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Study design and rationale for comparison of the incidence of slow flow following rotational atherectomy to severely calcified coronary artery lesions between short single session and long single session: The randomized ROTASOLO trial

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Background

Severely calcified coronary artery disease is still the Achilles' heel in percutaneous coronary intervention (PCI) [1], although there were many developments in devices and techniques over the last two decades [2–6]. Rotational atherectomy (RA) has been a cornerstone for the treatment of severely calcified coronary artery disease for more than 20 years [7–9]. However, unique complications occur in PCI with RA [10–12]. Among unique complications, slow flow is the most common complication following RA [13–15]. The severity of slow flow varies widely from transient thrombolysis in myocardial infarction (TIMI) grade 2 flow to persistent TIMI grade 0 flow (no flow), which would be associated with serious periprocedural myocardial infarction (PMI) [16, 17]. Previous retrospective studies reported that slow flow following RA was positively associated with lesion length, angulation, and burr-to-artery ratio, and was inversely associated with reference diameter, systolic blood pressure just before RA, and primary RA strategy [13]. Moreover, the maximum number of reverberations in intravascular ultrasound (IVUS) and the greater arc of calcification at minimum lumen area were also associated with slow flow following RA [18]. Although the clinical expert consensus document from the Japanese Association of CardioVascular Intervention and Therapeutics recommends appropriate burr size, short ablation time, and avoiding excessive speed down [19], the methods to prevent slow flow have not been established. The present retrospective study showed that a short single session was inversely associated with slow flow [13]. Thus, it was hypothesized that the short single session strategy would prevent the occurrence of slow flow following RA irrespective of total ablation time. This paper describes the study design and rationale for "Comparison of the Incidence of Slow Flow Following ROTAtional Atherectomy to Severely Calcified Coronary Artery Lesions between ShOrt Single Session Versus LOng Single Session: The Randomized ROTASOLO Trial" [UMIN000047231].

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Methods

Study design

The design of the ROTASOLO trial, which is currently ongoing, is an open-label randomized study to compare the incidence of slow flow following RA between the short single session strategy and the long single session strategy. The short single session strategy was defined as repeating short single session (no more than 15 s) RA until the burr crosses the target lesion, whereas the long single session strategy was defined as repeating long single session (20–30 s) RA until the burr crosses the target lesion. The trial will include 300 patients undergoing RA at the following 3 hospitals: (1) Saitama Medical Center, Jichi Medical University, (2) JCHO Saitama Medical Center, and (3) Nerima-Hikarigaoka Hospital in Japan. The planned enrollment period is 36 months. The primary outcome will be assessed immediately after RA in each procedure. The study was approved by the Institutional Review board of Saitama Medical Center, Jichi Medical University [S21–105], JCHO Saitama Medical Center [22–17], and Nerima-Hikarigaoka Hospital [22051201].

Inclusion criteria for the participation in the ROTASOLO trial are as follows: (1) patients with ischemic heart disease including acute coronary syndrome and chronic coronary syndrome who undergo PCI using RA, (2) patients who gave written informed consent, (3) angiographically severe calcification in target lesions, and (4) and intravascular imaging shows over 180-degree superficial calcification/calcified nodule, intravascular imaging devices cannot cross the lesion due to severe stenosis, or an intravascular imaging device (typically optical coherent tomography [OCT]) cannot provide valid images due to severe stenosis. Meanwhile, the exclusion criteria are as follows: (1) less than 20 years-old, and (2) contraindication in instructions-for-use of Rotablator.

Randomization

Pre-screening will be performed by investigators according to the findings of coronary angiography and/or computed tomography (CT)-angiography. If the patients are considered suitable for PCI with RA, investigators would explain the detail of the study. Each patient would provide written informed consent. Then, investigators would make a tentative registration for the study via REDCap (Research Electronic Data Capture; Vanderbilt University) [20, 21]. The ROTAPRO (Boston Scientific, Marlborough, MA) would be used for all RA procedures. During PCI, investigators would check all inclusion and exclusion criteria for the study. First, the operators would try intravascular imaging (IVUS or OCT) to the angiographically severe calcified lesions. After intravascular imaging, the operators would decide the initial burr size and the type of RotaWire (Floppy type or Extra-Support type) before randomization. After the operators decide the initial burr size and the type of RotaWire, patients would be centrally randomized at a 1:1 ratio using REDCap. The randomization was done using random permuted blocks, with block sizes ranging from 2 to 6, and was stratified according to center. The trial flow diagram is shown in Figure 1.

