Study Protocol

Registry Name	**ROVUS** (Evaluate Safety and Effectiveness of **Ro**tational Atherectomy and Intra**v**asc**u**lar Ultra**s**ound for Heavily Calcified Coronary Lesion) Asia Registry
Version No.	Version 3
Date	17th January 2021
Sponsor	National Heart Centre Singapore (NHCS) Boston Scientific Corporation
Type of clinical trial	Investigator-initiated
Study hypothesis	Rotational atherectomy with or without other calcium debulking therapies is a safe adjunctive procedure for patients with severe coronary calcification requiring PCI
Study population	All patients with signed informed consent for percutaneous coronary intervention (PCI) and are eligible for calcium debulking treatment with rotational atherectomy with or without other forms of calcium debulking therapies will be enrolled into this study
Study aim	1. To describe the use of RA in real world practice in Asia 2. To determine predictors of procedural success 3. To determine predictors of major procedural complications: perforation and no-reflow phenomenon 4. To assess the clinical outcome of patients undergoing RA for heavily calcified coronary lesions.
Study equipment	1. ROTABLATOR™ or ROTAPRO™ (Rotational Atherectomy System) 2. Opticross or Opticross HD (IVUS) - *preferred* 3. SYNERGY or SYNERGY XD (DES) - *preferred* 4. Other calcium debulking equipments used e.g. *Orbital atherectomy, shockwave lithotripsy, laser, very high-pressure balloon, angiosculpt, cutting balloon etc*

	Final selection of imaging platform, type of stents, adjunctive calcium debulking strategies and use of pre-/post-dilation is left to operator's discretion
Device specification	1. The ROTABLATOR™ or ROTAPRO™ (Rotational Atherectomy System) consist of hardware (console, high-pressure gas tank and foot pedal) and disposable components (wire guide, burr head and advancer). 2. The burr head sizes are 1.25mm,1.5mm,1.75mm, 2.0mm, 2.25mm, 2.38mm, 2.5mm 3. Other equipments used are subject to respective device specifications
Study design	Regional prospective, multicenter observational study
Estimated sample size	1000 patients to be enrolled, with each site enrolling at least 65 to 120 patients.
Proposed study countries/ Sites	1. Singapore: National Heart Centre Singapore, National University Hospital, Tan Tock Seng Hospital 2. Japan: Kokura Memorial Hospital, Sapporo Cardiovascular Clinic, Sendai Kousei Hospital 3. Malaysia: Serdang Hospital, Cardiac Vascular Sentral Kuala Lumpur 4. Thailand: Central Chest, King Chulalongkorn 5. Vietnam: Cho Ray Hospital, Bach Mai Hospital
Patient selection	**<u>Inclusion Criteria</u>** Subjects MUST fulfill ALL the following requirements in order to be eligible for the study: 1. At least 21 years of age of any gender 2. Able to understand and sign an informed consent form 3. Presence of clinical indication for PCI and/or stent placement 4. Subjects willing to comply with all research and follow-up requirements 5. Angiographic criteria (ONE of the following criteria MUST be met)

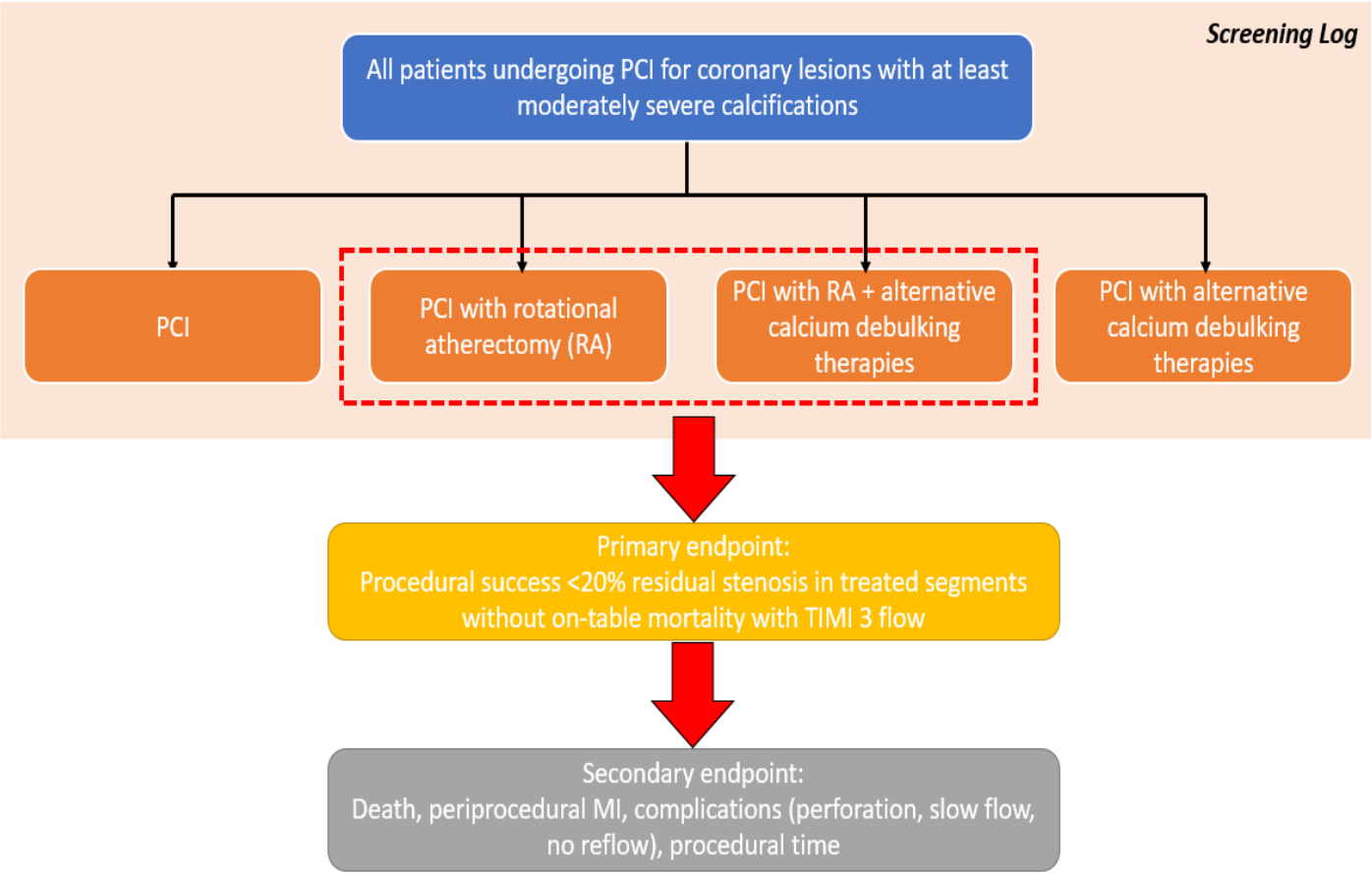
	a. Target lesions visually have at least moderate calcifications* b. Target lesion balloon dilatation failure c. Inability of devices (microcatheters, balloons, stents or imaging devices) to pass through the target lesion d. Intravascular imaging shows severe calcification* 6. Procedural criteria a. All patients treated with RA with or without other forms of debulking therapy ** Moderate calcification is defined as radio-opacities noted only during cardiac cycle prior to contrast injection whereas severe calcification is defined as radio-opacities seen without cardiac motion prior to contrast injection, usually affecting both sides of the arterial lumen*[1]
Study duration	2-year recruitment period with a minimum 1-year of clinical follow-up. Patients will be enrolled into the study at the point of treatment with rotational atherectomy
Primary efficacy endpoint	Procedural success defined as < 20% residual stenosis in treated segment without on-table mortality with TIMI 3 flow
Primary safety endpoint	All rotational atherectomy related complications
Secondary study endpoints	1. Death (in-hospital and at 1-year follow-up) 2. Periprocedural myocardial infarction (MI) defined as either (within 48 hours of procedure) a. Peak CK-MB ≥ 10x ULN OR ≥ 5x ULN + new pathologic Q waves in ≥ 2 contiguous leads/ new persistent LBBB[2] OR b. Peak Troponin T or I > 5x ULN + new pathologic Q waves/ ischemic ECG changes[3] 3. Complications: Significant coronary perforation defined as (within 48 hours of procedure) a. At least Type II, III or III CS based on Ellis classification[4] 4. Complication: no-reflow or slow flow (within 48 hours of procedure) 5. Procedural time defined as

