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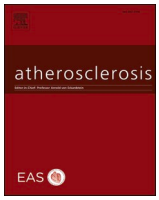

Effects of renin-angiotensin-aldosterone-system inhibitors on coronary atherosclerotic plaques: The PARADIGM registry

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ABSTRACT

Background and aims: Inhibition of Renin-Angiotensin-Aldosterone-System (RAAS) has been hypothesized to improve endothelial function and reduce plaque inflammation, however, their impact on the progression of coronary atherosclerosis is unclear. We aim to study the effects of RAAS inhibitor on plaque progression and composition assessed by serial coronary CT angiography (CCTA).

Methods: We performed a prospective, multinational study consisting of a registry of patients without history of CAD, who underwent serial CCTAs. Patients using RAAS inhibitors were propensity matched to RAAS inhibitor naïve patients based on clinical and CCTA characteristics at baseline. Atherosclerotic plaques in CCTAs were quantitatively analyzed for percent atheroma volume (PAV) according to plaque composition. Interactions

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between RAAS inhibitor use and baseline PAV on plaque progression were assessed in the unmatched cohort using a multivariate linear regression model.

Results: Of 1248 patients from the registry, 299 RAAS inhibitor taking patients were matched to 299 RAAS inhibitor naïve patients. Over a mean interval of 3.9 years, there was no significant difference in annual progression of total PAV between RAAS inhibitor naïve *vs* taking patients (0.75 *vs* 0.79%/year, $p = 0.66$). With interaction testing in the unmatched cohort, however, RAAS inhibitor use was significantly associated with lower non-calcified plaque progression (Beta coefficient −0.100, adjusted $p = 0.038$) with higher levels of baseline PAV.

Conclusions: The use of RAAS inhibitors over a period of nearly 4 years did not significantly impact on total atherosclerotic plaque progression or various plaque components. However, interaction testing to assess the differential effect of RAAS inhibition based on baseline PAV suggested a significant decrease in progression of non-calcified plaque in patients with a higher burden of baseline atherosclerosis, which should be considered hypothesis generating.

1. Introduction

Over the last 15 years, coronary CT angiography (CCTA) has become a novel tool in the diagnosis and risk stratification of patients with coronary artery disease (CAD) [1–5]. In addition to having superior sensitivity and specificity for the diagnosis of CAD than traditional methods such as exercise stress testing [6–8], it has the ability to non-invasively identify non-obstructive plaque in patients who would benefit from escalation of medical therapy to prevent major adverse cardiovascular events (MACE). The ability of CCTA to improve patient outcomes has already been demonstrated, with relative risk reductions in CAD death or myocardial infarction of up to 40% over 5 years [9]. Furthermore, it has also been shown to improve prognostication over conventional risk scores and functional testing independently [10]. It has achieved a Class I recommendation as part of the diagnostic workup for patients with chest pain [11].

In addition to identifying and risk stratifying CAD, this tool has allowed clinicians and researchers insights into the natural history of atherosclerosis. The Progression of AtheRosclerotic PlAque DetermIned by Computed TomoGraphic Angiography IMaging (PARADIGM) registry, previously described [12], is a large observational registry of patients with serial CCTA studies that has allowed researchers to observe changes in plaque volumes, distribution and morphology over time [13–16], as well as exploring plaque changes as they relate to patient risk factors (such as age, gender, diabetes, hypertension, smoking) [17,18]. This registry has previously provided insights into the potential effects of statins, demonstrating a reduction in the rate of plaque progression and increase in the proportion of calcified plaque associated with statin therapy [19].

Activation of the renin-angiotensin-aldosterone system (RAAS) has been thought to play a role in the pathophysiology of CAD, and its inhibition has been hypothesized to improve endothelial function and reduce progression of atherosclerosis [20–26], though the proposed mechanisms of this benefit vary significantly by drug, and further studies are needed to understand the complete mechanisms of these processes including off-target effects. Previous fundamental science studies have established potential mechanisms of ACE inhibitors and ARBs in slowing plaque progression or stabilizing plaque in models [27,28]. Further, landmark studies have demonstrated that the use of RAAS inhibitors has decreased MACE in patients at high risk of cardiovascular events, including those without overt LV dysfunction or diabetes [20,29,30], but there are few studies that have investigated the effect that RAAS inhibitors have on coronary artery plaque burden or morphology in humans over time, and none that have used cross sectional imaging to answer this question. Given their ubiquity in the treatment of cardiovascular disease, it is important to understand their effects on the atherosclerotic process. The objective of this study is to evaluate the effects that RAAS inhibitors have on the progression of atherosclerosis with regards to total plaque burden, as well as plaque composition over time.

2. Patients and methods

2.1. Study design

The PARDIGM Registry is a large, observational database of prospectively collected data on patients who have undergone serial CCTA studies for clinically indicated purposes. The purpose of this registry was to use demographic, clinical, and imaging data to better understand the natural history of coronary atherosclerosis and the impact clinical factors have on the process. The details and design of the registry have previously been described in detail and the study protocol was approved by the institutional review boards of all participating centers [12].

2.2. Study population

The PARADIGM registry is composed of 2252 patients across 13 study sites in 7 different countries who underwent serial CCTAs at least 2 years apart, denoted as CCTA-1 (baseline) and CCTA-2 (follow-up). Patients in this registry were excluded from the present study if they met any of the following criteria: 1) missing clinical data at baseline or follow-up, 2) missing data regarding use of RAAS inhibitors at baseline or follow-up, 3) patients with an uninterpretable CCTA-1 or CCTA-2 due to technical reasons or 4) patients with established CAD prior to CCTA-1. RAAS inhibitors within this registry included any patient taking an ACE inhibitor or ARB. Patients were categorized into RAAS inhibitor naïve patients if they were not taking this class of medications at CCTA-1 and CCTA-2, and conversely, they were categorized as taking RAAS inhibitors if they were documented to be taking these medications at the time of CCTA-1 and CCTA-2. Patients taking RAAS inhibitors at CCTA-2 but not CCTA-1 were excluded, as it was not possible to quantify the duration of RAAS inhibitor use. Changes in the dose or type of RAAS inhibitor is not available within the database.

