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Research paper

The angiography-guided spot versus entire stenting in patients with long coronary lesions trial: Study design and rationale for a randomized controlled trial protocol

Ju Yeol Baek [a], Seung Woon Rha [b,*], Byoung Geol Choi [b], Cheol Ung Choi [b], Kyoung-Ha Park [c], Byung Hee Hwang [d], Seung-Jin Lee [e], Young Keun Ahn [f], Jae Woong Choi [g], In-Ho Chae [h], Won Ho Choi [i], Young-Hyo Lim [j], Ji Hoon Ahn [k], Woong Gil Choi [l]

[a] Division of Cardiology, Department of Internal Medicine, Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul, Republic of Korea
[b] Division of Cardiology, Department of Internal Medicine, Korea University Guro Hospital, Seoul, Republic of Korea
[c] Division of Cardiology, Department of Internal Medicine, Hallym University Medical Center, Hangang Sacred Heart Hospital, Seoul, Republic of Korea
[d] Department of Internal Medicine, St. Paul's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea
[e] Department of Internal Medicine, Soonchunhyang University Medical College, Cheonan, Republic of Korea
[f] Department of Cardiovascular Medicine, Chonnam National University Medical School, Gwangju, Republic of Korea
[g] Division of Cardiology, Department of Internal Medicine, Eulji General Hospital, Eulji Medical College, Seoul, Republic of Korea
[h] Department of Internal Medicine, Seoul National University Bundang Hospital, Gyeonggi, Republic of Korea
[i] Division of Cardiology, Department of Internal Medicine, H PLUS Yangji Hospital, Seoul, Republic of Korea
[j] Department of Internal Medicine, Hanyang University College of Medicine, Seoul, Republic of Korea
[k] Division of Cardiology, Department of Internal Medicine, Soonchunhyang University Gumi Hospital, Gumi, Republic of Korea
[l] Division of Cardiology, Konkuk University Chungju Hospital, Chungju, Republic of Korea

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ABSTRACT

Background: /Purpose: Long-stenting, even with a second-generation drug-eluting stent (DES), is an independent predictor of restenosis and stent thrombosis in patients with long coronary lesions. Spot-stenting, i.e., selective stenting of only the most severe stenotic segments of a long lesion, may be an alternative to a DES. The purpose of this study is to compare the one-year clinical outcomes of patients with spot versus entire stenting in long coronary lesions using a second-generation DES.

Method: This study is a randomized, prospective, multi-center trial comparing long-term clinical outcomes of angiography-guided spot versus entire stenting in patients with long coronary lesions (≥25 mm in length). The primary endpoint is target vessel failure (TVF) at 12 months, a composite of cardiac death, target vessel-related myocardial infarction, and target vessel revascularization (TVR). A total of 470 patients are enrolled for this study according to sample size calculations. This study will be conducted to evaluate the non-inferiority of spot stenting compared to entire stenting with zotarolimus-eluting stents (ZES).

Results: This study is designed to evaluate the clinical impact of spot-stenting with ZESs for TVF due to possible edge restenosis or non-target lesion revascularization. Theoretically, spot-stenting may decrease the risk of TVR and the extent of endothelial dysfunction.

Conclusion: This SPOT trial will provide clinical insight into spot-stenting with a current second-generation DES as a new strategy for long coronary lesions.

1. Introduction

Drug-eluting stents (DESs) reduce angiographic restenosis and the need for repeat revascularization compared to bare-metal stents in patients with diffuse long lesions undergoing percutaneous coronary intervention (PCI) [1–4]. Also, multiple overlapping DESs that fully cover diffuse long lesions have been safe and effective [5–7]. However, the incidence of late-stent thrombosis is increased with long DESs compared to bare-metal stents, probably due to chronic inflammation and delayed healing of the arterial wall in long lesions. Others have

* Corresponding author. Cardiovascular Center, Korea University Guro Hospital, 148, Gurodong-Ro, Guro-gu, Seoul, 08308, Republic of Korea
E-mail address: megaroad1000@gmail.com (S.W. Rha).

