Study Title	**Assessment of *Cu*tting-Balloon Angioplasty with Novel Bioabsorbable *P*olymer-Coated, Everolimus-Eluting Stent in the Treatment of Calcified Coronary Lesions Guided by *I*ntravascular Ultrasoun*d*: Study Design and Protocol**
Study Title (Short Description)	**CUPID trial**
Principle Investigator	**Jon Suh, MD., PhD.**
Institution Name & Location	**SoonChunHyang University Hospital** **170 Jomaru-ro, Bucheon-si, Gyeonggi-do, 14584, Rep. of KOREA**
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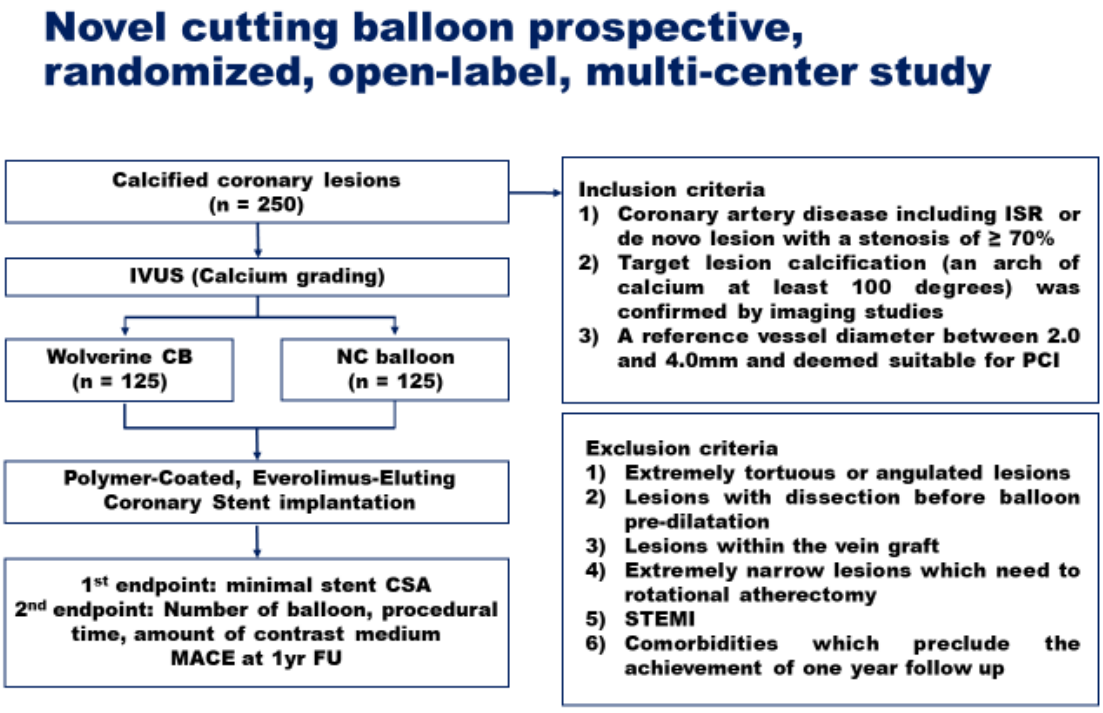
Document date : November 20, 2023

1. Study protocol



This clinical trial is designed as a prospective, observational, open-label, multi-center trial that will investigate the noninferiority of cutting balloon pre-dilatation compared with NC-balloon pre-dilatation in the treatment of calcified lesion who underwent bioabsorbable polymer-coated, everolimus-eluting coronary stent implantation.

Planned number of sites: 5 institutions in South Korea

1. SoonChunHyang University Hospital, Bucheon
2. SoonChunHyang University Hospital, Cheonan
3. Eulji Medical Center, Eulji University, Daejeon
4. Seoul St.Mary's Hospital, Seoul
5. Hanil General Hospital, Seoul

2. Study Outcomes

5.1. Primary endpoint: the efficacy of cutting balloon

① Minimal stent CSA (cross-section area) with IVUS at calcium site

5.2. Secondary endpoint: comparing the clinical outcomes

① MACE (major adverse cardiac events): composite of death, MI, TVR at 1yr follow-up

