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Impact of Combination Therapy with Ezetimibe/Simvastatin Treatment on the Neointimal Response to Biodegradable Polymer Biolimus-Eluting Stent Implantation in Patients with Acute Myocardial Infarction: Serial Assessment with Optical Coherence Tomography

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Abstract: The aim of this study was to compare the neointimal response at 12-month follow-up between ezetimibe/simvastatin (Vytorin, manufactured by Merck) 10/10 mg and Vytorin 10/40 mg after biodegradable polymer Biolimus-eluting stent (BP-BES) implantation in patients with acute myocardial infarction (AMI). A total of 20 patients requiring revascularization were randomly assigned to receive either Vytorin 10/10 mg (n = 9) or Vytorin 10/40 mg (n = 11). Baseline optical coherence tomography (OCT) was performed after stent implantation, and follow-up OCT was scheduled at 12 months. We performed follow-up OCT in 18 patients (Vytorin 10/10 mg (n = 9) or Vytorin 10/40 mg (n = 9)). A total of 842 frames and 8552 struts were analyzed at initial and follow-up OCT. At follow-up, the percentage of uncovered struts was not significantly different between both groups (6.61 ± 10.29% vs. 7.57 ± 6.45%, $p = 0.815$). The percentage of malapposed struts was also similar between both groups (0.69 ± 1.58% vs. 1.55 ± 2.72%, respectively, $p = 0.422$). Mean percent neointimal hyperplasia area was not significantly different between both groups (6.53 ± 3.26% vs. 6.37 ± 8.96%, $p = 0.961$). This OCT study showed that both high- and moderate-intensity dosing of Vytorin was associated with relatively lower percentages of uncovered struts and malapposed struts after Biolimus A9-eluting stent implantation in patients with AMI.

Keywords: acute coronary syndrome; ezetimibe/simvastatin combination; drug-eluting stent; optical coherence tomography

1. Introduction

Despite the fact that drug-eluting stent (DES) implantation has demonstrated marked reduction in restenosis as compared with the bare metal stent (BMS), the occurrence of late stent thrombosis has been a major concern [1–4]. Animal studies have demonstrated that DES induced greater fibrin deposition, late neointimal thickening, and delayed endothelialisation compared with BMS [5]. Furthermore, incomplete neointimal coverage of covered struts, the most powerful indicator of endothelialisation, was the best morphometric predictor of late stent thrombosis in a pathologic study [6]. Recently, studies have demonstrated that uncovered and malapposed struts were frequently observed in patients

with very late stent thrombosis, occurring beyond one year after DES implantation [7,8]. Therefore, assessment of appropriate endothelialisation and late apposition status of DES is the key factor for the prevention of stent thrombosis.

A large randomized controlled trial, IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT), demonstrated the efficacy of combination therapy with ezetimibe/simvastatin (Vytorin, manufactured by Merck) on the reduction of low-density lipoprotein (LDL) cholesterol and improving long-term clinical outcomes [9]. Therefore, as of recently, guidelines recommend that the combination of statin and ezetimibe should be considered in patients with statin intolerance [10,11].

The biodegradable polymer Biolimus-eluting stent (BioMatrix Flex™, Biosensors Inc., Newport Beach, CA, USA) consists of a stainless-steel platform coated by an abluminal layer of biodegradable polymer which is degraded by surface hydrolysis to lactide during a period of 6 to 12 months [12]. However, data is scarce on the process of neointimal coverage and late apposition status of the biodegradable polymer Biolimus-eluting stent (BP-BES) when implanted in the highly thrombogenic setting of acute myocardial infarction (AMI) after combination therapy with statin and ezetimibe.

Intracoronary frequency domain optical coherence tomography (OCT) provides high-resolution (10 μm) imaging which enables the visualization of various vascular structures and detection of strut coverage, malapposition, and the characterization of neointimal tissue in the setting of AMI when compared with intravascular ultrasound (IVUS) [13–19]. OCT has almost 10 times higher axial resolution than IVUS. Therefore, we performed this study to compare the neointimal response, assessed by serial OCT, at 12-month follow-up between Vytorin 10/10 mg and 10/40 mg after BP-BES implantation in patients with AMI.

2. Methods

2.1. Study Design and Study Population

This was a prospective, single-centre, randomized study, designed to compare the neointimal response according to the different doses of Vytorin after BP-BES implantation in patients with AMI, including ST-elevation myocardial infarction (STEMI). This present study was conducted according to the Declaration of Helsinki. The study protocol was approved by the Institutional Review Board of Chonnam National University Hospital (approval number: CNUH-2013-080), and written informed consent was obtained from each patient.