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reported an increased incidence of major adverse cardiac events using multiple overlapping DESs [8,9]. Although the use of overlapping stents with second-generation DESs for long lesions can be effective and safer than first-generation DESs, for extremely long stenting, high rates of target lesion revascularization (TLR) and restenosis have been reported with frequent periprocedural myocardial infarctions (MI) up to 23% [10–13].

Spot-stenting to cover only the maximally stenotic segment may overcome the limitations of long stenting in the clinical setting. Demosthenes et al. demonstrated that it is an appropriate therapeutic alternative to diffuse long lesions using first-generation DESs with favorable clinical outcomes [14–16]. Thus, this study will be a clinical comparison of angiography-guided entire stenting with all lesion coverage versus angiography-guided spot-stenting with selective coverage of short segments using second-generation DESs.

2. Method

2.1. Study design

We hypothesize that the 12-month target vessel failure (TVF) of angiography-guided spot-stenting will be non-inferior to that of angiography-guided entire stenting in patients with long coronary lesions. To test this hypothesis, a prospective, randomized, multi-center trial will be conducted to compare the 12-month target vessel failure of spot versus entire stenting with zotarolimus–eluting stents (ZES) for the long lesion length (≥25 mm). This trial protocol is registered with the Clinical Research Information Service (CRiS) of South Korea (trial registration number: KCT0003082). A brief flow chart of the entire study is presented in Fig. 1.

2.2. Study population

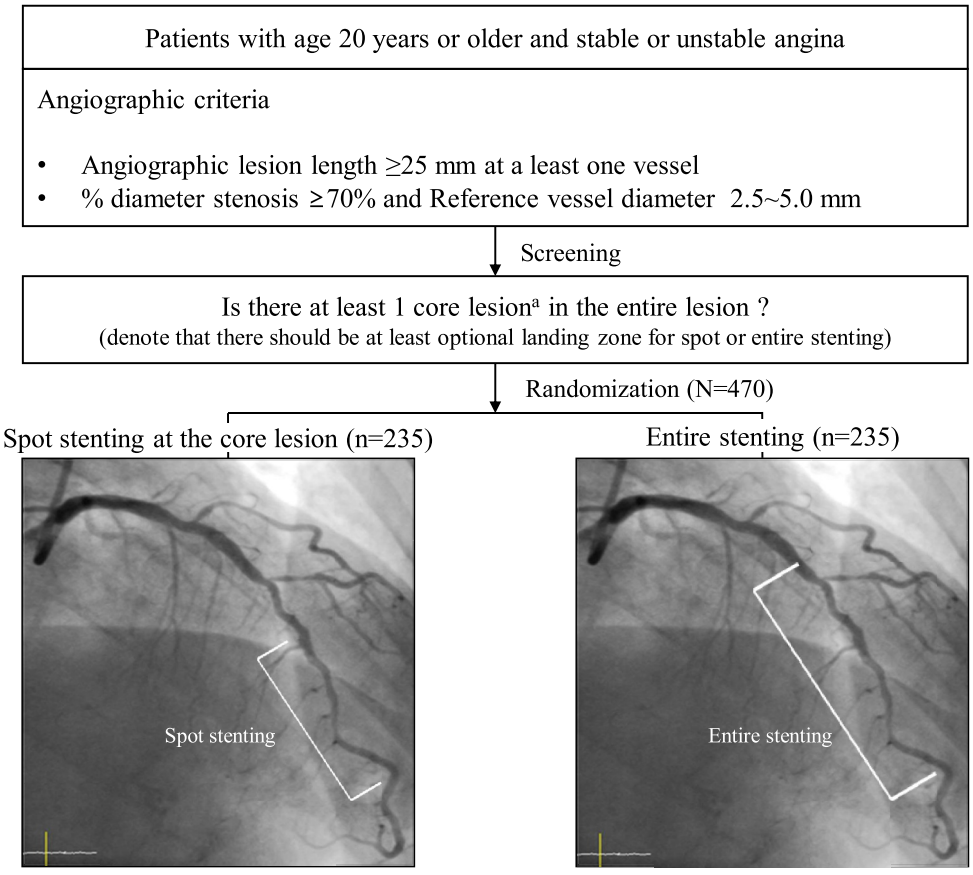
The study population comprises 470 patients enrolled at 12 centers in Korea. Patients who present to the cardiac catheterization laboratory for non-emergent PCIs are eligible to participate in this study. Detailed inclusion and exclusion criteria are listed in Table 1.