② TLR (target lesion revascularization) at 1yr follow-up

③ Procedure time, the total amount of contrast, and the number of balloons

3. Analysis plan

6.1. Study period: 24 months

6.2. Enrollment: 12 months

6.3. Follow-up: 12 months

6.4. Analysis and result report: 2 months

4. Sample size calculation for the primary analysis

4.1. Hypothesis:

This trial is a 1:1 matched comparative cohort clinical trial, with patients being assigned to either the cutting balloon or the NC balloon group (1: 1 ratio) during the study period. It will test the noninferiority of a strategy of cutting balloon pre-dilatation compared with NC balloon pre-dilatation in the treatment of calcified coronary lesion. minimal CSA at the calcium site assessed by IVUS is the primary endpoint. Limited similar clinical trials on cutting balloon for the treatment of de novo various degree calcified coronary lesions have achieved differing results. The result of a previous study that investigates the efficacy of cutting balloon indicates that the mean CSA after cutting balloon treatment for native coronary artery disease are 6.26mm and 5.03 mm in the NC balloon group (18). We hypothesize that stent implantation after the cutting balloon pre-dilatation will not be inferior to pre-dilatation with NC balloon for the treatment of de novo calcified coronary lesions. Using double-sided inspection, $\alpha = 0.05$ and $\beta = 0.2$, and considering the expected loss to follow-up of 20%, the number of cases to be included should be at least 250. Therefore, we aim for 125 cases for each group. Nevertheless, the sample size proposed was 250 patients in each group to further increase the power and account for possible protocol deviation.

4.2. Assumption

Data for all endpoints will be evaluated using an intention-to-treat analysis. All data will be expressed as mean ± standard deviation. The unpaired Student's t-test and Mann–Whitney U test will be used to compare continuous variables. Categorical variables will be compared using the chi-square and Fisher's exact tests. All time-to-event outcomes of MACEs will be summarized using Kaplan–Meier survival estimates and compared between the two groups using log-rank tests. $p < 0.05$ is considered statistically significant. All statistical analyses will be performed using SPSS software (version 20.0, SPSS Inc., Chicago, IL, USA).

4.3. Final sample size

Total number = 250 (Wolverine cutting balloon = 125, Non-compliant balloon = 125)

5. Methods

5.1. PCI procedure and medication:

PCI and stent implantation will be performed according to the current guidelines using standard interventional techniques (reference). Before PCI, all patients will be administered loading doses of aspirin (200–300 mg), clopidogrel (300–600 mg), ticagrelor (180 mg), or prasugrel (60 mg). After sheath insertion at the arterial access site, weight-adjusted unfractionated heparin will be administered at a bolus dose of 100 U/kg, with an additional bolus to maintain an activated clotting time of 250–300 s. Additional intravenous and intracoronary injections of platelet glycoprotein IIb/IIIa receptor blockers will be administered at the discretion of the operator. The interventional strategy, balloon size, and stent selection will be based on the discretion of the same operator for all patients. However, modification of the calcific atheroma using rotational atherectomy can be performed at the operator's discretion in cases of balloon-uncrossable lesions, and these cases will be excluded from enrollment. All patients who undergo PCI will receive aspirin (100 mg daily) with clopidogrel (75 mg daily), ticagrelor (180 mg), or prasugrel (60 mg) because a dual antiplatelet

maintenance regimen for at least 12 months is recommended. Cilostazol (100–200 mg daily) will be administered as an adjunct to the dual antiplatelet regimen at the treating physician's discretion. In-hospital stay and after-discharge medications include aspirin, clopidogrel, ticagrelor, prasugrel, beta-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and lipid-lowering agents such as statins, which will be recorded and entered into a dedicated computerized database with clinical information.

5.2. Quantitative coronary angiography:

Coronary angiography will be digitally recorded at baseline and immediately after the procedure (post-ballooning and post-stenting) and assessed offline in the angiographic core laboratory. The quantitative coronary angiographic analysis will be performed using an automated edge-detection algorithm (CAAS-5; Pie-Medical, Best, Netherlands) with conventional methods by independent interventional cardiologists who are blinded to the type of balloon used, treatment outcomes, and IVUS analysis. All measurements will be performed using cineangiograms recorded after the intracoronary injection of nitroglycerin. The interpolated reference diameter will be considered as the reference segment diameter. The lesion length is defined as the distance from the proximal shoulder to the distal shoulder at the lesion site. Standard qualitative and quantitative analyses and definitions will be used for quantitative coronary angiography (QCA) (qca 1, 2 references).

