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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Disclosures

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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
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Hypothesis

Primary

- Valsartan will reduce progression of carotid bulb 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
- 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

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

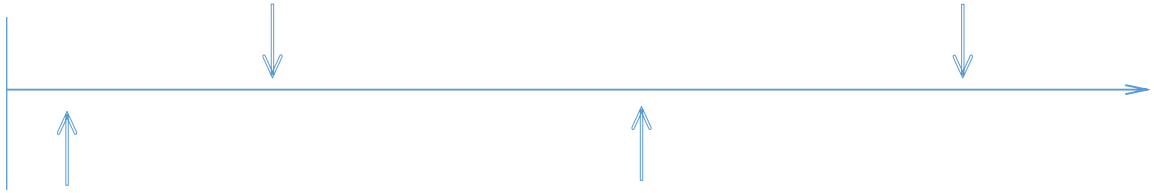
- History and Physical Exam
- CBC, Chemistry, and Lipid profile
- Oxidative Stress Markers
- Inflammatory Markers
- Vascular Function

12 Months

- History and Physical Exam
- CBC, Chemistry, and Lipid profile
- Oxidative Stress Markers
- Inflammatory Markers
- Vascular Function
- **Carotid MRI**

24 Months

- History and Physical Exam
- CBC, Chemistry, and Lipid profile
- Oxidative Stress Markers
- Inflammatory Markers
- Vascular Function
- **Carotid MRI**



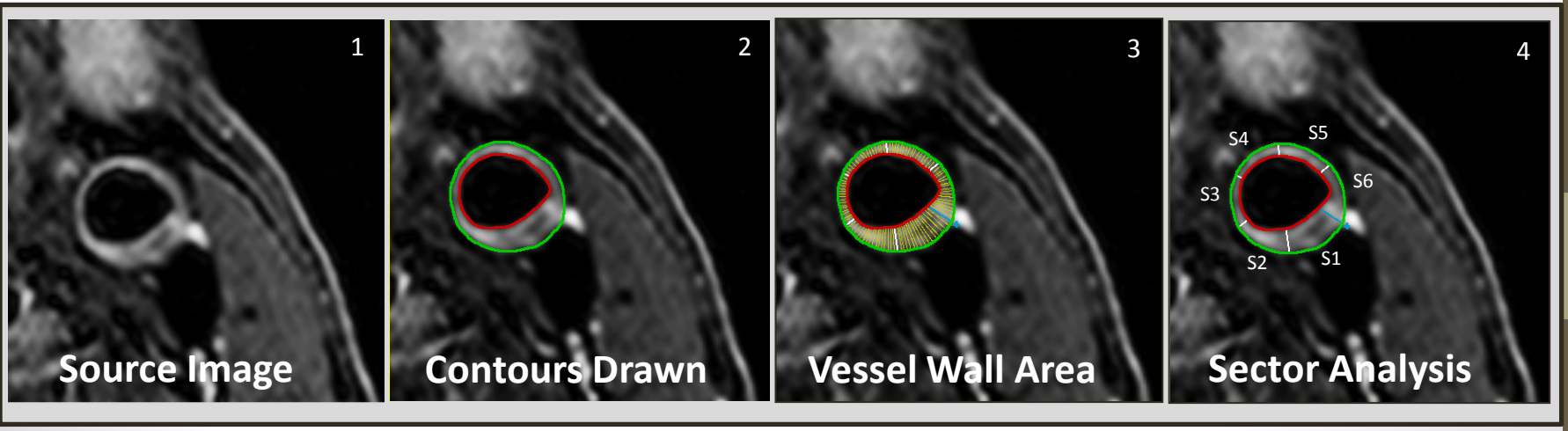
Methods: Carotid MRI

- 1.5 or 3T MRI system
- T2-weighted, black-blood, turbo spine echo (TSE) sequence
- 3 mm slice thickness, 0.3 mm x 0.3 mm spatial resolution