2.3. Ethics and informed consent

The study protocol will be approved by the institutional review board at each participating institution and written informed consent will be obtained from all patients. This study will be conducted according to the provisions of the Declaration of Helsinki and the International Conference on Harmonization of Good Clinical Practice. Prior to participation, the investigator will inform the patients of the scope and purpose, rights, duties, and possible risks and benefits of participation. An identification code and randomization number will be used for patient identification to maintain patient confidentiality. Patients may voluntarily terminate their participation in this study at any time.

2.4. Randomization and procedures

Patients who undergo coronary angiography for stable or unstable angina are eligible for enrollment in this trial if they meet the enrollment criteria. Patients who visit the hospital for chest pain and undergo coronary angiography, showing significant stenosis corresponding to at least 70% or greater in one vessel and with lesions 25 mm or longer, with core lesions, will be selected and randomized. Using an interactive web-based response system, patients who fulfill all of the inclusion criteria and none of the exclusion criteria will be randomly assigned at 1:1 ratio



[a] Refers to the definition of core lesion at figure 2.

Fig. 1. Study flow chart.

Table 1
Inclusion and exclusion criteria.

Inclusion criteria
1. Age 20 or older. 2. Patients with stable or unstable angina. 3. Lesion length of ≥25 mm based on angiographic estimation. 4. Significant coronary artery stenosis in *de novo* lesions (≥70% estimated by QCA) indicated for coronary revascularization with stent implantation and reference vessel diameter of 2.5–5.0 mm by lesion assessment for coronary revascularization with stent implantation. 5. Patients with core lesions, which are indicated for spot-stenting (core lesions are defined in Method).
Exclusion criteria
• Contraindications for antiplatelet agents. • Left main disease (diameter stenosis of ≥50% based on visual estimates and graft vessel disease). • Recent history of hematologic disease, leukocyte count of ≤3000/mm^3 or platelets ≤100,000/mm^3 • Hepatic dysfunction with AST or ALT levels of >3 times the upper normal limit. • Serious non-cardiac comorbid disease with a life expectancy of < one year. • Acute myocardial infarction within 48 h. • Inability to follow the protocol.

AST; aspartate aminotransferase, ALT; alanine aminotransferase.

to receive either spot or entire stenting immediately after pre-PCI angiography. Patients enrolled in this study will be eligible for the final intention-to-treat analysis at the time of randomization. The definition of core lesions as a precondition for randomization is below.

2.5. Definition of a core lesion

A core lesion is an arbitrary definition used to select subjects. The presence of a core lesion will be decided according to lesion characteristics estimated visually in coronary angiography prior to randomization. A core lesion is a virtual small segment included in the whole range of arteriosclerotic lesions within the target vessel. These are the same segments or landing zones for spot-stenting (Fig. 2). Also, this evaluation will enable the investigator to determine if the lesions are appropriate for this study. Additionally, the selection of a segment for spot-stenting based on the definition of a core lesion will exclude complex and diffuse lesions contraindicated for spot-stenting. Core lesions are defined as follow:

1) Lesions with maximal percent diameter stenosis (%DS) ≥ 70%, differentiated from the surrounding segments. 2) Core lesions must show a landing zone, appropriate for spot-stenting. If the lesion meets the criteria defined above, the investigator will initiate randomization.

In the group of patients indicated for angiography-guided spot stenting, short-stenting will be conducted at the core lesion. Following implantation of the stent, high-pressure post-dilation is optional to achieve optimal results defined as angiographic residual diameter of <30% and the absence of angiographically detected dissection.