Enrolled patients with AMI were randomized after successful urgent coronary angiography (CAG). Computer-generated random numbers were used for the randomization. Exclusion criteria were: (1) patients with hypersensitivity or contraindication to antiplatelet or lipid-lowering drug treatment, (2) patients with a life expectancy shorter than one year, (3) unprotected left main coronary artery disease, (4) chronic renal failure with a baseline creatinine $\geq$2.0 mg/dL or regular hemodialysis state, (5) Killip classification $\geq$III, (6) unprotected left main coronary artery disease, (7) proximal lesions within 10 mm of the ostium of major artery, (8) bifurcation lesion with diameter $\geq$2 mm of side branch diameter, and (9) lesions with previous stent failure or severe calcification or chronic total occlusion.

2.2. Interventional Procedures

All patients who underwent percutaneous coronary intervention (PCI) received 300 mg aspirin and 300 or 600 mg clopidogrel, or 60 mg prasugrel, or 180 mg ticagrelor as a loading dose prior to the procedure. PCI was performed using current conventional techniques. The selection of PCI timing, vascular access, and use of glycoprotein IIb/IIIa inhibitor were at the physician's discretion. After PCI with BP-BES implantation, dual antiplatelet medications including aspirin and P2Y12 receptor inhibitor were prescribed as a maintenance dose for at least one year, and follow-up CAG after one year was planned for the entire study population.

2.3. Procedures for OCT Image Acquisition

OCT examination was performed using a frequency-domain OCT system (C7-XR OCT Intravascular Imaging System, St. Jude Medical, St. Paul, MN, USA) with a pullback speed of 20 or 25 mm/s according to a non-occlusive technique. All patients were given 3000 IU of intravenous heparin before procedures. The procedure was performed via radial or femoral access with a ≥6 Fr guiding catheter. The C7 Dragonfly^{TM} (St. Jude Medical) was advanced over the 0.014-inch PCI wire and the implanted stent was crossed after administration of intracoronary nitrates of 200 µg. For blood clearing, contrast media was injected through the guiding catheter with an automated power injector. The standard infusion rate was 3 mL/s for the right coronary artery (RCA) and 4 mL/s for the left coronary system. Follow-up OCT image acquisition was achieved with the same method.

2.4. OCT Image Analysis

Cross-sectional OCT images were analysed at 1-mm intervals and OCT analysis was performed by an independent investigator blinded to patient and procedural information at the intravascular image core laboratory in Chung-Ang University Hospital. OCT measurements and definitions have been based on previous studies [20,21]. Stent and luminal areas in every image were measured and mean values are reported in this study. Intra-stent thrombus was defined as a protruding mass in-between or over stent struts (Figure 1A). A malapposed strut was defined as a strut that has detached more than 120 µm from the vessel wall, as the strut thickness of BP-BES is 120 µm (Figure 1B,C). Neointimal hyperplasia (NIH) area was calculated as the stent area minus the luminal area (Figure 1D). Percent NIH area was calculated as NIH area × 100/stent area. The NIH thickness was defined as the distance between the luminal surface of the covering tissue and the luminal surface of the strut. An uncovered strut was defined as having the NIH thickness of 0 µm (Figure 1E,F). The percentage of malapposed or uncovered struts was calculated as the (malapposed or uncovered struts/total number of struts in each stent) × 100, respectively.