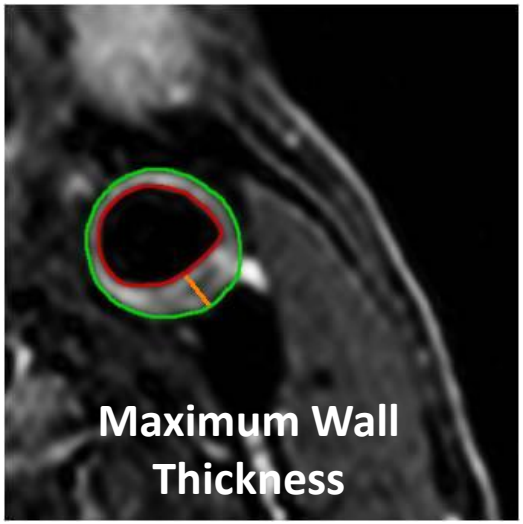
Analysis

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

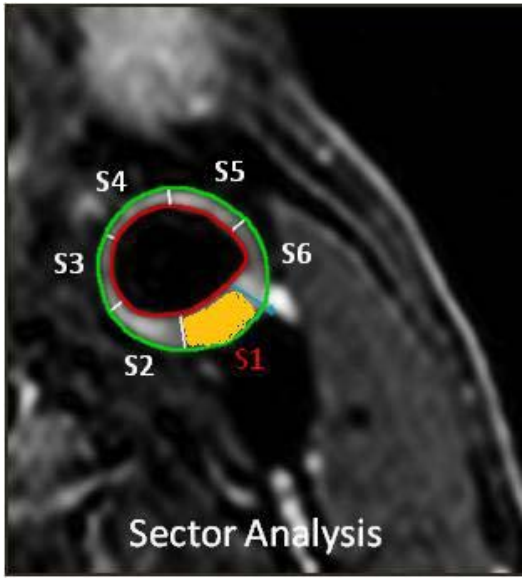
  Software Calculated Measures
  - Lumen area
  - Vessel wall area = total vascular area - lumen area
  - Mean wall thickness
  - Maximum wall thickness
  - Each cross sectional MRI slice divided into 6 sectors with the mean wall thickness calculated for each sector



