# Effect of the Renin Inhibitor Aliskiren on Progression of Coronary Atherosclerosis: AQUARIUS Study Results

SJ Nicholls, GL Bakris, JJP Kastelein, V Menon, B Williams, M Nicolaides, P Brunel, J Armbrecht, R Puri, D Bash, A Hsu and SE Nissen

SAHMRI HEART

C5 Research

Cleveland Clinic Coordinating Center for Clinical Research

# Disclosures

- Research support: AstraZeneca, Amgen, Anthera, Eli Lilly, Novartis, Resverlogix, InfraReDx, Roche and LipoScience

- Consulting and honoraria: AstraZeneca, Eli Lilly, Anthera, Omthera, Merck, Takeda, Resverlogix, Sanofi-Aventis, CSL Behring, Esperion, Boehringer Ingelheim

- AQUARIUS was sponsored by Novartis Pharma AG

# Steering Committee

- Steven Nissen (Chair)
- Stephen Nicholls (Principal Investigator)
- George Bakris
- John Kastelein
- Venu Menon
- Bryan Williams
- Juergen Armbrecht (non-voting)

# Background

- Guidelines recommend blood pressure (BP) reduction in hypertensive patients with a treatment goal of 140/90 mmHg for most individuals

- The benefit of additional BP lowering agents in patients at treatment goals has not been established .

- However, few trials have examined the benefits and risks of further intensifying BP treatment in patients with established coronary artery disease, who are in the pre-hypertensive range.

# Background

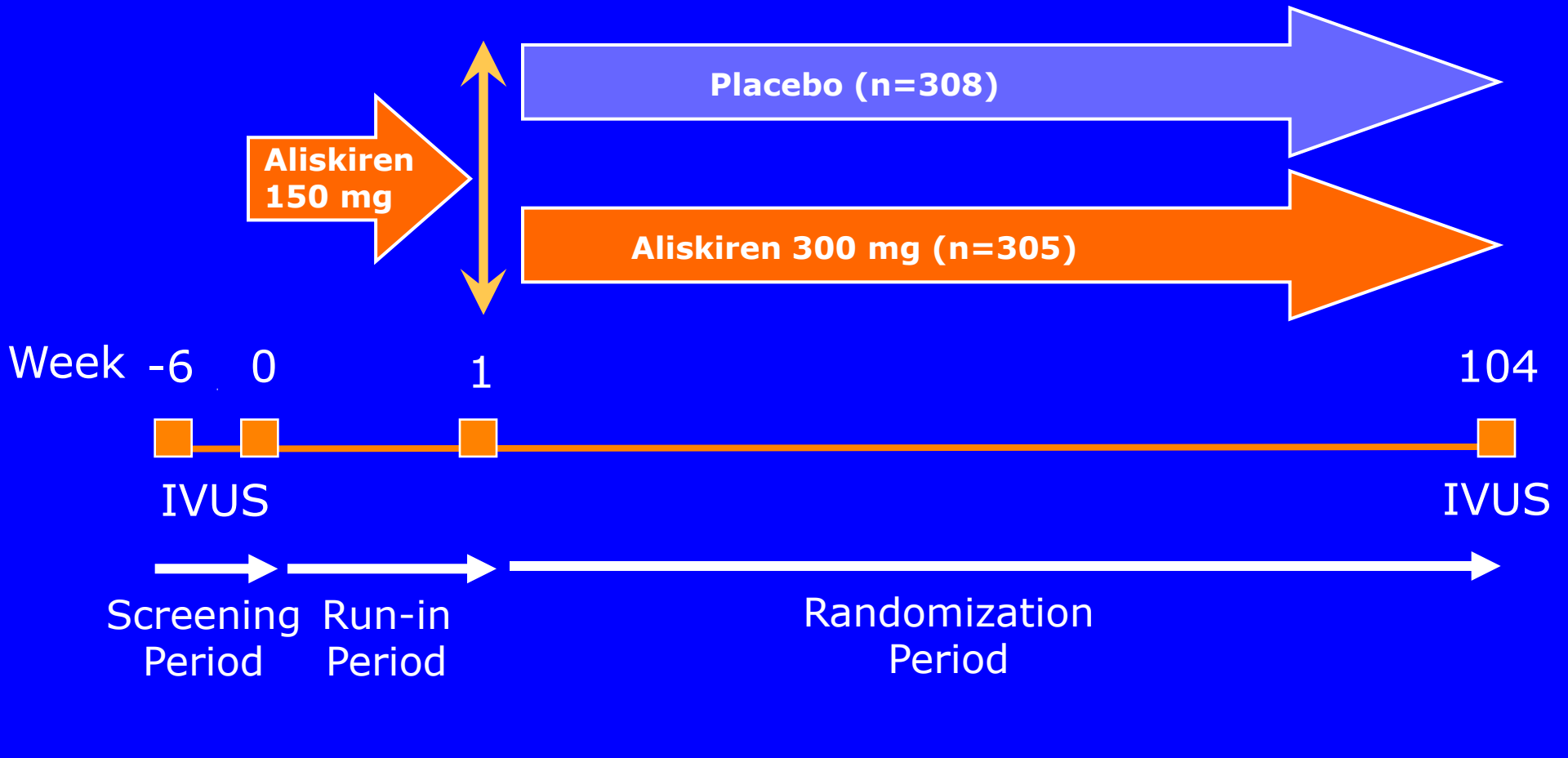
- Some studies have suggested a role of the renin-angiotensin-aldosterone system (RAAS) in atherosclerosis
- Preclinical models demonstrate favorable effects of renin inhibition with aliskiren on progression of atherosclerosis
- However, clinical trials of aliskiren have not yet shown a clinical outcomes benefit, and a trial in patients with high risk type 2 diabetes was terminated for futility and adverse clinical effects
- The effects of renin inhibition on atherosclerosis in humans has not been investigated

