Valsartan Improves Arterial Stiffness in Type 2 Diabetes Independently of Blood Pressure Lowering

Janaka Karalliedde, Andrew Smith, Lorenita DeAngelis, Vincenzo Mirenda, Albert Kandra, Jaco Botha, Philippe Ferber, Giancarlo Viberti

Abstract—Increased arterial stiffness, as estimated from aortic pulse wave velocity (Ao-PWV), and albuminuria are independent predictors for cardiovascular disease in type 2 diabetes mellitus (T2DM). Whether angiotensin receptor blockers (ARBs), drugs with cardio-renal protective effects, improve Ao-PWV to a greater extent than other equipotent antihypertensive medications remains unclear. After a 4-week washout phase, we compared the effects of valsartan (n=66), an ARB, with that of amlodipine (n=65), a calcium channel blocker on Ao-PWV in 131 T2DM patients with systolic blood pressure (SBP) ≥60 mm Hg and raised albumin excretion rate (AER) in a 24-week randomized, double-blind, parallel group study. Hydrochlorothiazide (HCTZ) 25 mg/d was added to valsartan 160 mg and amlodipine 5 mg/od uptitrated to 10 mg/od after 4 weeks to ensure equivalent BP control. After 24 weeks brachial and central aortic BP had fallen to a similar extent with attained mean (SD) brachial and central PP of 61.6 (13.6) and 47.3 (14.1) mm Hg in the valsartan/HCTZ group and 61.5 (12.2) and 47.3 (9.9) mm Hg in the amlodipine group, respectively. Ao-PWV showed a significantly greater reduction, mean (95% CI), −0.9 m/s (−1.4 to −0.3) for valsartan/HCTZ compared to amlodipine (P=0.002). AER fell significantly only with Val/HCTZ from 30.8(20.4, 46.5) to 18.2(12.5, 26.3) mcg/min, (P=0.01) with between treatment difference in favor of Val/HCTZ of −15.3mcg/min (P<0.001). Changes in AER and Ao-PWV were not correlated. Valsartan/HCTZ improves arterial stiffness and AER to a significantly greater extent than amlodipine despite similar central and brachial BP control. These 2 effects, which appear independent of each other, may explain the specific cardio-renal protective properties of ARBs. (Hypertension. 2008;51:1617-1623.)

Key Words: type 2 diabetes ■ hypertension ■ arterial stiffness ■ albuminuria ■ angiotensin receptor blockers

Cardiovascular disease (CVD) is the main cause of death in patients with type 2 diabetes mellitus (T2DM). In T2DM angiotensin type 1 (AT1) receptor blockers (ARB) reduce albumin excretion and prevent the progression of diabetic renal disease, and inhibition of the renin angiotensin system (RAS) may also provide cardio-protective benefits. These effects would appear independent of the brachial blood pressure lowering action of these drugs. However, some authors have questioned whether antihypertensive drugs offer cardio-renal protection beyond blood pressure lowering.

In T2DM systolic hypertension is often associated with albuminuria, and both are strong predictors of CVD mortality and morbidity and progressive renal failure. Recent evidence indicates that increased arterial stiffness, involving accelerated vascular aging of the aorta, is a powerful and independent risk factor for early mortality and provides prognostic information above and beyond traditional CVD risk factors such as blood pressure itself, age, gender, diabetes, smoking, and cholesterol. As arterial stiffness is the principal determinant of pulse pressure (PP), any increase would result in unfavorable hemodynamics which affect ventricular afterload and impair coronary perfusion.

Arterial stiffness can be assessed noninvasively by measurement of Aortic pulse wave velocity (Ao-PWV), along the thoracoabdominal aortic pathway by a simple and reproducible method. Ao-PWV as assessed by carotid-femoral PWV is considered the gold standard for the measurement of arterial stiffness and has emerged as the only measure of arterial stiffness able to predict outcome in subjects with T2DM, hypertension, and end-stage renal disease (ESRD). Changes in Ao-PWV are believed to be influenced by long term pressure dependent structural changes which may be slowed but not reversed by pharmacotherapy. However, recent work has suggested that improved arterial compliance may be obtained in patients with isolated systolic hypertension independently of peripheral blood pressure changes. The cardio-renal protection afforded by inhibitors of the RAS may therefore be mediated, at least in part, by drug-specific effects on arterial stiffness and...
aluminumuria. In this study we examined whether the ARB valsartan would improve arterial stiffness to a greater extent than an equivalent antihypertensive medication, the calcium channel blocker amlopidine, in T2DM patients with systolic hypertension and aluminumuria.

Methods

Patients

Patients with a diagnosis of T2DM as defined by the World Health Organization, aged between 40 and 80 years with a recorded history of elevated albumin excretion rate (AER; albumin:creatinine ratio ≥2.5 mg/mmol in men and ≥3.5 mg/mmol in women on more than 3 occasions and/or AER ≥20 mcg/min on at least 2 timed overnight urine collections) and systolic hypertension defined as brachial systolic blood pressure (SBP) ≥140 mm Hg and pulse pressure (PP) ≥60 mm Hg (a conservative PP criterion for the diagnosis of isolated systolic hypertension) were eligible for the study. Exclusion criteria were a history of Type 1 Diabetes Mellitus, clinical or biochemical evidence of renal impairment (creatinine >150 μmol/L), uncontrolled diabetes defined as fasting plasma glucose >11.1 mmol/L or HbA1c >10%, presence of connective tissue diseases known to affect arterial vasculature, atrial fibrillation or other cardiac rhythm disorders, history of nondiabetic or obstructive kidney disease, microscopic or macroscopic hematuria, pregnancy, and history of a cardiovascular or cerebrovascular event in the preceding 12 months. The concomitant use at entry of medications such as thyrxiene and sympathomimetic drugs which could influence measurement of Ao-PWV was an additional exclusion criterion.

