a Sonosite Titan (Sonosite, Inc., Bothell, Washington) is employed to measure intimal-media thickness 1 cm distal to the carotid bulb and to identify localized carotid plaques.

**MICRO-ALBUMINURIA.** A spot urine sample is analyzed for albumine/creatinine ratio.

**ELECTROCARDIOGRAPHY.** A standard 12-lead electrocardiogram is evaluated for evidence of hypertrophy, repolarization abnormalities, or conduction abnormalities.

**LEFT VENTRICULAR MASS INDEX.** Left ventricular (LV) ultrasound is performed with the Sonosite Titan, and LV mass index (LVMI) was calculated according the formula of Devereux.

**PLASMA B-TYPE NATRIURETIC PEPTIDE.** A venous blood sample is analyzed for plasma B-type natriuretic peptide (BNP) with a Biosite Triage Platform (Biosite Inc., San Diego, California).

Each test is scored as 0 if normal, 1 for borderline, and 2 for abnormal. The criteria for normal and abnormal has been established on the basis of large published databases, as reported previously (9). The 10 tests therefore provide a total score from 0 to 20, which is called the Rasmussen Disease Score (RDS). Table 1 summarizes the range of values for markers for the RDS. We have arbitrarily established, on the basis of experience in a large screened population, a score of 6 or more as indicative of definite CV abnormalities (9).

Entrance criteria for DETECTIV included an RDS of ≥6, BP below 140/90 mm Hg without or with antihypertensive therapy, and cholesterol levels controlled with or without statin therapy according to current guidelines.

### Table 1: Range of Values of Markers for RDS

<table>
<thead>
<tr>
<th>Test</th>
<th>Normal</th>
<th>Borderline</th>
<th>Abnormal</th>
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<tbody>
<tr>
<td>RDS</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Large artery elasticity (C2)</td>
<td>(age- and gender-dependent)</td>
<td>(age- and gender-dependent)</td>
<td>(age- and gender-dependent)</td>
</tr>
<tr>
<td>Small artery elasticity (C4)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Resting BP (mm Hg)</td>
<td>SBP &lt;130 and DBP &lt;85</td>
<td>SBP 130-139 or DBP 85-89</td>
<td>SBP ≥140 or DBP ≥90</td>
</tr>
<tr>
<td>Exercise BP (mm Hg)</td>
<td>SBP rise ≤30 and SBP &lt;169</td>
<td>SBP rise 30-39 or SBP 170-179</td>
<td>SBP rise ≥40 or SBP ≥180</td>
</tr>
<tr>
<td>Retinal vasculature</td>
<td>A/V ratio &gt;3.5</td>
<td>A/V ratio ≤3.0 or mild A/V crossing changes</td>
<td>A/V ratio ≤1.2 or A/V nicking</td>
</tr>
<tr>
<td>Carotid IM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Microalbuminuria (mg/mmol)</td>
<td>≤0.6</td>
<td></td>
<td>≥1.00</td>
</tr>
<tr>
<td>Electrocardiogram</td>
<td>No abnormalities</td>
<td></td>
<td>Non-specific abnormality</td>
</tr>
<tr>
<td>LV ultrasound LVMI (g/m²)</td>
<td>≤120</td>
<td>120-129</td>
<td>≥130</td>
</tr>
<tr>
<td>BNP (µg/dl)</td>
<td>≤50</td>
<td>65-99</td>
<td>≥100</td>
</tr>
</tbody>
</table>

A/V ratio = arteriole-to-venule ratio; BNP = B-type natriuretic peptide; BP = blood pressure; DBP = diastolic blood pressure; IMT = intima-media thickness; LV = left ventricular; LVMI = left ventricular mass index; RDS = Rasmussen Disease Score; SBP = systolic blood pressure.
Table 2
Baseline Demographics and Clinical Characteristics of the Study Population (n = 76)

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 38)</th>
<th>valsartan (n = 38)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>54 ± 11</td>
<td>57 ± 9</td>
</tr>
<tr>
<td>Male/female</td>
<td>22/16</td>
<td>24/14</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.72 ± 11</td>
<td>1.71 ± 11</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>82.0 ± 16.8</td>
<td>85.8 ± 18.7</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.8 ± 4.9</td>
<td>28.1 ± 6.3</td>
</tr>
<tr>
<td>Cholesterol (mg/dl)</td>
<td>194.1 ± 29.6</td>
<td>198.1 ± 34.4</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dl)</td>
<td>117.0 ± 25.3</td>
<td>125.3 ± 26.1</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dl)</td>
<td>52.3 ± 13.6</td>
<td>46.2 ± 15.3</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>126.3 ± 64.3</td>
<td>154.4 ± 119.4</td>
</tr>
<tr>
<td>Glucose (mg/dl)</td>
<td>89.6 ± 9.0</td>
<td>87.1 ± 9.0</td>
</tr>
</tbody>
</table>

There are no significant differences for all parameters at baseline between the placebo and valsartan groups.

BMI = body mass index; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

Exclusions included prescription for an ARB, another serious medical illness likely to limit survival, or unlikeliness to be compliant with the regimen.

After the initial screen, patients were randomly assigned double-blind to receive Val 160 mg once daily or matching placebo (Plac) for 6 months. At 6 months the full screening testing was repeated. Then all the study patients (Val and Plac group) were given Val 160 mg once/day for the next 6 months. At 12 months all the studies were repeated.

At baseline a fasting venous blood sample was taken for the determination of total cholesterol, triglycerides, low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol, and glucose.