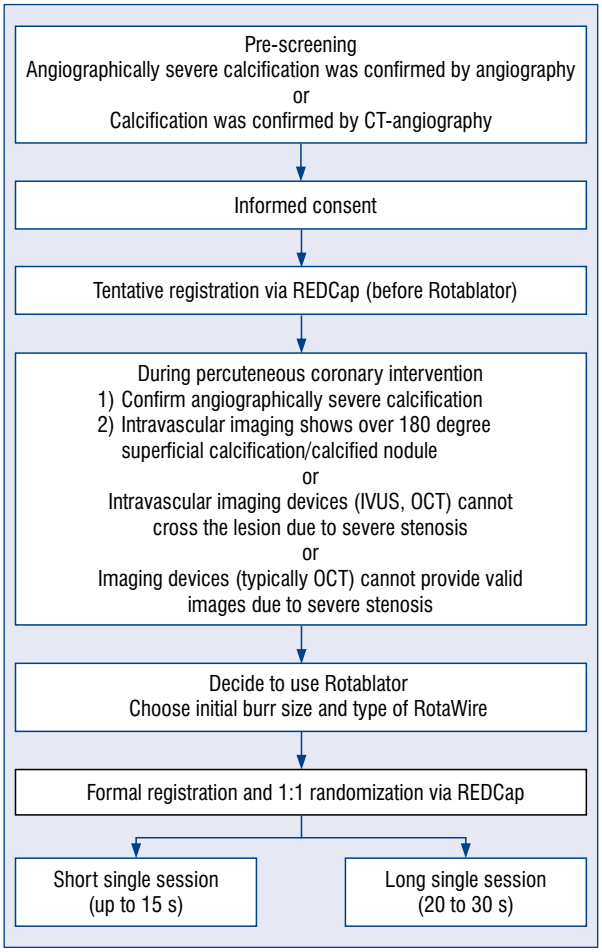

Figure 1. The trial flow diagram; CT — computed tomography; IVUS — intravascular ultrasound; OCT — optical coherence tomography.

The RA burr would be advanced over the wire to a position proximal to the lesion. The rotational speed would be set at the conventional range (140,000–190,000 rpm) with the burr proximal to the lesion. Techniques regarding RA would

Table 1. The detail of timing when to evaluate slow flow just after rotational atherectomy (RA).

Situation	Timing when we evaluate slow flow
The first burr crossed the target lesion (full RA). No second burr was used.	Just after the first burr crossed the target lesion.
The first burr crossed the target lesion (full RA). The second burr was used for burr size-up. The second burr crossed the target lesion (full RA).	Just after the first burr crossed the target lesion.
The first burr could not cross the target lesion. The second burr was used for burr size-down. The second burr crossed the target lesion (full RA).	Just after the second burr crossed the target lesion.
The first burr could not cross the target lesion, but switch to balloon dilatation (halfway RA). No further RA.	Just after the first burr attempt.
The first burr could not cross the target lesion. The second burr was used for burr size-down. However, the second burr also could not cross the target lesion (halfway RA).	Just after the second burr attempt.
The first burr could not cross the target lesion, but switch to balloon dilatation (halfway RA). However, balloon did not work. Then, switch to RA again. The second burr could cross the target lesion.	Just after the second burr crossed the target lesion.
The first burr could not cross the target lesion. The second burr was used for burr size-up. The second burr crossed the target lesion (full RA).	Just after the second burr crossed the target lesion.

