Effect of Angiotensin II Type I Receptor Blockade on Carotid Artery Atherosclerosis: A Double Blind Randomized Clinical Trial Comparing Valsartan and Placebo

The EFFERVESCENT Study

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Atlanta, GA
Disclosures

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[www.clinicaltrials.gov](http://www.clinicaltrials.gov) Identifier: NCT00208767
Background

- Angiotensin II plays a key role in the pathogenesis and progression of atherosclerosis
  - Oxidative stress
  - Inflammation
  - Thrombosis
  - Endothelial Function

- Angiotensin II AT-1 receptor blockade improves cardiovascular outcomes
  - Hypertension
  - Heart Failure
  - Myocardial Infarction

Nickenig G. Circulation. 2002; 105:393-396
Schieffer B. Circulation. 2000; 101:1372-1378
Prasad A. Circulation. 2000; 101:2349-2354
Pfeffer MA. NEJM. 2003; 349:1893-1906
Hypothesis

Primary

• Valsartan will reduce progression of carotid wall thickness and inhibit atherosclerotic plaque progression.

Secondary

• The effects of Valsartan on carotid disease will be mediated by improvements in oxidative stress, inflammation, and vascular function.
Study Design

- Single center, double-blind, placebo-controlled randomization of 120 subjects aged 21-80 years

- Carotid IMT >0.65 mm measured by ultrasound

- 2:1 randomization Valsartan (n=80) vs. placebo (n=40). Valsartan dose titrated to 320 mg/day

- Half of the subjects received statins and were stratified by statin use

- 24 months treatment period
Exclusion Criteria

- Premenopausal females with potential for pregnancy
- ACEi or ARB therapy in the previous 3 months
- Initiation or change in dose of statin therapy within 2 months
- Anticipated change in lipid lowering therapy
- LDL >160 mg/dl or >130 mg/dl in the presence of atherosclerotic plaque during screening carotid ultrasound and not receiving statin therapy
- Acute coronary or cerebrovascular event within 2 months
- Serum creatinine > 2.5 mg/dL
- HbA1c >8.5
- SBP>140 or DBP>90 mmHg
- Inability to give informed consent
- Current neoplasm
- Inability to undergo MRI

Premenopausal females with potential for pregnancy

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Study Protocol

Initial Visit
• History and Physical Exam
• CBC, Chemistry, and Lipid profile
• Oxidative Stress Markers
• Inflammatory Markers
• Vascular Function
• Carotid MRI

2 Weeks
• History and Physical Exam
• CBC, Chemistry, and Lipid profile
• Oxidative Stress Markers
• Inflammatory Markers
• Vascular Function
• Dose Titration

3 Months
• History and Physical Exam
• CBC, Chemistry, and Lipid profile
• Oxidative Stress Markers
• Inflammatory Markers
• Vascular Function

24 Months
• History and Physical Exam
• CBC, Chemistry, and Lipid profile
• Oxidative Stress Markers
• Inflammatory Markers
• Vascular Function
• Carotid MRI

12 Months
• History and Physical Exam
• CBC, Chemistry, and Lipid profile
• Oxidative Stress Markers
• Inflammatory Markers
• Vascular Function
• Carotid MRI
Methods: Carotid MRI

- 1.5 or 3T MRI system
- T2-weighted, black-blood, turbo spine echo (TSE) sequence
- 3 mm slice thickness of the R and L carotid bulbs, 0.3 mm x 0.3 mm spatial resolution

Analysis

- Dedicated vessel analysis package (VesselMASS, LUMC, Leiden, Netherlands)
- Outer and inner vessel contours traced by single blinded investigator

Software Calculated Measures

- Lumen area
- Vessel wall area = total vascular area - lumen area
- Mean wall thickness
- Maximum wall thickness
- Each cross sectional MRI slice divided into 6 sectors with the mean wall thickness calculated for each sector

Source Image  Contours Drawn  Vessel Wall Area  Sector Analysis
Plaque Definition