2.3. Coronary CTA analysis protocol

Image acquisition and post-processing for CCTAs in the PARADIGM registry were performed in accordance with the Society of Cardiovascular Computed Tomography guidelines [31,32].

Datasets from each participating site were transferred to a core laboratory for blinded image analysis. Coronary atherosclerosis was evaluated on multiplanar and cross-sectional CCTA images. All evaluations were performed by level III experienced readers masked to clinical results, using semi-automated plaque analysis software (QAngio CT Research Edition v2.1.9.1) with manual correction [33].

The details of the analysis have been described previously [12,19] but will be summarized below. The presence of atherosclerosis was defined as any tissue with $\geq$1 mm^2 within or adjacent to the lumen of the coronary artery that could be discriminated in two planes from surrounding structures including pericardial tissue, epicardial fat or lumen [34]. Plaque and vessel volume (mm^3) were obtained for all coronary arteries with a diameter $\geq$2 mm. Atherosclerotic plaque was

subclassified by composition, using predefined intensity cut-off values in Hounsfield units (HU) that have been validated relative to intravascular ultrasonography studies, into noncalcified plaque (−30 to 350 HU); encompassing necrotic core (−30 to 30 HU); fibro-fatty plaque (30–130 HU); fibrous plaque (131–350 HU); and calcified plaque (≥351 HU) [35,36]. Percent atheroma volume (PAV) was defined as: plaque volume/vessel volume x 100 (%) [37]. To determine progression and/or regression of the coronary atherosclerosis, annual change in PAV was defined as follows: ΔPAV/interval between CCTA examinations (%/year).

2.4. Study endpoints

The primary endpoint for this study was the annualized per patient change in PAV between CCTA-1 and CCTA-2 by RAAS inhibitor exposure. Secondary endpoints included annualized changes in various plaque components (non-calcified plaque, necrotic core, fibro-fatty plaque, fibrous plaque, and calcium).

2.5. Statistical analysis

Continuous variables are expressed as mean ± standard deviation, whereas categorical variables are presented as absolute counts and percentages. Differences between categorical variables were analyzed using the chi-square test and those between continuous variables using Student's t-test or Wilcox rank-sum test, as appropriate. Changes between CCTA-1 and CCTA-2 were assessed using paired t-tests or Wilcoxon signed-rank test.

Given the differences in baseline characteristics of patients between RAAS inhibitor naïve and RAAS inhibitor taking patients, a 1:1 propensity score matching was used. Patients were matched based on the following variables: age, body mass index, sex, hypertension, diabetes, dyslipidemia, smoking status, family history of premature atherosclerosis, aspirin use, statin use, CCTA scan interval and PAV at baseline. Propensity score matching was performed using the caliper method, with caliper width of 0.2. Patients with missing data were excluded from the analysis. Annualized progression of overall plaque burden was compared between groups, in addition to annualized progression of various plaque components.

Recognizing the importance of baseline PAV as a significant risk factor for plaque progression [14,18], a multivariate logistic regression analysis was performed to assess if there is a differential effect of RAAS inhibitor use on plaque progression in relation to baseline burden of disease. This analysis was performed on the unmatched cohort to minimize selection bias that may result from propensity score matching. This analysis was adjusted for age, sex, baseline PAV, baseline statin use, hypertension, diabetes, smoking status, family history of premature atherosclerosis and body mass index in the overall population, and effect sizes were reported.

A two-tailed p value < 0.05 was considered statistically significant. All statistical analyses were performed using STATA (version 16; StataCorp, College Station, TX, USA).

3. Results

3.1. Study population

The overall study population consisted of 2252 patients with repeat CCTA examinations, however, 1004 (45%) were excluded due to non-interpretable CT scans (n = 492, 22%), documented CAD before CCTA-1 (n = 227, 10%) or missing clinical data (n = 285, 13%) (Fig. 1). Of the remaining 1248 patients, mean age was 60.1 ± 9.0 years, 60% of