Study Design

This was a 24-week single-center, randomized, double-blind, parallel group, active-comparator controlled study. Patients receiving anti-hypertensive agents for systolic hypertension were permitted into the trial. Blood pressure medications were stopped for a wash out, run in phase of 4 weeks during which all patients received moxonidine (400 mcg/d) a central selective imidazoline receptor agonist. Moxonidine has minimal impact on the vessel wall properties and was used to avoid uncontrolled hypertension (SBP >150 mm Hg20 and pulse pressure >140 mm Hg20 and pulse pressure >140 mm Hg) was used to avoid uncontrolled hypertension (SBP >180 mm Hg). At the end of the run-in period patients with brachial PP ≥60 mm Hg and SBP ≥140 mm Hg were randomized to receive valsartan 160 mg or amlopidine 5 mg, and moxonidine was discontinued. Randomization was made to 1 of the 2 treatment arms and performed centrally using a validated system that automates the random assignment of treatment groups to randomization numbers. The randomization scheme was reviewed by a Biostatistics Quality Assurance Group at Novartis Pharma AG, the study sponsor, and locked after approval until all analyses were completed.

After 4 weeks hydrochlorothiazide (HCTZ) 25 mg/d was added to valsartan and amlopidine was up-titrated to 10 mg. HCTZ was added to valsartan 160 mg (the maximum dose licensed for use in the UK) to ensure equivalent BP-lowering between the treatment arms. HCTZ has no significant effect on arterial wall properties and thereby has a minimal effect on Ao-PWV.22 23 Amlopidine was chosen as a comparator in view of its potent antihypertensive action and previous clinical data, from patients with systolic hypertension, which suggested that amlopidine 10 mg would ensure equivalent BP control to the doses of valsartan/HCTZ (Val/HCTZ) used in this study. The use of other antihypertensive agents was not permitted during the trial as they could interfere with study evaluations and interpretation of results. However if brachial SBP and DBP exceeded the safety parameters of ≥180 mm Hg and ≥110 mm Hg, respectively, at any point during the study, patients were withdrawn from the study and treated accordingly. Similarly if SBP <100 mm Hg and DBP <60 mm Hg, patients were discontinued for safety reasons. Patients were reviewed at screening and at 2 and 4 weeks in the moxonidine run-in phase. Baseline assessments and measurements were performed at randomization visit and at 3 and 6 months.

All patients were recruited from the Diabetes Clinic at Guy’s and St Thomas Hospitals, London, United Kingdom and had to provide written informed consent to the study which was approved by the research ethics committee of Guy’s and St Thomas’ Hospitals and undertaken in adherence to the Declaration of Helsinki.

Measurements

All measurements and procedures were performed with the patients in the fasted state and having refrained from nicotine, alcohol, and caffeine for at least the previous 10 hours. Brachial and central blood pressure determinations including the aortic augmentation index (AIx) and Ao-PWV measurements were taken as previously described.26–28 Details of these measurements appear in the data supplement (available online at http://hyper.ahajournals.org).

Albumin concentration was measured by immunoturbidimetry using a Cobas Miras plus analyzer (Roche Diagnostics), and AER was calculated from the median of 3 nonconsecutive timed overnight urine specimens collected 1 week before Ao-PWV measurement. A fasting blood sample was taken for plasma glucose (enzymatic colorimetry), HbA1c (high-performance liquid chromatography [HPLC]), total cholesterol (enzymatic colorimetry), and serum creatinine (rate reaction) measurements by Beckman LX20 analyzer (Beckman Coulter). A panel of endothelial and oxidative markers which have been reported to influence vascular function were also studied at baseline and at the end of the study (see the data supplement).

Statistical Analysis

Detailed description of the statistical analysis plan is available in the data supplement. Briefly it was estimated that 52 patients per treatment group would provide 90% power at the 5% level (2-sided) to detect a difference in Ao-PWV between the valsalan 160 mg/HCTZ 25 mg and amlopidine 10 mg groups of 0.45 m/s (approximately equivalent to 5 years of vascular aging). Sample size calculations were performed using the software nQuery Advisor 4.0.

Groups were compared for demographic and baseline characteristics by summary statistics (mean, SD, median, and interquartile range for continuous variables depending on their distributions and proportions for nominal variables). Treatment comparability was examined using χ² tests for qualitative variables and using 1-way ANOVA F-tests for quantitative variables. AER values were log transformed before analysis in view of their skewed distribution and geometric mean and 95% confidence intervals are presented. The primary efficacy variable was the difference in change in Ao-PWV between the treatment groups, and the primary population used in this assessment was the intention to treat (ITT) population. The change in Ao-PWV was analyzed per prespecified statistical plan using analysis of covariance (ANCOVA) with treatment, gender, age, and operator as fixed factors and baseline mean PWV and baseline mean P as covariates. An additional model was also performed adding change from baseline to end of study in mean brachial PP. SAS version 8.02 was used to perform all the statistical analyses and P<0.05 was taken as being statistically significant.