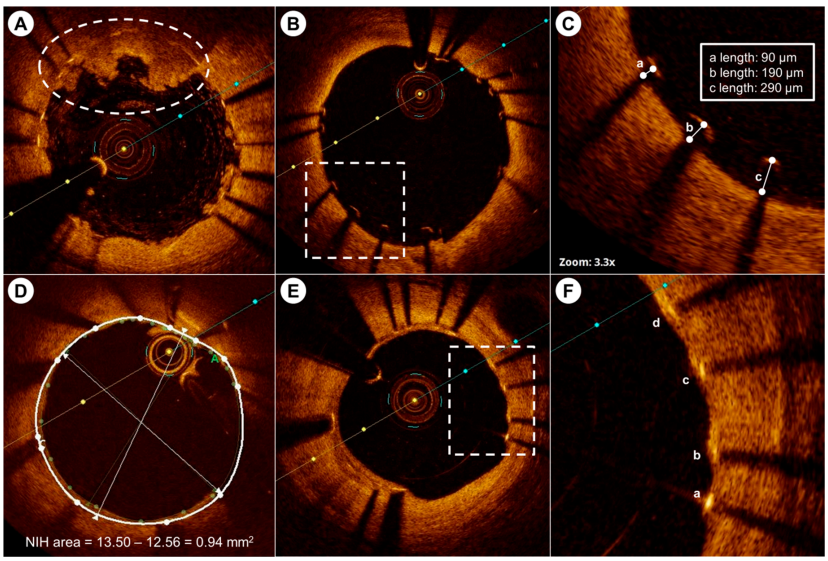

Figure 1. Representative images regarding the OCT analysis method. (**A**) Cross-sectional postimplantation OCT image showing intrastent white thrombus (white circle) and tissue prolapse. (**B**) OCT image showing the apposed and malapposed struts after stent implantation. (**C**) Zoomed-in image of the white box in Figure 1B demonstrating an apposed strut (a) and malapposed struts (b and c). (**D**) Follow-up OCT image demonstrating NIH area of 0.94 mm^2, defined as the stent area (13.50 mm^2) minus the luminal area (12.56 mm^2). (**E**) Follow-up OCT image showing the covered and uncovered struts. (**F**) Zoomed-in image of the white box in Figure 1E demonstrating an uncovered strut (a) and covered struts (b, c, and d). Abbreviations: OCT, optical coherence tomography; NIH, neointimal hyperplasia.

2.5. Study Endpoints

The primary endpoint of the study was the evaluation of the percentage of uncovered struts at follow-up OCT in all cross sections with analysis of 1-mm longitudinal intervals. The secondary endpoint was the percentage of malapposed struts and the characteristics of endothelialisation evaluated by OCT analysis at follow-up.

2.6. Statistical Analysis

All continuous variables were expressed as the mean with standard deviation or median with interquartile ranges, when appropriate. Categorical variables were reported as numbers with a percentage and compared using the χ^2 test or Fisher's exact test. The continuous variables were compared by the Mann–Whitney U test. A p value of <0.05 was considered statistically significant. All statistical analyses were performed using SPSS 22.0 for Windows (SPSS-PC, Chicago, IL, USA).

3. Results

3.1. Statistical Analysis

Twenty patients with AMI requiring revascularization were randomly assigned to receive either Vytorin 10/10 mg (n = 9) or Vytorin 10/40 mg (n = 11) between 8 June 2013, and 3 July 2017. Two patients in the Vytorin 10/40 mg group were excluded because of changing of Vytorin dose. During follow-up angiography with OCT, assessment was completely achieved in 18 subjects, nine of the Vytorin 10/10 mg group and nine of the Vytorin 10/40 mg group. The mean age of the total population was 60.2 ± 10.3 years, 15 patients (83.3%) were men, and six patients with STEMI were included. Baseline clinical and procedural characteristics and discharge medication of these patients are summarized in Table 1 and show no differences between the two groups in terms of age, gender, incidence of cardiovascular risk factors, angiographic findings, or medication.

Table 1. Characteristics of baseline clinical and procedures and discharge medication between the two groups.

Variables	Vytorin 10/10 mg (n = 9)	Vytorin 10/40 mg (n = 9)	p Value
Demographic			
Age, mean ± SD, y	57.0 (8.3)	63.4 (11.5)	0.222
Male	8 (88.9)	7 (77.8)	0.527
Cardiovascular risk factors			
Hypertension	3 (33.3)	6 (66.7)	0.157
Diabetes mellitus	2 (22.2)	4 (44.4)	0.317
Current smoking	7 (77.8)	4 (44.4)	0.147
STEMI	4 (44.4)	2 (22.2)	0.317
Culprit lesion			0.513
LAD	5 (55.6)	7 (77.8)	
LCx	1 (11.1)	1 (11.1)	
RCA	3 (33.3)	1 (11.1)	
Baseline QCA data, mean ± SD			
Reference vessel diameter, mm	3.40 ± 0.42	3.37 ± 0.38	0.931
Minimum lumen diameter, mm	0.12 ± 0.13	0.23 ± 0.21	0.297
Diameter stenosis, %	96.7 ± 3.5	92.8 ± 6.7	0.222
Implanted stent, median (IQR)			
No. of stents	1.0 (1.0–1.0)	1.0 (1.0–1.0)	0.730
Stent diameter, mm	3.5 (3.0–3.6)	3.5 (3.3–3.5)	1.000
Stent length, mm	24 (18–28)	18 (18–26)	0.340
Medication at discharge			
Aspirin	9 (100)	9 (100)	
Clopidogrel	1 (11.1)	3 (33.3)	0.257
Ticagrelor	4 (44.4)	4 (44.4)	
Prasugrel	4 (44.4)	2 (22.2)	0.317
ACEi/ARB	8 (88.9)	9 (100)	0.303
Beta-blocker	7 (77.8)	7 (77.8)	