In the group of patients with entire stenting under angiography guidance, stents of adequate size will be implanted to cover the whole lesion up to the segment defined as the atheroma-free area or with a stenosis of ≤30% in diameter. If the target vessel has a long lesion containing multiple core lesions, multiple spot-stenting or entire stenting with total lesion coverage can be conducted. No intravascular ultrasound will be allowed before or during PCI after randomization. DES implantation will be performed according to the standard techniques. For all PCI, the second-generation ZES (Onyx®, Medtronic Vascular, Korea) will be used for both groups to create identical stent effects. If a lesion cannot be covered with a stent, overlapping stents will be used. If a patient has more than one target vessel, all the vessels will be treated according to the standard protocols, except for the vessel under consideration for inclusion in this study. Prior to PCI, all patients will receive at least 75 mg of aspirin. A loading dose of 300 or 600 mg clopidogrel will be administered at least 12 h pre-PCI. However, if the loading dose of clopidogrel is not administered 12 h in advance, the patient will receive a 600 mg loading dose of clopidogrel in the catheterization laboratory prior to PCI. Unfractionated heparin will be administered to maintain an activated clotting time of >250 s. The use of glycoprotein IIb/IIIa inhibitors will be left to the investigator's discretion. After stent implantation, 100 mg daily aspirin will be prescribed indefinitely. The duration of clopidogrel administration (at a dose of 75 mg daily) will be at least 12 months following stent implantation. Lipid-lowering therapy with statins is additionally recommended for all patients after the procedure.

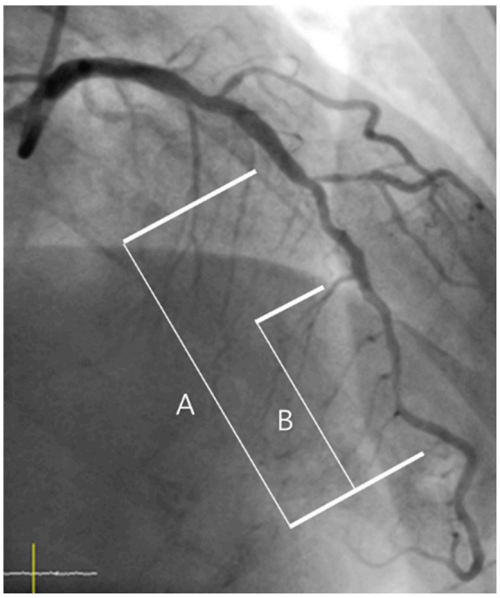


Fig. 2. Coronary angiogram and a core lesion. Core lesions are an arbitrary designation used to identify patients eligible for this study. (A) Segment with total lesion for entire stenting. (B) Core lesion for spot-stenting; Angiographic findings should show % diameter stenosis of ≥70% and reference diameter of ≥2.5 mm. There should be appropriate landing zones for the proximal and distal edges of the spot-stent.

2.6. Endpoints and follow-up

The primary endpoint is the occurrence of TVF, a composite of cardiac death and target vessel-related myocardial infarction (TV-MI), including Q wave, non-Q wave myocardial infarction (MI), and ischemia-driven target vessel revascularization (TVR), one year after the procedure (Table 2). Clinical events are defined according to the Academic Research Consortium criteria [17,18]. All deaths are considered cardiac deaths unless a definite non-cardiac cause is established. MI is defined as the presence of clinical symptoms, electrocardiographic changes, or abnormal imaging findings of MI, combined with increase in creatine kinase myocardial band fraction above the upper normal limit or an increase in troponin-T/troponin-I greater than the 99th percentile of the upper normal limit, unrelated to an interventional procedure during the initial hospitalization period. TV-MI is defined by the presence of randomized stented lesions in the MI-related target coronary artery. In the presence of a TV-MI, angiographic, echocardiographic, or electrocardiographic findings suggestive of TV-MI onset will be required to demonstrate that the coronary arteries with the stented lesions supply the corresponding territory of the infarcted myocardium. Stent thrombosis (ST) is defined according to the Academic Research Consortium (ARC) criteria based on timing, as well as diagnostic certainty. We will select "definite" or "probable" ST as the endpoints [19,20]. Ischemia-driven TVR is defined as a repeat PCI or bypass surgery of target vessels with either (1) ischemic symptoms or a positive stress test and (2) angiographic diameter stenosis of ≥70% based on quantitative

Table 2
Primary and secondary endpoints.