**Plaque:** Maximum chord > 2 mm
Statistical Methods

• Comparison between treatment groups was by linear mixed models that takes into account correlations between repeated measurements (left and right carotid arteries over time) on the same subjects.
Assessed for eligibility (n= 216)

Excluded (n= 96)
- Not meeting inclusion criteria (n= 72)
- Declined to participate (n= 23)
- Other reasons (n= 1)

Randomized (n= 120)

Allocation

Allocated to Valsartan (n= 80)
- Received allocated intervention (n= 80)
- On Statin Therapy (n= 40)

Allocated to placebo (n= 40)
- Received allocated intervention (n= 40)
- On Statin Therapy (n= 20)

Follow-Up

Lost to follow-up (n= 8)
Discontinued intervention (n= 19)
- Inadequate baseline MR images (n= 3)
- Death; acute respiratory failure (n= 1)
- Stroke (n= 1)
- Time constraints (n= 5)
- Relocation (n= 1)
- Statin side effects (n= 1)
- Frequent blood draws (n= 1)
- Nausea/Diarrhea (n= 3)
- Orthostatic hypotension (n= 1)
- Major injury/Accident (n= 1)
- GI bleed (n= 1)

Lost to follow-up (n= 3)
Discontinued intervention (n= 4)
- Inadequate baseline MR images (n= 2)
- Acute kidney injury n= 1
- Time constraints n= 1

Analysis

Analysed for final primary outcome (n= 49)
- Poor/missing images (n= 4)

Analysed for final primary outcome (n= 27)
- Poor/missing images at 24 months (n= 6)
## Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>All Patients N=120</th>
<th>Treatment N=80</th>
<th>Placebo N=40</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years, Mean ± SD)</td>
<td>60 ± 9</td>
<td>59 ± 9</td>
<td>62 ± 9</td>
<td>0.17</td>
</tr>
<tr>
<td>Male sex (%, N)</td>
<td>51 (61)</td>
<td>53 (42)</td>
<td>48 (19)</td>
<td>0.61</td>
</tr>
<tr>
<td>Caucasian race (%, N)</td>
<td>80 (96)</td>
<td>79 (63)</td>
<td>83 (33)</td>
<td>0.69</td>
</tr>
<tr>
<td>Hypertension (%, N)</td>
<td>39 (47)</td>
<td>35 (28)</td>
<td>48 (19)</td>
<td>0.19</td>
</tr>
<tr>
<td>Diabetes Mellitus (%, N)</td>
<td>7 (8)</td>
<td>6 (5)</td>
<td>8 (3)</td>
<td>0.8</td>
</tr>
<tr>
<td>Current and previous tobacco smoking (%, N)</td>
<td>35 (42)</td>
<td>33 (26)</td>
<td>40 (16)</td>
<td>0.65</td>
</tr>
<tr>
<td>Body mass index (kg/m(^2), Mean ± SD)</td>
<td>29 ± 9</td>
<td>29 ± 6</td>
<td>28 ± 5</td>
<td>0.22</td>
</tr>
<tr>
<td>Statin use (%, N)</td>
<td>60 (50)</td>
<td>40 (50)</td>
<td>20 (50)</td>
<td>1</td>
</tr>
</tbody>
</table>