Results

A total of 280 patients were screened of whom 144 were eligible to enter the study. These patients were randomized to Val/HCTZ (n=73) and amlopidine (n=71) groups.

Seven patients in the Val/HCTZ group (3 adverse events, 2 consent withdrawal, 1 lost to follow-up, and 1 administrative problem) and 6 patients in the amlopidine group (4 adverse events, 1 protocol violation, and 1 BP above acceptable value for physician in charge) dropped out of the study before obtaining a postbaseline measurement. This left 131 patients (Val/HCTZ=66 and amlopidine=65) which formed the intent to treat (ITT) population, defined as all randomized patients who provided baseline data and had at least 1 postbaseline measurement. A further 11 patients in the
Table. Baseline and End of Study Data for Selected Variables in Patients With T2DM, Systolic Hypertension, and Albuminuria Randomized to Valsartan/HCTZ or Amlodipine Treatment

<table>
<thead>
<tr>
<th>Variable</th>
<th>Valsartan/HCTZ</th>
<th>Amlodipine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brachial SBP, mm Hg</td>
<td>159.7 ± 10.7</td>
<td>156.3 ± 10.4</td>
</tr>
<tr>
<td>End of study</td>
<td>135.3 ± 18.7</td>
<td>137.2 ± 13.8</td>
</tr>
<tr>
<td>Change from baseline (95% CI)†</td>
<td>-23.7 (−28.5, −18.9)</td>
<td>-19.4 (−24.1, −14.6)</td>
</tr>
<tr>
<td>P value</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Brachial DBP, mm Hg</td>
<td>82.5 ± 9.3</td>
<td>82.4 ± 9.0</td>
</tr>
<tr>
<td>End of study</td>
<td>73.7 ± 10.7</td>
<td>75.7 ± 7.9</td>
</tr>
<tr>
<td>Change from baseline (95% CI)†</td>
<td>-9.4 (−11.9, −6.9)</td>
<td>-7.3 (−9.8, −4.9)</td>
</tr>
<tr>
<td>P value</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Brachial PP, mm Hg</td>
<td>72.2 ± 11.7</td>
<td>73.9 ± 10.0</td>
</tr>
<tr>
<td>End of study</td>
<td>61.6 ± 13.6</td>
<td>61.5 ± 12.2</td>
</tr>
<tr>
<td>Change from baseline (95% CI)†</td>
<td>-14.3 (−17.7, −10.8)</td>
<td>-12.2 (−15.5, −8.8)</td>
</tr>
<tr>
<td>P value</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Ao-PWV, m/s</td>
<td>12.5 ± 2.5</td>
<td>12.0 ± 2.5</td>
</tr>
<tr>
<td>End of study</td>
<td>10.7 ± 1.8</td>
<td>11.3 ± 2.6</td>
</tr>
<tr>
<td>Change from baseline (95% CI)‡</td>
<td>-1.8 (−2.4, −1.3)</td>
<td>-0.7 (−1.3, −0.2)*</td>
</tr>
<tr>
<td>P value</td>
<td>&lt;0.0001</td>
<td>0.01</td>
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<tr>
<td>AIX, %</td>
<td>28.2 ± 7.4</td>
<td>27.2 ± 7.3</td>
</tr>
<tr>
<td>End of study</td>
<td>22.7 ± 8.2</td>
<td>22.8 ± 7.7</td>
</tr>
<tr>
<td>Change from baseline (95% CI)‡</td>
<td>-4.3 (−6.7, −2.0)</td>
<td>-3.7 (−5.9, −1.4)</td>
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<tr>
<td>P value</td>
<td>0.0003</td>
<td>0.0015</td>
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<tr>
<td>Central aortic SBP, mm Hg</td>
<td>145.9 ± 14.6</td>
<td>142.0 ± 12.8</td>
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<tr>
<td>End of study</td>
<td>122.0 ± 18.8</td>
<td>122.5 ± 11.9</td>
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<tr>
<td>Change from baseline (95% CI)†</td>
<td>-23.6 (−28.7, −18.6)</td>
<td>-21.1 (−26.0, −16.3)</td>
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<td>P value</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
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<td>Central aortic DBP, mm Hg</td>
<td>84.4 ± 9.4</td>
<td>83.2 ± 8.5</td>
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<tr>
<td>End of study</td>
<td>74.7 ± 10.6</td>
<td>75.2 ± 6.4</td>
</tr>
<tr>
<td>Change from baseline (95% CI)†</td>
<td>-10.4 (−12.9, −7.9)</td>
<td>-9.1 (−11.5, −6.8)</td>
</tr>
<tr>
<td>P value</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Central aortic PP, mm Hg</td>
<td>61.6 ± 14.4</td>
<td>58.8 ± 12.2</td>
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<tr>
<td>End of study</td>
<td>47.3 ± 14.1</td>
<td>47.3 ± 9.9</td>
</tr>
<tr>
<td>Change from baseline (95% CI)†</td>
<td>-13.3 (−16.9, −9.7)</td>
<td>-11.9 (−15.4, −8.5)</td>
</tr>
<tr>
<td>P value</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
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Table. Continued