Primary endpoints
• A composite of cardiac death, target vessel-related myocardial infarction (TV-MI) and ischemic -driven target vessel revascularization (TVR) at 1-year follow up after the procedure.
Secondary endpoints
• All-cause death • Target lesion revascularization (TLR) • Non-target lesion revascularization (non-TLR) • Edge restenosis • Dissection • Any myocardial infarction • Periprocedural myocardial infarction.

coronary angiographic analysis. Routine angiographic follow-up is not recommended to reduce the bias from the oculo-stenotic reflex.

The secondary endpoint is pre-specified to assess the occurrence of all-cause death, TLR, non-target lesion revascularization (non-TLR), edge restenosis, dissection, any MI, and periprocedural myocardial infarction. TLR is defined as repeat PCI or bypass graft for restenosis at the lesion treated by randomization or within 5 mm of the PCI segment. Non-TLR is defined as revascularization of segments in the target vessel 5 mm away from the previous stent. Periprocedural myocardial infarction is defined by the third universal definition of myocardial infarction [19]. It is diagnosed by elevation in troponin-I or T values $>$ 5 x the 99th percentile upper reference limit in patients with normal baseline values or a rise in troponin values of $>$20% of the baseline value with either symptoms or other ischemic evidence after PCI. Edge restenosis is defined using the Mehran classification. Based on the coronary angiographies performed following the index PCI and during follow-up, the minimal lumen diameter and %DS will be measured within the stent (in-stent) and within 5 mm of the proximal and distal edges of the stent. Restenosis is defined as %DS $>$ 70% at the follow-up examination [21].

Post-procedural clinical assessment, including evaluation of cardiac symptoms and compliance with medications, will be performed in-hospital and at one, six, nine, and 12 months after the procedure during a visit to a physician's office. During follow-up, data will be collected and entered into computer database by a specialist from a clinical data management center. Patients with suspicious cardiac complaints will receive comprehensive clinical, electrocardiographic, and laboratory evaluations. When events occur at another hospital, the corresponding medical records (i.e., the discharge summaries, angiograms, and laboratory tests) will be requested by the investigators responsible for this study's participants. Patients will be followed for one year to monitor the occurrence of TVF and the secondary events. All events will be adjudicated and classified by the clinical event adjudication committee blinded to the treatment group information. Complications will be treated accordingly and reported to the Data Safety Monitoring Board.

2.7. Angiographic analysis

Quantitative coronary angiography will be performed using an off-line system (CASS system, Pie Medical Instruments, Maastricht, The Netherlands) before and after stent implantation by analysts blinded to the patient and treatment assignment (spot-stenting vs. entire stenting) in an independent core laboratory. Using the guiding catheter for magnification-calibration, the diameters of the reference vessel (the average of the proximal and distal reference lumen diameters) and the minimal luminal diameter will be measured before and after stenting from diastolic frames in single-matched view showing the smallest minimal luminal diameter.

2.8. Sample size calculation and statistical analysis

The primary analysis is a non-inferiority comparison of spot versus entire stenting with respect to the primary endpoint. Calculation of the sample size will be based on one-sided test. Based on previous studies, we assume that the overall incidence of TVF, including cardiac deaths, TV-MI, or ischemia-driven TVR, will be 7% at the one-year follow-up in the spot-stenting arm and in the entire-stenting arm. The non-inferiority margin will be 6% [16,22]. In the non-inferiority design, 235 patients are needed for each arm, assuming a one-sided alpha of 0.05, a statistical power of 80%, and an estimated dropout rate of 5%. The final results will be evaluated with intention-to-treat analysis.

