Effects of rosvastatin treatment on coronary artery ectasia in different patient age groups

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Abstract

Background: This study investigated the relationship between coronary artery ectasia (CAE) and serum levels of high-sensitivity C-reactive protein (Hs-CRP) to test our hypothesis that patient age is associated with the efficacy of anti-inflammatory therapy in CAE.

Method: We conducted a prospective analysis of 217 patients with CAE treated at the Department of Cardiology, Shanghai East Hospital, Shanghai East Hospital (Ji’an Campus), Cardiovascular Medicine of Baoshan People’s Hospital of Yunnan Province, from January 1, 2015, to July 30, 2019. Baseline data of patients, including sex, age, hypertension, hyperlipidemia, and diabetes, were collected from patient medical records. Study participants were grouped by age: CAE-A (age ≤50 years); CAE-B (50 years 70).

Results: All CAE patients received oral rosvustatin therapy (10 mg, QN quaque night) and maintained good follow-up, with a loss rate of 0.0% at the 6-month follow-up. The control group (NC Group, n = 73, with normal coronary arteries) received regular symptom-relieving treatments. Among these four groups, the inflammatory markers were significantly higher in patients with CAE than in the NC Group. The inflammatory markers in the CAE-A group were higher than in the CAE-B group, which were higher than the CAE-C group. Follow-up after 6 months of rosvustatin therapy showed a significantly greater reduction in Hs-CRP and interleukin-6 levels in the CAE-A group than the CAE-B group, which, again, were higher than the CAE-C group.

Conclusions: Anti-inflammatory therapy using rosvustatin was more effective in younger CAE patients, indicating the need for early statin therapy in CAE patients.

Background

Coronary artery ectasia (CAE) is an abnormal coronary dilatation, mainly diagnosed through coronary angiography, which provides information on the size, location, and number of dilatations. CAE is characteristically defined as a dilated coronary artery segment whose diameter is at least 1.5 times that of the adjacent normal coronary lumen [1], and is a relatively rare coronary artery abnormality (incidence < 5%) among coronary artery diseases [2]. The increased prevalence of CAE in recent years has generated greater focus on the incidence and influence of CAE [3]; however, the
etopathogenetic mechanism of CAE is incompletely known so far, although it may be related to systemic inflammation, stimulated nitric oxide production, coronary balloon angioplasty, nodular polyarteritis, and Kawasaki syndrome [4, 5]. Moreover, potential risk factors for CAE include an imbalance between matrix metalloproteinases (MMPs) and tissue inhibitor metalloproteinases (TIMPs), angiotensin-converting enzyme genotypes, elevated levels of homocysteine, cocaine usage, smoking, vascular trauma, and diabetes [6-9].

Conventionally, CAE has been considered a variant of coronary atherosclerosis [10]. Recent studies have found that inflammation plays a key role in active defense against various insults. Current consensus indicates that atherosclerosis is an inflammatory disease, although the triggering factors and atherosclerotic processes, including plaque rupture, coronary artery spasm, coronary slow flow, coronary microvascular dysfunction, asymptomatic myocardial ischemia, and restenosis, may be variable. Furthermore, CAE is closely related to myocardial infarction; however, there are currently no standard treatment guidelines specified for CAE. The anti-inflammatory and endothelium-protective effects of rosuvastatin have been proven to improve symptoms in patients with coronary artery disease [11]. However, there is no conclusive evidence of the therapeutic efficacy and optimal timepoint for rosuvastatin therapy in CAE patients from different age groups. We conducted the present study to compare the inflammatory status and therapeutic effects of rosuvastatin in CAE patients of different age groups.

