Impact of age on Stent Strut Coverage and Neointimal Remodeling as assessed by Optical Coherence Tomography

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Abstract: While older age associates with adverse percutaneous coronary intervention (PCI) outcomes, detailed information relating age to stent strut coverage and neointimal characteristics is lacking. One hundred ninety patients with 230 sirolimus-eluting stents (SESs) were divided into 3 groups: group A (<55 years), group B (56–65 years), and group C (>65 years). At 6 and 12 months of follow-up, optical coherence tomography was performed to assess strut coverage and neointimal remodeling.

At 6 months, the proportion of uncovered struts increased with age: 6.1% in group A versus 7.3% in group B versus 11.7% in group C (P < 0.001) while the proportion of embedded struts decreased: 72.1% versus 57.0% vs. 55.0%, respectively (P < 0.001). Mean neointimal thicknesses were 90 μm versus 60 μm versus 60 μm, respectively (P < 0.001), and neointimal areas were 0.82 mm² versus 0.52 mm² versus 0.57 mm² (P < 0.001). At 12 months, the proportion of uncovered struts increased with age (3.9% vs. 3.3% vs. 4.9 %; P < 0.001), while mean neointimal thicknesses were 100 versus 70 versus 80 μm (P < 0.001) and neointimal areas were 0.87 versus 0.60 versus 0.67 mm² (P < 0.001).

Patients <55 years receiving SES showed highest strut coverage and neointimal repair rate compared with the other 2 groups. A “catch-up phenomenon” appeared to occur in the oldest patients, as in the first 6 months the neointima showed lowest endothelial cell coverage and lowest neointimal proliferation rate, whereas from 6 to 12 months, the highest neointimal proliferation rate was seen in the oldest patients.

Abbreviations: ACEI = angiotensin-converting enzyme inhibitor, CAD = coronary artery disease, LAD = left anterior descending coronary artery, LCX = left circumflex coronary artery, OCT = optical coherence tomography, PCI = percutaneous coronary intervention, QCA = Quantitative coronary vessel analysis, RCA = right coronary artery, SAP = stable angina pectoris, SES = sirolimus-eluting stent, UAP = unstable angina pectoris.

INTRODUCTION
A high prevalence of coronary artery disease (CAD) is observed worldwide. As a result of this, revascularization procedures in CAD patients continue to be performed more frequently. Furthermore, with the population aging and approximately 25% of people over 75 years of age exhibiting cardiovascular disease, older people have become the principal recipients of percutaneous coronary intervention (PCI). A number of studies, however, suggest that elderly patients undergoing PCI tend to present with a higher incidence of comorbidities and exhibit a higher rate of adverse cardiac outcomes.

Thus, previous studies have shown that age was an independent predictor of mortality. Specifically, older patients with CAD differ from their younger counterparts in that they often present with more extensive atherosclerotic involvement, a higher frequency of multivessel disease, greater calcification of coronary vessels, and the presence of concomitant carotid and peripheral vascular disease. Moreover, age-related extra-cardiac conditions, including compromised renal and pulmonary function, likely contribute to a different response to PCI and poorer outcomes.

Stent implantation in patients older than 75 years results in an in-hospital mortality rate between 2.2% and 4.7%. As elderly patients with acute myocardial infarction (AMI) are less often treated with reperfusion therapy than younger patients and are often excluded from randomized clinical trials, questions remain as to the best approach for treating this subset of population. Despite widespread use of sirolimus-eluting stents (SESs) as a strategy for reducing the risk of subsequent restenosis, little is known about the impact of age, per se, on vessel response to SES implantation. In particular, the differences between elderly patients and younger patients in intimal healing remain unclear.

As PCI technology evolves and the Chinese population becomes proportionally older, assessing neointimal responses in the elderly is essential. However, to date, few studies have focused on strut coverage and neointimal responses after PCI in different age groups. The aim of the present study was, therefore, to observe the effects of age on neointimal coverage using optical coherence tomography (OCT).