The cumulative incidence of TVF as the primary endpoint at 12 months will be calculated using the Kaplan–Meier estimates. Comparison between the two groups will be performed using the log-rank test and the Cox proportional-hazards model. For variables other than clinical outcomes, comparisons between the two groups will be conducted using $\chi 2$ tests or Fisher's exact test for categorical variables and the Student's t-test or the Mann–Whitney test for continuous variables. A p-value < 0.05 is statistically significant.

2.9. Trial organization

This trial has been designed by the principal investigator and the executive committee. Besides the Executive Committee, a Steering Committee, a Data Safety Monitoring Board, and a Clinical Event Adjudication Committee will be involved in the execution, administration, and supervision of this trial. Study coordination, data management, and site management services will be performed at the Cardiovascular Center, Korea University Guro Hospital, Seoul, Korea. Designated trial monitors will review the investigational data at appropriate intervals for accuracy and completeness and ensure compliance with the protocol.

2.10. Executive Committee

The Executive Committee will include a chairperson and three members selected from the investigators. The committee is responsible for overseeing the administrative progress of this study and will approve the final trial design and protocol issued to the Data and Safety Monitoring Board (DSMB) and the clinical sites. This committee will also be responsible for reviewing the final results, determining the methods of presentation and publication, and selection of secondary projects and publications by members of the Steering Committee. The Executive Committee also holds the right to modify or discontinue this study prematurely based on DSMB recommendations.

2.11. Data Safety Monitoring Board

The frequency of DSMB meetings will be determined prior this study's commencement. Additionally, the DSMB may schedule a meeting at any time if a safety issue is suspected. The DSMB is responsible for issuing recommendations regarding safety or compliance issues throughout this study and may recommend to the Executive Committee appropriate modification or cessation of this study. However, all final decisions regarding study modifications are with the Executive Committee. All cumulative safety data will be reported to the DSMB and reviewed on an ongoing basis throughout the enrollment and follow-ups to ensure patient safety. Prior to the first review of the data, the DSMB charter will be drafted. The DSMB will develop a consensus understanding of all trial endpoints and definitions used in the event of adjudication. All DSMB reports will remain strictly confidential but will be made available to the regulatory body upon request.

2.12. Clinical Event Adjudication Committee

The Clinical Event Adjudication Committee (CEAC) is comprised of

three interventional and non-interventional cardiologists not engaged in this study. The CEAC is responsible for the development of specific criteria for the categorization of clinical events and clinical endpoints in this study, based on this study's protocol. At the onset of this trial, the CEAC will establish explicit rules outlining the minimum amount of data required and the algorithm to classify a clinical event. All members of the CEAC will be blinded to the primary results of this trial. The CEAC will meet regularly to review and adjudicate all clinical events. The CEAC will also review and rule on all deaths that occur throughout this trial.

2.13. Data coordination and site management

Data coordination and site management services will be provided at the Cardiovascular Center of the Korea University Guro Hospital.