# Objective

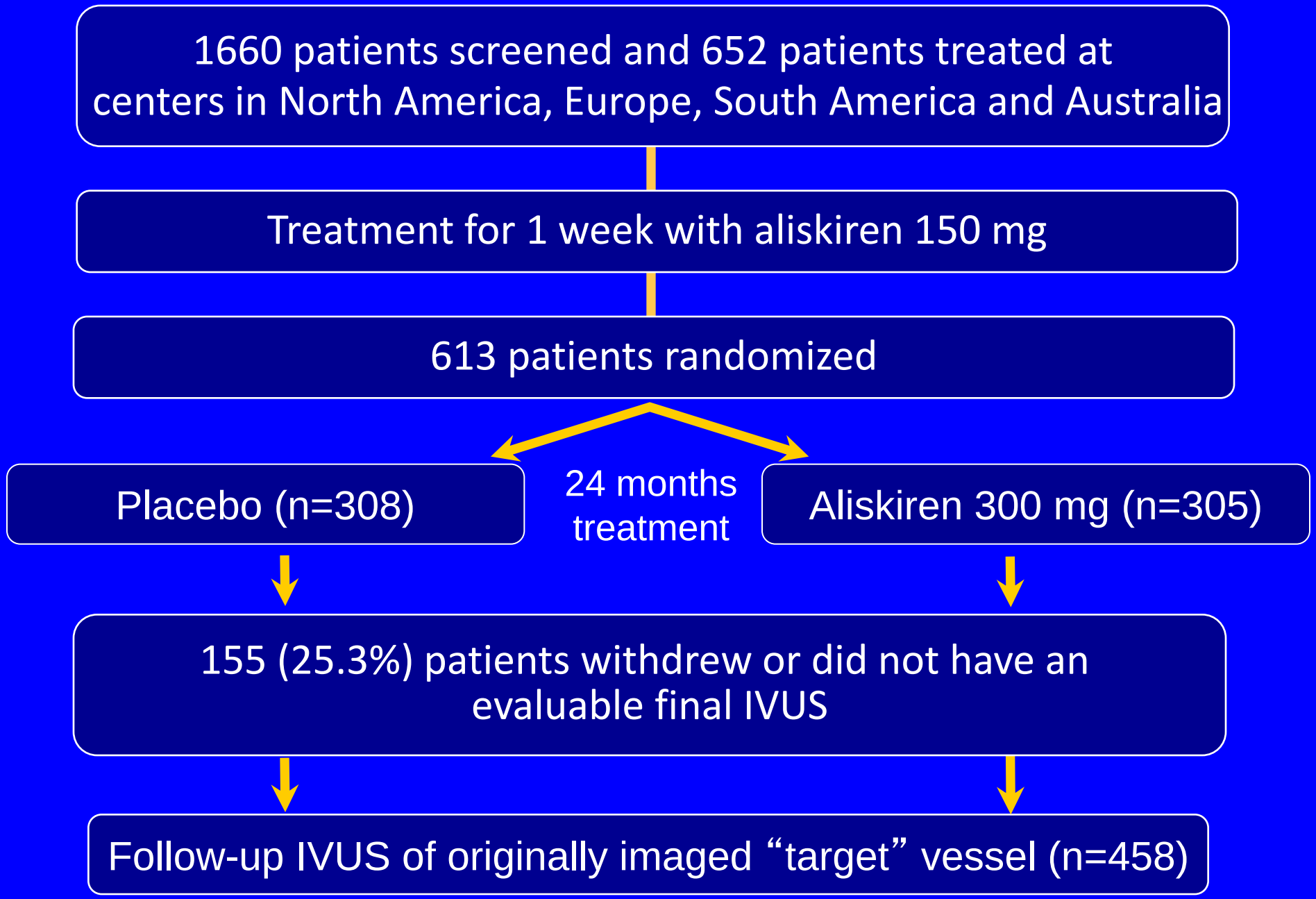
To compare the effects of aliskiren 300 mg versus placebo on progression of coronary atherosclerosis assessed by intravascular ultrasound in patients whose blood pressure is in the pre-hypertensive range.