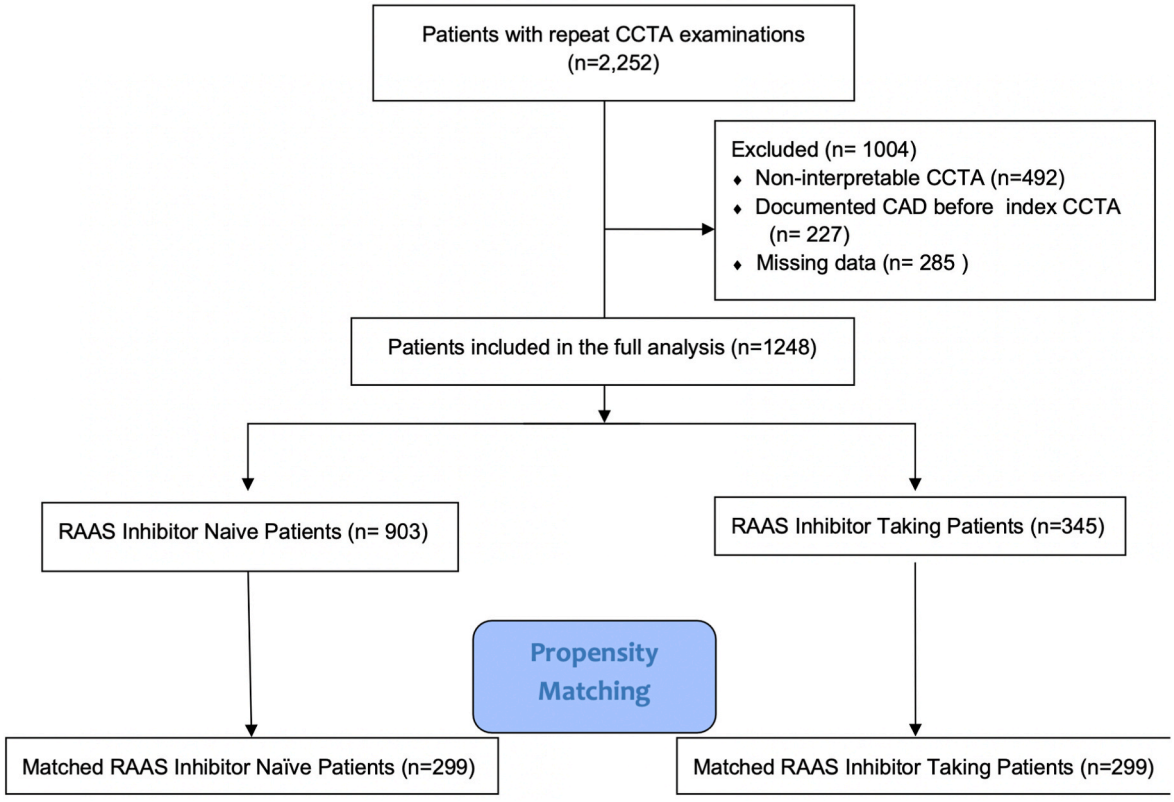

Fig. 1. Consort diagram.
The matched cohort consists of 299 patients in each of the RAAS inhibitor taking and RAAS inhibitor naïve groups. The unmatched cohort consists of the 1248 subjects who met inclusion and exclusion criteria, before propensity score matching was performed. CCTA = coronary CT angiography; CAD = coronary artery disease; RAAS = Renin-Angiotensin-Aldosterone System.

Table 1
Patient characteristics at baseline.

Variables	Total (n = 1248)	RAASi naïve (n = 903)	RAASi taking (n = 345)	*p* value
Age, year	60.1 ± 9.0	59.5 ± 9.1	61.7 ± 8.8	**<0.001**
Male gender	499 (40.0)	368 (40.8)	131 (38.0)	0.405
Body mass index, kg/m^2	25.3 ± 3.3	25.2 ± 3.2	25.7 ± 3.3	**0.008**
Hypertension	646 (51.9)	352 (39.1)	294 (85.2)	**<0.001**
Diabetes mellites	251 (20.1)	149 (16.5)	102 (29.6)	**<0.001**
Hyperlipidemia	506 (40.7)	338 (37.6)	168 (48.7)	**<0.001**
Family history of coronary artery disease	364 (29.2)	254 (28.1)	110 (31.9)	0.217
Smoker	478 (38.5)	343 (38.2)	135 (39.2)	0.773
Anti-platelet agent use	493 (39.5)	296 (32.8)	197 (57.1)	**<0.001**
SBP, mmHg	129.6 ± 17.5	128.6 ± 17.6	131.9 ± 17.2	**0.008**
DBP, mmHg	78.1 ± 10.5	77.7 ± 10.6	79.2 ± 10.4	**0.043**
Statin use	509 (41.0)	319 (35.7)	190 (54.6)	**<0.001**
Creatinine, mg/dL	1.0 ± 0.6	1.0 ± 0.3	1.1 ± 1.0	**0.004**
Total cholesterol, mg/dl	191.4 ± 40.1	195.2 ± 39.9	181.5 ± 38.8	**<0.001**
LDL, mg/dl	116.5 ± 34.9	119.8 ± 35.0	107.8 ± 33.5	**<0.001**
HDL, mg/dl	51.6 ± 14.3	52.1 ± 14.5	50.2 ± 13.6	**0.048**
Triglycerides, mg/dl	146.7 ± 89.2	144.6 ± 92.4	152.1 ± 80.2	0.222
CT interval, year	3.8 ± 1.6	3.8 ± 1.6	3.8 ± 1.5	0.481

Note: values are mean ± SD or raw numbers (%) and compared between groups using unpaired *t*-test or chi-square test. RAASi = Renin Angiotensin-Aldosterone System inhibitor; SBP = systolic blood pressure; DBP = diastolic blood pressure; LDL = low-density lipoprotein; and HDL = high-density lipoprotein.

which were male. Within this total population, 345 patients were taking RAAS inhibitors whereas 903 were RAAS inhibitor naïve, and the mean duration between CT scans was 3.8 ± 1.6 years. Patients taking RAAS inhibitors tended to be older (61.7 ± 9.6 years *vs* 59.5 ± 8.4 years, $p < 0.001$), and more likely to have hypertension (85.2% *vs* 39.1%, $p < 0.001$), diabetes mellitos (29.6% *vs* 16.5%, $p < 0.001$), hyperlipidemia (48.7% *vs* 37.6%, $p < 0.001$) and a higher SBP (131.9 *vs* 128.6, $p = 0.008$) (Table 1). Patients taking RAAS inhibitors were more likely to be on anti-platelet therapy (57.1% *vs* 32.8%, $p < 0.001$) and beta-blockers (38.1% *vs* 21.3%, $p < 0.001$). Table 2 shows baseline characteristics of patients after propensity matching. After matching, there were no significant differences between these groups. Propensity score distributions and AUC are illustrated in Supplementary Figs. 1 and 2. Unless otherwise stated, results are based on the propensity matched population.

3.2. Plaque composition at baseline

At baseline, propensity matched RAAS inhibitor naïve patients and RAAS inhibitor taking patients had no significant difference in percent atheroma volume (PAV) at 5.77 ± 7.06% and 5.83 ± 7.91%, respectively ($p = 0.45$) (Fig. 2). Similarly, there was no significant difference in plaque composition at baseline, with RAAS inhibitor naïve patients *versus* RAAS inhibitor taking patients demonstrating a fibrous PAV of 2.54 ± 3.11% and 2.51 ± 3.48% ($p = 0.31$), fibrofatty PAV of 1.14 ± 2.11% and 0.99 ± 1.61% ($p = 0.31$), necrotic core PAV of 0.16 ± 0.44% and 0.13 ± 0.34% ($p = 0.75$), and calcified PAV of 1.92 ± 3.43% and 2.20 ± 4.41% ($p = 0.55$), respectively (Table 3).