METHODS
Patient Population

The study centered on a retrospective analysis of 119 patients who underwent elective or urgent coronary stent implantation and subsequent OCT imaging between November...
To study the impact of age on strut coverage and neointimal remodeling, patients were divided into 3 groups according to age: Group A (≤55 years, n = 46), Group B (56–65 years of age, n = 39), and Group C (66–74 years, n = 34). In order to exclude the influence of baseline clinical characteristics and treatments, we also divided the affected patients into subgroups to separately analyze whether these factors impacted neointimal coverage across the 3 groups. Patients were excluded if they had significant left main CAD, renal insufficiency or congestive heart failure. In addition, if there were difficulties in advancing the OCT catheter subjects were also excluded. The protocol employed was approved by the Harbin Medical University Ethics Committee. Before the catheterization procedure, all patients signed an informed consent.

Quantitative Coronary Vessel Analysis (QCA)

QCA results were reviewed separately using a quantitative coronary angiogram program by 2 independent observers blinded to the patients’ information. The minimal luminal diameter (MLD) of the treated coronary artery “in-stent” segments, reference diameter, and percent diameter stenosis (DS%) were measured. Luminal loss was defined as the difference between the MLD immediate after the procedure and MLD at follow-up. The luminal loss rate was defined as neointimal hyperplasia area/lumen area relative to the time after implantation.

OCT Image Acquisition

OCT images were acquired in either the Frequency-Domain (C7XR system) or Time-Domain (M2/M3 system). During image acquisition, automated pullback was used with a short injection of contrast media through the guiding catheter in the C7XR system. In the M2/M3 system, during image acquisition, the proximal segment of the vessel was blocked by an occlusion balloon and the automatic pull back accompanied by continuous saline infusion.

OCT Image Analysis

OCT image analysis was performed as previously reported. In brief, cross-sectional OCT images were analyzed at 1 mm intervals. Stent and luminal area were measured at 1 mm intervals, and neointimal area was calculated as stent area minus luminal area. Maximum, minimum, and mean neointimal thickness (NIT), stent area, and lumen area were automatically calculated for each cross-sectional OCT image. Strut coverage, malapposition, protruding, embedded struts, and neointimal hyperplasia (NIH) were defined according to previously published criteria (Fig. 1). Strut struts in lesions with major side branches (diameter ≥2 mm) were excluded from OCT analysis. When a lesion needs to implant 2 stents, overlapping segments of the stent was not included in the measurements or comparisons. OCT images were analyzed by 2 experienced investigators. If discordance occurred between the 2 investigators, a third investigator was used to give a consensus reading.

Patient Clinical Data and Follow-Up

Follow-up information was available for all 119 patients at 6 and 12 months after stent implantation. Patient data including sex, weight, height, smoking, and history of past diseases such as hypertension, diabetes, and myocardial infarction were collected. Similarly, laboratory data for blood lipid levels and blood glucose levels were collected, and data regarding to treatment/drug interventions including PCI, statins, β-receptor blockers, angiotensin-converting enzyme inhibitors (ACEIs), and angiotensin receptor blockers (ARBs). Follow-up was performed at 6 and 12 months using patient readmission records.

Statistical Analysis

Baseline patient clinical characteristics and angiographic data were compared across these three groups. Comparisons of categorical data were analyzed using χ² statistics or Fisher exact test. Continuous variables were compared using Student t test or Mann–Whitney U test. The post hoc Tukey test was applied only when the P-value for ANOVA was less than 0.05. Variables were reported as mean ± standard deviation (SD) for continuous variables or as percentages for dichotomous variables. A P-value < 0.05 was considered as statistical significance.

RESULTS

Patient Clinical Data

The baseline clinical characteristics of the patients are shown in Table 1. The youngest patient group was characterized by a greater percentage of male patients (80.4% vs. 48.7% vs. 52.9%, P < 0.005), whereas the patients in the other older groups were more likely to have hypertension (52.2% vs. 79.5% vs. 61.8%, P < 0.05). Other characteristics including treatment and laboratory data showed no differences across the 3 groups.