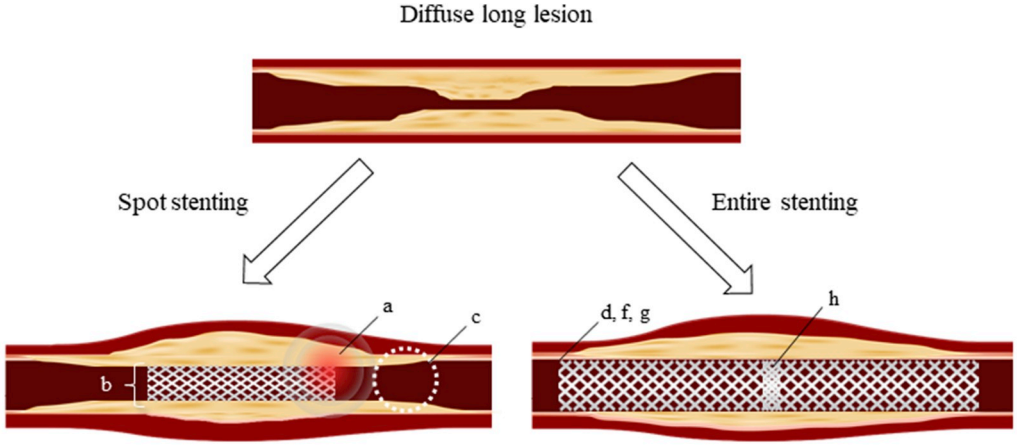
3. Discussion

This SPOT trial is a randomized, prospective, multi-center trial comparing 12-month TVF of angiography-guided spot versus entire stenting in patients with long coronary lesions. It is designed to suggest clinical implications of this study and generate hypotheses as follow: 1) Overall, the incidence of target vessel failure in spot-stenting, the selective implantation of a second-generation DES at the most stenosed lesion in patients with diffuse long lesions, will not be different from those undergoing entire stenting. 2) Without significant clinical differences, spot-stenting will reduce stent length to prevent stent thrombosis and TLR with increased cost-effectiveness or reduced stent numbers. 3) Additionally, to avoid excessive stent dilation on the residual plaque, investigators may prefer smaller stents in the group undergoing spot stenting. This is because stents are targeted to cover the most stenosed segment, which has a smaller reference diameter of the segment surrounded by mild residual plaque, than the landing zone of the entire stenting (Fig. 3).

Conversely, spot-stenting to address residual plaque burden has a concern of more distal or proximal edge response to injury involving residual stenosed plaque. It may cause edge restenosis proximal or distal to the landing zone. Edge restenosis can be predicted by the plaque burden associated with the post-stenting reference segment [23]. The SIRIUS trial findings showed that larger edge stent area/reference minimum lumen areas were associated with edge restenosis [24]. Also, residual stenosis suggests that an area beyond the spot-stenting zone (non-target lesions) may trigger disease progression observed during long-term follow-up. In contrast, additional benefits of spot-stenting could be anticipated. First, shorter DES lengths, theoretically, may reduce the risk of ST or TVR. Second, the extent of endothelial dysfunction may be shortened by spot-stenting and contribute to the physiological maintenance of vasomotor function [25], in addition to obviating the need for additional stent implantation. The stent numbers and procedural time are reduced, potentially decreasing the risk of TLR.

Entire stenting with long or multiple stents would lead to a relatively higher risk of ST compared to spot-stenting. When using multiple or longer stents for complex interventions, PCI can increase the risk of ST regardless of the conventional ST risk. Recent reports showed an association between stent length and increased clinical risk of ST after first-generation DES implantation [26,27]. Stent length of >31.5 mm is a threshold for ST in first-generation DES-treated patients [28]. Additionally, overlapping implantation of DESs for the treatment of long, native coronary lesions has been associated with increased TLR and periprocedural myocardial necrosis [12,13]. However, this fault associated with entire stenting would be offset by the use of second-generation DESs. In previous studies, the rate of major adverse cardiac events in patients treated with second-generation DESs for long lesions was lower than in patients treated with first-generation DESs. Recent reports demonstrated that the use of second-generation DESs for long lesions reduced the incidence of definitive ST [10]. Additionally, newer generation DESs, not associated with TVR and ST in patients with diffuse long lesions, have undermined the clinical impact of stent length in first-generation DESs [29].

To the best of our knowledge, few studies have directly compared the



	Arguments Pro	Arguments Contra
Spot-stenting	Convenient stent delivery	More distal edge response[a]
	Cost effective (fewer stent used)	Stent undersizing and underexpansion[b]
	Fewer clinical events ?	Non target lesion events due to uncovered lesion[c]
Entire-stenting	Complete coverage of target lesion[d]	Long stenting (with more stents)[h]
	Less edge response[f]	Long stent-related events
	More stent optimization[g]	Delivery problems

Fig. 3. Hypotheses and clinical issues of this SPOT trial.

clinical outcomes with different stent lengths using randomization for similar long lesions. Most studies only reported the clinical effects of long-stenting on diffuse long lesions associated with disease severity. Thus, this study was designed to demonstrate the efficacy and safety of spot-stenting when used with second-generation DESs in diffuse long lesions compared to entire stenting. This study will have some limitations. First, the spot-stenting method is arbitrary. Additionally, the selection of a landing zone for spot-stenting depends on the individual procedure adopted by each investigator. Second, the non-inferiority margin of the primary clinical endpoint is relatively large.