3.3. Plaque progression according to RAAS inhibitor use

Using baseline and follow-up CCTA data, annualized total plaque progression and progression of various plaque components were compared between RAAS inhibitor naïve and RAAS inhibitor taking groups (Table 3). In the matched cohort, RAAS inhibitor use did not appear to have an impact on total plaque atheroma volume progression over time, at 0.75 ± 1.04%/year and 0.79 ± 1.00%/year for RAAS inhibitor naïve patients *vs* RAAS inhibitor taking patients, respectively. Looking at the progression of various plaque compositions yielded similar results with no significant differences between groups, as show in Fig. 3. Annualized plaque progression in RAAS inhibitor naïve

Table 2
Baseline characteristics after propensity matching.

Variable	RAASi naïve (n = 299)	RAASi taking (n = 299)	*p* value
Age	61.7 ± 8.4	62.3 ± 9.6	0.403
Male	128 (42.8)	127 (42.5)	0.934
Body mass index, kg/m^2	25.5 ± 3.0	25.3 ± 3.3	0.577
Hypertension	252 (84.3)	252 (84.3)	1
Diabetes mellites	80 (26.8)	77 (25.8)	0.78
Hyperlipidemia	107 (35.8)	115 (38.5)	0.498
Family history of coronary artery disease	88 (29.4)	85 (28.4)	0.787
Smoker	58 (19.4)	52 (17.4)	0.527
Anti-platelet agent use	150 (50.2)	156 (52.2)	0.624
SBP, mmHg	131.8 ± 18.6	131.4 ± 16.9	0.79
DBP, mmHg	78.6 ± 11.9	78.6 ± 10.2	0.972
Statin use	147 (49.2)	149 (48.9)	0.87
Creatinine, mg/dL	1.0 ± 3.9	1.0 ± 0.2	0.256
Total cholesterol, mg/dl	186.9 ± 39.9	183.3 ± 40.5	0.292
LDL, mg/dl	113.6 ± 32.9	109.3 ± 33.8	0.127
HDL, mg/dl	48.7 ± 12.6	50.2 ± 13.8	0.192
Triglycerides, mg/dl	152.2 ± 96.5	149.4 ± 80.1	0.712
CT Interval, year	3.8 ± 1.6	3.9 ± 1.6	0.307
PAV (%)	5.77 ± 7.06	5.83 ± 7.91	0.918

Note: values are mean ± SD or raw numbers (%) and compared between groups using unpaired *t*-test or chi-square test. RAASi = Renin Angiotensin-Aldosterone System inhibitor; SBP = systolic blood pressure; DBP = diastolic blood pressure; LDL = low-density lipoprotein; and HDL = high-density lipoprotein; PAV = percent atheroma volume.

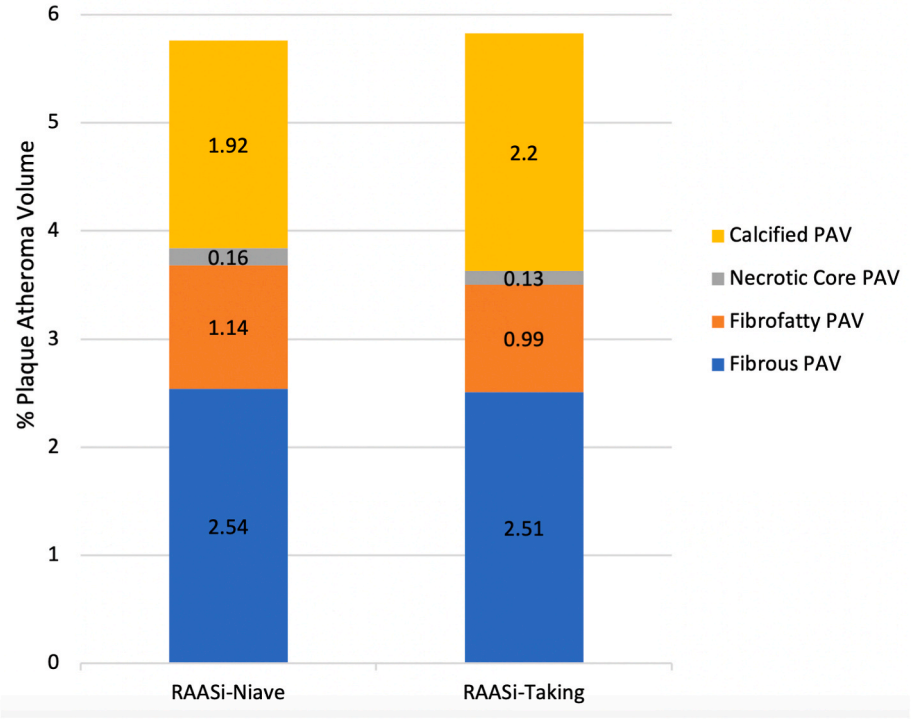

Fig. 2. Total plaque composition for patients at baseline.
RAASi = Renin Angiotensin-Aldosterone Antagonist inhibitor; PAV = percent atheroma volume.

patients *versus* RAAS inhibitor taking patients was 0.29 ± 0.64%/year and 0.25 ± 0.61%/year for fibrous plaque ($p = 0.91$), −0.03 ± 0.41%/year *vs* 0.03 ± 0.36%/year for fibrofatty plaque ($p = 0.67$), −0.02 ± 0.13%/year *vs* 0.002 ± 0.07%/year for necrotic core ($p = 0.09$), and 0.51 ± 0.79%/year *vs* 0.51 ± 0.84%/year for calcified plaque ($p = 0.37$).