	a. Time of guide engagement to removal of guide
Follow-up	All patients will be followed-up via telephone consultation at the 12-month mark from index rotational atherectomy procedure
Recommended management	**<u>Pre-procedural antiplatelet regimen</u>** (i) Aspirin: a. If aspirin naïve, 300mg loading followed by 100mg OM b. If already on aspirin 100mg OM, ensure daily compliance for at least 72 hours prior to procedure AND (ii) Clopidogrel: a. If clopidogrel naïve: 600mg loading followed by 75mg OM b. If already on clopidogrel 75mg OM, ensure daily compliance for at least 1 week prior to procedure OR (iii) Ticagrelor: a. If ticagrelor naïve: 180mg loading followed by 90mg BD b. If already on ticagrelor 90mg BD, ensure daily compliance for at least 24 hours OR (iv) Prasugrel a. If prasugrel naïve: 60mg loading on table if planned for PCI followed by 10mg OM b. If already on prasugrel 10mg OM, ensure daily compliance for at least 24 hours **<u>Intracoronary medications</u>** The administration of intracoronary glyceryl trinitrate (GTN) is recommended prior to coronary angiography of both right and left coronary artery.

	Use of any of the following intracoronary medications is left to operator discretion as per site practice and/ or product instructions (i) Calcium Channel blockers (CCB): Verapamil/ Diltiazem (ii) Adenosine (iii) Nitroprusside **<u>Anti-thrombotics</u>** Use of any of the following antithrombotic regimen is left to operator discretion as per site practice and/or product instructions (i) Heparin (ii) Bivalirudin (iii) Fondaparinux (iv) Group 2b/3a inhibitors e.g. eptifibatide (v) Cangrelor **<u>Pre-procedural preparation</u>** (i) For RCA/ dominant LCx lesions, operators can consider to standby atropine or temporary pacing wire (TPW) insertion if patient develops significant bradycardia/ cardiac conduction delays during the procedure **<u>Intracoronary imaging</u>** (i) The preferred intracoronary imaging platform is Intravascular Ultrasound (IVUS) i.e. Opticross or Opticross HD prior to intervention to evaluate target lesion characteristics and post-intervention to optimize stent expansion. However, the final selection is left to the discretion of the operators. (ii) Optical coherence tomography (OCT) is an alternative if deemed appropriate by the operators. **<u>Post-procedure</u>** (i) IV normal saline hydration based on clinical judgement to reduce risk of contrast induced nephropathy (CIN) (ii) If TPW was inserted but nil further brady-arrhythmia was noted, TPW can be safely removed prior to transfer out of cardiovascular laboratory (iii) To reduce post-procedural vasospasm, IV nitroglycerin can be administered

	(iv) The subjects should receive dual antiplatelet therapy (DAPT) – one being that of aspirin and the other being a P2Y12 inhibitor – post- procedurally. The dose and duration of treatment is to be determined by the operator. (v) All patients are recommended to be on DAPT for at least 6 months in duration post-PCI extendable to at least 12 months if they are deemed at low risk for bleeding.
Statistical analysis	All analysis will be performed using SAS or STATA Analysis will be conducted in two approaches, (1) according to the intention-to-treat (ITT) principle and (2) per-protocol analysis.
Sub-group analysis	This study will evaluate real world clinical outcomes of all enrolled patients who have undergone calcium debulking therapies. The following sub-groups listed below (but are not limited to) may be used for further analysis: (i) Acute coronary syndrome (ii) Lesion length (iii) Bifurcation lesions (iv) Multiple overlapping stents (≥ 2 stents for each epicardial coronary artery) (v) Chronic kidney disease (vi) Multivessel disease (≥ 2 vessel CAD) (vii) Left main (LM) equivalent (viii) Chronic total occlusions (CTO) (ix) Severely impaired LVEF i.e. ≤ 30% (x) IVUS subgroup
Primary site	National Heart Centre Singapore (NHCS)

Study flow chart



Data collection schedule

	Baseline	Follow-up
Time	≤ 48h after PCI	12m
Visit timeline	V_{start}	V_{end}
Informed consent	X	
Entry criteria	X	
History / demographic data	X	
Symptoms (CCS score)	X	X
Laboratory^	X	
DAPT use data*		X
Adverse events recording	X	X

Note:

Laboratory testing: full blood count, liver function (ALT, AST), renal function (BUN, creatinine), lipids (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides), glucose, coagulation panel (APTT/PT), myocardial injury markers include: CK, CK-MB, TnT / TnI.etc.

* DAPT recommendations may differ based on clinical situation/ stent use. Data collected will be type of antiplatelets and recommended duration for each antiplatelets used.

Note: All subjects will be followed up 12 months post PCI via telephone consult to check on symptoms, compliance, and development of adverse events. Medical records will also be reviewed at the end of 12 months for any clinically significant events.

Table of Contents

List of abbreviations

Abbreviations	Name/ Organisation
ACC	American College of Cardiology
ACS	Acute coronary syndrome
AE	Adverse Event
AHA	American Heart Association
ALT	Alanine Transaminase
AST	Aspartate Transaminase
BSC	Boston Scientific Corporation
CABG	Coronary Artery Bypass Graft
CAC	Coronary artery calcium score
CCS	Canadian Cardiovascular Society
CK	Creatine Kinase
CK-MB	Creatine Kinase-Myoglobin Band
CKD	Chronic Kidney Disease
CTRO	Clinical Trials and Research Office
CRF	Case Report Form
CTO	Chronic Total Occlusion
DAPT	Dual Antiplatelet Therapy
DES	Drug-Eluting Stent
DMC	Data Monitoring Committee
EC	Ethics Committee
ECG	Electrocardiogram
FDA	Food and Drug Administration
ITT	Intention to Treat
IVUS	Intravascular Ultrasound
LAD	Left Anterior Descending Coronary Artery
LBBB	Left Bundle Branch Block
LCX	Left Circumflex Coronary Artery
LL	Lesion length
LM	Left Main
LVEF	Left Ventricular Ejection Fraction
MACE	Major Adverse Cardiac Event
MI	Myocardial Infarction
MLD	Minimum Lumen Diameter

NHCS	National Heart Centre Singapore
NHLBI	National Heart, Lung, and Blood Institute
NSTEMI	Non ST elevation Myocardial Infarction
NTG	Nitroglycerin
OCT	Optical Coherence Tomography
PCI	Percutaneous Coronary Intervention
RA	Rotational Atherectomy
RCA	Right Coronary Artery
RVD	Reference Vessel Diameter
SAE	Serious Adverse Event
SCAI	Society for Cardiovascular Angiography & Intervention
ST	Stent Thrombosis
STEMI	ST Elevation Myocardial Infarction
TLF	Target Lesion Failure
TLR	Target Lesion Revascularization
TnI	Troponin I
TnT	Troponin T
TVF	Target Vessel Failure
TVR	Target Vessel Revascularization
UAP	Unstable Angina Pectoris

1. Research background

Coronary artery calcification is common especially in the elderly, diabetic or chronic kidney disease (CKD) population. While percutaneous coronary intervention (PCI) is a well-known and widely accepted treatment modality for obstructive coronary artery disease, severely calcified coronary lesions increase complexity of PCI with lower rates of procedural success as well as worse ischemic outcomes[5]. Given these technical challenges, lesion preparation strategies prior to stent implantation have been proposed to improve clinical outcomes with mixed results.