Methods
Subjects
We prospectively enrolled 6542 patients who were first diagnosed using coronary angiography at our centers from January 1, 2015 to July 30, 2019. Exclusion criteria included various malignant tumors, and intolerance to statin treatment, patients with dilated segments appearing within or directly associated with coronary bypass grafts, patients who developed a coronary dilation after coronary interventions, patients with a diagnosis of Kawasaki disease, patients with fistulas or coronary artery anomalies, patients with acute or chronic coronary total occlusion [12], or inability to complete a 6-month follow-up. Finally, 302 patients were diagnosed with CAE and 85 patients were excluded
(Fig. 1). We included 217 patients with CAE (grouped by age) and collected clinical data including blood lipids, blood routine, high-sensitivity C-reactive protein (Hs-CRP), and other biochemical indicators (Table 1). The primary outcome included changes in inflammatory markers. The secondary outcome included levels of inflammation. This study was approved by the medical ethics committee of Shanghai East Hospital, Shanghai East Hospital (Ji'an Campus), and Baoshan People's Hospital of Yunnan Province. According to the results of coronary angiography and patient age, participants were divided into four groups: CAE-A (age ≤ 50 years), CAE-B (50 years < age ≤ 70 years), CAE-C (age > 70 years), and a normal control group (NC Group; age matched) with normal coronary arteries.
Table 1
Basic information and laboratory findings of CAE patients and normal controls

| Groups                      | NC Group (n = 73) | CAE-A (n = 60) (age ≤ 50 years) | CAE-B (n = 83) (50 years < age ≤ 70 years) | CAE-C (n = 74) (age > 70 years) | Total CAE (A + B + C, n = 217) | p-value |
|------------------------------|------------------|---------------------------------|---------------------------------------------|---------------------------------|-----------------------------|---------|
| Sex (M), n (%)               | 42 (57.5)        | 39 (65.0)                       | 57 (68.7)                                  | 50 (67.6)                      | 146 (67.3)                 | 0.2794  |
| Diabetes mellitus, n (%)     | 13 (17.8)        | 11 (18.3)                       | 18 (21.6)                                  | 18 (24.3)                      | 47 (21.7)                  | 0.1712  |
| Hypertension, n (%)          | 23 (31.5)        | 19 (31.7)                       | 28 (33.7)                                  | 27 (36.5)                      | 74 (34.1)                  | 0.2142  |
| Waist circumference (cm)     | 90.3 ± 14.8      | 91.6 ± 12.7                     | 92.7 ± 16.1                                | 93.8 ± 19.1                    | 92.8 ± 16.2                | 0.5277  |
| Creatinine (mg/dL)           | 70.34 ± 11.6     | 67.6 ± 12.7                     | 77.8 ± 13.2                                | 87.8 ± 14.8                    | 78.48 ± 12.5               | 0.2560  |
| Smoking index                | 119.2 ± 15.5     | 110.3 ± 10.5                    | 135.5 ± 15.6                               | 130.2 ± 15.1                   | 126.7 ± 17.8               | 0.2391  |
| Total cholesterol (mmol/L)   | 4.89 ± 1.04      | 5.59 ± 1.21*                    | 5.39 ± 1.18                                | 4.95 ± 1.07                    | 5.30 ± 1.16*               | 0.0452  |
| Low-density lipoprotein-C (mmol/L) | 2.89 ± 0.36 | 3.92 ± 0.54*                    | 3.74 ± 0.51*                               | 3.73 ± 0.49*                   | 3.79 ± 0.52*               | 0.0237  |
| High density lipoprotein-C (mmol/L) | 1.08 ± 0.12 | 1.22 ± 0.27                     | 1.15 ± 0.19                                | 1.13 ± 0.15                    | 1.16 ± 0.16                | 0.9161  |
| Triglyceride (mmol/L)        | 1.56 ± 0.19      | 1.69 ± 0.19                     | 1.89 ± 0.21                                | 1.75 ± 0.18                    | 1.78 ± 0.15                | 0.8493  |
| Hypersensitive CRP (mg/L)    | 16.9 ± 3.82      | 32.3 ± 5.51*                    | 26.1 ± 4.23*                               | 22.5 ± 4.82*                   | 25.6 ± 4.65*               | 0.0213  |
| Glycated hemoglobin (%)      | 5.89 ± 1.12      | 5.90 ± 1.07                     | 6.50 ± 1.12                                | 6.89 ± 1.25                    | 6.46 ± 1.21                | 0.1421  |
| Ejection fraction (%)        | 56.3 ± 12.58     | 59.4 ± 9.14                     | 55.5 ± 9.23                                | 50.3 ± 8.47                    | 54.8 ± 8.53                | 0.3432  |
| Hemoglobin (g/L)             | 125.5 ± 26.5     | 131.1 ± 28.6                    | 125.1 ± 26.3                               | 119.1 ± 29.8                   | 123.8 ± 28.1               | 0.6535  |
| Red blood cell distribution width (%) | 36.8 ± 5.26 | 36.7 ± 5.95                     | 38.7 ± 4.94                                | 36.4 ± 4.68                    | 37.4 ± 5.59                | 0.8601  |
| Mean platelet volume (fL)    | 10.5 ± 1.26      | 10.7 ± 1.05                     | 11.2 ± 1.35                                | 10.5 ± 1.91                    | 10.8 ± 1.45                | 0.2503  |
| WBC (10^9/L)                 | 6.25 ± 2.56      | 8.85 ± 2.21                     | 8.35 ± 2.06                                | 8.25 ± 2.36                    | 8.38 ± 2.30                | 0.0763  |
| Interleukin6 (pg/dL)         | 4.1 ± 0.6        | 12.3 ± 1.5*                     | 10.9 ± 1.3*                                | 8.9 ± 1.1*                     | 10.6 ± 1.3*                | 0.001   |