Angiographic Findings

A total of 123 stents in the 119 patients were studied. Each patient had only 1 lesion, whereas 4 patients received 2 stents overlapped in 1 lesion. Fifty-eight stents were placed in the left anterior descending coronary artery (LAD), 31 in the circumflex (LCX), and 34 in the right coronary artery (RCA). With respect to age the number of subjects and stents was as follows: youngest group (≤55 years, 46 patients/46 stents), older group...
(56–65 years of age, 39 patients/40 stents), and eldest (66–74 years, 34 patients/37 stents). Four lesions had overlapping segments (2 stents), where older group have 1 overlapping segment, 3 overlapping segments in eldest group (Table 1).

OCT Findings

Vascular and Stent Parameters and Lesion Type

Vascular and stent parameters and lesion type are listed in Table 2. No significant differences in distribution of plaques in the treated lesions were observed.

Strut Coverage

At 6 months of follow-up, Group A exhibited the thickest neointima (90 μm vs. 60 μm vs. 60 μm, P < 0.001) compared the other age groups (Fig. 2A). An age-related increase in the proportion of uncovered struts was observed (6.1% vs. 7.3% vs. 11.7%, P < 0.001) (Fig. 2C). Correspondingly, the proportion of embedded struts decreased (72.1% vs. 57.0% vs. 55.0%, P < 0.001) as age increased. The proportion of protruding struts also was observed to increase with age (26.7% vs. 41.9% vs. 42.6%, P < 0.001) (Fig. 2E).

At 12 months of follow-up, Group A have the thickest neointima (100 μm vs. 70 μm vs. 80 μm, P < 0.001) (Fig. 2B). Group C continued to show the highest proportion of uncovered struts (3.9% vs. 3.3% vs. 4.9%, P < 0.001) (Fig. 2D). Conversely, Group A had the highest proportion of embedded struts (76.3% vs. 64.1% vs. 71.5%, P < 0.001) (Fig. 2F).

The baseline clinical characteristics of the patients were similar between the groups with the exception of sex. In order to exclude the influence of the baseline differences, we selected the affected patients and analyzed them separately to evaluate neointimal coverage. However, no influences were detected across the 3 age groups. Table 3 shows the impact of age on neointimal characteristics according to gender. For both male and female patients, the youngest group also showed the highest proportion of embedded struts (76.3% vs. 64.1% vs. 71.5%, P < 0.001) in male patients and 74.4% vs. 62.5% vs. 70.7%, P < 0.001 in female patients). Group A had the greatest area of neointimal hyperplasia (0.81 mm² vs. 0.61 mm² vs. 0.63 mm² in male patients, P < 0.001) and female patients, P < 0.001 and 70 vs. 70 vs. 70 mm² in patient, P < 0.001) and greatest mean neointimal thickness (90 μm vs. 70 μm vs. 80 μm in male patients, P < 0.001 and 120 vs. 70 vs. 70 μm in female patients, P < 0.001). Regardless of sex, the eldest group showed the highest proportion of uncovered struts between the 3 groups (4.32% vs. 3.8% vs. 5.4%, P < 0.001 in male patients and 1.3% vs. 2.6% vs. 4.2% in female patients, P < 0.001).

Figure 3 shows the increases in neointimal thickness occurred during 6 to 12 months after stent implantation. The data are presented as the differences between the median values at the 6- and 12-month follow-ups. As age increased, the Group C had the highest Δ median of neointimal hyperplasia thickness. And as in the first 6 months the neointima showed low
that a ratio of uncovered struts to total struts/section of related impairment of drug access.23 In the present study, the underlying plaque morphology, thrombus burden, and uncovered struts could be explained by many factors, including for favorable clinical outcomes.

Best morphometric predictor of LST.22 Such studies further show of uncovered stent struts to the total number of stent struts is the cation, it is associated with a high incidence of AMI and concerns.21,22 Although LST is a relatively infrequent complication of in-stent restenosis (ISR) by targeting proliferating cells.17

As a result of inhibition of endothelialization and delayed vascular healing to the endothelial damage, late stent thrombosis (LST, defined as 30 days up to 1 year) and very late stent thrombosis (VLST, >1 year) have emerged as major safety concerns.18–20 Although LST is a relatively infrequent complication of in-stent restenosis (ISR) by targeting proliferating cells.17