Data are expressed as No. (%) unless otherwise indicated; Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; IQR, interquartile range; LAD, left anterior descending artery; LCx, left circumflex artery; QCA, quantitative coronary angiography; RCA, right coronary artery; STEMI, ST-elevation myocardial infarction.

3.2. Initial and Follow-Up Laboratory Findings

Baseline initial laboratory findings for both groups are shown in Table 2. There were no statistically significant differences in the profiles of lipids, high-sensitivity C-reactive protein, and cardiac enzymes, except for apolipoprotein A1. Regarding follow-up lipid profiles, total cholesterol, LDL-cholesterol, and absolute change and degree of change of LDL-cholesterol were similar between the two groups. However, the Vytorin 10/40 mg group showed a significantly lower triglyceride and higher high-density lipoprotein cholesterol level than the Vytorin 10/10 mg group (Table 3).

Table 2. Laboratory characteristics of patients in both groups.

Laboratory Findings	Vytorin 10/10 mg (n = 9)	Vytorin 10/40 mg (n = 9)	*p* Value
Total cholesterol, mg/dL	184 (160–223)	174 (145–206)	0.605
Triglyceride, mg/dL	103 (75–178)	112 (78–162)	0.931
HDL-cholesterol, mg/dL	33 (30–35)	40 (35–49)	0.014
LDL-cholesterol, mg/dL	123 (88–143)	122 (85–138)	0.730
Apolipoprotein B, mg/dL	89 (82–107)	97 (0.8–1.1)	0.340
Apolipoprotein A1, mg/dL	114 (105–119)	126 (114–135)	0.040
Apolipoprotein B/Apo A1	0.74 (0.72–0.93)	0.79 (0.66–0.91)	0.666
hsCRP, mg/dl	0.50 (0.43–0.72)	0.61 (0.14–1.20)	0.863
Peak CK-MB, ng/ml	54 (12–154)	21 (10–189)	0.387
Peak troponin-I, ng/ml	12.1 (8.8–47.3)	9.3 (4.8–40)	0.546

Data are expressed as median (IQR); Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; CK, creatine kinase.

Table 3. Lipid profiles at follow-up between the two groups.

Laboratory Finding	Vytorin 10/10 mg (n = 9)	Vytorin 10/40 mg (n = 9)	*p* Value
Total cholesterol, mg/dL	126 (106–151)	117 (95–133)	0.387
Triglyceride, mg/dL	178 (137–414)	112 (59–137)	0.008
HDL-cholesterol, mg/dL	33 (27–37)	44 (40–47)	0.004
LDL-cholesterol, mg/dL	61 (53–70)	55 (41–75)	0.489
Δ LDL-cholesterol, mg/dL	55.7 ± 25.0	61.7 ± 22.6	0.605
Degree of change of LDL-cholesterol, %	46.0 ± 10.7	50.5 ± 13.7	0.387

Data are expressed as median (IQR) or mean ± SD; Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein.

3.3. OCT Analysis at the Index Procedure and Follow-Up

Initial and follow-up OCT measurements are shown in Table 4. The median follow-up time was 12 months (range: 7 to 38 months) and showed no difference in both groups. At the strut analysis, a total of 842 frames (430 in the initial OCT and 412 in the follow-up OCT) and 8552 struts (4328 in the initial OCT and 4224 in the follow-up OCT) were analyzed at initial and follow-up OCT. Regarding initial OCT analysis, there were no significant differences between the two groups in terms of mean lumen area, mean stent area, percentage of malapposed or uncovered struts, and presence of intrastent thrombi. At the follow-up OCT analysis, the percentage of uncovered struts was not significantly different between the Vytorin 10/10 mg and 10/40 mg groups (6.61 ± 10.29% vs. 7.57 ± 6.45%, $p = 0.297$) (Figure 2). Moreover, there was no significant difference in the percentage of malapposed struts between the two groups (0.69 ± 1.58% vs. 1.55 ± 2.72%, $p = 0.489$) (Figure 3). Neointimal coverage including mean NIH area and mean percent NIH area were also similar in both groups. Intrastent thrombi were recognized in two individuals in the Vytorin 10/10 mg group and in none in the Vytorin 10/40 mg group at follow-up.