*: p < 0.05 vs NC Group; the p-value listed in the table refers to the comparison between the total CAE and NC groups.

Measurement of related indicators

Hypertension is defined as a systolic blood pressure (SBP) ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg; BP was measured three times on the same day without the use of any antihypertensive drugs. The smoking index was calculated as the number of cigarettes smoked per day × the number of years of smoking. Fasting venous blood samples of all subjects were collected to measure hematological parameters and biochemical indices. The red blood cell distribution width, hemoglobin, mean platelet volume, and white blood cell (WBC) counts were analyzed using a Horiba
The serum glucose and creatinine, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), triglycerides (TG), Hs-CRP, and interleukin-6 (IL-6) were detected with enzymatic colorimetric methods using a fully automatic biochemical analyzer (Roche Cobas c702) in the Shanghai East Hospital, Shanghai East Hospital (Ji’an Campus), and Baoshan People’s Hospital of Yunnan Province.

**Coronary angiography**
The Siemens Artis zeego III was used to conduct coronary angiography with a routine radial artery approach. X-ray photography was performed with the injection of a contrast agent. Blood-vessel diameter measurements were performed by skilled coronary intervention doctors. CAE was defined as local or diffuse dilated coronary arteries with a diameter exceeding 1.5-fold of the adjacent normal coronary lumen. The coronary artery images considered indicative of CAE after qualitative comparative analysis by two independent operators were included in this study (Fig. 2).

Pharmacological therapy was withheld at least 24 h before angiography.

**Statistical analysis**
Statistical analysis was conducted using SPSS19.0 software. Data from continuous variables are presented as means ± standard deviations; non-normally distributed data are presented as medians. A comparison between two groups was conducted with an independent samples t-test, and qualitative data were evaluated by Fisher’s exact test. A comparison of continuous variables between the three groups was performed by one-way ANOVA with post hoc Dunnett’s correction. A p-value < 0.05 was considered statistically significant. Logistic regression analysis and stepwise methods were applied to screen the factors showing correlations with CAE, with the entry criteria set at p < 0.05 and rejection criterion at p > 0.1.

**Results**
The baseline characteristics of the risk factors associated with CAE, including sex (male), hypertension, diabetes, hyperlipidemia, and smoking history, were similar between the total CAE group and normal controls. Laboratory findings such as total cholesterol, LDL-C, Hs-CRP, WBC, and IL-6 were elevated in the total CAE group compared to that in the NC Group (p < 0.05). The levels of total cholesterol, LDL-C, Hs-CRP, and IL-6 were significantly higher in the CAE-A group than in the
CAE-B, CAE-C, or NC group ($p < 0.05$), furthermore the levels of TC, LDL-C, Hs-CRP, and IL-6 in the CAE-B group were higher than in the CAE-C or NC group. Under similar circumstances, the levels of TC, LDL-C, Hs-CRP, and IL-6 in the CAE-C group were higher than in the NC group. There were no statistical differences in sex, hypertension, diabetes, waist circumference, smoking index, triglyceride, glycosylated hemoglobin red blood cell distribution width (RBW), and mean platelet volume among the three different age groups of CAE patients ($p > 0.05$; Table 1).