Plaque Definition

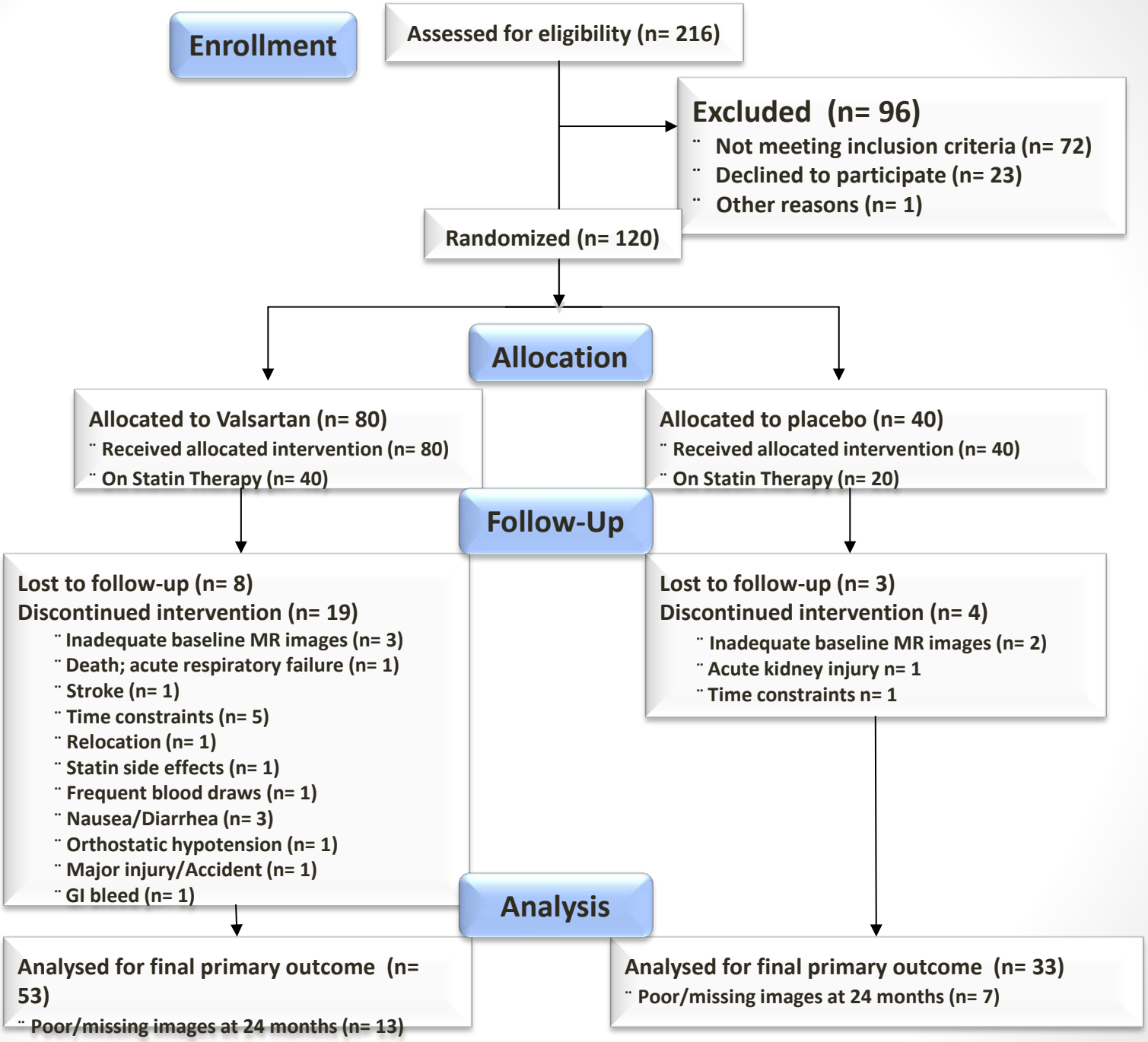


Plaque: Maximum chord > 2 mm



Statistical Methods

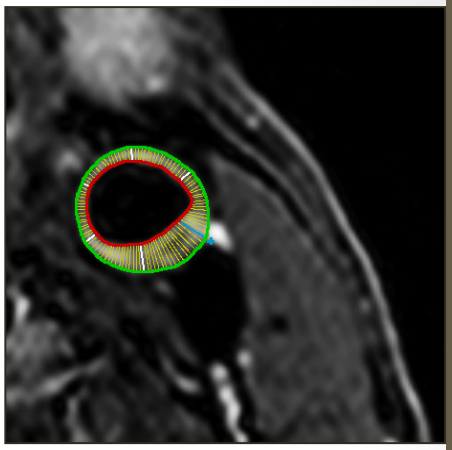
- Comparison between treatment groups was by linear mixed models that take into account correlations between repeated measurements on the same subjects.
  - Model-based means are unbiased with unbalanced and incomplete data
  - Dropouts assumed to be independent of the unobserved measurements
  - Compound symmetry was assumed