5.3. IVUS procedure and analysis:

After regular coronary angiography, IVUS will be performed at baseline (before pre-dilatation) and repeated immediately after stent implantation in all cases. IVUS will be performed using an OptiCross 60 MHz (Scientific Corporation, Maple Grove, MN, USA). After intracoronary injection of nitroglycerin, the IVUS catheter will be carefully advanced distal to the culprit lesion under fluoroscopic guidance and then withdrawn automatically at 0.5 mm/s to perform the imaging sequence, which begins 20 mm distal to the culprit lesion and ends at the aorto-

ostial junction. IVUS imaging will be recorded on the compact disc for offline analysis by a single experienced observer who is unaware of the clinical and angiographic information. IVUS measurements will be performed in accordance with the American College of Cardiology Clinical Expert Consensus Document on the Standards for Acquisition, Measurement, and Reporting of Intravascular Ultrasound Studies. The ischemia-related vessel is identified as narrow (≥ 70%) using angiography. The culprit lesion site selected for analysis is the image slice with the lowest luminal cross-sectional area (CSA). The proximal and the distal reference segments are defined as the most normal-looking cross-sections within the same arterial segment, typically ≤ 10 mm from the lesion, but before any large side branch.

We will measure the lumen in the minimum lumen area slice. The lumen CSA will be measured every 1 mm of the culprit lesion segment, and the average lumen CSA will be calculated. The maximum calcium arc, calcium length, and calcium ratio (calcium length/lesion length) will be measured. After stent implantation, we will measure the minimum stent CSA, minimum and maximum stent diameters, and acute CSA gain. Acute CSA gain = minimum stent CSA − minimum CSA. Stent symmetry = minimum stent diameter/maximum stent diameter. Stent expansion = minimum stent CSA/reference lumen CSA. Incomplete stent apposition is defined as insufficient close contact between the struts and the underlying wall. Stent asymmetry is defined as stent symmetry of at least one section < 0.7. Stent under expansion is defined as a stent expansion rate of < 0.8.

6. Study device

1) Wolverine (Boston Scientific, Natrick, MA, USA) cutting balloon

2) bioabsorbable polymer-coated everolimus-eluting coronary stent (Synergy ™, Boston Scientific Corporation, Marlborough, MA, USA)

3) NC balloon (the type of NC balloon will be decided at the operator's discretion)

4) IVUS will be performed using an OptiCross 60 MHz (Scientific Corporation, Maple Grove, MN, USA).

7. Study Population

7.1. Inclusion criteria

1) coronary artery disease including in-stent restenosis (ISR) or de novo lesion with stenosis of ≥ 70%,
2) target lesion calcification confirmed by an imaging study: various degrees of calcium deposition along the coronary artery wall (an arch of calcium at least 100 degrees) confirmed at baseline coronary angiography, computed tomography, and IVUS),
3) reference vessel diameter between 2.0 and 4.0 mm, deemed suitable for percutaneous coronary intervention (PCI).

7.2. Exclusion criteria

1) extremely tortuous or angulated lesions,
2) lesions with dissection before balloon pre-dilatation,
3) lesions within the vein graft,
4) extremely narrow lesions which need rotational atherectomy,
5) ST-elevation myocardial infarction (STEMI).
6) Comorbidities that preclude the achievement of one-year follow-up.

8. Expected study period

- Enrollment: 12 months
- Follow-up: 12 months
- Data analysis: 2 months
- Publication including target journal and presentation:

  JACC: Cardiovascular Interventions

  Circulation: Cardiovascular Interventions

  TCT 2025

9. Safety Reporting including DSMB

9.1. Potential risk and adequacy of protection against risks

In patients undergoing intervention and revascularization, treatment decisions should be based on clinical indication, regardless of sex, or race or ethnicity, and efforts to reduce the disparities of care are warranted. In patients undergoing revascularization, decision should be patient-centered *that is, considerate of the patient's preferences and goals, cultural beliefs, health literacy, and social determinants of health* and made in collaboration with the patient's support system. In patients undergoing coronary angiography and revascularization, adequate information benefits, risks, therapeutic consequences, and potential alternatives in the performance of percutaneous and surgical myocardial revascularization, when feasible, with sufficient time for informed decision-making to improve clinical outcomes.

