Effects of angiotensin receptor blockers on neointimal characteristics in angina patients requiring stent implantaion: optical coherence tomography analysis

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Abstract

Background: Angiotensin receptor blockers (ARBs) are known for its anti-inflammatory and anti-proliferative effects. The aim of the study was to evaluate long-term effects of ARBs on morphologic characteristics of stent restenosis in patients with coronary artery disease requiring stent implantation by optical coherence tomography (OCT).

Methods: Patients with coronary artery disease having history of drug-eluting stent implantation (n = 407) were analyzed on the basis of ARB therapy as the ARB group (n = 162) and the non-ARB group (n = 245). Neointimal characterizations were performed at lesions with diameter stenosis >30% with OCT in each group. Major adverse cardiovascular events (MACEs), lumen area, stent area, neointimal area, neointimal thickness, nonapposed struts, uncovered struts, and intraluminal mass between two groups were also observed.

Results: More patients in the ARB group revealed homogeneous and layered neointimal pattern (44.9% vs. 35.6%, P < 0.001, and 16.8% vs. 10.6%, P < 0.001, respectively), and whereas patients in the non-ARB group revealed heterogeneous neointimal pattern (1.1% vs. 7.6%, P < 0.001). Mean neointimal area (1.09 ± 1.00 mm² vs. 1.38 ± 1.24 mm²) and mean neointimal thickness (140.6 ± 112.0 μm vs. 189.6 ± 423.1 μm) with OCT were smaller in the ARB group when compared to the non-ARB group. Percentage of covered stents was significantly higher in the ARB group when compared to the Non-ARB group (97.3% vs. 92.6%, P = 0.015). Other factors such as follow-up % diameter stenosis, late lumen loss, binary restenosis, MACEs, various neointimal characteristics analyzed by image analyzing software did not show significant differences.

Conclusion: The use of ARBs after drug-eluting stent implantation demonstrated difference in neointimal characteristics, less amount of neointimal area and fewer number of uncovered stent struts during the follow-up OCT, indicating the anti-proliferative and anti-inflammatory effects of ARBs.

Keywords: Angiotensin receptor blockers, Neointima, Drug-eluting stents, Optical coherence tomography

Background

Angiotensin receptor blockers (ARBs) have been widely used in hypertensive patients with coronary artery disease (CAD) requiring stent implantation. In addition to its antihypertensive effect, ARBs are also known for their anti-inflammatory and anti-proliferative effects. The renin–angiotensin system has been implicated in the pathogenesis of restenosis and acute coronary syndrome [1–6] and, thus, may be a potential target for the prevention of in-stent restenosis and atherothrombotic events in patients who have CAD. It is well known that direct vascular effects of angiotensin II include vasoconstriction, inflammation, endothelial dysfunction, and stimulation of growth processes and remodeling, which are mediated by type 1 receptors [3, 7]. The single-center VALsartan for Prevention of REstenosis after Stenting of Type B2/C lesions (VAL-PREST) trial documented the remarkable therapeutic effects of the ARB valsartan on restenosis after stenting in complex coronary lesions [8]. In that trial, the ARB was more effective than
placebo for preventing in-stent intimal proliferation and its superiority over an angiotensin-converting enzyme (ACE) inhibitor can be predicted from the result that 68% of patients in the placebo group were taking an ACE inhibitor.

Optical coherence tomography (OCT) is an emerging intracoronary diagnostic modality that provides high-resolution images of coronary artery in vivo [9]. In addition to tissue characterization in native coronary plaques, OCT has been applied to characterize neointima after stent implantation [10]. Indeed, several OCT studies revealed the development of lipid-laden neointima inside the stents, and OCT has become the modality of choice to study athereosclerotic change of neointima [11–13]. However, correlation between anti-proliferative effect of ARB and change of neointimal characterization has not been studied yet. We investigated and compared the long-term effects of ARBs on neointimal characteristics in patients with CAD requiring stent implantation by OCT image analysis.