# AQUARIUS Study Design

613 patients with symptomatic CAD (angiographic stenosis >20%), systolic BP 125-139 mmHg, diastolic BP <90 mmHg and two additional CV risk factors



# AQUARIUS Trial: Flow of Patients



# Clinical Characteristics

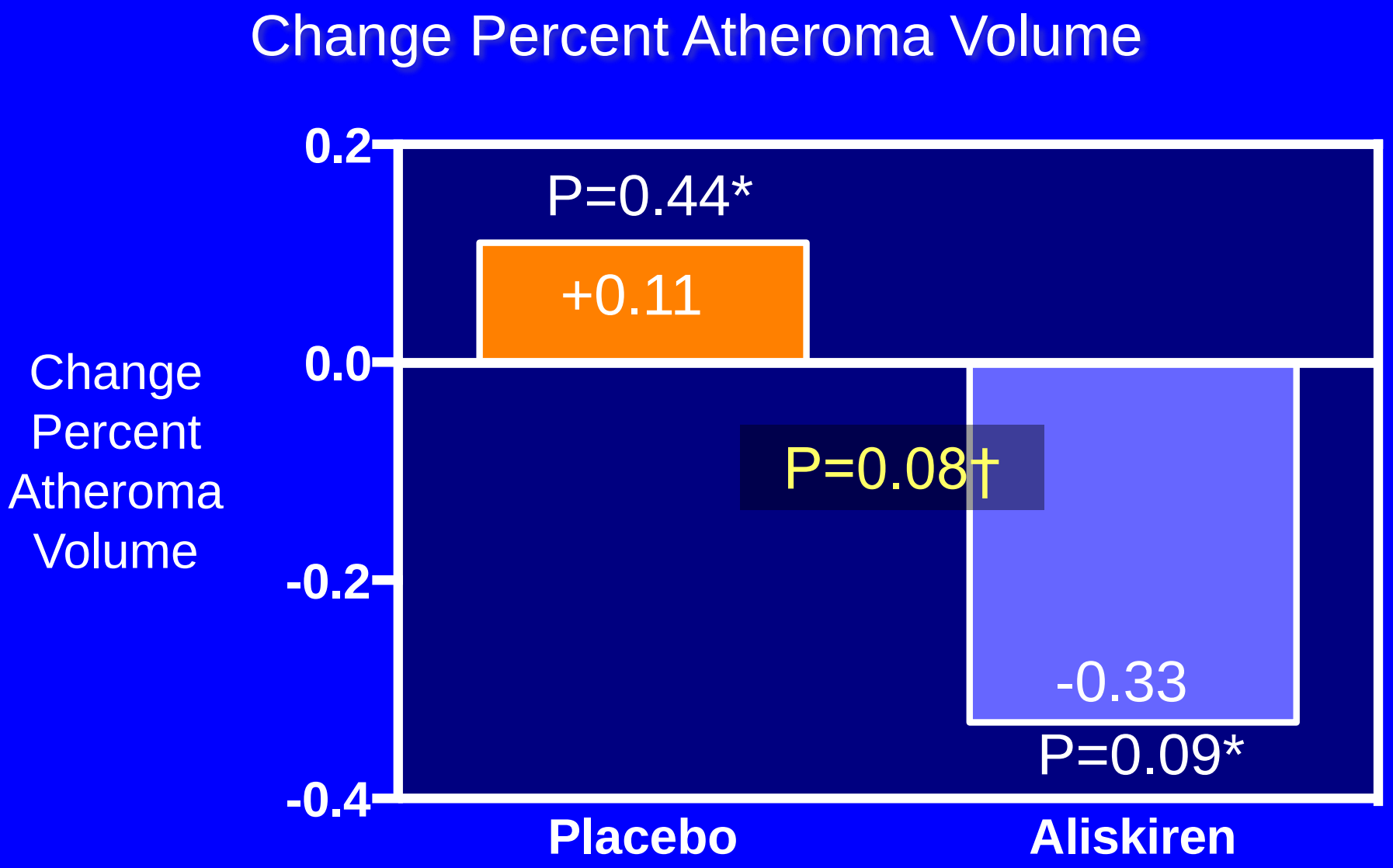
| Parameter | Placebo (n=308) | Aliskiren (n=305) |
|---|---|---|
| Mean age in years | 59.2 | 60.2 |
| Males | 77.6% | 74.8% |
| History of Hypertension | 86.0% | 81.6% |
| History of Diabetes | 29.2% | 29.2% |
| Concomitant Medications | | |
| Statins | 93.5% | 90.5% |
| Anti-platelet Therapy | 97.7% | 95.4% |
| Beta-blockers | 79.5% | 78.4% |
| ACE Inhibitors | 62.0% | 53.4% |
| Angiotensin II Receptor Blockers | 22.7% | 22.6% |
| Calcium Channel Blockers | 44.2% | 41.0% |