3.4. Interaction testing in the unmatched cohort

Given the known importance of baseline PAV in predicting plaque progression and progression to obstructive disease [14,18], it was hypothesized that there may be a differential effect of RAAS inhibitors for patients with higher baseline risk as a result of higher baseline total PAV.

A multivariable linear prediction model on the unmatched cohort revealed significant interactions between RAAS inhibitor use and baseline PAV on non-calcified and fibrous plaque progression (Table 4). β-coefficients for the interaction between baseline PAV and RAAS inhibitor use were −0.100 ($p = 0.038$) and −0.214 ($p < 0.001$) for non-calcified plaque and fibrous plaque respectively, indicating RAAS inhibitor use was significantly associated with lower non-calcified plaque and fibrous plaque progression in patients with higher baseline PAV. Linear prediction models for non-calcified and fibrous plaque progression based on these coefficients are shown in Fig. 4A and B, respectively. There was no significant interaction between baseline PAV and RAAS inhibitor use on calcified plaque progression (p for interaction = 0.699).

4. Discussion

In the analysis of this large, prospective, observational cohort of patients with stable CAD with serial CCTA, use of RAAS inhibitors did not significantly alter the progression of coronary atherosclerosis or its composition in the matched cohort. However, the linear regression analysis performed on the unmatched cohort suggested that patients with a higher baseline plaque burden showed a statistically significant reduction in non-calcified plaque progression with RAAS inhibitor use compared to those without, having adjusted for clinical risk factors including statin use (Fig. 5). This finding should be considered hypothesis generating.

RAAS inhibitors have many potential on- and off-target mechanisms for slowing or preventing plaque progression, influencing plaque remodeling, and impacting plaque stability [26–28]. However, this complex interplay of canonical and non-canonical signaling of multiple pathways may be influenced by pharmacologic agent, dose, stage of disease, and underlying host genetics and demographics [38,39]. While fundamental and translational science continue to dissect these pharmaceuticals and their mechanisms of action as it related to plaque, clinical tools like CCTA allow us to continue to discern their real-world impact.

Previous studies evaluating the effect of RAAS inhibitors on coronary atherosclerosis have shown mixed results. The two largest trial are the OLIVUS [24] and PERSPECTIVE [40] trials, which randomized patients with stable CAD to ACE inhibitor or ARB *vs* placebo, and used Intravascular Ultrasound (IVUS) to evaluate changes in plaque volume for a specific lesion over time. The OLIVUS trial randomized 247 patients with a follow-up of 14 months, and found that in a multiple linear regression model, ARB olmesartan was associated with reduced risk of progression, whereas age, sex, statin use and diabetes were not. Conversely, the PERSPECTIVE trial randomized 244 patients to perindopril or placebo with a follow-up period of 3 years, and found no significant difference in plaque progression between groups. Importantly, neither of these studies looked at plaque composition. Findings in other vascular beds including serial assessment of carotid arteries have also shown mixed results [41,42]. We extend these findings by looking at a larger cohort, a longer follow-up period, and by using CT data to evaluate total atherosclerosis and plaque composition rather than specific segments of coronary arteries. Similar to the PERSPECTIVE trial, our findings did not show an impact of RAAS inhibitors on total atherosclerotic progression, but by evaluating changes in plaque composition, we found that patients with a higher burden of underlying atherosclerosis had reduced rates of progression of non-calcified

Table 3
Total percent atheroma volume and plaque composition annualized progression in the matched cohort.

Variables	RAASi naïve (n = 299)	RAASi taking (n = 299)	*p* value
Total PAV (%)			
Baseline CCTA	5.77 ± 7.06	5.83 ± 7.91	0.45
Follow-up CCTA	8.45 ± 9.07	8.67 ± 10.27	0.59
p value (baseline vs follow-up)	<0.001	<0.001	
Annualized progression, %/year	0.75 ± 1.04	0.79 ± 1.00	0.66
Fibrous PAV (%)			
Baseline CCTA	2.54 ± 3.11	2.51 ± 3.48	0.31
Follow-up CCTA	3.53 ± 4.01	3.32 ± 3.87	0.50
p value (baseline vs follow-up)	<0.001	<0.001	
Annualized progression, %/year	0.29 ± 0.64	0.25 ± 0.61	0.91
Fibrofatty PAV (%)			
Baseline CCTA	1.14 ± 2.11	0.99 ± 1.61	0.60
Follow-up CCTA	1.06 ± 1.75	1.07 ± 1.88	0.74
p value (baseline vs follow-up)	0.325	0.258	
Annualized progression, %/year	−0.03 ± 0.41	0.03 ± 0.36	0.67
Necrotic core PAV (%)			
Baseline CCTA	0.16 ± 0.44	0.13 ± 0.34	0.75
Follow-up CCTA	0.11 ± 0.26	0.13 ± 0.38	0.86
p value (baseline vs follow-up)	0.064	0.917	
Annualized progression, %/year	−0.02 ± 0.13	0.002 ± 0.07	0.09
Calcified PAV (%)			
Baseline CCTA	1.92 ± 3.43	2.20 ± 4.41	0.55
Follow-up CCTA	3.75 ± 5.52	4.15 ± 6.92	0.66
p value (baseline vs follow-up)	<0.001	<0.001	
Annualized progression, %/year	0.51 ± 0.79	0.51 ± 0.84	0.37
Non-calcified PAV (%)			
Baseline CCTA	3.84 ± 4.90	3.63 ± 4.74	0.45
Follow-up CCTA	4.70 ± 5.51	4.52 ± 5.47	0.57
p value (baseline vs follow-up)	<0.001	<0.001	
Annualized progression, %/year	0.24 ± 0.85	0.29 ± 0.81	0.67

Note: Values were compared between groups using Wilcoxon rank sum test.
RAASi = Renin Angiotensin-Aldosterone System inhibitor; PAV = percent atheroma volume; and CCTA = coronary CT angiogram.

plaques, which are a recognized marker of increased risk of MACE [43].