4. Authorship responsibility and contributions

- ***Conception and Design***

SW Rha, JY Baek, BG Choi, Choi CU.

- ***Analysis and Interpretation of Data***

JY Baek, BG Choi, KH Park, BH Hwang, WH Choi, YH Lim, JH Ahn, WG Choi.

- ***Acquired the data and assisting the data handling and analysis***

BG Choi, SJ Lee, YK Ahn, JW Choi.

- ***Drafting of the Manuscript or Revising it Critically for Important Intellectual Content***

JY Baek, BG Choi.

- ***Final Approval of the Manuscript Submitted***

SW Rha, IH Chae, YK Ahn.

5. Trial status

Trial registration number: KCT0003082.

Trial register: Clinical Research Information Service (CRiS) in South Korea.

Final protocol version number and date: Version 1–2, January 16, 2019.

Approximate recruitment completion date: December 30, 2021.

6. Supplement

6.1. Participating centers

- Division of Cardiology, Department of Internal Medicine, Korea University Guro Hospital, Seoul, Korea.
- Division of Cardiology, Department of Internal Medicine, Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul, Korea.
- Division of Cardiology, Department of Internal Medicine, Hallym University Medical Center, Hangang Sacred Heart Hospital, Seoul, Korea.
- Department of Internal Medicine, St. Paul's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea.
- Department of Internal Medicine, Soonchunhyang University Medical College, Cheonan, Korea
- Department of Cardiovascular Medicine, Chonnam National University Medical School, Gwangju, Korea.
- Division of Cardiology, Department of Internal Medicine, Eulji General Hospital, Eulji Medical College, Seoul, Korea.
- Department of Internal Medicine, Seoul National University Bundang Hospital, Gyeonggi, Korea.
- Division of Cardiology, Department of Internal Medicine, H PLUS Yangji Hospital, Seoul, Korea.
- Department of Internal Medicine, Hanyang University College of Medicine, Seoul, Korea.
- Division of Cardiology, Department of Internal Medicine, Soonchunhyang University Gumi Hospital, Gumi, Korea.
- Division of Cardiology, Konkuk University Chungju Hospital, Chungju, Korea.

6.2. Committee

Steering Committee.

SW Rha (Chair)	Korea University Guro Hospital, Seoul, Korea.
In–Ho Chae	Seoul National University Bundang Hospital, Gyeonggi, Korea.
Jae Woong Choi	Eulji General Hospital, Eulji Medical College, Seoul, Korea.
Young Keun Ahn	Chonnam National University Medical School, Gwangju, Korea.

Executive Committee.

Cheol Ung Choi (Chair)	Korea University Guro Hospital, Seoul, Korea.
Ju Yeol Baek	Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul, Korea.
Byung Hee Hwang	St. Paul's Hospital, The Catholic University of Korea, Seoul, Korea.
Seung-Jin Lee	Soonchunhyang University Medical College, Cheonan, Korea.

Data Safety Monitoring Board.

Yong Hoon Kim	Kangwon National University Hospital, Chuncheon, Korea.
Yun-Hyeong Cho	Myongji Hospital, Goyang, Gyeonggi, Korea.
Taesoo Kang	Dankook University Hospital, Cheonan, Korea.
Wonho Kim	Eulji University Hospital, Daejon, Korea.

Clinical Event Adjudication Committee.

Tae Hoon Ahn	Gacheon University Gil Hospital, Incheon, Korea.
Joon Hyuk Kong	Mediplex Sejong Hospital, Bucheon, Gyeonggi, Korea.
Min-Ho Lee	Soonchunhyang University Seoul Hospital, Seoul, Korea.

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Declaration of competing interest

The author(s) have no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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