# On-Treatment BP and Lab Values

| Parameter | Placebo (n=233) | Aliskiren (n=225) | P Value |
|---|---|---|---|
| Systolic BP (mmHg)† | 130.4 | 128.3 | 0.007 |
| Diastolic BP (mmHg)† | 76.8 | 75.3 | 0.003 |
| LDL cholesterol (mg/dL)† | 93.0 | 94.8 | 0.36 |
| hsCRP (mg/L)* | 1.8 | 1.9 | 0.97 |
| Plasma renin activity (ng/mL/h)* | 1.5 | 0.2 | <0.01 |
| Plasma renin concentration (ng/L)* | 19.8 | 88.8 | <0.01 |

*Median; †Least squares mean

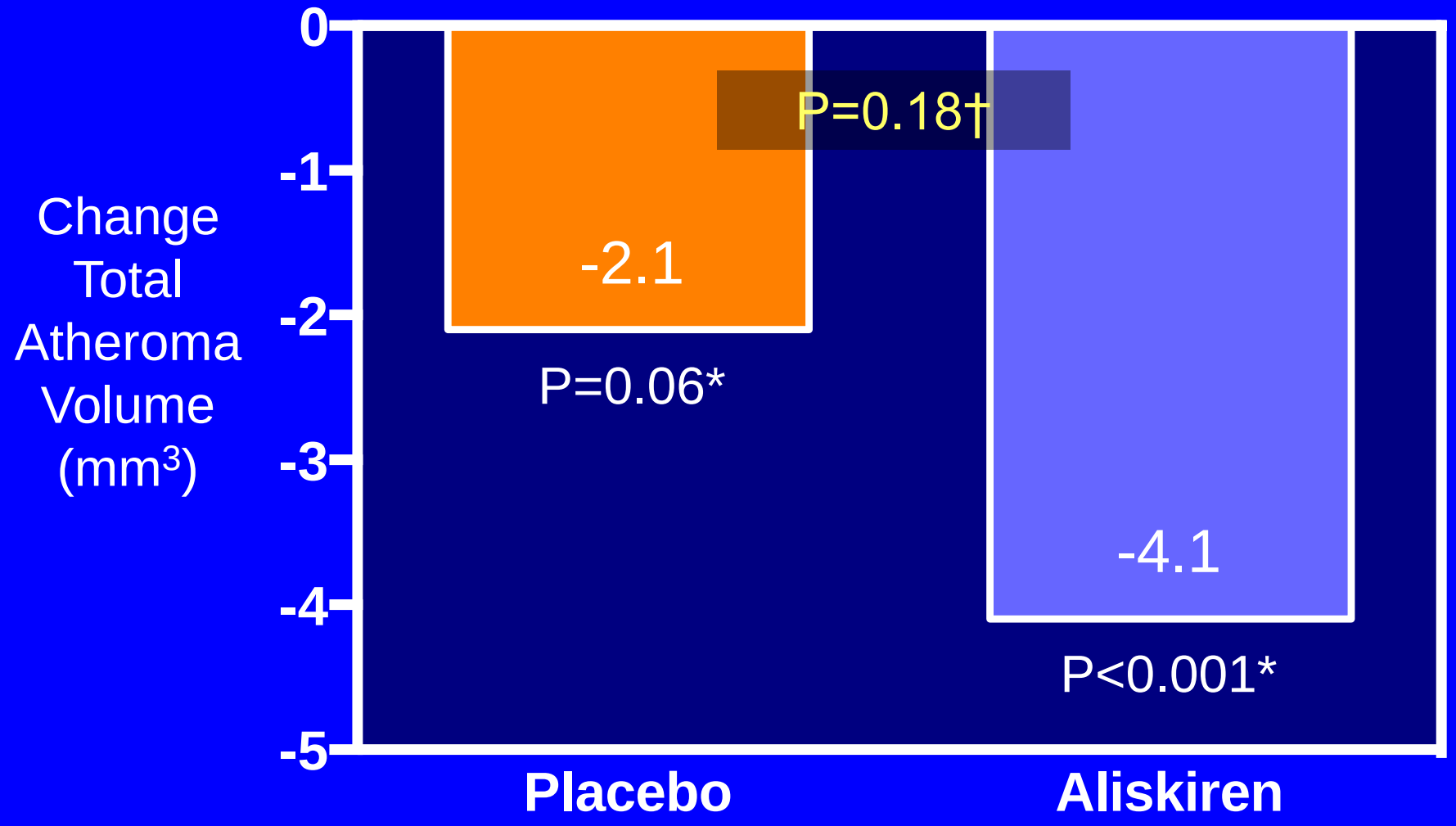
# Primary IVUS Efficacy Parameter




Least squares mean change. † comparison between groups. * comparison from baseline