Logistic regression analysis was performed to identify the independent risk factors associated with CAE. In stepwise method analysis, covariant factors included hypertension, diabetes mellitus, Hs-CRP, LDL-C, smoking, triglycerides, WBC, and IL-6. Multivariate analysis showed that increased levels of Hs-CRP and IL-6 were independent predictors of CAE ($p < 0.05$; Table 2).

**Table 2**  
Multivariate analysis of variables associated with CAE

|                      | OR    | 95% CI       | p-value |
|----------------------|-------|--------------|---------|
| Hypertension         | 1.364 | 0.932–1.648  | 0.248   |
| Diabetes mellitus    | 1.407 | 0.802–2.053  | 0.198   |
| Waist circumference  | 1.448 | 0.967–1.938  | 0.124   |
| LDL-C                | 1.492 | 0.986–2.091  | 0.099   |
| Smoking              | 1.119 | 0.932–1.422  | 0.176   |
| TG                   | 1.238 | 0.836–1.865  | 0.236   |
| WBC                  | 1.690 | 0.990–1.785  | 0.061   |
| Hs-CRP               | 1.782 | 1.124–2.014  | 0.021*  |
| Interleukin-6        | 1.584 | 1.112–1.986  | 0.030*  |

CAE: coronary artery ectasia; Hs-CRP: hypersensitive C-reactive protein; LDL-C: low-density lipoprotein cholesterol; TG: triglycerides; WBC: white blood cells. *: $p < 0.05$ vs NC Group

The baseline drug treatments of patients with a confirmed diagnosis of CAE at study inclusion are shown in Table 3. Each CAE patient was subjected to rosuvastatin treatment, with or without other drugs such as ACEI/ARB, beta-receptor blocker, calcium channel blocker, diuretics, aspirin, and clopidogrel. The patients of the NC Group received non-statin treatments. There were not significant differences in the selection of therapeutic medications among the three CAE groups and the NC Group, except for rosuvastatin ($p > 0.05$).
Table 3
Baseline medication selection of CAE patients after confirmed diagnosis

| Treatments          | Group NC (n = 73) | CAE-A (n = 60) (age ≤ 50 years) | CAE-B (n = 83) (50 years < age ≤ 70 years) | CAE-C (n = 74) (age > 70 years) | Total CAE (A + B + C, n = 217) | p-value |
|---------------------|-------------------|---------------------------------|---------------------------------------------|---------------------------------|-------------------------------|---------|
| ACEI/ARB            | 18                | 16                              | 27                                          | 28                              | 71                            | 0.895   |
| β-receptor blocker  | 21                | 25                              | 36                                          | 28                              | 89                            | 0.424   |
| Calcium channel blocker | 16             | 18                              | 15                                          | 17                              | 50                            | 0.310   |
| Diuretics           | 14                | 15                              | 13                                          | 16                              | 44                            | 0.769   |
| Aspirin             | 35                | 42                              | 56                                          | 50                              | 148                           | 0.424   |
| Clopidogrel         | 12                | 15                              | 12                                          | 13                              | 30                            | 0.582   |

p-value: total CAE vs NC.

After the 6-month treatment with rosuvastatin, serum levels of Hs-CRP and IL-6 were differentially reduced in the three CAE age groups (Table 4), supporting the efficacy of rosuvastatin as an anti-inflammatory agent. Among the three CAE age groups, the CAE-A (age ≤ 50 years) group showed the highest compliance to rosuvastatin treatment, as evidenced by the most significant reduction in serum levels of Hs-CRP and IL-6. The CAE-A group showed the greatest reduction in serum levels of Hs-CRP and IL-6 followed by the CAE-B group and then the CAE-C group.