Full RA means that the burr could cross the target lesion. Halfway RA means that RA was tried, but the burr could not cross the target lesion. Even if the burr could not reach to the midpoint of the target lesion, RA attempts that eventually could not cross the target lesion would be classified as halfway RA.

be consistent with those that were recommended by the clinical expert consensus document on RA from the Japanese Association of Cardiovascular Intervention and Therapeutics [19]. In the short single session group, operators would control the single session time up to 15 s. In the long single session group, operators would control the single session time from 20 s to 30 s. In both groups, operators can add sessions until the first burr crosses the target lesion. If the operator decides to use the second burr (i.e., burr size-up) after the first burr crosses the target lesion, operators can set the single session time freely. In other words, operators do not need to follow the short or long single session strategy after the first burr crosses the target lesion. The console of ROTAPRO clearly display each run time, which is open to the main- and sub-operators. Clinical engineers in catheter rooms call the time of each session. The time of each session in this study is recorded before the first burr crosses the target lesion.

Primary outcome

The primary outcome was slow flow just following RA. Although slow flow is usually defined as TIMI grade ≤ 2 [22], this TIMI grade ≤ 2 was not adopted in the current study as the definition of slow flow in the ROTASOLO trial, because the borderline between TIMI grade 2 and TIMI grade 3 is sometimes ambiguous. Furthermore, the TIMI flow grade is a subjective parameter. In the ROTASOLO trial, slow flow just after RA was defined as ([initial TIMI-frame count before RA] × 1.1 minus [TIMI-frame count just after RA]) less than 0. Absence of slow flow was defined as ([initial TIMI-frame count before RA] × 1.1 minus [TIMI frame count just after RA]) not lower than 0. For the present TIMI-frame count evaluation, the frame rate was set as 15 frames per second (15 fps). Initial TIMI-frame count before RA was multiplied 1.1-fold, because TIMI frame count would be influenced by not only slow flow, but also injection speed, the dose of contrast media, the depth of guide-catheter, and the presence of guidewire. In other words, if the TIMI-frame count just after RA is slightly higher than the TIMI-frame count before RA, it may be a margin of error rather than slow flow caused by RA. Therefore, initial TIMI--frame count before RA × 1.1 was compared with TIMI-frame count just after RA.

If ≥ 2 burrs are used for RA, slow flow will be evaluated only after the first burr crosses the lesion. Once the first burr crossed the lesion, slow flow would not be evaluated for this study after the second burr crosses the lesion. If the first burr could not cross the lesion and the second burr (typically smaller burr) could cross the lesion, slow flow would be evaluated for this study after

the second burr crosses the lesion. If halfway RA is performed [23], slow flow will be evaluated just after halfway RA. In other words, slow flow just after RA is evaluated only one time per PCI. The detail of timing when slow flow is evaluated just after RA is shown in Table 1. Secondary outcomes are PMI and complications such as vessel perforation.

Definitions of variables

All clinical information and study outcomes will be collected as electronic data capture (EDC) via REDCap. Patient characteristics include age, sex, height, body weight, hypertension, diabetes mellitus, dyslipidemia, current smoker, creatinine level at admission, hemodialysis, peritoneal dialysis, history of heart failure requiring hospitalization, use of statin, use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers/ /angiotensin receptor neprilysin inhibitor, and use of beta-blockers. Lesion characteristics include type of lesion, presence of visible thrombus, chronic total occlusion, in-stent lesion, target vessel, ostial lesion, reference diameter, lesion length, and lesion angle. Procedure characteristics include use of balloon before RA, guide catheter size, use of intra-aortic balloon pumping, use of veno-arterial extracorporeal membrane oxygenation, type of RotaWire, number of used burrs, initial burr size, maximum burr size, initial burr to artery ratio, maximum burr to artery ratio, total run time, mean single run time, mean rotational speed, blood pressure before RA, heart rate before RA, use of halfway RA, and type of final procedure. Study outcomes include final TIMI-flow grade, type III vessel perforation, burr entrapment, PMI, and in-hospital death. Hypertension was defined as a systolic blood pressure > 140 mmHg, diastolic blood pressure > 90 mmHg, or medical treatment for hypertension [24]. Diabetes mellitus was defined as a hemoglobin A1c level > 6.5% or treatment for diabetes mellitus [24]. Dyslipidemia was defined as a total cholesterol level > 220 mg/dL, a low-density lipoprotein cholesterol level > 140 mg/dL, or treatment for hyperlipidemia [24]. Creatine kinase and creatine kinase-myocardial band (CK-MB) at the day after RA will be collected. PMI was defined as CK-MB ≥ 10 upper limit of normal [25]. The reference diameter and lesion length will be calculated by quantitative coronary angiography [13]. The burr-to-artery ratio was defined as the burr size divided by the reference diameter [13].