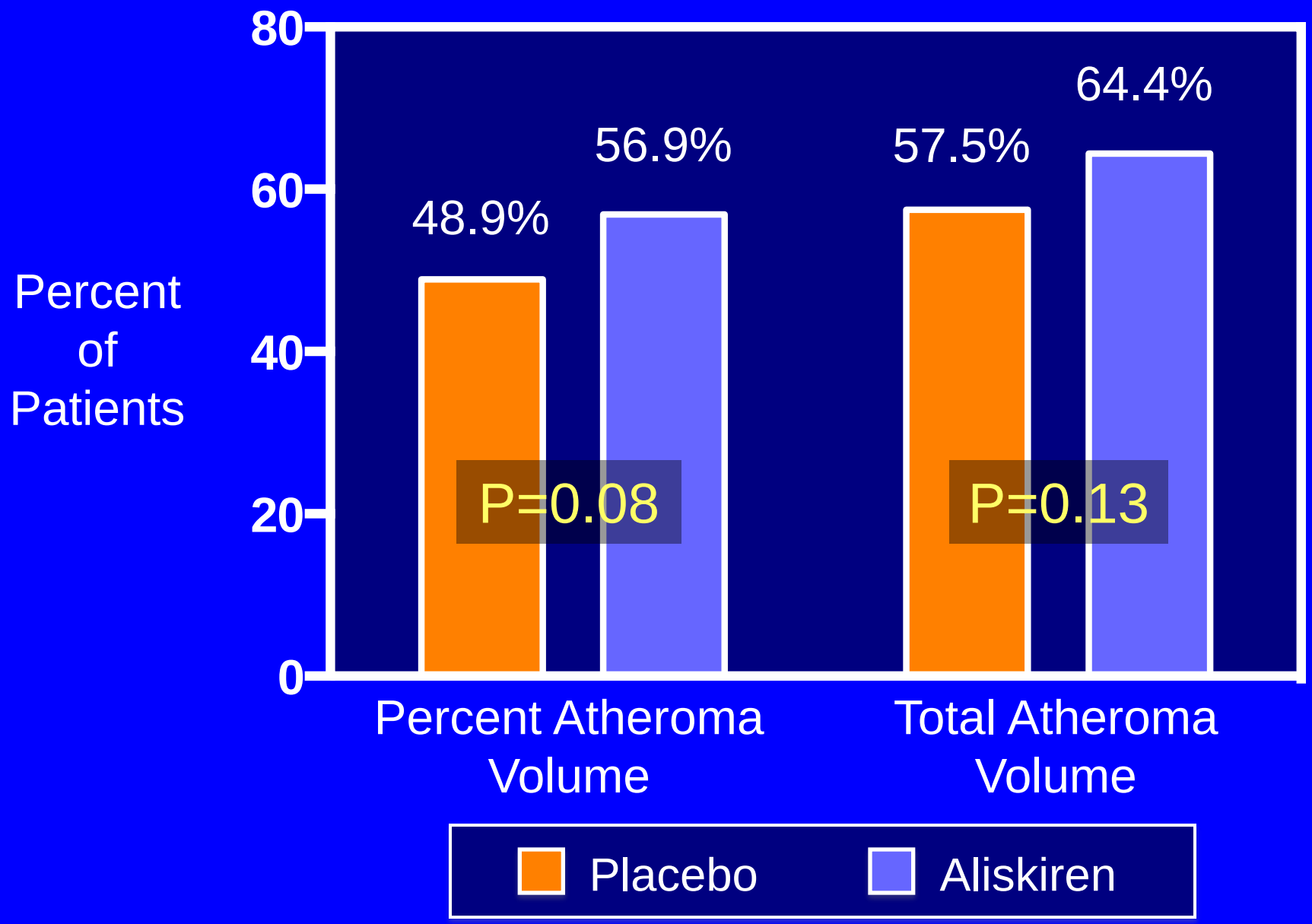
# Secondary IVUS Efficacy Parameter

## Change in Total Atheroma Volume




Least squares mean change. † comparison between groups. * comparison from baseline