<table>
<thead>
<tr>
<th>Variable</th>
<th>Valsartan/HCTZ</th>
<th>Amlodipine</th>
</tr>
</thead>
<tbody>
<tr>
<td>AER, mcg/min</td>
<td>30.8 (20.4, 46.5)</td>
<td>27.5 (17.4, 43.5)</td>
</tr>
<tr>
<td>End of study</td>
<td>18.2 (12.5, 26.3)</td>
<td>32.6 (19.5, 54.5)</td>
</tr>
<tr>
<td>Change from baseline (95% CI)†</td>
<td>-34.6% (−53.0, −8.9)</td>
<td>23.7% (−10.0, 69.9)*</td>
</tr>
<tr>
<td>P value</td>
<td>0.0125</td>
<td>0.1873</td>
</tr>
</tbody>
</table>

SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; Ao-PWV, Aortic pulse wave velocity; AER, albumin excretion rate; HCTZ, Hydrochlorothiazide. Data are mean ± SD except AER where data are presented as geometric mean and 95% CI.

*P < 0.005 for between treatment difference.
†Treatment and previous ACE inhibitor/ARB treatment as fixed factors and baseline value as covariate.
‡Treatment, gender, age, and operator as fixed factors and baseline value and baseline mean PP included as covariates.

Val/HCTZ group (6 adverse events, 3 BP above, and 1 BP below acceptable value for physician in charge and 1 lost to follow-up) and 12 in the amlodipine group (7 adverse events, 1 BP above acceptable value for physician in charge, 1 protocol violation, 1 withdrawal of consent, 1 lost to follow-up, and 1 administrative problem) were withdrawn before the end of the study, leaving 55 patients in the Val/HCTZ group and 53 patients in the amlodipine group who completed the study. These discontinued patients were, however, part of the ITT population for efficacy assessment as they all had postbaseline measurements. Please see Figure S1 for details of patient enrollment and outcomes. There were no significant baseline differences in anthropometric, clinical, or biochemical variables. Please see the data supplement and Table S1 for baseline demographic, clinical, and biochemical features of the ITT populations in the 2 treatment groups. The numeric differences in baseline PP and SBP did not reach conventional statistical significance. Gender and ethnic distribution was similar between the 2 groups. Patients of white origin were 47% and 48% in the Val/HCTZ and amlodipine groups, respectively, of Afro-Caribbean origin 36% and 35%, and other ethnic groups were 18% and 17%. Information on concomitant medications and clinical conditions are reported in the data supplement.

The Table shows baseline and end of study data for selected hemodynamic and biochemical variables for the ITT population in each group. Other variables that were measured but are not shown in the Table did not change significantly between the 2 groups. Glycemic control was similar between groups at baseline and in the Val/HCTZ group HbA1c rose from, mean (SD), 7.1% (1.1) to 7.5% (1.3) P = 0.03 at the end of the study whereas there was no significant change in the amlodipine group (7.4 [1.1] % to 7.6 [1.4] %). Fasting total, LDL, and HDL cholesterol did not change significantly during the course of the study, and there were no significant differences between the 2 groups at baseline and at the end of the study. All patients had serum creatinine below 115 μmol/L. Plasma electrolytes and serum creatinine did not differ at baseline and did not change significantly during the course of the study.
After treatment there was a significant fall in brachial SBP, DBP, and PP in both groups. However, at study end there was no significant difference in brachial SBP, DBP, and PP between treatment groups (Table). Mean (95% CI) falls in brachial SBP [Val/HCTZ versus amlodipine −23.7 (−28.5, −18.9) versus −19.4 (−24.1, −14.6) mm Hg, brachial DBP −9.4 (−11.9, −6.9) versus −7.3 (−9.8, −4.9) and brachial PP −14.3 (−17.7, −10.8) versus −12.2 (−15.5, −8.8) mm Hg were similar between groups after adjustments for baseline differences and previous treatment with inhibitors of the RAS. Similarly we found no between group difference in mean arterial pressure (MAP) and MAP change (data not shown).

Mean (SD) heart rate was similar at baseline (Val/HCTZ versus amlodipine 77.0 (16.2) versus 75.9 (12.0)) and at the end of the study (75.9 (13.5) versus 76.5 (10.4)).

Mean (95% CI) Ao-PWV was reduced from baseline by 1.8 (−2.4 to −1.3) m/s in Val/HCTZ group $P<0.0001$ and by 0.7 (−1.3 to −0.2) in amlodipine group $P=0.01$ (Table). The estimated mean (95% CI) difference in Ao-PWV change from baseline between the Val/HCTZ and amlodipine group was −1.1 m/s (−1.8 to −0.5); $P=0.001$, from the prespecified statistical model, which included adjustment for the nonsignificant baseline differences in blood pressures. When further adjustments were made for change in brachial PP from baseline to end of study the treatment difference in Ao-PWV was $-0.9 \text{ m/s} (-1.4 \text{ to } -0.3, P=0.0019; \text{Figure 1})$.

This differential impact on Ao-PWV by the 2 treatments occurred early after 12 weeks treatment, and this separation persisted until the end of the study (Figure 2).