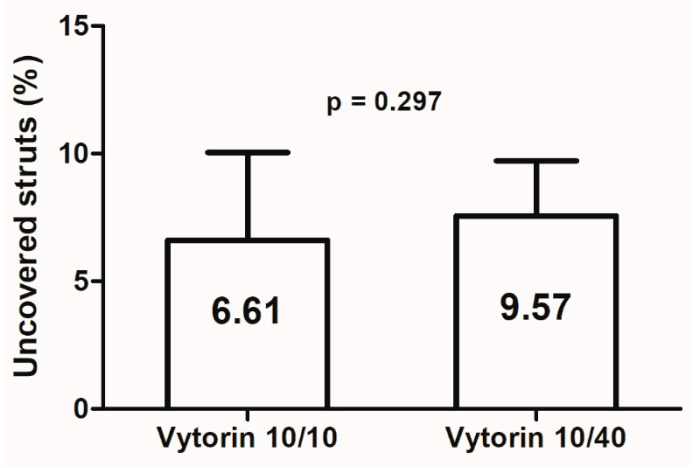

Figure 2. Percentage of uncovered struts at follow-up OCT in the Vytorin 10/10 mg and 10/40 mg groups. Abbreviation: OCT, optical coherence tomography.

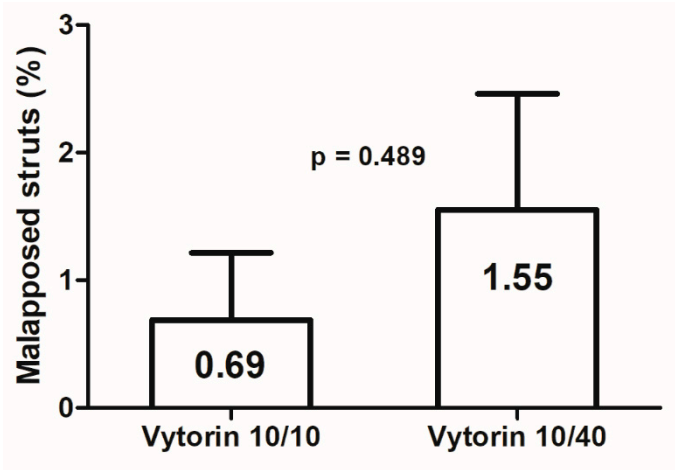

Figure 3. Percentage of malapposed struts at follow-up OCT in the Vytorin 10/10 mg and 10/40 mg groups. Abbreviation: OCT, optical coherence tomography.

Table 4. Optical coherence tomography analysis.

Variables	OCT Analysis Immediately after PCI			Follow-Up OCT Analysis		
	Vytorin 10/10 mg (n = 9)	**Vytorin 10/40 mg (n = 9)**	***p* Value**	**Vytorin 10/10 mg (n = 9)**	**Vytorin 10/40 mg (n = 9)**	***p* Value**
Time interval to OCT (month)				12.3 ± 4.4	17.6 ± 11.6	0.489
Number of total cross sections	222	208		200	212	
Analysis of all cross sections						
Number of total struts	2251	2077		2101	2123	
Mean lumen area (mm^2)	8.17 ± 2.39	8.49 ± 2.28	0.666	9.11 ± 3.36	8.43 ± 2.03	0.863
Mean stent area (mm^2)	8.40 ± 2.47	8.50 ± 1.98	0.730	9.75 ± 3.62	9.01 ± 1.99	0.730
Percentage of uncovered struts (%)	87.53 ± 10.98	91.34 ± 8.86	0.387	6.61 ± 10.29	7.57 ± 6.45	0.297
Percentage of malapposed struts (%)	3.88 ± 2.79	7.32 ± 7.32	0.387	0.69 ± 1.58	1.55 ± 2.72	0.489
Presence of intra-stent thrombus	9 (100%)	6 (66.7%)	0.058	2 (22.2%)	0 (0%)	0.134
Mean NIH area (mm^2)				1.41 ± 2.28	0.65 ± 0.76	0.297
Mean percent NIH area (%)				6.53 ± 3.26	6.37 ± 8.96	0.190
Mean NIH thickness (μm)				47 ± 29	56 ± 103	0.190

Data are expressed as mean ± SD or No. (%); Abbreviations: NIH, neointimal hyperplasia; OCT, optical coherence tomography; PCI, percutaneous coronary intervention.