Methods
Study design and patients
This study was based on a retrospective observational data on patients who underwent OCT in Korea university Anam hospital between January 2011 and December 2012. Patients with CAD having history of drug-eluting stent (DES) implantation were analyzed on the basis of ARB therapy. Type of ARB or DES was not limited and administering other medications such as aspirin, β-blocker, calcium channel blocker for angina was not prohibited. Patients were divided in terms of taking ARBs as the ARB group and the non-ARB group. Inclusion criteria were: age between 40 to 75 years, CAD requiring drug-eluting stent implantation, diagnosed with hypertension or under antihypertensive medications, and OCT measurements during the follow-up. Patients with left main CAD, previous history of coronary artery bypass graft, acute myocardial infarction (MI), chronic total occlusion, ejection fraction <50%, unsuccessful reperfusion after coronary stent implantation, and liver or renal dysfunction were excluded from this study. Age and risk factor matching (diabetes, hyperlipidemia, smoking, family history of CAD) was performed. Major adverse cardiovascular events (MACEs) such as all-cause death, non-fatal MI, stroke, and target lesion revascularization (TLR) were compared between the two groups during the follow-up.

Quantitative coronary angiography
Offline quantitative coronary angiography (QCA) was conducted using the view that revealed the highest degree of stenosis. Severity of coronary stenosis was measured using the Cardiovascular Measurement System (MEDIS Medical Imaging System; Leiden, The Netherlands). For every patient, angiograms were analyzed at the time of OCT examination. Lesion length, reference diameter, minimal luminal diameter, and percent diameter stenosis were calculated by a single operator who was blinded to clinical characteristics. Analysis of angiographic frames was performed in the end-diastolic stage. Angiographic restenotic lesion type was classified as follows: focal restenosis, <10 mm in length (A) (articulation or gap [IA], margin [IB], focal body [IC], multifocal [ID]), or diffuse intrastent restenosis (B), >10 mm in length (intrastent [II], proliferative [III]) [14].

OCT examination and analysis
OCT examination and analysis was performed during the follow-up (LightLab Imaging Inc., Ilumien Offline review workstation, Ver D.O 2, MA, USA). Under guidance of a 0.014 in. angioplasty wire, OCT imaging catheter (C7 DragonflyTM, LightLab Imaging Inc., MA, USA) was advanced into the distal end of the DES implantation site. The entire length of the stent was imaged with an automatic pullback device moving at 15 mm/s and the OCT image clearly visualized the stent cross-section.

Neointimal characterizations were performed with OCT images at lesions of diameter stenosis >30% and were analyzed into two groups with same lesions by experienced observers using established criteria [10, 15]. The first group was categorized simply with patterns defining neointimal tissue structure of homogeneous, heterogeneous or layered (Fig. 1). Another group was classified into seven categories using densitometric analysis with image analyzing software (Image Pro Plus 7.0, Media cybernetics Inc., Bethesda, MD, USA): (1) macrophage, (2) cholesterol plaque, (3) fibrous plaque, (4) proteoglycan rich plaque, (5) calcified plaque, (6) lipid plaque, and (7) neovascularization. With densitometry, ranging from contrast of minimum 0(darkest) to maximum 255(brightest), lipid or calcified plaque or neovascularization was set to 0–69 (purple), proteoglycan plaque to 70–108 (yellow), fibrous plaque to 109–194 (orange) and macrophage or cholesterol crystal to 195–255 (red) (Fig. 2). Overlapping categories (macrophage or cholesterol crystal and lipid plaque or calcified plaque or neovascularization) could not be differentiated by densitometry; therefore, setting

Fig. 1 Neointimal characterizations. a Homogeneous b Heterogeneous c Layered
boundaries manually between overlapping categories and calculating ratio with pixels was done manually (Fig. 3). Lumen area, stent area, neointimal area, neointimal thickness, nonapposed struts, uncovered struts, and intraluminal mass were also observed.

**Study endpoints**
Primary end point was to compare neointimal characteristics and neointimal area with OCT during the follow-up. The secondary end point was to compare major adverse cardiovascular events (MACEs defined as non-fatal MI, death, stroke, and TLR) and late lumen loss, diameter stenosis, in-stent restenosis (defined according to the Academic Research Consortium criterion) [16] during the follow-up.