However, the beneficial reductions in neointima formation and ISR are accompanied by impaired endothelial regenerative and vascular healing that has created a number of new concerns.18–20 As a result of inhibition of endothelialization and delayed vascular healing to the endothelial damage, late stent thrombosis (LST, defined as 30 days up to 1 year) and very late stent thrombosis (VLST, >1 year) have emerged as major safety concerns.21,22 Although LST is a relatively infrequent complication of in-stent restenosis (ISR) by targeting proliferating cells.17

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Previous reports have shown that a higher prevalence of uncovered struts could be explained by many factors, including the underlying plaque morphology, thrombus burden, and related impairment of drug access.23 In the present study, patients aged over 65 years had the highest uncovered rate, both at 6 and 12 months of follow-up. Conversely, the patients ≤55 years old showed the highest proportion of embedded struts and had the greatest neointima area and neointima thickness. Examination of the clinical characteristics of our study groups showed no differences in coexisting diseases or drug treatments but some apparent differences in sex. Despite this, when we investigate the impact of age on neointimal characteristics according to gender, no statistical differences were noted. A tentative conclusion from these results is that age was the dominant factor for neointima formation in the present study. Previous OCT studies have reported that the incidence of uncovered struts was 8.9% to 13.3% at 6 months and 12.2% at 9 to 12 months after SES implantation.24 In the present study, at 6 months, the uncovered rate was 16.7%, whereas at 12 months, the uncovered rate had decreased to 8.0%. As patient age increased, the proportion of uncovered struts and protruding struts increased, and the younger patients had the high proportion of embedded neointima. Further, the neointima was thicker in the younger patients than in the 2 older groups at both 6 and 12 months. These results are consistent with those of previous studies showing that aging is associated with a decreased viability of vascular cells.25 These observations offer an explanation for the outcomes in late thrombosis which are seen in the clinic and may provide a theoretical foundation for antiplatelet therapy in patients receiving SES stents.

Previous studies have reported that increased numbers of adverse events in elderly patients may be related to an accumulation of inflammatory cells at the site of stent implantation. Monocytes, in particular, have been implicated in neointimal

### Table 2. Vascular and Stent Parameters and Lesion Type Analysis at Baseline and Follow-up

| Baseline | ≤55 (n = 46) | 55–65 (n = 39) | ≥65 (n = 34) | P<sub>1v2</sub> | P<sub>1v3</sub> | P<sub>2v3</sub> |
|----------|-------------|----------------|-------------|----------------|----------------|----------------|
| Stent area, mm<sup>2</sup> | 7.16 ± 2.21 | 6.95 ± 2.22 | 6.78 ± 2.41 | 0.047 | 0.001 | 0.172 |
| Stent length (mm) | 23.93 ± 5.56 | 24.07 ± 5.93 | 24.56 ± 6.73 | 0.91 | 0.652 | 0.746 |
| Stent diameter (mm) | 2.92 ± 0.468 | 2.85 ± 0.422 | 2.79 ± 0.51 | 0.498 | 0.236 | 0.553 |
| Min lumen diameter (mm) | 2.60 ± 0.52 | 2.59 ± 0.45 | 2.61 ± 0.44 | 0.527 | 0.667 | 0.29 |
| Max lumen diameter (mm) | 2.90 ± 0.56 | 2.86 ± 0.47 | 2.91 ± 0.47 | 0.039 | 0.79 | 0.089 |
| Min-NIH (mm) | 0.04 ± 0.06 | 0.03 ± 0.04 | 0.03 ± 0.03 | <0.001 | <0.001 | 0.014 |
| Mean-NIH (mm) | 0.12 ± 0.10 | 0.09 ± 0.07 | 0.09 ± 0.05 | <0.001 | <0.001 | 0.098 |
| Max-NIH (mm) | 0.21 ± 0.15 | 0.17 ± 0.11 | 0.18 ± 0.10 | <0.001 | <0.001 | 0.202 |

NIH = Neointimal hyperplasia.