4. Discussion

To the best of our knowledge, this is the first study reporting the comparison of neointimal responses at long-term follow-up, assessed by OCT, according to the different doses of Vytorin after BP-BES implantation in patients with AMI. In this study, we did not find a significant difference between the Vytorin 10/10 mg and 10/40 mg groups in the percent of uncovered struts, despite marked reduction in uncovered struts at follow-up when compared with acute results. A sub-study of the LEADERS (Limus Eluted from A Durable vs. ERodable Stent coating) demonstrated better strut coverage of BP-BES as compared with a first-generation sirolimus-eluting stent (SES) at nine months (0.6% in the BP-SES group vs. 2.1% in SES group, $p = 0.04$) [22]. Another sequential OCT study showed that the proportion of uncovered struts tended to be lower in BP-BES than in SES at nine months (2.8% in the BP-BES group vs. 5.7% in the SES group, $p = 0.31$) [23]. In our study, the mean percentage of uncovered struts was 7.1% in the entire study population. The follow-up OCT results of our study showed higher uncovered struts when compared with two previous studies (7.1% vs. 0.6% and 2.8%, respectively). However, our study only enrolled patients with acute myocardial infarction (AMI). Other two studies enrolled patients with ischemic heart disease including angina, only 35–40% of enrolled patients with AMI. AMI is completely different pathophysiology from angina patients. This difference of enrolled patients might induce the proportion of uncovered struts between our study and other two studies. In one OCT study, a number of uncovered struts was observed in 12.8% of OCT-guided and 16.8% of image-guided primary PCI patients with STEMI at 9 months [24].

Regarding strut malapposition, our study showed that the percent of malapposed struts was similar in both groups. However, follow-up OCT of all individuals showed that the mean percentage of malapposed struts significantly decreased from 5.6 ± 5.6% after the index PCI to 1.1 ± 2.2% at follow-up ($p = 0.004$). Although the healing process of malapposition has not yet been fully understood, the improved apposition of BP-BES observed at follow-up can be explained by the reduced late-acquired malapposition due to the absence of a hypersensitivity reaction against the biodegradable polymer [20]. In the PESTO (Morphological Parameters Explaining Stent Thrombosis assessed by OCT) registry, malapposition was frequently observed in all stent thrombosis (ST) types, including acute/subacute and late/very late stent thrombosis [25]. The potential advantage of BP-BES might lead to improved long-term clinical outcomes, especially a lower risk of cardiac events associated with very late ST between one and four years [26].

The mean thickness of NIH was 47 μm and 56 μm in the 10/10 mg and 10/40 groups, respectively, and the mean was 51 ± 74 μm in all 18 patients. It was quite thin when compared to an estimation on the basis of two previous studies [27,28]. A substudy from the RESOLUTE all-comers (Randomized Comparison of a Zotarolimus-Eluting Stent (ZES) With an Everolimus-Eluting Stent (EES) for Percutaneous Coronary Intervention) trials demonstrated that neointimal thickness was 116 μm in ZES and 142 μm in EES at 13 months after stent implantation [27]. In another sequential OCT study, neointimal thickness at 9 months' follow-up was 139 μm and 124 μm in the ZES and EES groups, respectively [28]. The presence of abluminal coating and the biodegradable polymer might be the reason that possibly explains the differences in neointimal thickness between the stents, although further studies should be conducted for confirmation.

There were several limitations in this study. First, this is a single-centre study with the limitations of a small sample size, even though our study is a randomized trial. Second, inter-observer and intra-observer variability were not evaluated regarding the OCT analysis. Third, although the high resolution of OCT is able to assess the characteristics of neointima, it may be difficult to differentiate neointima from other material, such as fibrin and thrombi.

5. Conclusions

This prospective randomized OCT study showed that both high- and moderate-intensity dosing of Vytorin was associated with relatively lower percentages of uncovered struts and malapposed

struts after BP-BES implantation in patients with AMI. Moreover, follow-up OCT demonstrated thin neointimal thickness and good tissue coverage in BP-BES regardless of Vytorin dose.

Author Contributions: Y.J.H. and Y.Y. conceived and designed the experiments; M.H.J., Y.A., Y.K., Y.J.H., J.H.K., D.S.S, and M.C.K. performed the experiments; Y.K. and S.W.K. analysed the data; Y.K. wrote the first draft of the article.

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