AI x did not differ at baseline [mean (SD), 28.2% (7.4) in the Val/HCTZ group versus 27.2% (7.3) in the amlodipine group] and fell similarly in both groups to 22.7% (8.2) and 22.8% (7.7), respectively ($P=0.0003$ for change from baseline in the Val/HCTZ group and $P=0.0015$ in the amlodipine group), with no significant between group difference. At baseline there were no significant between group differences in central aortic SBP, DBP, and PP. Please see Table S1. Central aortic SBP, DBP, and PP fell significantly and similarly in both groups after treatment with no significant differences between the 2 treatment groups at study end. Mean (95% CI) reductions in central aortic SBP (Val/HCTZ versus amlodipine −23.6 [−28.7, −18.6] versus 21.1 [−26.0, −16.3] mm Hg), central aortic DBP −10.4 (−12.9, −7.9) versus −9.1 (−11.5, −6.8) mm Hg and central aortic PP −13.3 (−16.9, −9.7) versus −11.9 (−15.4, −8.5) mm Hg were similar between groups after adjustments for baseline differences and previous treatment with inhibitors of the RAS (Table).

Geometric mean (95% CI) AER fell significantly from 30.8 (20.4, 46.5) to 18.2 (12.5, 26.3) mcg/min, $P<0.001$ in the Val/HCTZ group as compared to a nonsignificant rise from 27.5 (17.4, 43.5) to 32.6 (19.5, 54.5) mcg/min in the amlodipine group. This translated to a fall in AER of 35% in the Val/HCTZ group as compared to a nonsignificant rise in the amlodipine group with a ratio of the geometric means (95% CI) between groups that was highly significant in favor of Val/HCTZ of $-47\%$ ($-25\%, -63\%; P=0.0004$) after adjustments for baseline AER and previous RAS inhibitor treatment (Figure 3). This corresponded to a 15.3 mcg/min difference in the AER lowering effect between treatment groups. The changes in AER did not correlate with changes in Ao-PWV in either group.

Mean (SD) ferric reducing ability of plasma (FRAP) levels rose significantly from 997.1 (213.6) μmol/L to 1121.9
(228.0) μmol/L with Val/HCTZ treatment (P=0.0003) as compared to a fall from 938.4(161.9) μmol/L to 921.4 (180.5) μmol/L with amldipine (P=0.11). This translated into a 16% increase in favor of Val/HCTZ compared to amldipine (P<0.0001). There were no significant between treatment differences in the other measured markers of endothelial function and oxidative stress.

Safety Data
There were no deaths during the study and the adverse event profile was similar between groups (Please see data supplement).

Discussion
Treatment with Val/HCTZ reduced Ao-PWV by 0.9 m/s more than amldipine in patients with T2DM, systolic hypertension, and albuminuria despite similar attained brachial and central aortic PP in both groups at the end of the study. This difference roughly corresponds to 9 years of vascular aging.28 The effect of Val/HCTZ on reducing Ao-PWV was seen early after 12 weeks of treatment and continued until the end of the study. Amlodipine, although to a significantly lesser extent, also lowered Ao-PWV in the first 12 weeks, but no further reduction was seen by week 24. The different responses in improvement of Ao-PWV in the face of no significant differences in SBP or PP changes as well as similar attained brachial and central aortic blood pressures suggest that ARBs reduce arterial stiffness beyond what would be expected from their antihypertensive effects and support the view that in this patient group arterial wall properties are ameliorated to a greater extent and more durably by ARBs than calcium channel blockers. There is some discrepancy in the literature about the effect of calcium channel blockers on Ao-PWV. In nondiabetic patients with essential hypertension some authors23,31 have reported a reduction in Ao-PWV and brachial ankle pulse wave velocity (Ba-PWV) with felodipine and amldipine, respectively, but other studies have found no effect of amlodipine or nifedipine on Ao-PWV and Ba-PWV after 6 months treatment.32,33 Often in these studies the comparator drug(s) were thiazide diuretics which are known to have a negligible impact on arterial stiffness and the patients’ population of these studies was entirely different from the group we investigated. There are no previous reports in T2DM with systolic hypertension and albuminuria about the effect of calcium channel blockers or ARBs on arterial stiffness. Our findings are consistent with reports that valsartan reduced Ba-PWV compared with a calcium channel blocker despite similar brachial BP control in patients with essential hypertension.33 In that study, however, no significant reduction in Ba-PWV from baseline was seen with calcium channel blockade; furthermore Ao-PWV, as a measure of arterial stiffness, was not evaluated and submaximal doses of antihypertensive agents were used.