### Discussion

Drug-eluting stents (DESs) have greatly reduced the problem of in-stent restenosis (ISR) by targeting proliferating cells.17 However, the beneficial reductions in neointima formation and ISR are accompanied by impaired endothelial regenerative and vascular healing that has created a number of new concerns.18–20 As a result of inhibition of endothelialization and delayed vascular healing to the endothelial damage, late stent thrombosis (LST, defined as 30 days up to 1 year) and very late stent thrombosis (VLST, >1 year) have emerged as major safety concerns.21,22 Although LST is a relatively infrequent complication, it is associated with a high incidence of AMI and mortality. Histopathological studies have suggested that the ratio of uncovered stent struts to the total number of stent struts is the best morphometric predictor of LST.22 Such studies further show that a ratio of uncovered struts to total struts/section of >0.3 is predictive of LST. Therefore, optimal neointimal coverage with complete endothelialization after DES implantation is required for favorable clinical outcomes.

Previous reports have shown that a higher prevalence of uncovered struts could be explained by many factors, including the underlying plaque morphology, thrombus burden, and related impairment of drug access.23 In the present study, patients aged over 65 years had the highest uncovered rate, both at 6 and 12 months of follow-up. Conversely, the patients ≤55 years old showed the highest proportion of embedded struts and had the greatest neointima area and neointima thickness. Examination of the clinical characteristics of our study groups showed no differences in coexisting diseases or drug treatments but some apparent differences in sex. Despite this, when we investigate the impact of age on neointimal characteristics according to gender, no statistical differences were noted. A tentative conclusion from these results is that age was the dominant factor for neointima formation in the present study. Previous OCT studies have reported that the incidence of uncovered struts was 8.9% to 13.3% at 6 months and 12.2% at 9 to 12 months after SES implantation.24 In the present study, at 6 months, the uncovered rate was 16.7%, whereas at 12 months, the uncovered rate had decreased to 8.0%. As patient age increased, the proportion of uncovered struts and protruding struts increased, and the younger patients had the high proportion of embedded neointima. Further, the neointima was thicker in the younger patients than in the 2 older groups at both 6 and 12 months. These results are consistent with those of previous studies showing that aging is associated with a decreased viability of vascular cells.25 These observations offer an explanation for the outcomes in late thrombosis which are seen in the clinic and may provide a theoretical foundation for antiplatelet therapy in patients receiving SES stents.

Previous studies have reported that increased numbers of adverse events in elderly patients may be related to an accumulation of inflammatory cells at the site of stent implantation. Monocytes, in particular, have been implicated in neointimal
hyperplasia and stent restenosis.26,27 Such studies also indicate that neointimal hyperplasia will progress into the formation of neoatherosclerosis. Subsequently, this may rupture and present as an acute coronary syndrome or myocardial infarction a likely mechanism contributing to LST.11,28 Excellent vascular responses to SES implantation are seen as early as 4 months after the procedure, and the neointima of the SES thickens gradually over 4 years.29–31 Studies have revealed that the time point for detecting neoatherosclerosis was approximately 14 months after implantation of a DES.32,33 In the present study, we found that elderly patients show uncovered struts coexisting with heterogeneous neointimal hyperplasia around the area of the struts. This finding is consistent with the elderly patients having a higher incidence of acute thrombosis and LST. This suggests that for elderly patients with implanted SESs, more attention should be given not only to neointimal delay but also neointimal hyperplasia and the formation of neoatherosclerosis after stent placement. Moreover, while differing types of plaque in the treated lesions could impact stent coverage no significant differences in plaque distribution ($P = 0.198$) were observed in the present study, and we intend on further investigating this point in future studies.

The present study showed that in the youngest patient group, neointimal growth was greater in the first 6 months after stent implantation and slowed in the subsequent 6–12-month period. In contrast to this, the elderly group exhibited slow growth in the first 6 months and a relatively higher growth rate in months 6 to 12. Although the present study presents only observations, it is tempting to speculate that age impacts the mechanisms underlying endothelial cell proliferation, which consistent with previous study.34 Also supporting this hypothesis are angiography-based reports of elderly patients having a higher rate and degree of endothelial cell hyperplasia after long-term follow-up.35 Further, clinical studies have suggested that there is a “late catch-up phenomenon” in some patients after DES implantation.35 Consistent with this, we also observed what could be termed a “catch-up phenomenon” in that the neointima in the early stages (0–6 months) of the oldest patient
group showed a high rate of noncoverage and a low rate of neointimal proliferation, whereas in the 6- to 12-month period, this appeared to change to a higher rate of neointimal proliferation with a suggestion of neointimal hyperplasia perhaps progressing to neoatherosclerosis. 