Understanding the physiology of RAAS inhibitors in patients with stable CAD is critical, given their widespread clinical use. The landmark trials of HOPE in 2000 [20] and EUROPA in 2003 [29] demonstrated just over 20% relative risk reduction in MACE for patients with known CAD or at high risk of CAD, but these were placebo controlled and both documented better blood pressure control in the ACE inhibitor groups. Subsequent studies, however, have not demonstrated this benefit. The PEACE trial [44] randomized over 8000 patients post-MI with normal or slightly reduced ejection fraction to ACE inhibitor or placebo and found no difference in MACE outcomes. Similarly, CAMELOT [45] randomized patients with CAD and normal blood pressure to enalapril, amlodipine or placebo, and found a statistically significant reduction in MACE with amlodipine, but not enalapril. A meta-analysis by Bangalore et al. [30] summarizes this effect, ultimately demonstrating that in patients with CAD without heart failure, RAAS inhibitors reduced MACE only when compared to placebo, not active controls. This is reflected in the 2019 ESC guidelines for stable CAD, with no blanket recommendation for ACE inhibitors unless patients are at high risk for cardiovascular events [46]. The findings from this study are supportive of this recommendation, with the linear regression analysis demonstrating a reduction in progression of non-calcified plaque in patients at higher baseline risk based on a larger burden of underlying atherosclerosis, independent of risk factors such as diabetes, hypertension or statin use. The current study offers a possible mechanism for the protective effects of RAAS inhibitors, above and beyond those of blood pressure lowering, cardiac remodeling or flow-mediated vasodilation of arteries, but it also suggests a role for a tailored approach to their use as the overall matched cohort of those with CAD did not show benefit with regards to atherosclerosis progression. Importantly these positive results were identified by interaction testing, are hypothesis generating, and would require further study before stronger recommendations can be made.

With the growing use of CCTA, there may be future opportunities to better risk stratify patients with CAD based on plaque burden and morphology, allowing clinicians to offer individualized pharmacotherapy based on a combination of clinical risk factors, and CT findings. Given the limited number of clinical endpoints within this cohort, we cannot comment on any potential benefit from the use of RAAS inhibitors outside their effects on atherosclerosis. The ongoing WARRIOR CCTA (NCT 05035056) sub-study evaluating plaque changes by serial CCTA in which symptomatic women with non-obstructive CAD are randomized to usual care vs intensive medical therapy (statin, ACEi, ASA) may shed further light on the effects of RAAS inhibitors on the atherosclerotic process, in addition to acute coronary syndromes, strokes and cardiac mortality.

This study has many strengths. It is the first study to use CT-derived plaque volumes to evaluate the effect that RAAS inhibitors have on total plaque burden, as well as plaque morphology over time, providing a unique insight into the effect this class of medication has on the natural history of this disease above and beyond previous invasive coronary angiography studies. Furthermore, it is drawing from a large, multinational, prospective registry that represents a diverse range of ages and ethnicity. Lastly, it is the largest study with the longest follow-up period to date to assess the effect of RAAS inhibitors on coronary artery total plaque burden in addition to morphology changes.

There are, however, several limitations. Given the observational nature of this study, despite rigorous propensity matching, there may be confounding variables that were not accounted for in the analysis as well as bias by indication. Second, we do not have data on the type of RAAS inhibitor, nor the dose taken, which may be relevant in interpretation. Third, propensity score matching caused reduced sample size and may have contributed to being underpowered to note an effect. Lastly, there were limited clinical endpoints to assess the effect of RAAS inhibitors on MACE within this cohort, and thus we cannot comment on their role in preventing myocardial infarction, stroke, heart failure or cardiovascular death through mechanisms that are independent of progression of underlying atherosclerosis.

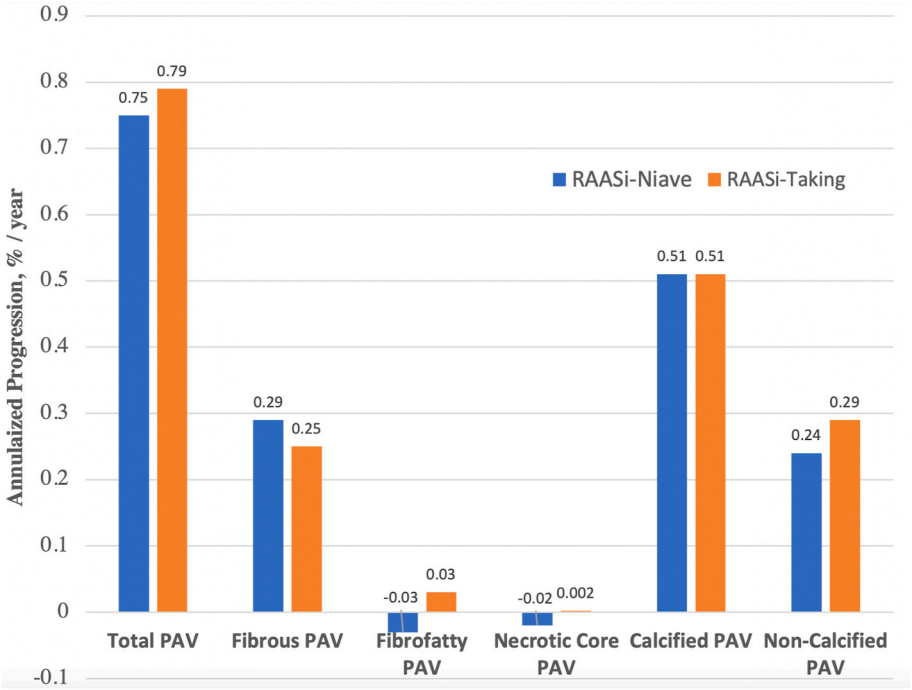

Fig. 3. Annualized progression of total PAV, fibrous PAV, fibrofatty PAV, necrotic Core PAV, and calcified PAV for RAAS inhibitor naïve and RAAS inhibitor taking patients.
RAASi = Renin Angiotensin-Aldosterone System inhibitor and PAV = percent atheroma volume.