Table 4
Comparison of serum Hs-CRP and IL-6 levels in CAE patients treated with rosuvastatin

| Groups          | CAE-A (n = 60) (age ≤ 50) | CAE-B (n = 83) (50 < age ≤ 70) | CAE-C (n = 74) (age > 70) | p-value |
|-----------------|---------------------------|--------------------------------|---------------------------|---------|
|                  | Pre-treatment | Post-treatment | p-value | Pre-treatment | Post-treatment | p-value | Pre-treatment | Post-treatment | p-value |
| Hs-CRP          | 32.3 ± 5.51       | 17.5 ± 2.38    | 0.0001  | 26.1 ± 4.23   | 18.8 ± 2.74   | 0.023  | 22.5 ± 4.82   | 19.8 ± 2.98   | 0.310  |
| IL-6            | 12.3 ± 1.54      | 6.4 ± 1.7*     | 0.021   | 10.9 ± 1.3    | 7.5 ± 2.0*    | 0.043  | 8.9 ± 1.1     | 7.6 ± 2.3     | 0.519  |

CAE: coronary artery ectasia. Hs-CRP: hypersensitive C-reactive protein. IL-6: Interleukin-6. Pre-treatment: values measured at study inclusion. Post-treatment: after 6-month treatment with rosuvastatin. *: p < 0.05 vs corresponding pre-treatment group.

Discussion

Dyslipidemia is a well-recognized, major risk factor for atherosclerosis [13, 14]. The increased serum lipids, especially LDL-C, will deposit in the arterial wall, and gradually form atherosclerotic plaques, which can consequently block the native artery and cause cardiovascular diseases such as coronary heart disease [15]. Increased inflammation is the core process in all stages of atherosclerosis. With the application and development of many techniques such as anti-inflammatory therapy, antithrombotics, thrombolysis drugs, and catheter treatment in recent decades, the incidence and mortality of atherosclerosis or obstructive vascular diseases have been significantly reduced [16, 17].
CAE is a multifactorial disease and the pathogenic mechanism has not yet been fully elucidated. CAE was considered a variation of atherosclerosis, mainly resulting from the thinning and/or destruction of the myocardial membrane. However, the dilatation process may be independent from the atherosclerotic process because it can be found as an isolated lesion in coronary arteries and other vascular systems [18]. It has been found that elevated inflammatory markers, such as plasma IL-6, and plasma soluble adhesion molecules are closely linked to the presence of coronary artery dilation [19–21]. Long-term exposure to nitrites, herbicide sprays, acetylcholine inhibitors, cocaine, and smoking can also lead to degeneration of the endometrium of the coronary arteries through oxidative stress-induced inflammation, which can eventually cause CAE [10]. Research on inflammation and CAE has characterized CAE-related inflammation, which includes elevated Hs-CRP and IL-6 levels [22].

Accumulation of excess circulating LDL-C was associated with an overproduction of reactive oxygen species and an increase in pro-inflammatory cytokines in the coronary endothelium, linking elevated cholesterol with cardiovascular inflammation [23].

Rosuvastatin is a selective hydroxy methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor widely used in the field of coronary atherosclerotic heart disease [24]. The liver is the main target organ of rosuvastatin, where it can lower cholesterol levels and increase the number of LDL receptors on the surface of liver cells, thereby improving lipid metabolism by promoting LDL absorption and inhibiting hepatic synthesis of very-low-density lipoprotein (VLDL) [25]. Statin therapy can exert pleiotropic effects in atherosclerotic processes such as regulating inflammatory responses, endothelial function, and thrombus formation based on the reduction in LDL-C levels [26]. Rosuvastatin can also stabilize or reverse atherosclerotic plaque through suppressing MMP expression and protect the vascular endothelium against inflammation [27, 28].