Although further studies are needed to verify the above hypothesis, the present study suggests that in older patients undergoing stent implantation, more emphasis needs to be placed on early antithrombotic treatment. However, after intimal coverage has been achieved, attention should be shifted to excessive neointimal proliferation and prevention of the development of neoatherosclerosis.

**LIMITATIONS**

Despite a number of interesting observations, there are several limitations in our study. We report a single-center experience, possibly limiting the general applicability of our results. The number of patient was also relatively small, making it difficult to assess any contributions of comorbidities and ongoing treatments/interventions. Finally, it should be noted that strut coverage, as assessed by intravascular OCT, must be interpreted with caution as it does not provide resolution to the single-endothelial cell level nor does it provide functional information. Nevertheless, our data indicate a significant effect of age on stent maturation/remodeling, and this finding should stimulate further detailed studies.

### TABLE 3. Impact of Age on Neointimal Characteristics According to Gender

|                | Age ≤ 55 (n = 37) | Age >55–≤65 (n = 19) | Age >65 (n = 18) | P-Value | P1v2 | P1v3 | P2v3 |
|----------------|-------------------|----------------------|-----------------|---------|------|------|------|
| Struts, n      | 6316              | 3538                 | 2720            |         |      |      |      |
| Uncovered struts, n (%) | 272 (4.3)        | 136 (3.8)            | 146 (5.4)       | 0.012   | 0.269| 0.028| 0.004|
| Malapposition, n (%) | 71 (1.1)         | 92 (2.6)             | 22 (0.8)        | <0.001  | <0.001| <0.001| <0.001|
| Protruding, n (%) | 1405 (22.2)       | 1130 (31.9)          | 739 (27.2)      |         |      |      |      |
| Embedded, n (%)  | 4840 (76.6)       | 2316 (65.5)          | 1959 (72.0)     |         |      |      |      |
| NIH area (mm²)  | 0.81 (0.57,1.24)  | 0.6 (0.40,0.93)      | 0.72 (0.50,1.09)| <0.001  | <0.001| <0.001| 0.001|
| Mean NIH thickness (mm) | 0.09 (0.06,0.14) | 0.07 (0.05,0.11)    | 0.08 (0.06,0.11)| <0.001  | <0.001| 0.001| <0.001|

Females at 12 months

|                | Struts, n | 1061 | 2874 | 1890 |
|----------------|-----------|------|------|------|
| Uncovered struts, n (%) | 14 (1.3) | 76 (2.6) | 80 (4.2) | <0.001| <0.001| <0.001| <0.001|
| Malapposition, n (%) | 25 (2.4) | 35 (1.2) | 31 (1.6) | <0.001| <0.001| 0.017| <0.001|
| Protruding, n (%) | 247 (23.3) | 1043 (36.3) | 523 (27.7) | <0.001| <0.001| <0.001| <0.001|
| Embedded, n (%) | 789 (74.4) | 1796 (62.5) | 1336 (70.7) | <0.001| <0.001| <0.001| <0.001|
| NIH area (mm²) | 1.08 (0.78,1.56) | 0.61 (0.42,0.91) | 0.63 (0.43,0.85) | <0.001| <0.001| <0.001| 0.487|
| Mean NIH thickness (mm) | 0.12 (0.09,0.18) | 0.07 (0.05,0.10) | 0.07 (0.05,0.10) | <0.001| <0.001| <0.001| 0.625|

NIH = Neointimal hyperplasia.
REFERENCES

1. Mozaffarian D, Benjamin EJ, Go AS, et al. Heart disease and stroke statistics—2015 update: a report from the American Heart Association. Circulation. 2014;131:e29–e322.

2. Williams MA, Fleg JL, Ades PA, et al. Secondary prevention of coronary heart disease in the elderly (with emphasis on patients > or =75 years of age): an American Heart Association scientific statement from the Council on Clinical Cardiology Subcommittee on Exercise, Cardiac Rehabilitation. Circulation. 2002;105:1735–1743.