Our novel findings that in T2DM patients with systolic hypertension and albuminuria an ARB modulates arterial stiffness independently of brachial and central BP lowering and of the passive effect of pressure on arterial elastic properties (no change in MAP) may, at least in part, explain the favorable cardio-renal protective effects observed in this population with RAS inhibition in several previous studies.7–5,34 Increased aortic stiffness is likely to be attributable to an increase in intrinsic wall stiffness rather than raised BP alone.35 As higher Ao-PWV can adversely affect central pressure and cardiac function, simply lowering peripheral BP may be insufficient. Tropeano et al have indeed reported that in T2DM with hypertension high dose perindopril (8 mg od) increased carotid artery distensibility independently of brachial blood pressure supporting the view that the RAS modulates intrinsic arterial wall stiffness. At variance with our study they measured carotid arterial stiffness, rather than Ao-PWV, and preselected patients to be responsive to perindopril.36

Our results showed that Alx and central aortic pressures fell significantly and similarly in both groups. Central aortic pressures and Alx measurements do not necessarily reflect the same arterial wall properties as measured by Ao-PWV. Central aortic pressures and Alx mirror changes in pressure wave reflection from distal sites (resistance vessels) where impedance mismatch occurs and are only indirect surrogate markers of arterial stiffness. Although increased arterial stiffness is responsible for the velocity of the pressure wave transmission, the intensity of the wave reflection, and thereby central aortic pressures and AIx, is determined primarily by the reflective properties of the vasculature which can be modulated independently of arterial stiffening.37,38 As central blood pressure is determined primarily by 3 major factors, stroke volume, aortic stiffness, and wave reflection, it is conceivable that Val/HCTZ treatment may have resulted in a decrease in stroke volume as a result of a fall in end diastolic volume and reduction in cardiac preload.39 By contrast dihydropyridine calcium channel blockers such as amldipine have limited effect on preload and end diastolic ventricular volumes.39,40 This would explain the similar effect on central blood pressures and reduction in AIx but the differential impact on Ao-PWV observed in the 2 treatment groups.

A recent study in patients with essential hypertension and additional cardiovascular risk factors has shown that combination therapy of an ACE inhibitor, perindopril, and a calcium channel blocker, amldipine, resulted in lower central aortic pressures when compared with the β blocker atenolol despite similar brachial BP lowering effects.41 These differences, which were not unexpected in view of the limited vasodilatory effects of β blockers, resulted in fewer cardiovascular and renal events in the perindopril/amldipine group.41 This study, which differs from ours because it did not measure Ao-PWV sequentially and did not compare directly the effects of the ACE inhibitor versus the calcium channel blocker, is nevertheless consistent with our results that both inhibition of the RAS and calcium channel blockade lower central aortic pressures. Although no clinical trial to date has demonstrated that differential lowering of Ao-PWV with medical treatment results in different cardiac or renal outcomes our work establishes a platform to address this important question in future clinical studies. The importance of such studies is underscored by the epidemiological evidence that Ao-PWV per se is an independent risk factor for CVD morbidity and mortality.13–15
We have previously demonstrated that in T2DM elevated albumin excretion rate is associated with higher Ao-PWV, an effect likely to be mediated at least in part by arterial blood pressure. In patients with T2DM and albuminuria, overactivation of the RAS occurs and angiotensin II mediates a number of effects from increased collagen synthesis to proliferation of smooth muscle cells, arterial wall fibrosis, accumulation and activation of inflammatory cells, and increased vascular permeability, which result in premature vascular and renal complications. We confirmed in this study our previous observation that, as monotherapy, valsartan results in a significantly greater reduction in albuminuria than that obtained by amlodipine despite similar brachial BP lowering effects in T2DM. We found no relationship between the change in arterial stiffness and the reduction in albuminuria with valsartan, suggesting that blockade of the AT1 receptor affects these 2 variables through different mechanisms.

Albuminuria is driven to a large extent by the pressure changes in the microvasculature. Pressure and angiotensin II induced formation of excess reactive oxygen species, partly via NAD(P)H oxidase inhibition, may also contribute to microvessel permeability changes. It is interesting that in our study levels of FRAP, an index of plasma antioxidant capacity, rose significantly with Val/HCTZ but not with amlodipine. Blood pressure induced changes in the smaller diameter arterioles supplying the glomerulus and alterations in the wall properties of these vessels are likely to be discordant with the remodeling of the larger diameter and more elastic vessel walls that influence Ao-PWV. The effect of Val/HCTZ on arterial stiffness is more likely to involve changes in extracellular matrix metabolism. We did not specifically address this issue, but Zieman et al have demonstrated that 8-week treatment with an AGEs cross link breaker, Alagebrum, which downregulated markers of collagen synthesis and other extracellular glycoproteins, resulted in reduction of carotid arterial stiffness. However cross link breakers have also been found to have peripheral blood pressure lowering effect.

There are limitations to our study. We did not make direct measurements of the mechanical properties of the vessel wall. This would require an invasive technique not applicable in a clinical study and Ao-PWV, measured by planimetry and tonometry, is a well established, accurate, and sensitive marker of central arterial stiffness. Further, Ao-PWV is a validated and independent predictor of CVD in many studies. The administration of HCTZ with valsartan which was used to ensure equivalent BP control in the 2 arms may have affected our findings. However, thiazide diuretics have also been found to have peripheral blood pressure lowering effect.