**Statistical analysis**
Categorical variables are expressed as numbers and percentages. Continuous variables are expressed as mean ± SD. Comparisons between groups were performed with 2-tailed Student t test for continuous variables and with χ² or Fisher exact test for categorical variables. The reproducibility of qualitative variables was assessed with κ test. A P < 0.05 was considered statistically significant. All statistical analyses were performed using SPSS (SPSS 12.0; Chicago, IL) software.

**Results**
**Participant characteristics and baseline assessments**
In total, we included 407 patients who were diagnosed as CAD having history of DES implantation and underwent OCT. Of these patients, 162 (39.8%) were in ARB group and 245 (60.2%) were in non-ARB group. Patient baseline characteristics were well matched in the study groups except sex. In the ARB group, fewer patients were male compared with the non-ARB group (66.0% vs. 79.6%, P = 0.002). Regarding as a retrospective data, various types of ARB were used in this study but difference of other medication use for angina was not statistically significant except CCB (24.1% vs. 68.9%, P < 0.001) (Table 1).
Target lesion characteristics and QCA analysis

Target arteries or types of target lesion did not differ within both groups (Table 2). Atherosclerotic lesions were located in left anterior descending artery (LAD) mainly (72.8% vs. 68.7%, \( P = 0.129 \)), and angiographic restenotic lesion type C took the largest portion in both groups (44.1% vs. 43.3%, \( P = 0.939 \)). Although several types of DES used in the study, there was no significant difference. Also, QCA findings on baseline, postprocedure and OCT follow-up revealed no significant differences in any parameters between the 2 groups (Table 3).

Endpoints

Described above, neointimal characteristics obtained by OCT were analyzed in two different methods, three patterns of homogenous, heterogeneous or layered and seven categories of using image analyzing software. As we analyzed with former method, all three patterns were differed with statistical significance between two groups (Table 4).

Homogeneous and layered pattern existed more in the ARB group (44.9% vs. 35.6%, \( P < 0.001 \)) and 16.8% vs. 10.6%, \( P < 0.001 \), respectively), whereas heterogeneous pattern was more seen in the non-ARB group (1.1% vs. 7.6%, \( P < 0.001 \)). By using latter method, both groups were statistically similar (Table 4), but macrophage seemed to be lower in the ARB group (0.98% vs. 1.23%, \( P = 0.225 \)). Secondary endpoints consist with comparing major adverse cardiovascular events and late lumen loss, diameter stenosis, in-stent restenosis during the follow-up did not show any statistical significance, although patients in the ARB group were more likely to occur TLR than the non-ARB group (15.4% vs. 9.4%, \( P = 0.077 \)). In quantitative OCT findings, stent struts were covered more likely in the ARB group than the non-ARB group (97.3% vs. 92.6%, \( P = 0.015 \)) (Table 5).

Discussion

Stent restenosis is an infrequent but poorly understood clinical problem in the drug-eluting stent era and its...
treatment is challenging. Experimental and clinical studies have identified excessive neointimal hyperplasia as leading cause of stent restenosis [17–19]. Neointima was composed of various characteristic lesions, such as fibrous tissue, proteoglycan-rich tissue, approved by pathologic examination of restenosis in bare-metal stent (BMS) and in DES in tissue samples obtained by atherectomy [20]. In the other hand, ARBs inhibit atherosclerosis as reduced plaque burden in atherosclerotic vessels and reduced incidence of in-stent restenosis [21]. In this concept of anti-inflammatory and anti-proliferative effect of ARBs toward atherosclerosis and neointimal growth, our present study assessed difference of neointimal characterization in use of long term ARBs by OCT. Furthermore, we tried to discover changes of specific neointimal component related to ARBs use.

Neointimal characterization in OCT was analyzed into two groups: a group which is classified conventionally into three patterns of homogeneous, heterogeneous and layered, and another group of specific neointimal component described above in methods. Considering former group, although currently no OCT criteria have been validated with histology for the identification of these tissue types, there are consumptions of each pattern correlating