3. Batchelor WB, Anstrom KJ, Mulhauser LH, et al. Contemporary outcome trends in the elderly undergoing percutaneous coronary interventions: results in 7,472 octogenarians. National Cardiovascular Network Collaboration. J Am Coll Cardiol. 2000;36:723–730.

4. De Gregorio J, Kobayashi Y, Alibero R, et al. Coronary artery stenting in the elderly: short-term outcome and long-term angiographic and clinical follow-up. J Am Coll Cardiol. 1998;32:577–583.

5. Klein LW, Block P, Brindis RG, et al. Percutaneous coronary interventions in octogenarians in the American College of Cardiology-National Cardiovascular Data Registry: development of a nomogram predictive of in-hospital mortality. J Am Coll Cardiol. 2002;40:394–402.

6. Cohen H, Williams DO, Holmes DR, et al. Impact of age on procedural and 1-year outcome in percutaneous transluminal coronary angioplasty: a report from the NHLBI Dynamic Registry. Am Heart J. 2003;146:513–519.

7. Abizaid AS, Mintz GS, Abizaid A, et al. Influence of patient age on acute and late clinical outcomes following Palmaz-Schatz coronary stent implantation. Am J Cardiol. 2000;85:338–343.

8. Xu B, Li J, Yang Y, et al. Age-based clinical and angiographic outcomes after sirolimus-eluting stent implantation in patients with coronary artery disease. Chin Med J (Engl). 2007;120:447–451.

9. Muñoz IC, Alonso JJ, Duran JM, et al. Coronary stent implantation in patients older than 75 years of age: clinical profile and initial and long-term (3 years) outcome. Am Heart J. 2002;143:620–626.

10. Takano M, Inami S, Jang I-K, et al. Evaluation by optical coherence tomography of neointimal coverage of sirolimus-eluting stent three months after implantation. Am J Cardiol. 2007;99:1033–1038.

11. Hou J, Qi H, Zhang M, et al. Development of lipid-rich plaque inside bare metal stent: possible mechanism of late stent thrombosis? An optical coherence tomography study. Heart. 2010;96:1187–1190.

12. Jia H, Abthian F, Aguirre AD, et al. In vivo diagnosis of plaque erosion and calcified nodule in patients with acute coronary syndrome by intravascular optical coherence tomography. J Am Coll Cardiol. 2013;62:1748–1758.

13. Finn AV, Joner M, Nakazawa G, et al. Pathological correlates of late drug-eluting stent thrombosis: strut coverage as a marker of endothelialization. Circulation. 2007;115:2435–2441.

14. Mehanna EA, Attizzani GF, Kyonon H, et al. Assessment of coronary stent by optical coherence tomography, methodology and definitions. Int J Cardiovasc Imaging. 2011;27:259–269.

15. Regar E, Co-chair WC, Akasaka T, et al. consensus standards for acquisition, measurement, and reporting of intravascular optical coherence tomography studies: a report from the international working group for intravascular optical coherence tomography standardization and validation. J Am Coll Cardiol. 2012;59:1058–1072.

16. Barlis P, Dimopoulou K, Tanigawa J, et al. Quantitative analysis of intracoronary optical coherence tomography measurements of stent strut apposition and tissue coverage. Int J Cardiovasc Imaging. 2010;14:151–156.

17. Kastrati A, Mehilli J, Pache J, et al. Analysis of 14 trials comparing sirolimus-eluting stents with bare-metal stents. N Engl J Med. 2007;356:1030–1039.

18. Pfisterer M, Brunner-La Rocca HP, Buser PT, et al. Late clinical events after clopidogrel discontinuation may limit the benefit of drug-eluting stents: an observational study of drug-eluting versus bare-metal stents. J Am Coll Cardiol. 2006;48:2584–2591.

19. Nakazawa G, Vorpahl M, Finn AV, et al. One step forward and two steps back with drug-eluting-stents: from preventing restenosis to causing late thrombosis and nouveau atherosclerosis. JACC Cardiovasc Imaging. 2009;2:625–628.