9.2. Event adjudication and reporting, data safety and monitoring plan

1) Data safety and monitoring plan

The principal investigator will make the monitoring manager to visit and examine coordinating centers regularly. A designated trial monitor will review data not only for completeness, but also for accordance of the hospital data and eCRF data. Compliance with the protocol and adverse events will be also examined. This trial monitor may inspect all documents and required records that are maintained by the Investigator/site, including medical records (office, clinic, or hospital) for the subjects in this trial. The coordinating centers will permit access to such records.

Type of Report	Prepared by Staffs for:	Time limit of notification
Serious adverse event	IRB	According to IRB regulation of Site
	DCC/EC/Principal investigator DSMB	Within 48 hours
Annual progress report	EC/Principal investigator	Submitted per 1 year
Deviations from investigational plan	IRB	According to IRB regulation of Site
	EC/Principal investigator	Notify within 7 days.

Final summary report	EC/Principal investigator	Within 1 month

*DCC: Data Coordinating Center, EC: Executive Committee (Co-researchers)

2) Executive Committee

	Name	Center	Position
Chairman	Jon Suh	Department of Cardiology, SoonChunHyang University Bucheon Hospital, SoonChunHyang University College of Medicine	MD, PhD.
Committee members	Sang Ho Park	Department of Cardiology, SoonChunHyang University Cheonan Hospital, SoonChunHyang University College of Medicine	MD, PhD
	Jihun Ahn	Department of Internal Medicine, Daejeon Eulji Medical Center, Eulji University School of Medicine	MD, PhD
	Tae-Hoon Kim	Department of Cardiology, Hanil General Hospital, Seoul	MD, PhD
	Min Gyu Kong	Department of Cardiology, SoonChunHyang University Bucheon Hospital, SoonChunHyang University College of Medicine	MD, PhD
	Kwan Yong Lee	Department of Cardiology, Seoul St. Mary's Hospital, The Catholic University of Korea	MD, PhD
	Inki Moon	Department of Cardiology, SoonChunHyang University Bucheon Hospital, SoonChunHyang University College of Medicine	MD.

3) Serious Adverse Events

The definition of serious adverse events is in the following paragraph. It must be reported to the principal investigator within 48hours after recognition of the event and to the IRB according to IRB regulation of site.

① Results in persistent or significant disability or incapacity (significant, persistent or permanent change or disruption in subject's body function/structure, physical activity or quality of life)

② Requires in-patient hospitalization or prolongs hospitalization

③ Results in a congenital anomaly/birth defect or,

④ Life-threatening events or death

4) Event adjudication committee

	Name	Center	Position
Chairman	Je Sang Kim	Cardiovascular Center, Dongguk University Ilsan Hospital, Dongguk	MD, PhD

		University	
Committee members	Jeong-Hun Shin	Division of Cardiology, Department of Internal Medicine, Hanyang University Guri Hospital	MD, PhD
	Ha Wook Park	Department of Cardiology, Sejong General Hospital, Bucheon	MD.

5) Data safety and monitoring board

	Name	Center	Position
Chairman	In Hyun Jung	Department of Cardiology, Yongin Severance Hospital, Yonsei University College of Medicine	MD, PhD
Committee members	Hun Soo Chang	Department of Microbiology and BK21 FOUR Project, SoonChunHyang University College of Medicine,	PhD.
	Inki Moon	Department of Cardiology, SoonChunHyang University Bucheon Hospital, SoonChunHyang University College of Medicine	MD

The DSMB reviews the safety data and delivers recommendations for it. The DSMB may convene a meeting at any time if it deems that there is a safety problem.

The DSMB Charter is drafted before the DSMB's first data review. The plan defines its regulations when clinical trials are suspended due to safety concerns. At the first meeting of the DSMB, understanding and discussion of all elements of the plan and determination of the frequency of DSMB meetings are made. DSMB develops an understanding of all evaluation variables in this clinical trial and all definitions used in the judgment.

The Commissioners do not directly coordinate the client of this clinical trial. The committee members have no interest in the central analysis room or with the researchers of this clinical trial. The configuration of the DSMB includes at least two cardiovascular intervention specialists. The names of the actual members are not published and can be provided to regulators as needed. DSMB functions in accordance with relevant regulations.

The DSMB Chairman shall notify the DCC if he deems that there is a problem with safety or compliance with the plan. The Commission may, if necessary, recommend an early suspension in accordance with the safety-related early discontinuation principle determined prior to the start of a clinical trial, or if clinically significant results are found in the safety-related data. All DSMB reports must be strictly confidential and provided at the request of regulators.