Rotational atherectomy (RA; ROTABLATOR™ OR ROTAPRO™) was first developed by David Auth and colleagues in 1988[6]. The first RA procedure was performed in 1988 by Bertrand et. al. with subsequent US Food and Drug Administration (US FDA) approval for commercial use in 1993. Initial adoption RA was tempered by reports of high rates of restenosis in the pre-drug eluting stent (DES) era[7,8] but there is a resurgence of interest given the rapidly ageing population with increasing complexity of coronary lesions encountered for percutaneous coronary intervention (PCI)[9].

In our current era of DES, the use of atherectomy has shifted from plaque debulking to plaque modification prior to PCI to promote stent expansion. This switch in emphasis was driven by outcomes from the Study to Determine Rotablator and Transluminal Angioplasty Strategy (STRATAS) and Coronary Angioplasty and Rotablator Atherectomy Trial (CARAT) clinical trials[10,11]. In these 2 trials, aggressive strategy with large burrs to achieve maximum debulking as lesion debulking strategy was associated with higher rates of angiographic complications (e.g. perforation), target lesions revascularization (TLR), and periprocedural CK-MB release compared to lesion modification strategy with use of smaller burrs. This change in emphasis has allowed for widespread adoption of smaller burrs, guide catheters and sheaths without compromising safety and efficacy. Several studies have shown that RA can improve procedural success for PCI with no increase in adverse MACE outcomes[12]. As such, the 2011 ACC/AHA/SCAI guidelines on coronary intervention has given a Class IIa Evidence Level C recommendation for the use of RA in the treatment of heavily calcified coronary lesions[13].

Thus far, a staggering 900,000 RA procedures have been performed globally since its inception. The US, being the country which first developed RA, is currently carrying out approximately 20,000 cases of RA yearly with a utilization rate of 2% of all PCIs. Likewise, European centers have a comparable reported RA utilization rate of 2-3% while Japan's utilization rate is roughly 2.8%[14]. China's recent Rota Registry reported a much lower utilization rate of only 0.4%. However, thus far, there are limited reported data on utilization rates as well as outcomes in other Asian countries such as Singapore, Malaysia, etc.

Therefore, this study aims to evaluate the real-world use of rotational atherectomy with or without other calcium debulking therapies in Asian countries in terms of clinical practice, safety as well as effectiveness outcomes and provide future basis/ platform for further research in this area.

1.1 Introduction to disease

1.1.1 Disease Profile

Coronary artery calcification (CAC) is a consequence of calcium phosphate composite deposition in the wall of coronary artery resulting in hardening. In these cases, PCI is challenging in view of difficulty to dilate or cross the lesions, often leading to suboptimal stent expansion, poor adherence and subsequently increasing incidence of major adverse cardiovascular events (MACE).

1.1.2 Epidemiology and risk factors

The prevalence of CAC is age and sex dependent and occurs in at least 90% of men and 67% of women aged 70 years and above[15,16]. In multi-ethnic epidemiological studies, risk factors for CAC beyond age include hypertension, hyperlipidemia, diabetes and chronic kidney disease, similar to traditional cardiovascular risk factors[17]. Even after adjusting for the above risk factors, patients of Chinese descent are 77% more likely to have coronary artery calcifications compared to their Caucasian and Afro-American counterparts[18]. In addition, some retrospective studies have also shown that the risk factors aforementioned not only increase likelihood of CAC but also accelerates progression of calcification in patients with established coronary calcifications.

1.1.3 Pathophysiology and classification

Calcium regulatory mechanisms play an integral role not only in bone formation but also CAC. Vascular smooth muscles produce matrix vesicles which regulates mineralization in the vascular intima and media[19,20]. Other cell types e.g. microvascular pericytes also have the potential to generate mineralized matrix and undergo osteoblastic differentiation, leading to calcified deposits[20].

There are 2 widely recognized types of CAC i.e. atherosclerotic/intimal calcification and medial artery calcification. Intimal calcification occurs primarily due to atherosclerotic processes potentiated by inflammatory mediators as well as elevated lipid content in the lesions resulting in osteoblastic differentiation of the vascular smooth muscles[19]. On the other hand, medial artery calcification is linked to traditional risk factors of advanced age, diabetes and chronic kidney disease and results in arterial stiffness.

1.1.4 Detection of CAC

Coronary angiography has low-moderate sensitivity compared to IVUS or CT in detection of CAC but very high specificity. On the other hand, intravascular ultrasound (IVUS) is significantly more accurate with a sensitivity of at least 90 to 100% and specificity of 99 to 100%. Optical coherence tomography (OCT) provides higher resolution imaging (10-20 μm) than grayscale IVUS (150-200μm) with a comparable sensitivity of 96% and specificity of 97% for coronary calcification detection[21]. Both IVUS and OCT has been shown to be useful in evaluating calcium thickness and angle which predicts stent expansion[22]. A maximum calcium angle of more than 180 degrees with greater amount of calcium can lead to a smaller and more eccentric shaped stent area. However, as ultrasound does not penetrate calcium, IVUS is unable to determine calcium thickness. In contrast, as light penetrates calcium, OCT is able to determine calcium thickness in most of the cases as well as measure calcium volume[23].

1.2 Introduction to treatment

1.2.1 Rotational atherectomy

To date, rotational atherectomy (RA) has been the most used atherectomy modality since its first inception in 1988. RA uses high speed rotation (140,000 – 180,000 rpm) to ablate inelastic plaque, resulting in debris averaging 5μm in size[24]. The main focus of RA in the era of DES stent has been on plaque modification rather that plaque debulking with more papers showing improved PCI success rates. However, the use of RA has not been shown to reduce rates of MACE or stent restenosis[25]. The contemporary ROTAXUS trial showed that there is no difference in MACE outcomes at 2-year mark in calcified coronary lesion patients treated with or without RA but there were higher angiographic success rates compared to standalone PCI[26]. In the multicenter ROTATE trial, Kawamoto et. al. showed that planned RA is associated with shorter procedural/ fluoroscopy time, lower contrast volume as well as number of pre- dilation balloon catheters used compared to unplanned/ provisional RA[27]. Thus far, RA has been given a Class IIa Evidence level C for use in fibrotic or severely calcified coronary lesions that might not be crossed by a balloon catheter or adequately dilated before stent implantation in the 2011 ACC guidelines although the same guideline also cautions against routine use of RA in de novo lesions or in-stent restenosis (class III, level evidence A)[13].

1.3 Introduction to equipment

1.3.1 Structure and basic principle of ROTABLATOR™

The rotational atherectomy device (ROTABLATOR™ OR ROTAPRO™; Boston Scientific, Natick, MA) comprises of the following components – console, foot pedal, air supply, advancer and the burr (Figure 1-4).

There are several key components of the ROTABLATOR™.

(1) Guidewire: Divided into 2 types i.e. floppy or extra support guidewire. Both guidewires have a 0.014” maximum spring tip diameter and an outer diameter of 0.009”.

(2) Burr head: Diamond-encrusted elliptical burr with an outer diameter of 20μm with a wide range of burr sizes ranging from 1.25 – 2.5mm with 0.25mm increment in size from the smaller burr head to the next bigger burr head.

(3) Polytetrafluoroethylene sheath tube: Has a diameter of 0.058”. This is used to encase the drive shaft to minimize driving axis injuries to the arteries when the drive shaft is introduced into the lesion. The RotaGlide lubricant is also used to lubricate the drive shaft to reduce friction and improve tactile feel.

(4) Advancer: Atherectomy device that controls forward and backward motion of the burr head via the advancer knob.

(5) Console: Important for controlling the rotational speed of burr head and monitoring duration of use.

(6) Pedals: On and off pedals that is connected to the pressurized gas tank

(7) Air supply: Recommended to use compressed air or nitrogen with pressure regulator adjusted to 6.5-7.5bar and a gas flow rate that is not less than 140L/min.