# Fraction of Patients Exhibiting Regression

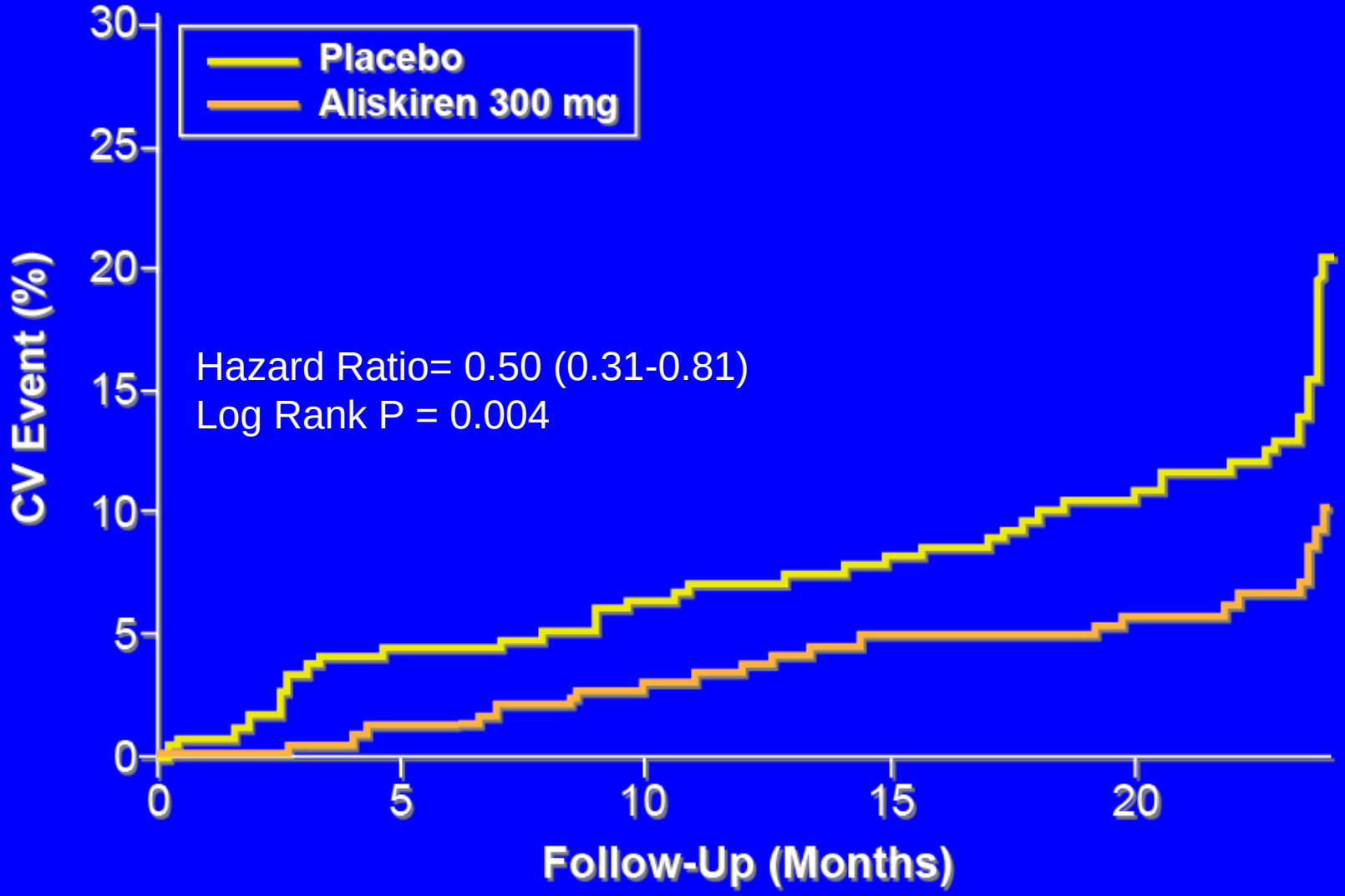


# Exploratory Analysis: Major Adverse Cardiovascular Events (MACE)

| | Placebo (n=308) | Aliskiren (n=305) | P Value |
|---|---|---|---|
| MACE | 50 | 26 | 0.004 |
| Death | 6 | 1 | 0.07 |
| MI | 8 | 1 | 0.02 |
| Stroke | 4 | 1 | 0.19 |
| Revascularization | 35 | 24 | 0.13 |
| ACS | 9 | 4 | 0.18 |

P values from log rank test. ACS: acute coronary syndrome, MI: myocardial infarction

# Kaplan Meier Curves: Time to Major Adverse Cardiovascular Events (MACE)



# Analysis Based Upon Diabetes Status

| | No Diabetes | | | Diabetes | | | P Value# |
|---|---|---|---|---|---|---|---|
| | Placebo (n=173) | Aliskiren (n=170) | P Value† | Placebo (n=60) | Aliskiren (n=55) | P Value† | |
| ΔPAV (%) | 0.01 P=0.95* | -0.53 P<0.01* | 0.06 | 0.33 P=0.40* | 0.15 P=0.70* | 0.74 | 0.55 |
| ΔTAV ($mm^3$) | -2.7 P=0.03* | -5.3 P<0.01* | 0.15 | -0.4 P=0.86* | -1.3 P=0.58* | 0.79 | 0.62 |
| | Placebo (n=218) | Aliskiren (n=216) | P Value† | Placebo (n=90) | Aliskiren (n=89) | P Value† | |