Sample size calculations and statistical methods

Sample size calculations were based on previously published data. The present retrospective study includes 513 lesions treated with RA, the incidence of slow flow was 14.7% in lesions that received short single session (no more than 15 s), whereas the incidence of slow flow was 28.8% in lesions that received long single session (20–30 s) [13]. If the cut-off of the probability of a type-I error (α) was set as 5% (0.05) and the cut-off of the probability of a type-II error (β) as 20% (0.2), a total of 266 lesions would be needed to detect the difference between the two groups. It was anticipated that substantial cases would be excluded by this strict imaging criteria, a total of 300 patients were chosen as the sample size for the ROTASOLO study. The primary outcome (incidence of slow flow) will be compared between the short single session group and the long single session group using the Fisher exact test.

Monitoring and auditing

The ROTASOLO study will be monitored via REDCap by the Center for Clinical Investigation in Jichi Medical School. The Center for Clinical Investigation in Jichi Medical School will monitor (1) progress of enrollment, (2) delay of input on EDC, (3) deviation from the protocol, and (4) serious adverse events every 1 year. Monitoring will be applicable to all participants with formal registration and randomization.

The ROTASOLO study will be audited by the Center for Clinical Investigation in Jichi Medical School. The Center for Clinical Investigation in Jichi Medical School will audit (1) the accuracy of documents of written informed consent and (2) the eligibility for the study participants twice during the enrollment period. Auditing will be applicable to selected participants (maximum 30 cases).

Discussion

The results of the ROTASOLO trial will determine whether a short single session strategy can reduce the incidence of slow flow following RA. Because the number of RA cases per operator is inversely associated with adverse events [26, 27], refinement of RA procedures would be important to reduce complications related to RA. However, RA procedures vary widely among RA experts. Although a total of 3 expert consensus documents

on RA have been published from Europe, North America, and Japan [19, 28, 29], recommendations to prevent slow flow are not sufficiently supported by robust evidence. The ROTASOLO trial will shed light on refinement of RA procedures to prevent slow flow after RA.

Slow flow includes both permanent severe slow flow and transient mild slow flow. Transient mild slow flow would be recovered immediately if operators stop RA procedures and inject intracoronary vasodilators. However, if operators ignore transient slow flow during RA, it can progress to permanent severe slow flow, which would be associated with PMI and subsequent death. The prevention and early management of slow flow is an important step to reduce unique complications in RA [19].

The ROTASOLO study has several limitations. First, quantitative coronary angiography and the evaluation of slow flow will not be performed by independent core laboratories. Second, the present definition of slow flow using TIMI-frame count has not been validated by other groups. Third, although the ROTASOLO study was designed as a multicenter study, only 3 institutions were included in this study. Fourth, the inability to blind operators might impact the trial results. Finally, our definition of PMI, which uses CK-MB as biomarker, is not sensitive enough to detect minor PMI.

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Conflict of interest: Dr. Kenichi Sakakura has received speaking honoraria from Boston Scientific; he has served as a proctor for Rotablator for Boston Scientific; and he has served as a consultant for Boston Scientific. Dr. Hiroyuki Jinnouchi has received speaking honoraria from Boston Scientific. Dr. Kei Yamamoto has received speaking honoraria from Boston Scientific, and has served as a consultant for Boston Scientific. All other authors had nothing to disclose.

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