**Prior History of:**

<table>
<thead>
<tr>
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<th>Treatment N=80</th>
<th>Placebo N=40</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary artery disease (%, N)</td>
<td>12 (14)</td>
<td>11 (9)</td>
<td>13 (5)</td>
<td>0.84</td>
</tr>
<tr>
<td>Myocardial infarction (%, N)</td>
<td>7 (8)</td>
<td>6 (5)</td>
<td>8 (3)</td>
<td>0.8</td>
</tr>
<tr>
<td>Cerebrovascular disease (%, N)</td>
<td>13 (15)</td>
<td>13 (10)</td>
<td>13 (5)</td>
<td>1</td>
</tr>
<tr>
<td>Stroke (%, N)</td>
<td>3 (3)</td>
<td>4 (3)</td>
<td>0 (0)</td>
<td>0.22</td>
</tr>
</tbody>
</table>
## Patients’ Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Valsartan</th>
<th>Placebo</th>
<th>Change between Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline 24 Months</td>
<td>Baseline 24 Months</td>
<td>P value</td>
</tr>
<tr>
<td><strong>Blood Pressure (mean ± SD)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>122 ± 13 114 ± 20</td>
<td>129 ± 16 124 ± 15</td>
<td>0.011</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>74 ± 10 69 ± 8</td>
<td>76 ± 12 72 ± 12</td>
<td>0.003</td>
</tr>
<tr>
<td><strong>Fasting Lipid Profile (mean ± SD)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>All Patients</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>180 ± 31 173 ± 34</td>
<td>172 ± 28 175 ± 33</td>
<td>0.11</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>119 ± 61 120 ± 72</td>
<td>108 ± 67 106 ± 55</td>
<td>0.87</td>
</tr>
<tr>
<td>High density lipoprotein (mg/dL)</td>
<td>50 ± 16 55 ± 18</td>
<td>56 ± 14 62 ± 15</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Low density lipoprotein (mg/dL)</td>
<td>104 ± 26 94 ± 28</td>
<td>93 ± 25 91 ± 27</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>Statin Group</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>170 ± 33 161 ± 30</td>
<td>167 ± 33 166 ± 35</td>
<td>0.13</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>111 ± 64 120 ± 71</td>
<td>118 ± 77 114 ± 51</td>
<td>0.34</td>
</tr>
<tr>
<td>High density lipoprotein (mg/dL)</td>
<td>48 ± 14 52 ± 16</td>
<td>58 ± 14 61 ± 15</td>
<td>0.008</td>
</tr>
<tr>
<td>Low density lipoprotein (mg/dL)</td>
<td>97 ± 29 85 ± 26</td>
<td>85 ± 25 83 ± 27</td>
<td>0.037</td>
</tr>
<tr>
<td><strong>No Statin Group</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>193 ± 24 191 ± 32</td>
<td>179 ± 20 188 ± 26</td>
<td>0.61</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>130 ± 57 120 ± 74</td>
<td>94 ± 49 94 ± 61</td>
<td>0.37</td>
</tr>
<tr>
<td>High density lipoprotein (mg/dL)</td>
<td>53 ± 19 58 ± 21</td>
<td>54 ± 14 65 ± 15</td>
<td>0.006</td>
</tr>
<tr>
<td>Low density lipoprotein (mg/dL)</td>
<td>114 ± 16 108 ± 25</td>
<td>103 ± 21 104 ± 22</td>
<td>0.13</td>
</tr>
<tr>
<td><strong>Biomarkers (mean ± SD)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Potassium (mmol/L)</td>
<td>4.3 ± 0.3 4.4 ± 0.3</td>
<td>4.5 ± 0.4 4.4 ± 0.3</td>
<td>0.045</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>0.98 ± 0.17 0.92 ± 0.27</td>
<td>0.96 ± 0.21 0.94 ± 0.23</td>
<td>0.054</td>
</tr>
</tbody>
</table>
Effect of Valsartan on Carotid Bulb Vessel Wall Area

At 24 months, vessel wall area decreased significantly with Valsartan \( (P=0.008) \) compared to an insignificant change with placebo \( (P=0.28) \)
Effect of Valsartan on Carotid Bulb Vessel Wall Thickness

After 24 months, mean circumferential wall thickness of the carotid bulb decreased with Valsartan (P = 0.0035) compared to an insignificant change with placebo (P = 0.34)
After 24 months, maximum wall thickness of the carotid bulb increased with placebo ($P = 0.001$) compared to an insignificant change with Valsartan ($P = 0.61$).
Effect of Valsartan on Carotid Bulb Plaque Thickness

Atherosclerotic plaque, defined as mean WT of maximum sector in subjects with maximum WT >2mm (n=86).