| Variable          | ARB Group (n = 162) | Non-ARB Group (n = 245) | P value |
|-------------------|---------------------|-------------------------|---------|
| Number of lesions stented | 195 | 307 |         |
| Target coronary artery | 142 (72.8%) | 211 (68.7%) | 0.129  |
| LAD (15.9%) | 49 (16.0%) | 47 (15.3%) | 0.91   |
| LCX (11.3%) | 22 | 47 (15.3%) | 0.91   |
| RCA | 22 | 47 (15.3%) | 0.91   |
| Type of lesion (%) | 5 (2.6%) | 11 (3.6%) | 0.104  |
| A | 35 (17.9%) | 56 (18.2%) | 0.636  |
| B1 | 69 (35.4%) | 107 (34.9%) | 0.877  |
| B2 | 86 (44.1%) | 133 (43.3%) | 0.945  |
| C | 121 (62.1%) | 175 (57.0%) | 0.939  |
| Stent type | | | |
| EES | 105 (64.8%) | 147 (60.0%) | 0.288  |
| BES | 29 (17.9%) | 47 (19.2%) | 0.768  |
| ZES | 16 (9.9%) | 32 (13.1%) | 0.342  |
| SES | 11 (6.8%) | 20 (8.2%) | 0.622  |

Table 2: Target lesion characteristics

| Variable          | Value | Value | P value |
|-------------------|-------|-------|---------|
| Number of lesions stented | 195 | 307 |         |
| Target coronary artery | 142 (72.8%) | 211 (68.7%) | 0.129 |
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Table 3: QCA Measurements at baseline

| Variable          | ARB Group (n = 162) | Non-ARB Group (n = 245) | P value |
|-------------------|---------------------|-------------------------|---------|
| Baseline          |                     |                         |         |
| RD (mm)           | 2.54 ± 0.21         | 2.58 ± 0.16             | 0.454   |
| MLD (mm)          | 0.63 ± 0.25         | 0.58 ± 0.31             | 0.323   |
| % stenosis        | 75 ± 6              | 78 ± 8                  | 0.401   |
| Mean lesion length (mm) | 19.5 ± 8.5 | 22.2 ± 10.4 | 0.287   |
| Postprocedure      |                     |                         |         |
| RD (mm)           | 2.65 ± 0.28         | 2.68 ± 0.32             | 0.128   |
| MLD (mm)          | 2.53 ± 0.27         | 2.52 ± 0.29             | 0.323   |
| % stenosis        | 5 ± 4               | 6 ± 4                   | 0.709   |
| Acute gain (mm)   | 1.9 ± 0.3           | 1.9 ± 0.4               | 0.892   |
| Mean stent length (mm) | 23.1 ± 7.9 | 250 ± 7.5 | 0.564   |
| Mean stent diameter (mm) | 2.64 ± 0.37 | 2.65 ± 0.36 | 0.768   |

QCA quantitative coronary angiography, RD reference diameter, MLD minimal lumen diameter

Values are expressed as mean ± SD for quantitative variables or as n (%) for qualitative variables.
with neointimal characteristics. Homogeneous pattern is regarded identical to fibrous plaque, which was shown predominance in DES comparing with BMS [20]. Heterogeneous pattern is believed to be a mixture of various neointimal components within whole portion of neointimal growth that might result to show different optical properties [10]. Layered pattern could be visualized in OCT based on pathologic examinations that have demonstrated the density and orientation of smooth muscle cells vary within restenotic tissue compared to the inner luminal

### Table 4 Primary endpoint. Neointimal characterization by OCT

| Analyzing patterns | ARB Group (n = 162) | Non-ARB Group (n = 245) | P value |
|-------------------|---------------------|------------------------|---------|
| Number of lesions analyzed | 89 | 132 | |
| Homogenous pattern | 40 (44.9%) | 47 (35.6%) | <0.001 |
| Layered pattern | 15 (16.8%) | 14 (10.6%) | <0.001 |
| Heterogeneous pattern | 1 (1.1%) | 10 (7.6%) | <0.001 |

### Analyzing with Image Pro

| Number of lesions analyzed | 57 | 81 | |
| Macrophage (%) | 0.98 | 1.23 | 0.225 |
| Cholesterol plaque (%) | 0.01 | 0.00 | 0.355 |
| Fibrous plaque (%) | 55.63 | 58.36 | 0.479 |
| Proteoglycan rich plaque (%) | 26.4 | 25.7 | 0.705 |
| Calcified plaque (%) | 0.21 | 0.11 | 0.568 |
| Lipid plaque (%) | 16.73 | 13.28 | 0.198 |
| Neovascularization (%) | 0.04 | 0.19 | 0.217 |