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Valsartan Improves Arterial Stiffness in Type 2 Diabetes Independently of Blood Pressure Lowering
Janaka Karalliedde, Andrew Smith, Lorenita DeAngelis, Vincenzo Mirenda, Albert Kandra, Jaco Botha, Philippe Ferber and Giancarlo Viberti

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Supplement files for: Valsartan improves arterial stiffness in Type 2 diabetes independently of blood pressure lowering

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Measurements

Blood pressure determinations were taken in a temperature controlled (22°C) quiet room after 15 minute rest in the supine position at each visit. Brachial BP was measured from the non-dominant arm, three times at 5 minute intervals by an automated sphygmomanometer (Omron Digital Blood Pressure Monitor HEM907, Bannockburn, IL). The mean values of the last two readings for both brachial SBP and DBP were used for calculation. Brachial PP was calculated as SBP–DBP. Following the last measurement three successive recordings, each over 10 seconds, of the radial artery pressure wave forms were sampled by applanation tonometry (Millar tonometer, Millar Instruments, Houston, TX) using the Sphygmocor system (Atcor, Sydney, Australia). Data that met the automatic quality controls specified by the Sphygmocor software were used to derive central aortic pressure waveforms by a previously validated generalised transfer function, from which central aortic SBP, DBP and PP values were obtained. Brachial arterial blood pressure was used to calibrate the radial pressure pulse. Aortic pressure waveforms were subjected to further analysis by the Sphygmocor software to calculate the aortic augmentation index (AIx). AIx is defined as the increment in pressure from the first systolic shoulder (inflection point) to the peak pressure of the aortic pressure waveform expressed as a percentage (of peak pressure) and provides a quantitative measure of augmentation of central BP. AIx data were corrected for a heart rate of 75 beats per minute. Ao-PWV was determined from carotid and femoral pressure waveforms obtained non-invasively by applanation tonometry (Millar tonometer, Millar Instruments, Houston, TX) using the Sphygmocor system (Atcor, Sydney, Australia). Waveforms were referenced to a concurrently recorded ECG and carotid to femoral transit time (ΔT) was computed from the foot to foot time difference between carotid and femoral waveforms. The distance between the surface markings
of the sternal notch and the carotid (d_c) and femoral artery (d_f) were used to estimate the path length between the carotid and femoral arteries (L = d_f - d_c) and Ao-PWV computed as L/ΔT. The within-subject standard deviation of Ao-PWV assessed using this method in our laboratory is 0.5 m/s and the intraobserver and interobserver coefficient of variation 3.0% and 3.5% respectively.

Enzyme-Linked ImmunoSorbent Assays (ELISA) were used to measure soluble vascular cell adhesion molecule-1 (sVCAM) [R&D Systems, Abingdon, UK], Von Willebrand factor (vWF) [Corgenix, Westminster, CO] and oxidized low density lipoprotein (LDL) [Mercodia, Uppsala, Sweden]. Ferric reducing ability of plasma (FRAP) which is an index of anti-oxidative capacity and protection was measured using a UV/Visible Spectrophotometer (LKB Ultrospec Plus Pharmacia, Uppsala, Sweden)⁴ and serum glutathione by HPLC. The FRAP assay is an automated test measuring the ferric reducing ability of plasma using the principle that ferric to ferrous ion reduction causes a coloured ferrous-tripryridyltriazine complex to form. As non enzymatic anti-oxidants can also be described as reductants the FRAP assay measures this reducing ability using a colorimetric method. The FRAP assay has a limit of detection of <2.0 μmol/l of antioxidant power and gives a linear response over a wide concentration range of various known antioxidants and has been shown to be an index of antioxidant potential.⁵

**Statistical analysis**

The primary efficacy variable was the difference in change in Ao-PWV between the treatment groups and the primary population used in this assessment was the intention to treat (ITT) population. The null hypothesis tested was H₀: μvalsartan/HCTZ - μamlodipine = 0, where μ was the mean change from baseline to endpoint for each treatment group. Secondary efficacy variables were changes from baseline in AER, central aortic SBP, DBP, PP and AIx and the time course
of Ao-PWV changes. Exploratory analyses of changes from baseline in oxidative and endothelial markers were also performed to gain insight into possible mechanisms of action of the two drugs. For the inferential statistics, values of the markers were log transformed to correct for the skewed distribution and geometric mean and 95% confidence intervals are presented. Least square estimates of the means, confidence intervals, and p-values are derived from an ANCOVA model with treatment and previous ACE/ARB treatment as factors and (log) baseline value as covariate. For the oxidative and endothelial markers (e.g. FRAP) a factor for smoking status (smokers and ex-smoker/non-smoker) was also included in the ANCOVA.

**Results**
The majority of patients in each group were on oral agents for their diabetes with 85% in Val/HCTZ and 78% in the amlodipine group on metformin, 29% and 39% on sulphonylureas and 40% and 50% were on oral agents plus insulin respectively. These differences were not statistically significant. Sixty five (98.5%) patients in the Val/HCTZ and 62 (95.4%) in the amlodipine group had a prior history of anti-hypertensive treatment for systolic hypertension. One patient in the Val/HCTZ group and 3 in the amlodipine group were newly diagnosed with systolic hypertension and on no previous medications. Of the patients previously treated for their hypertension 92% in Val/HCTZ and 89% in amlodipine group were receiving inhibitors of the RAS. Similar numbers of patients in each group were previously treated with amlodipine (34% vs. 30%) and thiazide diuretics (18% vs. 25%) with no significant difference between the two groups. More than 65% of patients in both groups were on lipid lowering therapy and 55% on aspirin with no significant difference between the two groups. There was a similar number of smokers in each group with 12 % in the Val/HCTZ group and 15% in amlodipine group.
Thirteen patients (18%) in Val/HCTZ group and 9 (13%) in the amlodipine group had previous history of CVD and 10% and 4% respectively had a history of peripheral vascular disease. Forty seven patients (65%) in Val/HCTZ group and 44 (62%) patients in amlodipine group had a history of documented diabetic retinopathy.