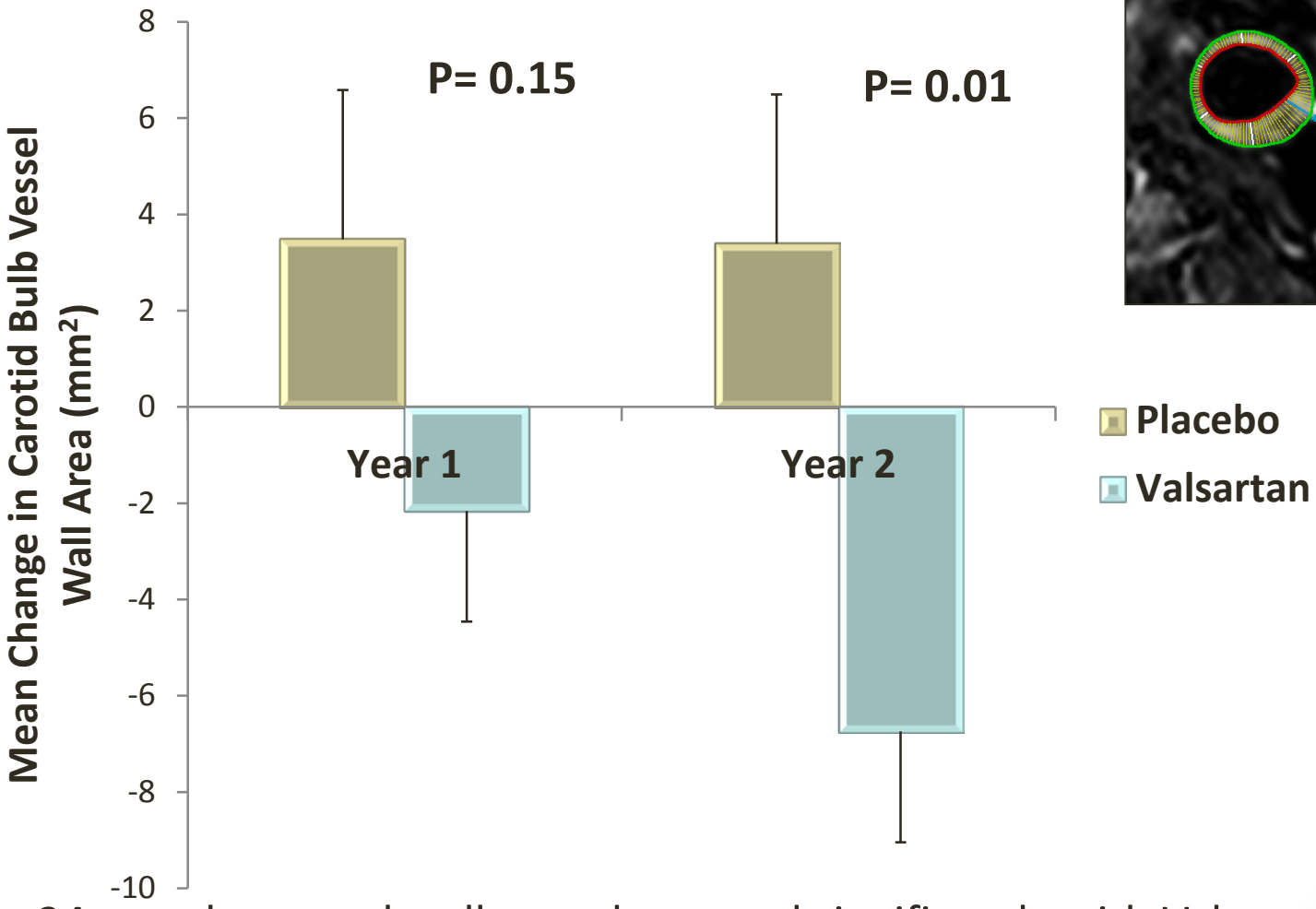

Enrollment
Assessed for eligibility (n= 216)
Excluded (n= 96)
¨ Not meeting inclusion criteria (n= 72)
¨ Declined to participate (n= 23)
¨ Other reasons (n= 1)
Randomized (n= 120)
Allocation
Allocated to Valsartan (n= 80)
¨ Received allocated intervention (n= 80)
¨ On Statin Therapy (n= 40)
Allocated 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= 53)
¨ Poor/missing images at 24 months (n= 13)
Analysed for final primary outcome (n= 33)
¨ Poor/missing images at 24 months (n= 7)