There are limited studies focused on the inflammatory status of different age groups of CAE patients. In this study, the cholesterol, LDL-C, Hs-CRP, and IL-6 levels were significantly higher in the total CAE groups than in the NC Group (Table 1). The total cholesterol and LDL-C levels are important for the risk evaluation of coronary heart disease, which benefits from statin therapy through the reduction of LDL-C, Hs-CRP, and IL-6 [29]. Moreover, comparisons between CAE groups of different ages revealed
that the highest serum levels of Hs-CRP and IL-6 were found in younger CAE patients (CAE-A), suggesting that cardiovascular inflammation related to CAE may occur at a comparatively younger age (Table 4). There are some potential explanations for this result. First, younger patients are more likely to be stressed resulting in a more primed or activated inflammatory status [30]. In addition, younger patients responded more strongly to physical and emotional stimulation [31] which can lead to increased levels of inflammatory markers. There are other life factors that can also lead to inflammation, such as cocaine abuse and trauma [8].

Previous retrospective studies have also found that statins could efficiently slow down the growth rate of an abdominal aortic aneurysm compared with controls [32]. In the present study, the efficacy of rosuvastatin in CAE patients among different age groups was investigated and compared. The results of follow-up found that younger patients had a greater reduction in the serum levels of Hs-CRP and IL-6, suggesting that rosuvastatin had a greater anti-inflammatory effect in younger patients (Table 4, Fig. 3, Fig. 4). This may be explained by higher levels of inflammatory markers in younger patients compared to older patients, thus the same dose of rosuvastatin could be more likely to produce a greater anti-inflammatory effect. Moreover, a smaller percentage of younger people have never taken rosuvastatin before. Older patients had a higher proportion of rosuvastatin history because of arteriosclerosis, hyperlipidemia, stroke, among other health complications. Therefore, the lipid-lowering effect of rosuvastatin may be more potent, which boosts its anti-inflammatory effects in young patients. The Cholesterol Treatment Trialists' Collaboration reported that the efficacy of statin therapy in older patients was lower than that in younger patients [33]. Furthermore, younger individuals have a higher basal metabolism level in lipid synthesis and degradation [34], therefore, younger CAE patients could be more sensitive to rosuvastatin treatment. After rosuvastatin treatment, the Hs-CRP and IL-6 levels of the CAE-A group reduced to comparable levels with the NC Group, while those in the CAE-C group were only partially reversed, indicating that the inflammatory status of younger CAE patients was more severe but reversible, while inflammation in older CAE patients was comparatively mild, persistent, and irreversible.

Study Limitations
First, this study is based on a relatively small number of patients, although a large sample size was examined. Second, although specific exclusion criteria were selected, some confounding factors may still cause interference such as the accurate assessment of coronary artery diameter, which may be limited due to uncertainty in identifying the reference part of the vessel. It would be better to use intravascular ultrasound or optical coherence tomography to provide more accurate information about the vessel. Third, pharmacological therapy was withheld at least 24 h before cardiac catheterization but may not be enough to exclude the possible effects of drugs on plasma inflammatory markers.

Conclusion
Younger CAE patients had higher levels of inflammatory markers than older CAE patients. The highest efficacy of anti-inflammatory treatment was found in younger CAE patients, suggesting that the clinical focus of rosvastatin in the treatment of CAE patients should be prescribed at a comparatively early stage.

Abbreviations
ACEI angiotension converting enzyme inhibitors; ARB:Angiotensin Receptor Blocker; CAE:coronary artery ectasia; Hs-CRP:high-sensitivity C-reactive protein; IL-6:interleukin-6; LDL-C:Low density lipoprotein-cholesterol; PO:peros; QN:quaque night; WBC:White blood cell.

Declarations
**Ethics approval and consent to participate:**

The ethics committee of Shanghai East Hospital, Shanghai East Hospital (Ji’an Campus), and Cardiovascular Medicine of Baoshan People’s Hospital of Yunnan Province approved the study, and all patients gave written informed consent for participating in the study.

**Conflict of interest:**
Not applicable.

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Authors’ contributions:
CHF and YH contributed equally to this work. CHF acquired, analyzed and interpreted data, wrote the manuscript. YH acquired, analyzed and interpreted data, revised the manuscript. RLL designed the study, acquired, analyzed and interpreted the data. LY revised the manuscript, XLL, YHL and ZHH acquired the data. All authors read and approved the final manuscript.