Table 4
Effect sizes (β coefficients) and interactions between RAAS inhibitor use and baseline PAV on plaque progression in the unmatched cohort.[a]

	Baseline PAV	RAASi use	Interaction term (baseline PAV x RAASi use)	Interaction *p*-value
Total plaque	0.088	0.449	−0.078	0.069
Non-calcified plaque	−0.049	0.935	**−0.100**	**0.038**
Fibrous plaque	0.118	0.114	**−0.214**	**<0.001**
Fibrous fatty plaque	−0.242	0.023	0.095	0.047
Necrotic Core	−0.154	0.001	0.072	0.141
Calcified plaque	0.638	0.012	0.014	0.699

RAASi = Renin Angiotensin-Aldosterone System inhibitor; PAV = percent atheroma volume.
[a] Adjustment for age, sex, baseline PAV, baseline statin use, hypertension, diabetes, smoking statis, family history of premature atherosclerosis and body mass index.

4.1. Conclusions

Our findings demonstrated that in patients with stable CAD, the use of RAAS inhibitors did not have a measurable impact on progression of total coronary atherosclerotic plaque for the matched cohort. Linear regression analysis on the unmatched cohort, however, did show a decrease in progression of non-calcified plaque in patients with higher burdens of baseline atherosclerosis. This should be considered hypothesis generating, but offers a potential mechanism for reduction on major adverse cardiac events in patients with a higher baseline risk.

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CRediT authorship contribution statement

Curtis Williams: lead the research study, developing the research question and, Methodology, interpreting the results and, Writing – original draftwriting the manuscript, with extensive collaboration from Jonathon Leipsic and Christopher Fordyce (senior investigators) in addition to Donghee Han and Hidenobu Takagi. **Donghee Han:** performed the statistical, Formal analysis, using STATA, lead the research study, developing the research question and, Methodology, interpreting the results and, Writing – original draft, with extensive collaboration from Jonathon Leipsic and Christopher Fordyce (senior investigators) in addition to Donghee Han and Hidenobu Takagi. **Hidenobu Takagi:** lead the research study, developing the research question and, Methodology, interpreting the results and, Writing – original draft, with extensive collaboration from Jonathon Leipsic and Christopher Fordyce (senior investigators) in addition to Donghee Han and Hidenobu Takagi. **Christopher B. Fordyce:** lead the research study, developing the research question and, Methodology, interpreting the results and, Writing – original draft, with extensive collaboration from Jonathon Leipsic and Christopher Fordyce (senior investigators) in addition to Donghee Han and Hidenobu Takagi. **Stephanie Sellers:** contributed in the review process, providing expertise in the basic science aspects of RAAS inhibitors in atherosclerosis. **Philipp Blanke:** were integral in the creation and maintenance of the PARADIGM registry, and provided invaluable feedback during the, Writing – original draft, process. **Fay Y. Lin:** were integral in the creation and maintenance of the PARADIGM registry, and provided invaluable feedback during the, Writing – original