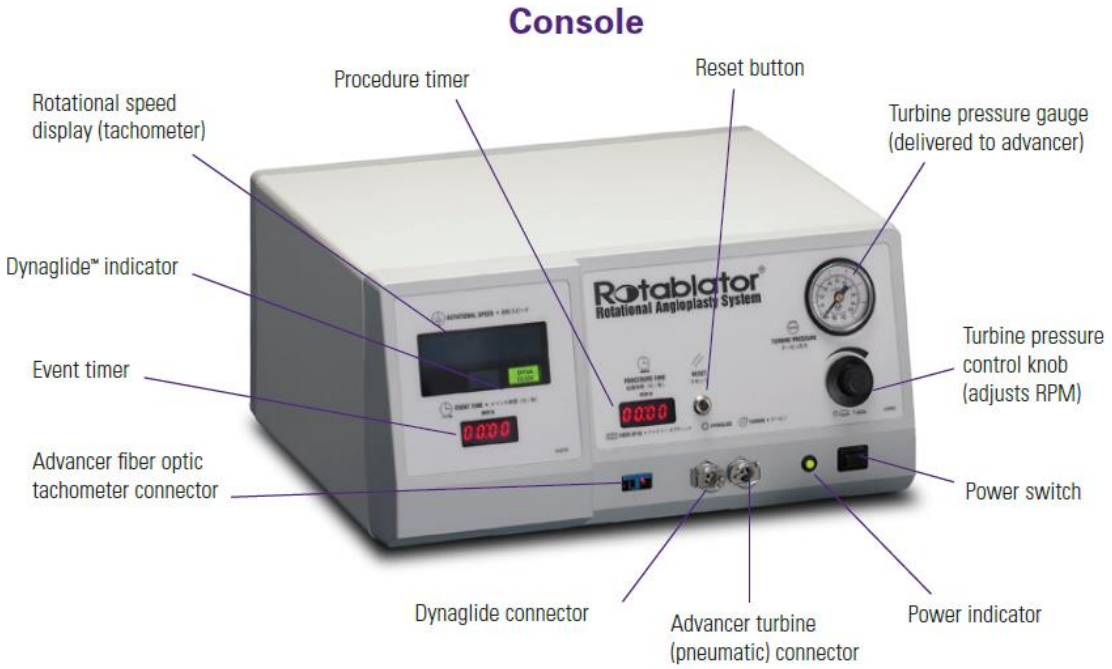


Figure 1: Console system of ROTABLATOR™ and its components. Source: Boston Scientific user manual

Figure 2: Foot pedal and air supply components of ROTABLATOR™. Source: Boston Scientific user manual

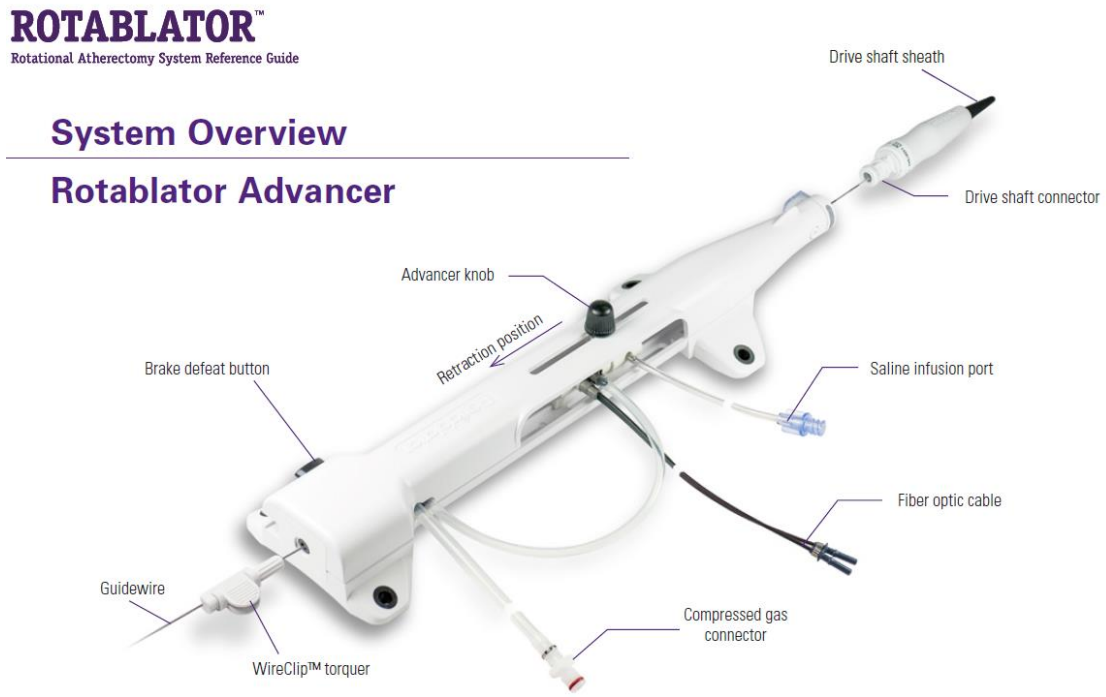


Figure 3: The rotablator advancer of ROTABLATOR™ and its components. Source: Boston Scientific user manual

Figure 4: ROTABLATOR™ Burr heads in different sizes. Source: Boston Scientific user manual

1.3.2 Principle

RA ablates using a diamond-encrusted elliptical burr which rotates at speeds of 140,000 – 180,000 rpm driven by a helical draft shaft that is advanced across a lesion over a guidewire. The burr causes "differential cutting" and preferentially ablates hard, inelastic, calcified plaques that are unable to stretch away from the RA burr compared to healthy arterial tissue (Figure 5). While RA has been shown to selectively remove calcium deposits, IVUS studies have also shown that adjacent endothelial cells may be abraded during the process leading to vasospasm[28]. However, high speed RA generally generates low friction during the creation of smooth lumen-atheroma interface with incidence of coronary artery dissection significantly lower than balloon

angioplasty alone[28]. On the other hand, low speed RA tend to cause fissures and debris formation between plaque and membrane, creating an irregular wall in the process.

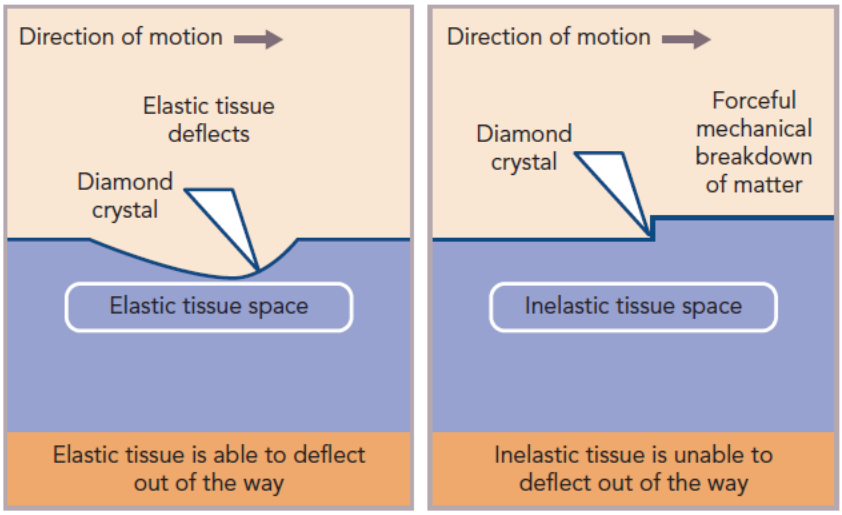


Figure 5: Differential cutting of ROTABLATOR™. Source: Barbato et.al. 2017

At rotational speed of 160,000 to 200,000 rpm, the RA burr head will pulverize atherosclerotic plaque into granules. Studies have found that a vast majority of the particles produced during atherectomy have a < 10-15µm size which will be cleared by the phagocyte system. It does not cause capillary thrombosis nor negatively affect left ventricular function. Despite this, the heat generated during the forward grinding can lower rotational speed with possibility of generating larger particles especially when the rotational speed drops below 75,000 rpm.

2. Study Aim

1 To describe the use of RA in real world practice in Asia
2 To determine predictors of procedural success
3 To determine predictors of major procedural complications: perforation and no-reflow phenomenon
4 To assess the clinical outcome of patients undergoing RA for heavily calcified coronary lesions.