At 24 months, plaque thickness decreased with Valsartan (P=0.014) but was unchanged with placebo (P=0.16).
Summary of Findings

In subjects with abnormal CIMT, there was:

• Significantly greater reduction in carotid bulb wall thickness and plaque thickness with Valsartan compared to placebo

• No significant change in the mean vessel lumen area in either group

• Effects of Valsartan were unaffected by statin use

• No correlations between the magnitude of change in carotid wall dimensions and changes in either blood pressure or lipid levels
# Effect of Valsartan on Biomarkers and Vascular Function

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<tr>
<td></td>
<td>Baseline</td>
<td>24 Months</td>
<td>P value</td>
</tr>
<tr>
<td><strong>Oxidative Stress</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cysteine (µM)</td>
<td>9.3 ± 2.5</td>
<td>9.2 ± 4.0</td>
<td>0.87</td>
</tr>
<tr>
<td>Cystine (µM)</td>
<td>85.9 ± 19.6</td>
<td>93.6 ± 21.5</td>
<td>0.016</td>
</tr>
<tr>
<td>Glutathione (µM)</td>
<td>1.3 ± 0.6</td>
<td>1.5 ± 0.6</td>
<td>0.069</td>
</tr>
<tr>
<td>Glutathione Disulfide (µM)</td>
<td>0.03 ± 0.02</td>
<td>0.06 ± 0.05</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cysteine-glutathione disulfide (µM)</td>
<td>2.4 ± 0.8</td>
<td>3.1 ± 1.2</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Inflammation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C-reactive protein (mg/L)</td>
<td>3.5 ± 6.1</td>
<td>2.9 ± 3.4</td>
<td>0.47</td>
</tr>
<tr>
<td>Fibrinogen (g/L)</td>
<td>2.5 ± 0.8</td>
<td>2.7 ± 0.8</td>
<td>0.32</td>
</tr>
<tr>
<td><strong>Vascular Function</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flow-mediated dilation (%)</td>
<td>5.5 ± 3.9</td>
<td>6.0 ± 3.6</td>
<td>0.43</td>
</tr>
<tr>
<td>Nitroglycerin-mediated dilation (%)</td>
<td>19.2 ± 5.0</td>
<td>22.4 ± 7.3</td>
<td><strong>0.004</strong></td>
</tr>
</tbody>
</table>
Effect of Valsartan on Biomarkers and Vascular Function

• There was improvement in oxidative stress (Cysteine-glutathione disulfide) with Valsartan.

• There were trends to improvement in fibrinogen levels and endothelium-independent function with Valsartan.
Conclusions

• Long term blockade of AT$_1$R with Valsartan resulted in significant reverse remodeling of the carotid arteries, manifested as regression in carotid wall thickness and carotid plaque without significant changes in lumen size.

• These effects of Valsartan were independent of changes in lipid levels, statin use, or blood pressure.

• Valsartan therapy was associated with lower oxidative stress, reduced fibrinogen levels, and improved endothelium-independent vascular function.
Implications

• In subjects with carotid wall thickening and mild subclinical atherosclerosis, AT$_1$R antagonists impede progression of disease.

• These effects may translate to long-term reduction in cardiovascular events in individuals with subclinical atherosclerosis.

• Outcome studies in this relatively low risk population may be warranted.
Effervescent Investigators

- **Principal Investigator**
  - Arshed A. Quyyumi, MD

- **Cardiology Fellows**
  - Ronnie Ramadan, MD
  - Saurabh Dhawan, MD

- **Imaging**
  - John N. Oshinski, PhD
  - Ayman Khoder, MD
  - Charles B. Kitchen

- **Oxidative Stress Lab**
  - Dean P. Jones, PhD

- **Biostatistics**
  - Jose Nilo G. Binongo, PhD

- **Vascular testing:**
  - Salman Sher MD

- **Study coordinators**
  - Hamid Syed, MD
  - Asad Ghafoor, MD
  - Muhammad Ali, MD
  - Christina Neissner, MD