**Safety data**
There were 4 serious adverse events (SAEs) in each group of which one in the Val/HCTZ group (increased blood glucose following excessive alcohol intake) and one in the amlodipine group (collapse probably syncopal episode) resulted in withdrawal. The other reported SAE which did not result in discontinuation, were in the Val/HCTZ group: exacerbation of diverticular disease resulting in hospitalization, breast infection and poor diabetic control; and in the amlodipine group: abdominal pain, lower respiratory tract infection and exacerbation of chronic obstructive pulmonary disease. Eight patients in the Val/HCTZ group (6 headache, 1 hypotension and 1 raised serum creatinine) and 10 in the amlodipine group (8 joint swelling and peripheral oedema, 2 headache) had adverse events which led to withdrawal. There was one reported case of hypokalaemia (serum potassium $\leq 3.2$mmol/l) in Val/HCTZ group which resolved without intervention.
References


**Table S1.** Baseline demographic, clinical and biochemical characteristics of patients with T2DM, systolic hypertension and albuminuria randomised to Valsartan/HCTZ or amlodipine treatment.

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>Val/HCTZ</th>
<th>Amlodipine</th>
<th>Val/HCTZ vs. amlodipine p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (M/F)</td>
<td>77/54</td>
<td>66 (39/27)</td>
<td>65 (38/27)</td>
<td>0.94</td>
</tr>
<tr>
<td>Age, yrs (range)</td>
<td>59.5(40-82)</td>
<td>59.7(40-78)</td>
<td>59.3(41-82)</td>
<td>0.80</td>
</tr>
<tr>
<td>Duration of diabetes, yrs</td>
<td>10.0±6.7</td>
<td>10.4±7.2</td>
<td>9.4±6.2</td>
<td>0.40</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>104.3±14.4</td>
<td>103.7±13.8</td>
<td>104.9±15.1</td>
<td>0.88</td>
</tr>
<tr>
<td>BMI, kg/m2</td>
<td>31.6±5.8</td>
<td>31.8±5.3</td>
<td>31.5±6.2</td>
<td>0.81</td>
</tr>
<tr>
<td>Brachial SBP, mmHg</td>
<td>158.0±10.7</td>
<td>159.7±10.8</td>
<td>156.3±10.4</td>
<td>0.06</td>
</tr>
<tr>
<td>Brachial DBP, mmHg</td>
<td>82.5±9.1</td>
<td>82.5±9.3</td>
<td>82.4±9.0</td>
<td>0.94</td>
</tr>
<tr>
<td>Brachial PP, mmHg</td>
<td>75.6±11.0</td>
<td>77.2±11.7</td>
<td>73.9±10.0</td>
<td>0.08</td>
</tr>
<tr>
<td>Ao-PWV, m/s</td>
<td>12.1±2.6</td>
<td>12.5±2.5</td>
<td>12.0±2.5</td>
<td>0.19</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>7.2±1.1</td>
<td>7.1±1.1</td>
<td>7.4±1.1</td>
<td>0.18</td>
</tr>
<tr>
<td>Fasting total cholesterol, mmol/l</td>
<td>4.4±1.0</td>
<td>4.5±1.2</td>
<td>4.3±0.9</td>
<td>0.33</td>
</tr>
<tr>
<td>LDL mmol/l</td>
<td>2.6±0.8</td>
<td>2.6±0.8</td>
<td>2.5±0.7</td>
<td>0.76</td>
</tr>
<tr>
<td>AER mcg/min*</td>
<td>29.1 (21.5,39.5)</td>
<td>30.8(20.4,46.5)</td>
<td>27.5(17.4,43.5)</td>
<td>0.71</td>
</tr>
</tbody>
</table>
Abbreviations:
BMI-body mass index, SBP-systolic blood pressure, DBP-diastolic blood pressure, PP-pulse pressure, Ao-PWV-Aortic pulse wave velocity, AER- albumin excretion rate, LDL-low density lipoprotein. HCTZ-Hydrochlorothiazide. Data are mean ±SD except *AER where data are presented as geometric mean and 95% CI.
Figure S1 Patient Enrolment and Outcomes.

280 Patients screened

144 met inclusion and exclusion criteria and randomised to Val/HCTZ or amlodipine groups

73 Received Val/HCTZ

- 3 Adverse events
  - 2 Patient withdrew consent
  - 1 Lost to follow up
  - 1 Administrative problem

66 assessed on ITT basis

55 completed study

71 Received Amlodipine

- 4 Adverse events
  - 1 Abnormal test procedures*
  - 1 protocol violation

65 assessed on ITT basis

53 completed study

3 Adverse events

2 Patient withdrew consent

1 Lost to follow up

1 Administrative problem

6 Adverse events

4 Abnormal test procedures**

1 Lost to follow up

- 1 Abnormal test procedures***
- 1 Protocol violation
- 1 Patient withdrew consent
- 1 Lost to follow up
- 1 Administrative problem

* BP above acceptable value for physician in charge
** BP above (3) and below (1) acceptable value for physician in charge
*** BP above acceptable value for physician in charge
Legend for Figure S1

Patient Enrolment and Outcomes.