3. Selection and exit criteria

3.1 Inclusion criteria

Subjects MUST fulfill ALL of the following requirements in order to be eligible for the study:

1. At least 21 years of age of any gender
2. Able to understand and sign an informed consent form
3. Presence of clinical indication for percutaneous coronary intervention (PCI) and/or stent placement
4. Subjects willing to comply with all research and follow-up requirements
5. Angiographic criteria (ONE of the following criteria MUST be met)
    a. Target lesions visually have at least moderate calcifications*

   b. Target lesion balloon dilatation failure
   c. Inability of devices (microcatheters, balloon, stents or imaging devices) to pass through the target lesion
   d. Intravascular imaging shows severe calcifications*
6. Procedural criteria
   a. All patients treated with RA with or without other forms of debulking therapy

*Moderate calcification is defined as radio-opacities noted only during cardiac cycle prior to contrast injection whereas severe calcification is defined as radio-opacities seen without cardiac motion prior to contrast injection, usually affecting both sides of the arterial lumen[1].

3.2 Exclusion criteria

1. Patient unable to or decline to give consent

3.3 Exit criteria

Participation in this study is optional and patients are free to withdraw their participation from this study at any time point during the study process without the need to provide any justification. Withdrawal from this study will not affect participants' future medical treatment.

Patients who have withdrawn their participation are not obligated to continue further follow-up and will not be replaced by new participants in this study. A reasonable sample size has been calculated to account for patient attrition.

Should the reason for withdrawal from the study be due to issues related to either safety or effectiveness of the study device, the investigator shall obtain a new separate consent from the subject, independent of the original study consent, to continue tracking his/her clinical progress/ situation.

3.4 Early termination

The study sponsors reserve the right to terminate the study at any stage should the need arise but will exercise this right only for valid scientific or administrative reasons. The study sponsors, relevant ethics committee and regulatory agencies (if applicable) will be notified in writing at the time of study termination.

3.4.1 Study termination criteria

Study termination refers to the cessation of all tests or follow-up during the progress of a clinical trial program. The main purpose is to protect the rights and interest of clinical subjects, maintain quality assurance testing and to minimize unnecessary economic losses.

Causes for early termination includes (but not limited to) the following:

1. Inability to continue research on grounds of medical and/or ethical considerations
2. Slow enrollment progress such that the study cannot be completed within a reasonable and acceptable time window

3. Decision from Ethics Committee/Board to terminate the study
4. Availability of new information which impacts standard of care (such as product safety/ performance)
5. Boston Scientific Corporation decides to suspend/ halt the development of the study/ test equipment

3.4.2 Study site termination criteria

If a study/ research site (i) is unable to recruit any patients, (ii) has an enrollment rate that is significantly lower than expected (iii) violated the study protocol without due justification or in spite of remedial measures, the study sponsors/ National Heart Centre Singapore (NHCS) reserve the right to remove the study site from the research study.

4. Study design

4.1 Research design

This is a prospective observational multicenter cohort study of all patients with calcified coronary lesions undergoing RA in participating centres across Asia. Patients will be required to provide informed consent for data collection, including follow-up data and uploading of data on a web-based data collection platform (de-identified).

Operators/ institution coordinators will fill up hardcopy or electronic (web-based) forms including patient's baseline demographics, co-morbidities, clinical data, laboratory test results, echocardiography results, coronary angiography findings with subsequent interventions performed as well as follow-up clinical and laboratory results.

Note that while detailed data for individual patients will only be collected if there is informed consent, data from each institution will also be collected for aggregate data regarding procedural volume (eg. total cases with debulking therapy and specifically for ROTABLATOR^{TM}). This will give a sense of representativeness of data collected. This screening data will also include the following fields: age, gender, ethnicity, co-morbidities, target vessel, prior revascularization (PCI/CABG), clinical presentation, procedural urgency, angiographic procedural details (RA and PCI) and in-hospital complication and mortality. The use of this retrospective data will require appropriate approval and will only utilize anonymized data. Only in-hospital data will be obtained and no follow up data is required from these controls.

Should these data not be available in any of the participating sites, a minimum baseline demographics, procedural and inpatient outcome data with reasons for non-participation in registry should be provided for records purposes. This shall be accepted as a limitation of the study. Sub-site analysis may be performed in centres with availability of all data in this group of patients to address generalisability of the data collected.

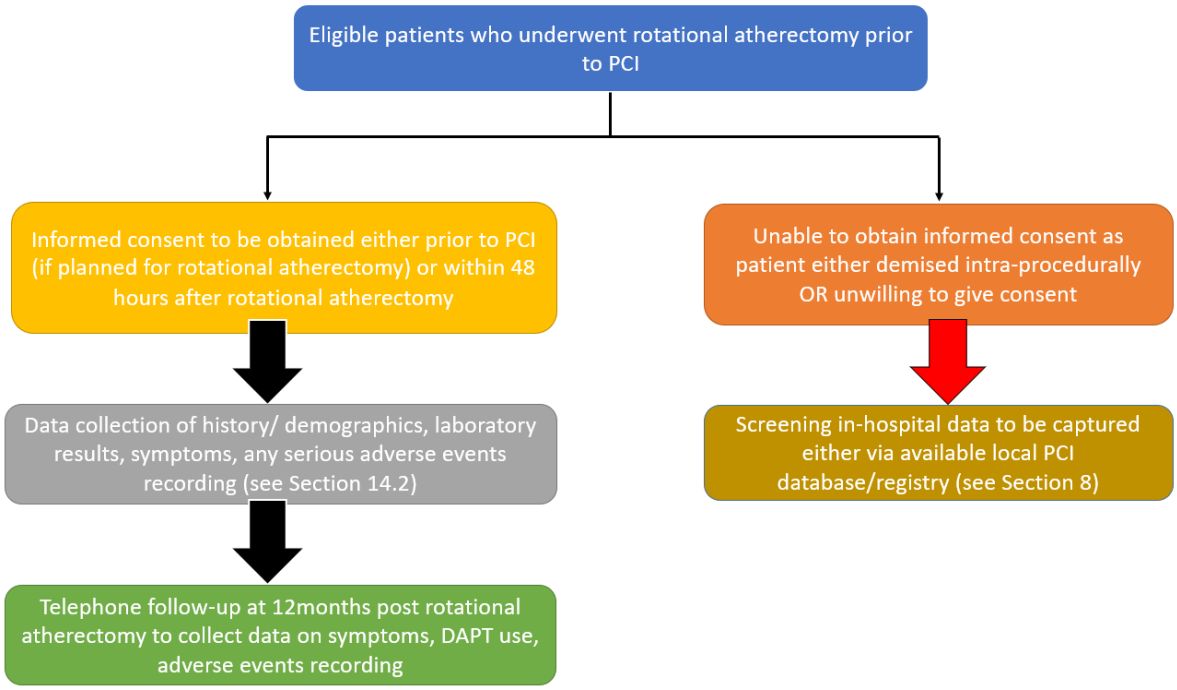


Figure 6: Data collection workflow for (i) patients who provide consent vs (ii) patients who declined to provide consent/ unable to give timely consent in view of unexpected demise

4.2 Study stages

4.2.1 Index visit: Within 48 hours of PCI

The following information will be captured during this index visit:

1. Demographics: Age, gender, ethnicity
2. Clinical characteristics: Clinical presentation (STEMI, NSTEMI, UAP, Angina, cardiac arrest), Symptoms (CCS angina score), Co-morbidities (diabetes mellitus, hypertension, hyperlipidemia, atrial fibrillation, smoking status, CKD/ ESRF, prior MI, prior PCI, prior CABG, prior CVA)
3. Laboratory results: full blood count, creatinine, electrolytes, fasting lipids/ glucose, HbA1c, cardiac injury markers i.e troponin T or I, CK, CK-MB)
    a. If either troponin T or I is to be measured AFTER PCI with rotational atherectomy, a total of 3 sets are recommended at specific time intervals of 0-1 hours (1st set), 4-8 hours (2nd set) and 12-24 hours (3rd set) POST-PCI to ensure uniformity of sample collection across all sites.
    b. Sites are to also provide the upper limit of normal values for their laboratory assay tests.
4. Medications: prior to PCI, during PCI, on discharge
5. ECGs (a post procedural ECG is required)
6. Echocardiographic data (LVEF)
7. Procedural data: Coronary anatomy (artery dominance, number of diseased vessels, presence of bypass grafts), target lesion (location by artery/grafts, proximal vs mid vs distal, branches (ramus, diagonal, OM, RPDA, graft)), rotational atherectomy (lubricant, burr size, run time, burr speed, number of passes, maximum rotational speed), adjunctive devices (guideliners, guide size, guide shape), PCI (type of PCI performed - POBA vs DEB vs DES, number of stents, pre and post-dilatation, stent overlap),

angiographic outcomes (TIMI flow, angiographic complications) procedural details (fluoroscopic duration, total contrast media)

8. Intravascular imaging data (OCT/ IVUS)
    a. Sites will also send CDs of their angiograms and intravascular imaging
9. Outcomes data: Primary (residual stenosis in treated segment with TIMI 3 flow without mortality), Secondary (Death, periprocedural MI, complications (coronary perforation, no reflow, slow flow)
10. Primary operator data: ie. Operator initials (further anonymized prior to analysis), Age band, years of interventional cardiology practice, number of procedures. (PCI) performed preceding year (range), approximate number of rotablator performed last year (range)
11. Limited hospital data: number of years with rotablator therapy, approximate number of PCI preceding year, number of rotablator preceding year, availability of orbital atherectomy/ shockwave lithotripsy

Patient will also be asked to sign study consent form (in addition to institutional procedural consent form) to certify agreement to participate in current research study.

4.2.2 Follow-up at 12 months: telephone contact

The following information will be captured during this 12-month follow-up visit: Symptoms (CCS score), medications (antiplatelet therapy, statins, non-statins LDL lowering therapy), outcomes (death, MI, TLR, stent thrombosis, and stroke).

4.3 Data collection of patients excluded from registry

1. Demographics: Age, gender, ethnicity
2. Abbreviated clinical characteristics: Clinical presentation (STEMI, NSTEMI, UAP, Angina, cardiac arrest), Symptoms (CCS score), Co-morbidities (diabetes mellitus, hypertension, hyperlipidemia, atrial fibrillation, smoking status, CKD/ ESRF, prior MI, prior PCI, prior CABG, prior CVA)
3. Abbreviated laboratory results: full blood count, creatinine, fasting lipids, HbA1c, cardiac injury markers i.e troponin T or I, CK, CK-MB)
4. Medications: on discharge
5. Echocardiographic data (LVEF)
6. Procedural data: Coronary anatomy (artery dominance, number of diseased vessels, presence of bypass grafts), target lesion (location by artery/grafts, proximal vs mid vs distal, branches (ramus, diagonal, OM, RPDA, graft)), use of alternative calcium debulking devices, PCI (type of PCI performed - POBA vs DEB vs DES, number of stents, pre and post-dilatation, stent overlap), angiographic outcomes (TIMI flow, angiographic complications) procedural details (fluoroscopic duration, total contrast media)
7. Outcomes data: Primary (residual stenosis in treated segment with TIMI 3 flow without mortality), Secondary (Death, periprocedural MI, complications (coronary perforation, no reflow, slow flow)

5. Medications

All participants are recommended to be initiated on dual antiplatelet therapy (DAPT), one of which must be aspirin and the other is a P2Y12 inhibitor (clopidogrel or ticagrelor) prior to PCI. The duration of DAPT is to be determined by the interventionist. The following recommendations are for physician reference.

(i) Aspirin

If the subject has been taking aspirin daily for ≥ 72 hours prior to PCI, loading of aspirin is not necessary.

If the subject is aspirin naïve or has taken aspirin for less than 72 hours prior to PCI, loading of aspirin prior to PCI is recommended. Dose of aspirin loading is to be determined by the interventionist.

If aspirin is to be loaded, it is recommended to be at least 2-hour prior to PCI.

Patient should be continued on long term aspirin subsequently.

(ii) P2Y12 inhibitors

If the subject has taken P2Y12 inhibitors (e.g. clopidogrel, ticagrelor or prasugrel) ≥ 7 days, loading of P2Y12 is not necessary.

If the subject is P2Y12 inhibitor naïve or has not taken P2Y12 daily for at least 7 days, loading of P2Y12 prior to the PCI is recommended. The dose of P2Y12 is to be determined by the interventionist. Generally, at least 300-600mg of clopidogrel is required for loading, while ticagrelor loading dose is 180mg.

If P2Y12 is to be loaded, it is recommended to be at least 2-hour prior to PCI for both clopidogrel and ticagrelor.

For prasugrel, loading dose of 60mg should only be given once coronary anatomy is known and PCI is planned on table.

The subject should be treated with P2Y12 inhibitor for a minimum duration of 6 months and continued up to at least 12 months if the risk of bleeding is deemed to be low.

(iii) Intraprocedural anticoagulation

The choice of anticoagulation is dependent on operator's discretion to maintain a recommended ACT range of 200-300 seconds.

(iv) Intracoronary medications

The administration of intracoronary glyceryl trinitrate (GTN) is recommended prior to coronary angiography of both left and right coronary artery system.

The use and choice of other intracoronary vasodilators such as CCB, adenosine is left up to operator's discretion/ individual site practice.

(v) Guideline directed medical therapy

Other medications such as statins, ACEi/ ARB, Beta-blockers, calcium antagonists and other drugs use are as per international or local guidelines such as ACC or ESC.

6. Procedure

6.1 Preparation prior to rotational atherectomy

Access planning for an individual patient must balance the need to provide sufficient support for RA and vascular complications that may arise. Generally, a 6 Fr system is adequate to support RA in most cases and is able to accommodate burr sizes up to 1.75mm, thereby permitting either trans-radial or trans-femoral approach. Radial approach has been associated with equivalent procedural success to that of femoral access[29,30]. As such, radial approach should not be abandoned in patients who have planned RA. In addition, additional support can be enhanced by either using a long sheath, supportive guide catheter or a child-in-mother catheter. In contrary, if a 2.0mm or larger burr size is required or complex bifurcation PCI is planned, a 7Fr or larger catheter may be required, by which a trans-femoral approach may be preferred.

Prior to RA, it is paramount to position a RotaWire across the target lesion with its tip placed as far distally as possible. Primary wiring of target lesion with RotaWire can be challenging and thus initial wiring with either a workhorse or specialty 0.014" coronary guidewire within a micro-exchange catheter or over-the-wire balloon may be easier, subsequently permitting exchange for a RotaWire while concurrently divulging crossing properties of the lesion. In situations whereby the microcatheter is unable to cross the lesion, it is advisable to perform RA with the smallest (1.25mm) burr.

Burr size selection is key to procedural success. As shown in STRATAS and CARAT trial, smaller burrs (with burr: artery ratio < 0.7) have comparable angiographic and procedural success rates to larger burrs but with fewer angiographic complications, less peri-procedural myocardial injury, use of smaller sheaths and guide catheters with consequently lower vascular and bleeding complications[10,11]. A stepped burr strategy beginning with 1.25 or 1.50 burr with gradual escalation in size up to maximal burr: artery ratio of 0.7 is recommended especially in cases for which micro-exchange catheter will not cross the lesion or lesions with severe angulation, tortuosity or eccentricity.

During the RA process, a flush solution comprising of heparinized saline with RotaGlide lubricant is also recommended to lubricate device motion, prevent sudden decelerations and reduce heat generation. In some instances, vasodilators such as nitroglycerin (50-200µg), verapamil (100-200µg, up to a total amount of 1.0 – 1.5mg) or diltiazem (0.5-2.5mg, up to 5-10mg) can be incorporated into the flush solution to further reduce risk of microvascular obstruction.