Patients' Characteristics

Characteristics	Valsartan			Placebo			Change between Groups
	Baseline	24 Months	P value	Baseline	24 Months	P value	P Value
Blood Pressure (mean ± SD)							
Systolic blood pressure (mmHg)	122 ± 13	114 ± 20	**0.011**	129 ± 16	124 ± 15	0.14	0.56
Diastolic blood pressure (mmHg)	74 ± 10	69 ± 8	**0.003**	76 ± 12	72 ± 12	**0.043**	0.78
Fasting Lipid Profile (mean ± SD)							
All Patients							
Total cholesterol (mg/dL)	180 ± 31	173 ± 34	0.11	172 ± 28	175 ± 33	0.42	0.10
Triglycerides (mg/dL)	119 ± 61	120 ± 72	0.87	108 ± 67	106 ± 55	0.83	0.79
High density lipoprotein (mg/dL)	50 ± 16	55 ± 18	**<0.001**	56 ± 14	62 ± 15	**0.005**	0.39
Low density lipoprotein (mg/dL)	104 ± 26	94 ± 28	**0.01**	93 ± 25	91 ± 27	0.68	0.11
Statin Group							
Total cholesterol (mg/dL)	170 ± 33	161 ± 30	0.13	167 ± 33	166 ± 35	0.92	0.31
Triglycerides (mg/dL)	111 ± 64	120 ± 71	0.34	118 ± 77	114 ± 51	0.77	0.40
High density lipoprotein (mg/dL)	48 ± 14	52 ± 16	**0.008**	58 ± 14	61 ± 15	0.25	0.76
Low density lipoprotein (mg/dL)	97 ± 29	85 ± 26	**0.037**	85 ± 25	83 ± 27	0.59	0.23
No Statin Group							
Total cholesterol (mg/dL)	193 ± 24	191 ± 32	0.61	179 ± 20	188 ± 26	0.12	0.13
Triglycerides (mg/dL)	130 ± 57	120 ± 74	0.37	94 ± 49	94 ± 61	0.95	0.52
High density lipoprotein (mg/dL)	53 ± 19	58 ± 21	**0.006**	54 ± 14	65 ± 15	**0.004**	0.10
Low density lipoprotein (mg/dL)	114 ± 16	108 ± 25	0.13	103 ± 21	104 ± 22	0.93	0.27
Biomarkers (mean ± SD)							
Potassium (mmol/L)	4.3 ± 0.3	4.4 ± 0.3	**0.045**	4.5 ± 0.4	4.4 ±0.3	0.45	**0.07**
Creatinine (mg/dL)	0.98 ± 0.17	0.92 ± 0.27	0.054	0.96 ±0.21	0.94 ± 0.23	0.31	0.46

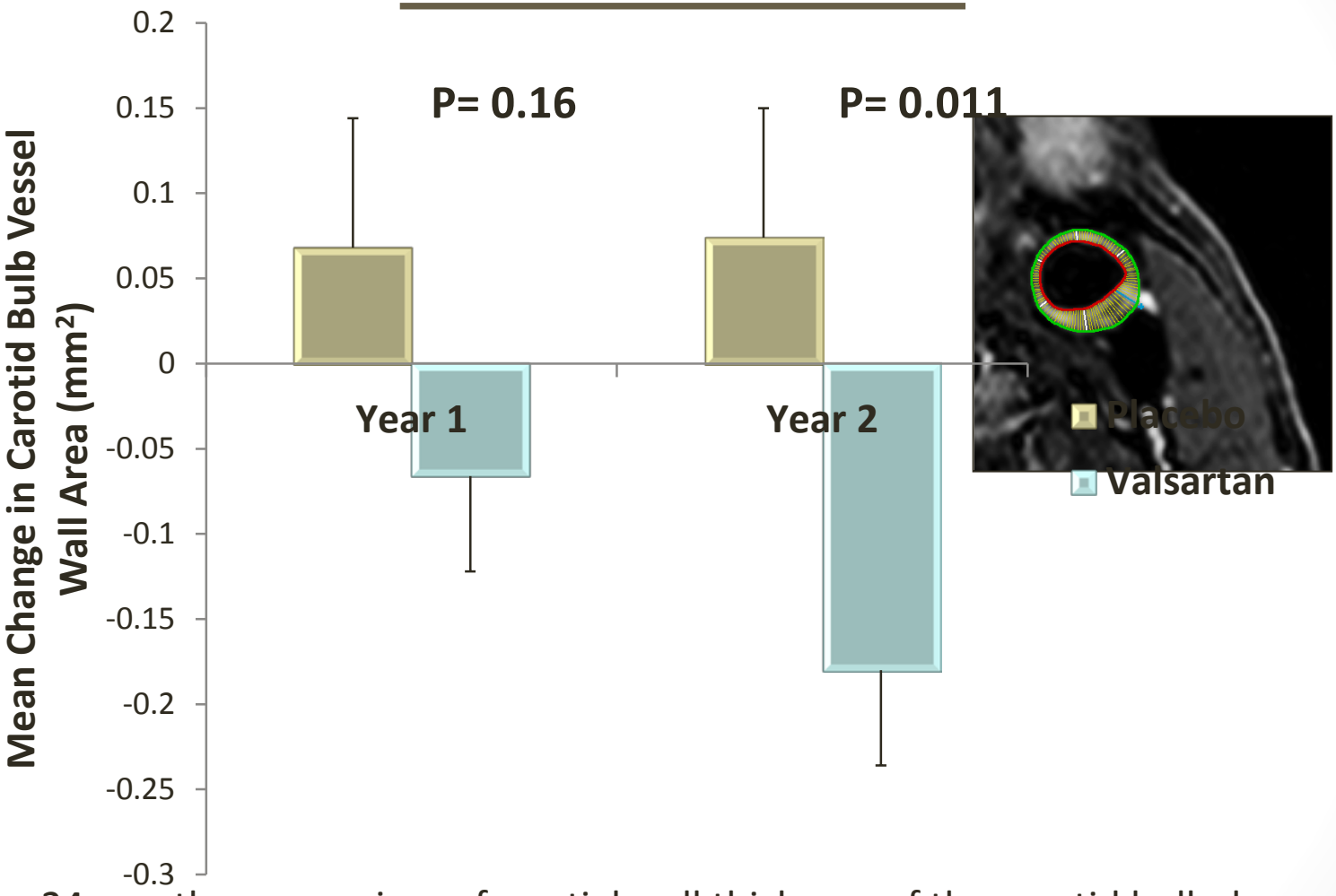
Effect of Valsartan on Carotid Bulb Vessel Wall Area