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References
1. Sheikh AS, Hailan A, Kinnaird T, Choudhury A, Smith D. Coronary artery aneurysm: evaluation, prognosis, and proposed treatment strategies. Heart Views. 2019;20:101-8.
2. Carino D, Agarwal A, Singh M, Meadows J, Ziganshin BA, Elefteriades JA. Coronary aneurysm: an enigma wrapped in a mystery. Aorta. 2019;7:71-4.
3. Tandon V, Tandon AA, Kumar M, Mosebach CM, Balakumaran K. Coronary artery aneurysms: analysis of comorbidities from the national inpatient sample. Cureus. 2019;11:e4876.
4. Ozturk S, Yetkin E, Waltenberger J. Molecular and cellular insights into the pathogenesis of coronary artery ectasia. Cardiovasc Pathol. 2018;35:37–47.

5. Kahraman F, Karabacak M, Türker Y. Serum nitric oxide level in patients with coronary artery ectasia. Anatol J Cardiol. 2017;17:341.

6. Raffetto JD, Khalil RA. Matrix metalloproteinases and their inhibitors in vascular remodeling and vascular disease. Biochem Pharmacol. 2008;75:346–59.

7. Koc F, Ardic I, Erdem S, Kalay N, Ozbek K, Yarlioglu M, et al. Relationship between L-arginine/asymmetric dimethylarginine, homocysteine, folic acid, vitamin B levels, and coronary artery ectasia. Coron Artery Dis. 2010;21:445–9.

8. Dendramis G, Paleologo C, Piraino D, Assennato P. Relationship between coronary artery ectasia, cocaine abuse, and acute coronary syndromes. World J Cardiol. 2016;8:351–5.

9. Rashid S, Gul U, Ali M, Sadiq T, Kiyani AM. Coronary artery ectasia: clinical and angiographic features. J Coll Physicians Surg Pak. 2018;28:824–8.

10. Aboeata AS, Sontineni SP, Alla VM, Esterbrooks DJ. Coronary artery ectasia: current concepts and interventions. Front Biosci (Elite Ed). 2012;4:00–310.

11. Gamboa CM, Safford MM, Levitan EB, Mann DM, Yun H, Glasser SP, et al. Statin underuse and low prevalence of LDL-C control among U.S. adults at high risk of coronary heart disease. Am J Med Sci. 2014;348:108–14.

12. Luo Y, Tang J, Liu X, Qiu J, Ye Zi, Lai Y, et al. Coronary Artery Aneurysm Differs From Coronary Artery Ectasia: Angiographic Characteristics and Cardiovascular Risk Factor Analysis in Patients Referred for Coronary Angiography. Angiology. 2017. doi:.

13. Petrie JR, Guzik TJ, Touyz RM. Diabetes, hypertension, and cardiovascular disease: clinical insights and vascular mechanisms. Can J Cardiol. 2018;34:575–84.

14. van Rooy MJ, Pretorius E. Obesity, hypertension and hypercholesterolemia as risk
factors for atherosclerosis leading to ischemic events. Curr Med Chem. 2014;21:2121-9.

15. Uygun T, Demir B, Tosun V, Ungan İ, Kural A, Çiftçi R, et al. Relationship between interleukin-17A and isolated coronary ectasia. Cytokine. 2019;115:84-8.

16. Iwańczyk S, Borger M, Kamiński M, Chmara E, Cieślewicz A, Tykarski A, et al. Inflammatory response in patients with coronary artery ectasia and coronary artery disease. Kardiol Pol. 2019;77:713-5.

17. Monte S, Macchia A, Pellegrini F, Romero M, Lepore V, D'Etto A, et al. Antithrombotic treatment is strongly underused despite reducing overall mortality among high-risk elderly patients hospitalized with atrial fibrillation. Eur Heart J. 2006;27:2217-23.

18. Tomioka T, Takeuchi S, Ito Y, Shioiri H, Koyama J, Inoue K. Recurrent acute myocardial infarction in a patient with severe coronary artery ectasia: implication of antithrombotic therapy. Am J Case Rep. 2016;17:939-43.