Statistical analysis. Descriptive values are expressed as mean ± SD for variables with normal distribution or medians and inter-quartile ranges for variables with non-normal distribution. Unpaired t test was used to compare the group means for variables with normal distribution. Mann-Whitney U test was used to compare medians and interquartile ranges for variables with non-normal distribution. A paired Student t test was used to compare the changes from baseline to 6 and 12 months within 1 group. Chi-square test was used to compare nominal variables. For all tests a p value < 0.05 was considered as statistically significant. Statistical analysis was performed with a standard statistical program package (STATVIEW, version 5.0, ABACUS CONCEPT Inc., Berkeley, California).

Results

Eighty subjects were initially randomized into DETECTIV; 6 withdrew early in the study, 2 because of an unrelated medical complication, and 4 because of withdrawn consent. The 76 subjects followed to completion are described in Table 2.

Table 3 summarizes the RDS of the 10 tests at baseline and after 6 months in Plac and Val groups and after 12 months when both groups were treated with Val. During the first 6 months of double-blind randomization to Val versus Plac, the RDS fell in both groups, but the fall was significantly (p = 0.03) greater in the Val group. The change in RDS from 6 to 12 months in the Plac group was highly significant (p < 0.0001). Patients assigned to Val at baseline exhibited modest further improvement from 6 to 12 months with continuation of Val (p = 0.01). After 12 months the decline in RDS in Val averaged 3.8 units, and a 44% reduction in the CV abnormalities identified. A similar reduction was noted in the initial Plac group treated the last 6 months with Val.

Because the RDS represents a scoring system based on threshold levels of individual components of the disease score, the individual measurement changes were compared. Small artery elasticity (C<sub>2</sub>) increased at 6 months by 57% in response to Val (p < 0.0001) but by only 9% in response to Plac (p = 0.38), and the difference was highly significant.
(p < 0.01). Systolic blood pressure (SBP) and diastolic blood pressure (DBP) decreased more in the Val arm compared with in the Plac arm (p < 0.01).

After 12 months’ therapy the Plac patients who had received Val for 6 months exhibited a significant 30% increase from baseline in small artery elasticity (p < 0.001), but this was significantly smaller (p < 0.02) than the 77% increase in the group that had received Val for 12 months. This improvement in elasticity was characterized by a progressive alteration in the arterial pulse wave with reduction in the late systolic reflected wave.

Structural markers of CV disease were not altered at 6 months, but by 12 months the group who had received Val for the entire trial exhibited a significant decrease in LVMI (p < 0.05). The other measures of vascular and cardiac function and structure were not significantly altered by Val.

Discussion

The pilot DETECTIV study allowed evaluation of the efficacy of Val versus Plac on the RDS and the 10 continuous variable components of the score in high-risk asymptomatic individuals with either prehypertension or controlled BP <140/90 mm Hg. During 6 months of Val, vascular function benefits, including improved small artery elasticity and a reduction in SBP and DBP within the normotensive range, were identified. These changes accounted for a significantly greater reduction in RDS at 6 months, further supported by a similar benefit from 6 months to 1 year in the group randomized to Val at 6 months.

The RDS is heavily dependent on structural abnormalities, and it is unlikely that 6 months would be a long enough time to detect gross benefits on structure. Nonetheless, treatment with Val for 12 months exerted a favorable effect on LVMI. Furthermore, from 6 to 12 months there was a further increase in small artery elasticity in the group randomized for 12 months to Val, and the improvement in elasticity was significantly greater after 12 months than after 6 months of therapy. This delayed increase in small artery elasticity is consistent with a slowly developing structural effect superimposed on the early functional benefit. These data on delayed cardiac and vascular effects suggest that longer-term therapy might display more dramatic benefits on structure of the vasculature and heart.

Angiotensin II has been implicated as a major contributor to endothelial dysfunction, hypertrophy of the vascular wall, arterial remodeling and inflammation, and consequently to reduced arterial compliance (8,10). Remodeling of small resistance arteries might be one of the earliest manifestations of target-organ damage and can be demonstrated before clinically apparent CV disease develops (11). Reducing BP might not suffice to improve outcomes in hypertension unless vascular remodeling is also corrected and endothelial function is improved. There is now growing evidence that ARB can favorably affect resistance artery structure and endothelial function. In recent studies in hypertensive patients, Val therapy has been demonstrated to improve compliance of the small and large arteries (12) and to improve endothelial function (13). Modest improvement of RDS in the Plac group during the first 6 months was related primarily to a decrease in BP and a modest increase in small artery elasticity. These effects might reflect the counseling regarding lifestyle changes and its positive influence on BP lowering and small artery elasticity. However this effect was less pronounced than compared with the first 6 months of Val.

The vascular and cardiac tests included in DETECTIV are all viewed as markers for disease progression that are predictive of CV risk. The disease identified by these markers progresses over many years, so it is not surprising that 6 to 12 months of therapy with an ARB was effective in improving only a few of the baseline abnormalities. A longer study in a larger population would likely provide more robust evidence for improvement in vascular and cardiac health.

As a pilot study DETECTIV was not designed to assess morbid events. Indeed, the population eligible for participation in DETECTIV had no evidence for overt disease that would place them at high immediate risk (14). The goal in this population is to slow disease progression from its earliest detection to hopefully delay or prevent morbid events during the patients’ productive years. Demonstration of this morbid event prevention would require a long study in a very large population. In the meantime, however, surrogate markers for the biological process in the arteries and heart that progress to morbid events should serve as an attractive means of identifying those at risk and demonstrating their response to therapy. Indeed, asymptomatic individuals with prehypertension or with BP controlled <140/90 mm Hg with high RDS might be candidates for pharmacotherapy, whereas those with low scores could be given life-style recommendations. The sensitivity and specificity of these scores would need to be documented in prospective studies.

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REFERENCES