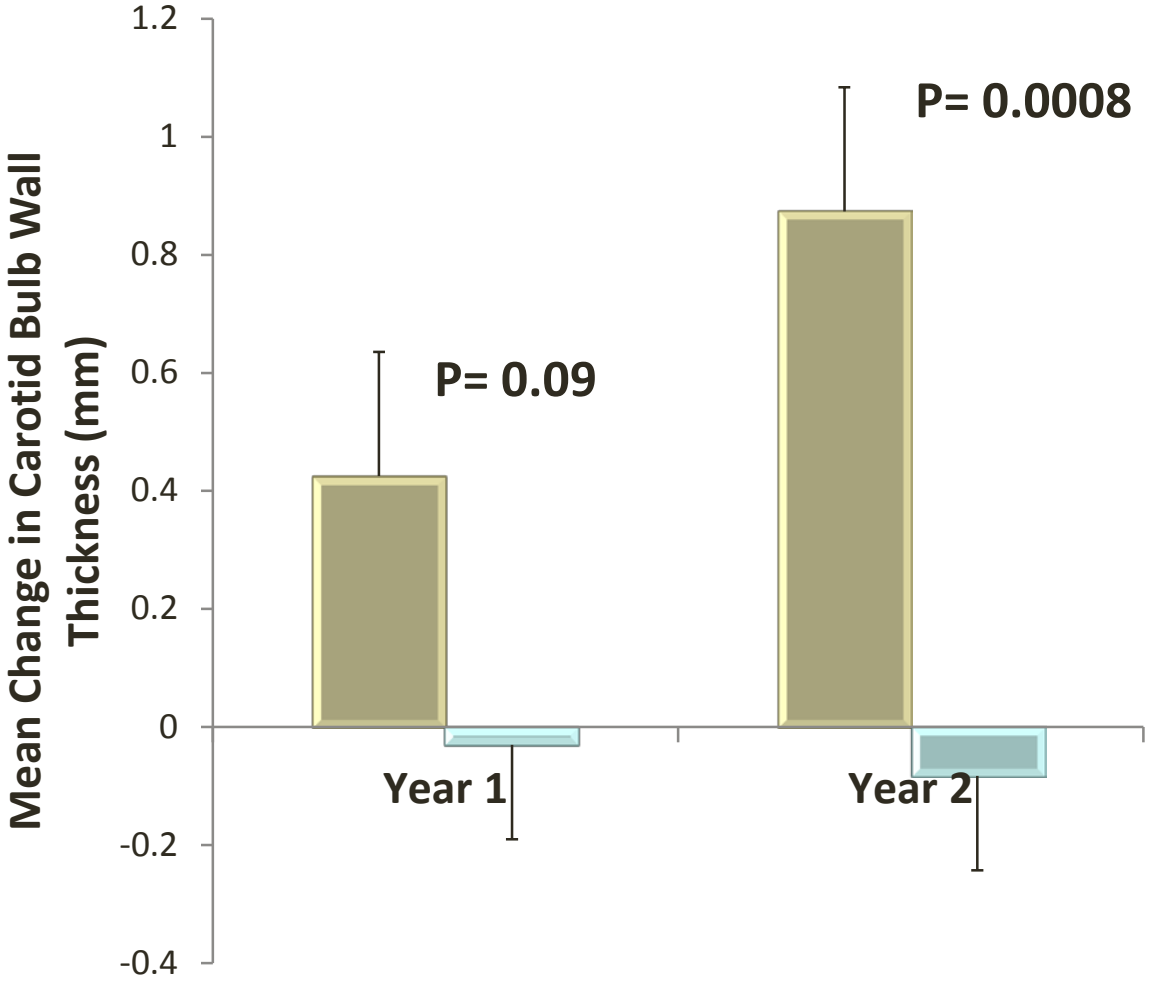
At 24 months, vessel wall area decreased significantly with Valsartan (**P= 0.008**) compared to an insignificant change with placebo (**P= 0.28**)