19. Brunetti ND, Salvemini G, Cuculo A, Ruggiero A, De Gennaro L, Gaglione A, et al. Coronary artery ectasia is related to coronary slow flow and inflammatory activation. Atherosclerosis. 2014;233:636-40.

20. Tokgozoglu L, Ergene O, Kinay O, Nazli C, Hascelik G. Hoscan Y. Plasma interleukin-6 levels are increased in coronary artery ectasia. Acta Cardiol. 2004;59:515-19.

21. Pranata R, Yonas E, Chintya V, Alkatiri AA. Is anticoagulant necessary in patients with coronary artery ectasia presenting with acute coronary syndrome? A systematic review of case reports. Int J Angiol. 2019;28:231-6.

22. Boles U, Wiklund U, David S, Ahmed K, Henein MY. Coronary artery ectasia carries a worse prognosis: a long-term follow-up study. Pol Arch Intern Med. 2019;129:833-5.

23. Catapano AL, Pirillo A, Norata GD. Vascular inflammation and low-density
lipoproteins: is cholesterol the link? A lesson from the clinical trials. Br J Pharmacol. 2017;174:3973-85.

24. Seker FB, Kilic U, Caglayan B, Ethemoglu MS, Caglayan AB, Ekimci N, et al. HMG-CoA reductase inhibitor Rosuvastatin improves abnormal brain electrical activity via mechanisms involving eNOS. Neuroscience. 2015;284:349-59.

25. Kim S, Kim CH, Vaziri ND. Upregulation of hepatic LDL receptor-related protein in nephrotic syndrome: response to statin therapy. Am J Physiol Endocrinol Metab. 2005;288:E813-7.

26. Tremoulet AH, Jain S, Jone P, Best BM, Duxbury EH, Franco A, et al. Phase I/IIa trial of atorvastatin in patients with acute Kawasaki disease with coronary artery aneurysm. J Pediatrics. 2019;215:107–17.

27. Chen J, Li D, Schaefer R, Mehta JL. Cross-talk between dyslipidemia and renin-angiotensin system and the role of LOX-1 and MAPK in atherogenesis studies with the combined use of rosvastatin and candesartan. Atherosclerosis. 2006;184:295–301.

28. Li Z, Wang L, Hu X, Zhang P, Chen Y, Liu X, et al. Effect of rosvastatin on atherosclerotic plaque stability: an intravascular ultrasound elastography study. Atherosclerosis. 2016;248:27-35.

29. Jafari J, Daum A, Abu Hamed J, Osherov A, Orlov Y, Yosefy C, et al. Low high-density lipoprotein cholesterol predisposes to coronary artery ectasia. Biomedicines. 2019;7:E79.

30. Hwang SY. Comparison of clinical manifestations and treatment-seeking behavior in younger and older patients with first-time acute coronary syndrome. J Korean Acad Nurs. 2009;39:888 – 98.

31. Gregoratos, G. Clinical manifestations of acute myocardial infarction in older patients. Am J Geriatr Cardiol. 2001;10:345-7.
32. Li Y, Lu G, Sun D, Zuo H, Wang DW, Yan J. Inhibition of endoplasmic reticulum stress signaling pathway: A new mechanism of statins to suppress the development of abdominal aortic aneurysm. PLoS ONE. 2017;12:e0174821.

33. Cholesterol Treatment Trialists' Collaboration. Efficacy and safety of statin therapy in older people: a meta-analysis of individual participant data from 28 randomised controlled trials. Lancet. 2019;393:407–15.

34. Thuresson M, Jarlov MB, Lindahl B, Svensson L, Zedigh C, Herlitz J. Thoughts, actions, and factors associated with prehospital delay in patients with acute coronary syndrome. Heart Lung. 2007;36:398–409.

Figures

The patient screening flow chart.
Representative coronary artery ectasia images of the left circumflex branch (LCX) and right coronary artery (RCA).
Figure 3

Comparison of serum Hs-CRP levels in CAE patients treated with rosvastatin.
Comparison of serum IL-6 levels in CAE patients treated with rosvastatin