### Table 5 Secondary endpoint. Cardiovascular events, QCA measurements and quantitative OCT findings during the follow-up period

| Cardiovascular events | ARB Group (n = 162) | Non-ARB Group (n = 245) | P value |
|-----------------------|---------------------|------------------------|---------|
| Non-fatal MI | 3 (1.9%) | 2 (0.8%) | 0.354 |
| Cardiac death | 1 (0.6%) | 0 | 0.319 |
| Stroke | 0 | 0 | 1.000 |
| TLR | 25 (15.4%) | 23 (9.4%) | 0.077 |

### QCA measurements

| Angiographic follow-up duration (months) | 19.0 ± 11.4 | 20.3 ± 14.1 | 0.523 |
| RD (mm) | 2.66 ± 0.30 | 2.68 ± 0.34 | 0.543 |
| MLD (mm) | 2.24 ± 0.29 | 2.21 ± 0.27 | 0.648 |
| % stenosis | 16 ± 8 | 19 ± 12 | 0.321 |
| Late lumen loss (mm) | 0.29 ± 0.28 | 0.32 ± 0.36 | 0.196 |
| Binary restenosis | 14 (8.6%) | 22 (9.0%) | 0.465 |

### Quantitative OCT findings

| Mean lumen area, mm² | 6.40 ± 2.49 | 6.74 ± 2.18 | 0.318 |
| Mean neointimal area, mm² | 1.09 ± 1.00 | 1.38 ± 1.24 | 0.096 |
| Mean neointimal thickness, μm | 140.6 ± 112.0 | 189.6 ± 423.1 | 0.217 |
| Malapposed strut No, % | 0.70% | 1.00% | 0.322 |
| Exposed strut No, % | 0.80% | 1.10% | 0.372 |
| Covered strut No, % | 97.30% | 92.60% | 0.015 |

OCT optical coherence tomography
Values are expressed as mean ± SD for quantitative variables or as n (%) for qualitative variables
Present study has several limitations. Unlike prior studies that revealed ARBs reduced incidence of in-stent restenosis, difference of TLR between two groups in our result revealed ARBs reduced incidence of in-stent restenosis, but valsartan, olmesartan and telmisartan appear to have a significant beneficial effect [21]. Also, various types of DES were used, from first generation (SES) to second generation (EES, BES, ZES), limiting this study that second-generation DES lead to a lower percentage of uncovered and malapposed struts, as well as a lower incidence of intra-stent thrombi, compared with first-generation DES [28, 29]. Measurement bias in analyzing densitometry with image analyzing software was described above in discussion.

Conclusions
In conclusion, the use of ARBs after DES implantation demonstrated different neointimal characteristics when compared with the non-ARB group, and stent struts were covered more likely with the use of ARBs during the follow-up OCT, indicating the anti-inflammatory effects of ARBs. For more definite conclusions, long-term clinical and serial OCT follow-up with a larger population will be needed in the future.

Abbreviations
ACE: Angiotensin converting enzyme; ARB: Angiotensin receptor blocker; BMS: Bare-metal stent; CAD: Coronary artery disease; DES: Drug-eluting stent; MACE: Major adverse cardiovascular event; OCT: Optical coherence tomography; QCA: Quantitative coronary angiography; TLR: Target lesion revascularization; VAL-PREST: Valsartan for prevention of restenosis after Stenting of Type B2/C lesions trial

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Availability of data and materials
This research was performed utilizing existing data from multiple EMRs within Korea University Anam Hospital. Data supporting the results reported in the article are available from the corresponding author on reasonable request.

Authors’ contributions
All named authors were involved in this project. SJH and DSL conceived and designed the study, provided methodological advice, participated in data interpretation and provided guidance and revisions for final draft of the manuscript. JYC assisted with study design and data analysis, performed literature study and wrote the first several drafts of the manuscript. All authors have read and approved the final draft of this manuscript.

Ethics approval and consent to participate
The institutional review board (IRB) of Korea University Anam Hospital approved this study with a waiver of informed consent.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.
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