20. Taniguchi Y, Otake H, Shanke T, et al. Two-year vessel healing after everolimus-eluting stent implantation: serial assessment by optical coherence tomography. J Cardiol. 2015;65:298–304.

21. Finn AV, Nakazawa G, Joner M, et al. Vascular responses to drug eluting stents importance of delayed healing. Arterioscler Thromb Vasc Biol. 2007;27:1500–1510.

22. Ong ATL, McFadden EP, Regar E, et al. Late angiographic stent thrombosis (LAST) events with drug-eluting stents. J Am Coll Cardiol. 2005;45:2088–2092.

23. Hwang C-W, Levin AD, Jonas M, et al. Thrombosis modulates arterial drug distribution for drug-eluting stents. Circulation. 2005;111:1619–1626.

24. Kim J-S, Hong M-K, Shin D-H, et al. Quantitative and qualitative changes in DES-related neointimal tissue based on serial OCT. JACC Cardiovasc Imaging. 2012;5:1147–1155.

25. Torella D, Leosco D, Indolfi C, et al. Aging exacerbates negative remodeling and impairs endothelial regeneration after balloon injury. Am J Physiol Heart Circ Physiol. 2004;287:H2850–H2860.

26. Eghbahieh SDD, Chowdhary P, Muto A, et al. Age-related neointimal hyperplasia is associated with monocyte infiltration after balloon angioplasty. J Gerontol A Biol Sci Med Sci. 2012;67:109–117.

27. Spinetti G, Wang M, Monticone R, et al. Rat aortic MCP-1 and its receptor CCR2 increase with age and alter vascular smooth muscle cell function. Arterioscler Thromb Vasc Biol. 2004;24:1397–1402.

28. Finn AV, Otsuka F. Neointimal hyperplasia: a culprit in very late stent thrombosis. Circ Cardiovasc Interv. 2012;5:6–9.

29. Nakano M, Virmani R. Histopathology of vascular response to drug-eluting stents: an insight from human autopsy into daily practice. Cardiovasc Interv Ther. 2015;30:1–11.

30. Attizzani GF, Bezerra HG, Ormiston J, et al. Serial assessment by optical coherence tomography of neointimal hyperplasia after implantation of an absorbable-coating Sirolimus-Eluting stent (from the first-in-human DESSOLVE I trial). Am J Cardiol Elsevier Inc. 2013;112:1557–1564.

31. Takano M, Yamamoto M, Mizuno M, et al. Late vascular responses after implantation of an absorbable-coating Sirolimus-Eluting stent (from the first-in-human DESSOLVE I trial). Am J Cardiol Elsevier Inc. 2013;112:1557–1564.

32. Yonetsu T, Kato K, Kim S-J, et al. Predictors for neoatherosclerosis: a retrospective observational study from the optical coherence tomography registry. Circ Cardiovasc Imaging. 2012;5:476–483.

33. Yonetsu T, Kato K, Kim S-J, et al. Predictors for neoatherosclerosis: a retrospective observational study from the optical coherence tomography registry. Circ Cardiovasc Imaging. 2012;5:476–483.

34. Stettler D, Wandel S, Allemand S, et al. Outcomes associated with drug-eluting and bare-metal stents: a collaborative network meta-analysis. Lancet. 2007;370:937–948.

35. Armstrong EJ, Xing L, Zhang J, et al. Association between leukocyte telomere length and drug-eluting stent strut coverage by optical coherence tomography. J Am Coll Cardiol. 2012;59:2218–2219.

36. Park KW, Kim C-H, Lee H-Y, et al. Does “late catch-up” exist in drug-eluting stents: insights from a serial quantitative coronary angiography analysis of sirolimus versus paclitaxel-eluting stents. Am Heart J. 2010;159:446.e3–453.e3.

37. Nakano M, Otsuka F, Virmani R. Letter by Nakano et al regarding “intracoronary optical coherence tomography of early and late vascular responses after implantation of an absorbable-coating Sirolimus-Eluting stent” (from the first-in-human DESSOLVE I trial). Am J Cardiol Elsevier Inc. 2013;112:e954author reply e955.

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