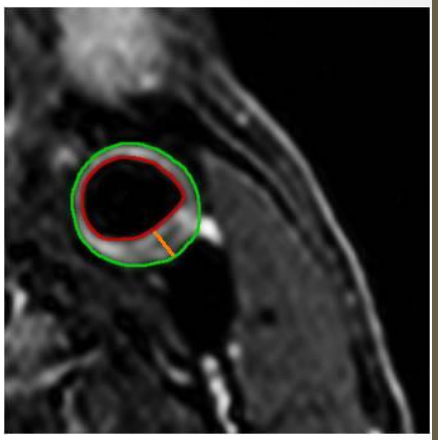
Effect of Valsartan on Carotid Bulb Vessel Wall Thickness



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**)

Effect of Valsartan on Carotid Bulb Maximum Wall Thickness

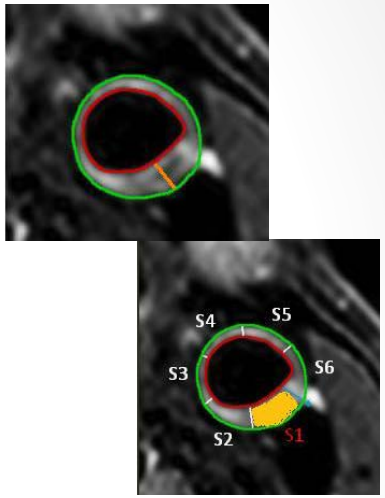


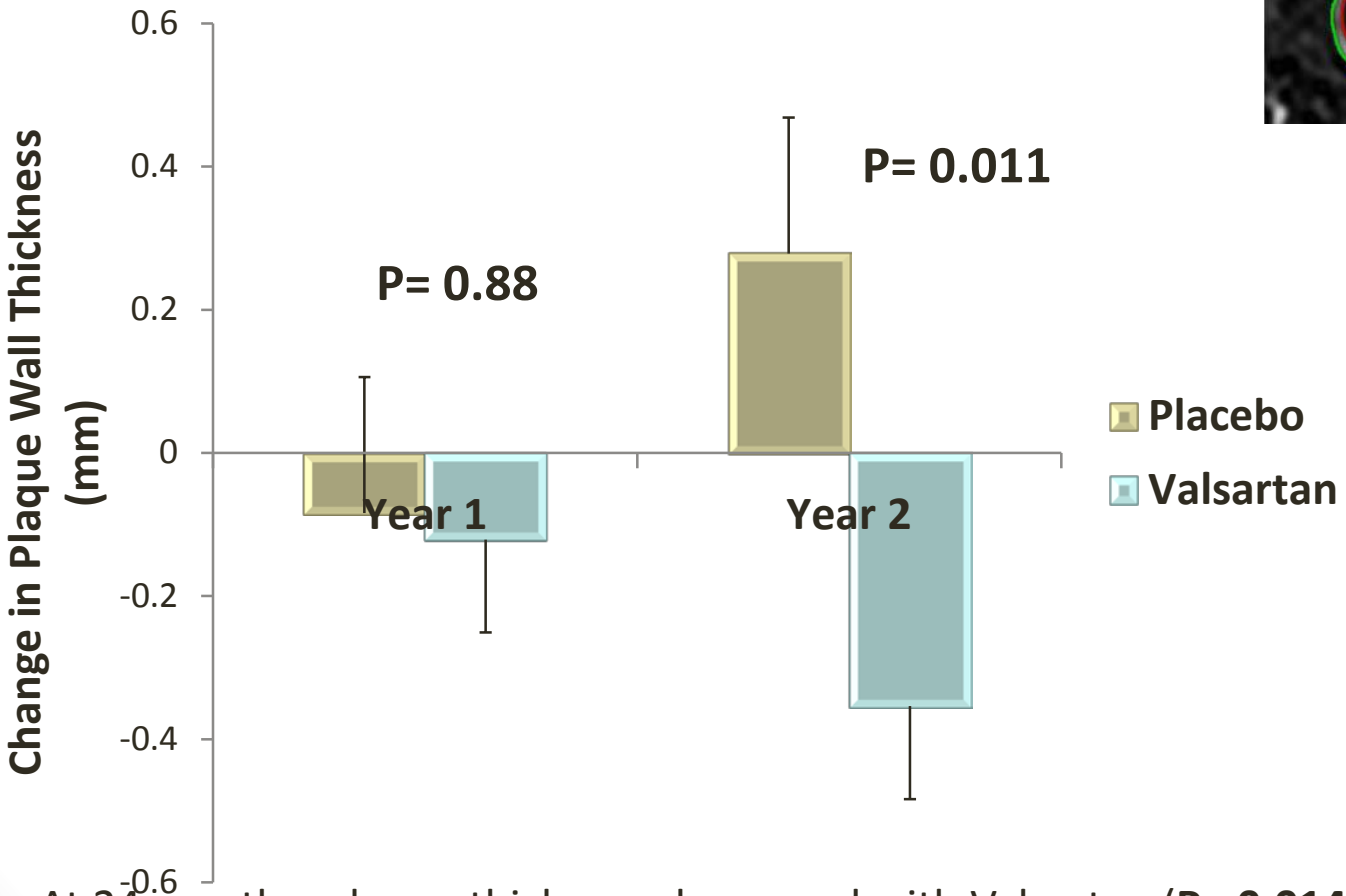


After 24 months, maximum wall thickness of the carotid bulb increased with placebo (**P= 0.001**) compared to an insignificant change with Valsartan (**P= 0.61**)

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

Characteristics	Valsartan			Placebo			Change between Groups
	Baseline	24 Months	P value	Baseline	24 Months	P value	P Value
Oxidative Stress							
Cysteine (µM)	9.3 ± 2.5	9.2 ± 4.0	0.87	9.2 ± 2.3	8.9 ± 2.5	0.71	0.91
Cystine (µM)	85.9 ± 19.6	93.6 ± 21.5	0.016	82.1 ± 11.3	92.1 ± 20.1	0.023	0.64
Glutathione (µM)	1.3 ± 0.6	1.5 ± 0.6	0.069	1.31 ± 0.52	1.65 ± 0.61	0.018	0.39
Glutathione Disulfide (µM)	0.03 ± 0.02	0.06 ± 0.05	<0.001	0.03 ± 0.02	0.06 ± 0.04	0.023	0.42
Cysteine-glutathione disulfide (µM)	2.4 ± 0.8	3.1 ± 1.2	0.001	2.28 ± 0.91	4.04 ± 2.06	<0.001	**0.007**
Inflammation							
C-reactive protein (mg/L)	3.5 ± 6.1	2.9 ± 3.4	0.47	2.26 ± 2.59	2.32 ± 2.65	0.91	0.55
Fibrinogen (g/L)	2.5 ± 0.8	2.7 ± 0.8	0.32	2.23 ± 0.48	2.54 ± 0.53	**0.007**	0.35
Vascular Function							
Flow-mediated dilation (%)	5.5 ± 3.9	6.0 ± 3.6	0.43	5.0 ± 3.8	5.0 ± 3.5	0.99	0.64
Nitroglycerin-mediated dilation (%)	19.2 ± 5.0	22.4 ± 7.3	**0.004**	19.9 ± 7.3	21.4 ± 7.7	0.48	0.49

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_1R 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, 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_1R 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

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  - Charles B. Kitchen
- **Oxidative Stress Lab**
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- **Biostatistics**
  - Jose Nilo G. Binongo, PhD
- **Study coordinators**
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  - Asad Ghafoor, MD
  - Muhammad Ali, MD
  - Christina Neissner, MD

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