RA involving right coronary artery, left dominant circumflex or use of large burr head (> 2.25mm) are prone to transient microvascular ischemia with consequent risk of bradycardia and conduction blocks. In such situations, prophylactic temporary pacing may be considered. Bradycardia in these situations occur especially during forward grinding spin of the burr and usually recovers after 5 to 60 seconds post cessation of atherectomy or on coughing.

6.2 Rotational atherectomy operational guide

6.2.1 System setup

Plug in console and turn on power switch. Connect the air supply hose to compressed air or nitrogen (minimum of 500 PSI in tank per procedure with 90-110 PSI flowing to console). Connect all 3 Dynaglide foot pedal hoses to the console (green and blue to the back while pink to the front). Then, connect the fiber-optic cables and air -line to the front of the console. Add the RotaGlide lubricant and other adjunctive vasodilators (as indicated) to the 1-liter sterile saline bag and connect it to the ROTABLATOR^{TM} infusion port and pressurize the bag to 150 - 200mmHg.

6.2.2 Procedure preparation

Place both the guide sheath and guidewire sequentially into the target vessel. Advance the guidewire beyond the target lesion and backload burr, stopping just proximal to the sheath. Grasp the proximal tip of the guidewire and thread this end into the hole in the tip of the burr. Continue feeding the wire into the catheter until it appears at the rear of the advancer. Then, grasp the exposed wire and pull it gently until the burr is a few centimeters from the entrance to the guide sheath/ introducer sheath. Thereafter, attach a wireclip Torquer to the end of the guidewire. Ensure that advancer knob is fixed at 2cm from the distal end. Connect the air hose, fiber optic cable and saline infusion port subsequently.

Test the system outside the subject's body with foot pedal activated. Firstly, check the drip from the catheter sheath tip and beneath the advancer. Next, set the burr speed to desired RPM level followed by ensuring the free movement of the advancer knob. Finally, check that the wire is visible out of the advancer with torquer clip attached. Tug on wire during rotating to ensure brake is activated.

6.2.3 Burr positioning and ablation procedure

Under fluoroscopic guidance, gently push the burr through the guide sheath to a point proximally to the target lesion. Check that the burr size is compatible with vessel diameter by contrast injection. Stop the burr in free lumen and when the burr is 1-2cm proximal to the target lesion, retract the advancer knob fully to prevent the burr from darting forward during first activation.

Fully depress the foot pedal to activate the burr. Adjust your foot for optimum position on the foot pedal. Recheck the rotational speed reading to verify that the rotation rate is appropriate for the burr size and lesion type. Generally smaller burrs 1.25mm – 2.0mm burrs require rotational speed of 160,000-180,000 rpm whereas larger burrs of at least 2.15mm require lower rotational speed of 140,000-180,000 rpm.

Slowly push the advancer knob forward and observe progress of burr fluoroscopically. Advance in such a manner such that the burr speed does not decrease lower than beyond 5000 rpm from the unloaded platform speed. This can be assessed by firstly observing the console display initially followed by listening to the corresponding drop in audible pitch. It is recommended to advance and retreat the burr no more than 3cm at a time in a smooth pecking motion. Care should be taken to engage the lesion only minimally when resistance is met. Short individual runs of less than 30 seconds are recommended with total rotational procedure time not to exceed five minutes. In between each interval, small amount of contrast should be injected to assess for burr head position, confirm presence of coronary blood flow and evidence of vascular complications such as

perforation in addition to flushing microparticles to distal ends of vessels. If resistance to motion is encountered, retract the burr and stop treatment immediately. Reassess situation using fluoroscopy. Decision to stop further atherectomy attempts using current burr is dependent on absence of resistance felt throughout the entire length of diseased segments or rotational speed was not significant decreased during the run.

6.2.4 Burr exchange and procedure completion

When satisfactory RA attempt has been made using the first burr, activate the Dynaglide feature by pressing the button on the foot pedal to exchange burr. When this feature is activated, the RA system will rotate at reduced speed of 60,000 – 90,000 rpm and the guidewire will advance readily when the advancer is withdrawn. The guidewire must be held firmly using the wireclip Torquer whenever the advancer is operated under the Dynaglide mode. With the wireclip Torquer/guidewire combination in docking port, depress the brake defeat button and push forward on the Torquer until it stops, hence locking the brake defeat button in a depressed position. Thereafter, the burr can be withdrawn over the guidewire until a 7cm or larger loop of wire remains. Release the foot pedal then. Thereafter, switch to a larger burr if required or proceed with stent placement if desired treatment outcome has been achieved.

6.3 Intracoronary imaging

Where appropriate, the preferred imaging platform is intravascular ultrasound (IVUS), either with Opticross or Opticross HD. However, the final selection on the use of IVUS or optical coherence tomography (OCT) is subject to operator's discretion based on angiographic findings.

6.4 PCI post rotational atherectomy

For PCI, the preferred type of stent is drug eluting stent (DES), either with SYNERGY or SYNERGY XD per commercial availability. However, the final selection on stent type/ brand is subject to operator's discretion based on clinical indication as well as angiographic findings.

7. Outcomes

7.1 Primary efficacy endpoint

Procedural success defined as < 20% residual stenosis in treated segment without on-table mortality with TIMI 3 flow

7.2 Secondary outcome measures

1. Death (in-hospital and at 1-year follow-up)
2. Periprocedural myocardial infarction (MI) defined as either (within 48 hours of procedure)
    a. Peak CK-MB ≥ 10x ULN OR ≥ 5x ULN + new pathologic Q waves in ≥ 2 contiguous leads/ new persistent LBBB[2] OR
    b. Peak Troponin T or I > 5x ULN + new pathologic Q waves/ ischemic ECG changes[3]
3. Complications: Significant coronary perforation defined as (within 48 hours of procedure)
    a. At least Type II, III or III CS based on Ellis classification[4]

4. Complication: no-reflow or slow flow (within 48 hours of procedure)
5. Procedural time defined as
    a. Time of guide engagement to removal of guide.

8. Safety assessment

8.1 Primary safety endpoint

All RA-related complication rate

8.2 Safety index

The following safety data will be collected over the 12-months follow-up period:

1. All-cause death (cardiac/non-cardiac/sudden death/unknown)
2. Myocardial infarction
    a. Subset analysis on target vessel MI (TVMI) in those with data on repeat coronary angiography
3. Target lesion revascularization (TLR)
4. Definite/probable stent thrombosis
5. Major cardiovascular events (MACE)
    a. Defined as composite endpoint of cardiac death, MI, TLR, and stent thrombosis
6. Stroke
7. Device related adverse events
    a. Includes but are not limited to rotawire fracture/ breakage, rotawire unravelling/ fraying, burr dislodgement/ fracture and burr entrapment

8.2 Reporting of adverse events

The events listed in Section 12.1 are all considered serious adverse events (SAE). However, as the procedure is done in accordance to standard of care and RA has been extensively used in clinical settings worldwide, these safety data will only be collected for the purposes of this registry and does not require safety reporting to Institutional Review Board (IRB) or Ethics Committee (EC).

Should there be an SAE deemed reportable by the respective site PI, the site PIs are to report the event(s) to their respective local IRB or EC as per their own prevailing safety reporting guidelines.

9. Data management/ monitoring

9.1 Accountability of data, completion and handover of data entry form

All participants who have signed the study consent form and are eligible for participation will have all of the necessary information recorded in the data entry form.

9.2 Database design

A secure web-based database application i.e. REDCap will be used to collate study data and for the purposes of study analysis.

9.3 Data entry

Clinical research coordinator (CRC) and/or authorized study investigators will be able to input and edit the data from the case reporting form into the electronic database as accurately as possible.

9.4 Data verification

The database will be reviewed by the site investigators as well as lead investigators to ensure the veracity of the data collected. If there are any discrepancies noted, a manual enquiry will be raised and will be discussed between involved study sites and the primary study site i.e. NHCS.

9.5 Data security

After the CRC or researcher fills in the data completely, data managers, statisticians and lead PI will review the data and finalise the analysis/ outcomes of the study population before locking/ encrypting the database.