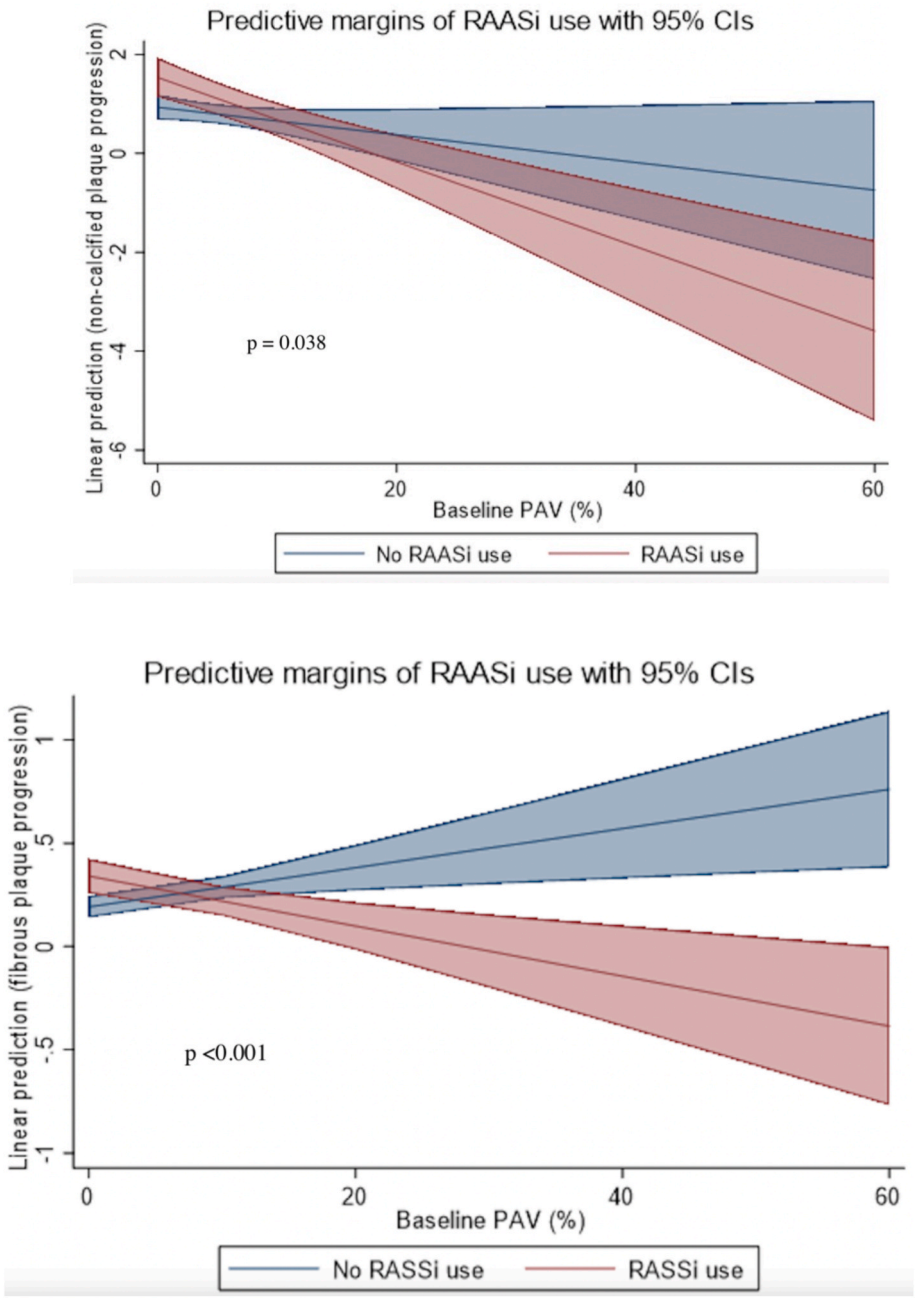

Fig. 4. Predictive margins of RAAS inhibitor use on (A) non-calcified plaque progression based on baseline PAV, and (B) fibrous plaque progression based on baseline PAV. These margins are the results of linear regression modelling performed on the unmatched cohort.
RAASi = Renin Angiotensin-Aldosterone System inhibitor; PAV = percent atheroma volume.

draft, process. **Leslee J. Shaw:** were integral in the creation and maintenance of the PARADIGM registry, and provided invaluable feedback during the, Writing – original draftmanuscript writing, process. **Sang-Eun Lee:** were integral in the creation and maintenance of the PARADIGM registry, and provided invaluable feedback during the, Writing – original draft, process. **Daniele Andreini:** were integral in the creation and maintenance of the PARADIGM registry, and provided invaluable feedback during the, Writing – original draft, process. **Mouaz H. Al-Mallah:** were integral in the creation and maintenance of the PARADIGM registry, and provided invaluable feedback during the, Writing – original draft, process. **Matthew J. Budoff:** were integral in the creation and maintenance of the PARADIGM registry, and provided invaluable feedback during the, Writing – original draft, process. **Filippo Cademartiri:** were integral in the creation and maintenance of the PARADIGM registry, and provided invaluable feedback during the, Writing – original draft, process. **Kavitha Chinnaiyan:** were integral in the creation and maintenance of the PARADIGM registry, and provided invaluable feedback during the, Writing – original draft, process. **Jung Hyun Choi:** were integral in the creation and maintenance of the PARADIGM registry, and provided invaluable feedback during the, Writing – original draft, process. **Edoardo Conte:** were integral in the creation and maintenance of the PARADIGM registry, and provided invaluable feedback during the, Writing – original draft, process. **Hugo Marques:** were integral in the creation and maintenance of the PARADIGM registry, and provided invaluable feedback during the, Writing – original draft, process. **Pedro de Araújo Gonçalves:** were integral in the creation and maintenance of the PARADIGM registry, and provided invaluable feedback during the, Writing – original draft, process. **Ilan**

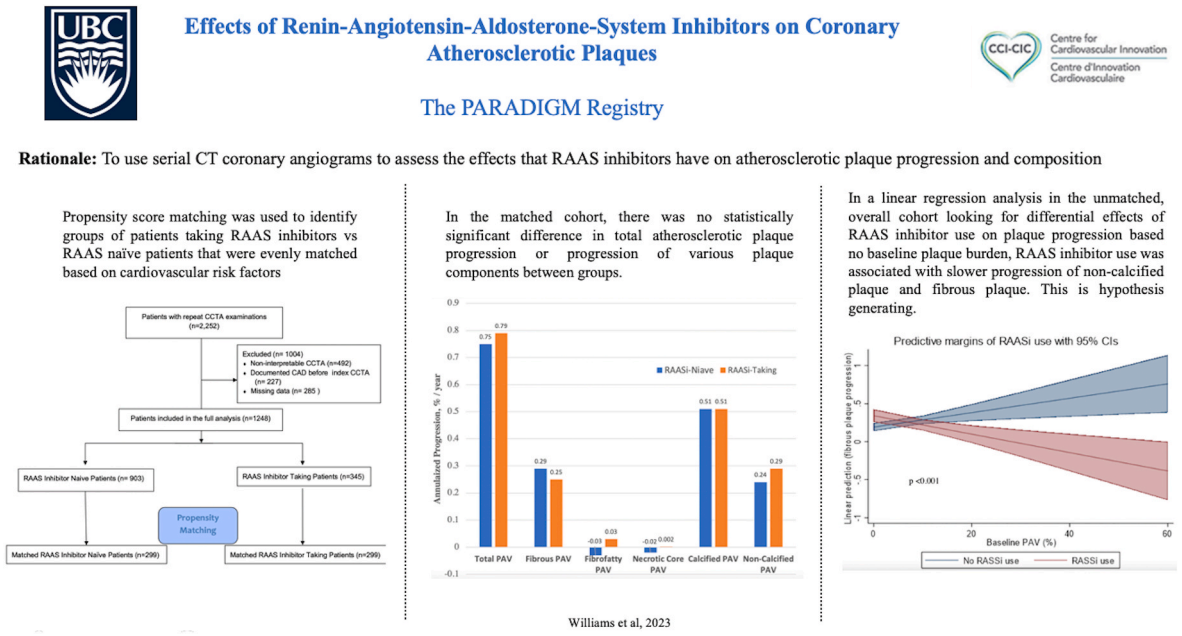

Fig. 5. Graphical abstract.
CCTA = Coronary CT Angiogram; RAASi = Renin Angiotensin-Aldosterone System inhibitor; PAV = percent atheroma volume.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2023.117301.

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