| MACE (%) | 16.1% | 6.5% | 0.002 | 16.7% | 13.5% | 0.55 | 0.10 |

MACE: major adverse cardiovascular events; PAV: percent atheroma volume; TAV: total atheroma volume
* P value for comparison with baseline; † P value for comparison between treatment groups
# P value for subgroup heterogeneity

# Adverse Events: Safety Population (n=613)

| Parameter | Placebo (n=308) | Aliskiren (n=305) |
|---|---|---|
| Discontinuation due to adverse events | 4.5% | 8.2% |
| Hypotension† | 3.9% | 7.2% |
| Renal and urinary disorders | 4.9% | 6.9% |
| Hyperkalaemia (≥5.5 mEq/L) | 9.8% | 10.7% |
| Creatinine >ULN | 2.0% | 1.3% |
| Blood urea nitrogen >ULN | 2.6% | 3.3% |

† P=0.04 for comparison between groups

# Conclusions

- Aliskiren 300 mg resulted in lower blood pressure and renin activity compared with placebo.
- For the primary endpoint, a trend to regression was observed with aliskiren, although this did not reach statistical significance (P=0.08).
- For the secondary endpoint, regression with aliskiren did not differ from placebo (P=0.18).
- Fewer cardiovascular events were observed in the aliskiren group (P=0.004).

Original Investigation

# Effect of Aliskiren on Progression of Coronary Disease in Patients With Prehypertension

## The AQUARIUS Randomized Clinical Trial

Stephen J. Nicholls, MBBS, PhD; George L. Bakris, MD; John J. P. Kastelein, MD, PhD; Vanu Menon, MD; Bryan Williams, MD; Juergen Armbrecht, MD; Patrick Brunel, MD; Marta Nicolaides, MD; Amy Hsu, MS; Bo Hu, PhD; Hui Fang, PhD; Rishi Puri, MBBS; Kiyoko Uno, MD, PhD; Yu Kataoka, MD, PhD; Dianna Bash, RN; Steven E. Nissen, MD

**IMPORTANCE** Blood pressure reduction and renin-angiotensin-aldosterone system inhibition are targets for treatment of atherosclerosis. The effect of renin inhibition on coronary disease progression has not been investigated.

**OBJECTIVE** To determine the effects of renin inhibition with aliskiren on progression of coronary atherosclerosis.

**DESIGN, SETTING, AND PARTICIPANTS** A double-blind, randomized, multicenter trial (Aliskiren Quantitative Atherosclerosis Regression Intravascular Ultrasound Study) comparing aliskiren with placebo in 613 participants with coronary artery disease, systolic blood pressure between 125 and 139 mm Hg (prehypertension range), and 2 additional cardiovascular risk factors conducted at 103 academic and community hospitals in Europe, Australia, and North and South America (enrollment from March 2009 to February 2011; end of follow-up: January 31, 2013).

**INTERVENTIONS** Participants underwent coronary intravascular ultrasound (IVUS) imaging and were randomized to receive 300 mg of aliskiren (n = 305) or placebo (n = 308) taken orally daily for 104 weeks. Disease progression was measured by repeat IVUS examination after at least 72 weeks of treatment.

**MAIN OUTCOMES AND MEASURES** The primary efficacy parameter was the change in percent atheroma volume (PAV) from baseline to study completion. Secondary efficacy parameters included the change in normalized total atheroma volume (TAV) and the percentage of participants with atheroma regression. Safety and tolerability were also assessed.

**RESULTS** Evaluable imaging data were available at baseline and follow-up for 458 participants (74.7%). The primary IVUS efficacy parameter, PAV, did not differ between participants treated with aliskiren (−0.33%; 95% CI, −0.68% to 0.02%) and placebo (0.11%; 95% CI, −0.24% to 0.45%) (between-group difference, −0.43% [95% CI, −0.92% to 0.05%]; $P = .08$). The secondary IVUS efficacy parameter, TAV, did not differ between participants treated with aliskiren (−4.1 $mm^3$; 95% CI, −6.27 to −1.94 $mm^3$) and placebo (−2.1 $mm^3$; 95% CI, −4.21 to 0.07 $mm^3$) (between-group difference, −2.04 $mm^3$ [95% CI, −5.03 to 0.95 $mm^3$]; $P = .18$). There were no significant differences in the proportion of participants who demonstrated regression of PAV (56.9% vs 48.9%; $P = .08$) and TAV (64.4% vs 57.5%; $P = .13$) in the aliskiren and placebo groups, respectively.

**CONCLUSIONS AND RELEVANCE** Among participants with prehypertension and coronary artery disease, the use of aliskiren compared with placebo did not result in improvement or slowing of progression of coronary atherosclerosis. These findings do not support the use of aliskiren for regression or prevention of progression of coronary atherosclerosis.

**TRIAL REGISTRATION** clinicaltrials.gov identifier: NCT00853827

JAMA. doi:10.1001/jama.2013.277169
Published online September 3, 2013.

Editorial

Supplemental content at jama.com

**Author Affiliations:** Author affiliations are listed at the end of this article.

**Corresponding Author:** Stephen J. Nicholls, MBBS, PhD, South Australian Health and Medical Research Institute, PO Box 11060, Adelaide, SA 5001, Australia (stephen.nicholls@sahmri.com).

JAMA®
The Journal of the American Medical Association

**Available at www.jama.com**

# A Final Thought

- The lack of statistical significance compared with placebo suggests that AQUARIUS is a neutral study.
- However, the trend towards favorable effects on plaque and clinical events suggests that there may be potential benefit from addition of blood pressure agents to patients considered at goal.
- Confirmation of a benefit of aliskiren on cardiovascular outcomes will require a larger clinical trial.