9.6 Core laboratory (Angiography/ Intravascular imaging – IVUS/OCT)

Dr Chin Chee Yang
Consultant
National Heart Centre Singapore

9.7 Statistical analysis team

Gao Fei
National Heart Research Institute (NHRI)
National Heart Centre Singapore (NHCS), Singapore

Dr. Tomohiro Shinozaki, PhD, MPH.
Department of Information and Computer Technology, Faculty of Engineering, Tokyo University of Science, Tokyo, Japan.

10. Statistical analysis

10.1 Sample size determination

10.1.1 Statistical hypothesis

The RA-related complications occur in 5% of all the RA procedures in Asian PCI centres

NOTE: See Appendix 1 and 2 for contemporary data on RA-related complication rates justifying selection of 5% incidence rate for all RA-related complications[31].

10.1.2 Assumptions

The target sample size is calculated based on the following assumptions:

1. The proportion of RA-related complications is 5%
2. 95% confidence intervals width is 3%.
3. Up to 20% of patients are assumed to drop out of this study

Confidence Level	Sample Size (N)	Target Width	Actual Width	Proportion (P)	Lower Limit	Upper Limit	Width if P = 0.5
0.95	1118	0.02	0.02	0.03	0.02	0.04	0.059
0.95	1476	0.02	0.02	0.04	0.03	0.05	0.051
0.95	1825	0.02	0.02	0.05	0.04	0.06	0.046
0.95	2167	0.02	0.02	0.06	0.05	0.07	0.042
0.95	497	0.03	0.03	0.03	0.015	0.045	0.088
0.95	656	0.03	0.03	0.04	0.025	0.055	0.077
0.95	**811**	**0.03**	**0.03**	**0.05**	**0.035**	**0.065**	**0.069**
0.95	963	0.03	0.03	0.06	0.045	0.075	0.063
0.95	280	0.04	0.04	0.03	0.01	0.05	0.117
0.95	369	0.04	0.04	0.04	0.02	0.06	0.102
0.95	457	0.04	0.04	0.05	0.03	0.07	0.092
0.95	542	0.04	0.04	0.06	0.04	0.08	0.084

Table 1: Numeric Results for Two-Sided Confidence Intervals for One Proportion Confidence Interval Formula: Simple Asymptotic

10.1.3 Final sample size

1000 subjects

10.2 Statistical analysis of data set

Full analysis set (FAS): Refers to the set of analysis established in accordance to intention-to-treat (ITT) principle. All subjects who signed informed consent form and met all the inclusion criteria with the use of RA with or without other calcium debulking therapies will be included in this analysis. For subjects who are unable to complete the study follow-up, the primary endpoint will be based on the last observation carry forward method.

Per-protocol set (PPS): Refers to the set of analysis pertaining to the whole treated study population who have completed the study excluding those not fulfilling selection criteria or use of devices/ equipments not provided in this research study.

Safety analysis set (SS): Refers to all study subjects that have been evaluated at least once for safety outcome. Those with missing data will not be carried forward.

Efficacy analysis will be carried out based on the full analysis set and the per-protocol set.

10.3 Statistical analysis plan

All demographic data, clinical characteristics, laboratory results, medications, electrocardiography, imaging, angiographic data, intravascular data, outcomes, primary operator data and hospital data will be analyzed. Continuous variables will be described using mean, median, standard deviation, interquartile range (IQR) and minimum/maximum values. Discrete variables will be described using frequency tables. A t-test will be used to assess if there is a significant difference ($p<0.05$) in continuous data and a chi-square test will be used in discrete data.

All statistical comparisons will be performed using two-sided tests with a significance level of 0.05. Statistical analysis will be performed using STATA or SAS software.

10.4 Primary efficacy endpoint analysis

Procedural success rate will be estimated and reported with 95% confidence interval.

10.5 Secondary endpoint analysis

All event rates within 48 hours of procedure will be estimated and reported with 95% confidence interval.

10.6 Safety evaluation

Kaplan-Meier curve will be used to construct 1-year cumulative event rates with 95% confidence interval.

10.7 Sub-group analysis

This study will collect all subjects who have undergone calcium debulking therapy and evaluate real-world clinical outcomes

The following sub-groups (but not limited to) may be utilised for analysis:

(i) Acute coronary syndrome
(ii) Lesion length
(iii) Bifurcation lesions
(iv) Multiple overlapping stents (≥ 2 stents for each epicardial coronary artery)
(v) Chronic kidney disease

(vi) Multivessel disease (≥ 2 vessel CAD)
(vii) Left main (LM) equivalent
(viii) Chronic total occlusions (CTO)
(ix) Severely impaired LVEF i.e. ≤ 30%
(x) IVUS subgroup

11 Study Management

11.1 Statement

This study complies with the requirements of the current Declaration of Helsinki as well as other relevant national regulations

11.2 Ethical section

In accordance to national policies and regulations, the site study investigators must provide the Ethics Committee with relevant study documents as required.

A copy of the approval from the local Ethics Committee together with the list of review documents must be submitted to the primary site i.e. National Heart Centre Singapore (NHCS) before the device will be delivered to the study sites. The approval document from the Ethics Committee must also be accompanied by a list detailing all the members involved in the approval and their respective roles in the committee.

Approval from Ethics Committee is mandatory prior to initiation of clinical trial.

Any changes to the study protocol must be submitted to the Ethics Committee for approval. Throughout the study, any serious or unintended adverse events pertaining to safety of patients must be reported to the Ethics Committee.

11.3 Verification of original records

Study investigators must ensure that all data obtained during this study is properly secured and encrypted to protect the privacy of subjects involved. In addition, study investigators must also consent to audit/ verification of database by auditors/ inspectors to ensure accuracy and accountability of data collected as well as update on progress of study. In the unfortunate event that the original records cannot be verified, the study investigator will need to assist the auditor in quality control of the data.

11.4 Quality assurance and audit

The study will be audited by personnel authorized by National Heart Centre Singapore/ Boston Scientific Corporation. Quality auditors will have access to all medical records, research-related documents/ correspondences, and informed consent for this study.

11.5 Informed Consent

It is the responsibility of the study investigator to explain the purpose, methods, benefits, and potential risks of this clinical trial to each subject. An informed consent (both written and verbal) must be obtained from the subject prior to inclusion in this study. Informed consent must be dated and signed by the participant him or herself. Participants who decline to provide informed consent will be excluded from this study. A copy of the signed inform consent and information sheet will be given to the participants.

By signing the informed consent form, the participant has agreed to allow National Heart Centre Singapore and Boston Scientific Corporation auditors to verify the data.

11.6 Modification of study protocol

Once the final version of the study protocol has been agreed upon, any further modifications to the protocol will be subjected to a detailed review of proposed changes with the proposer to initial against the proposed changes with date and time.

All proposed changes must be approved in writing by the Ethics Committee. All documents will need to be submitted to National Heart Centre Singapore (NHCS)

11.7 Case report form (CRF)

Operators/ institution coordinators will fill up hardcopy and/or electronic (web-based) forms including patient's baseline demographics, co-morbidities, clinical data, laboratory test results, echocardiography results, coronary angiography findings with subsequent interventions performed as well as follow-up clinical and laboratory results. Note that while detailed data for individual patients will only be collected if there is informed consent, data from each institution will also be collected for aggregate data regarding procedural volume (eg. Of total cased with debulking therapy and specifically for rotablator). This will give a sense of representativeness of data collected.

11.8 Audit

NHCS will request for participating centers to provide updates on recruitment progress as well as clinical outcomes of existing patients at regular intervals.

Finally, all original data collection forms, records, laboratory results must be readily available at every time point to all study investigators and auditors.

11.9 Confidentiality agreement and patient privacy

Study investigators must ensure the confidentiality of the information provided or disclose the requisite information as required with the authorization from NHCS.

The researcher must not disclose any confidential information obtained from NHCS, Boston Scientific, or from this study to third parties.

Researcher musts ensure that the data is anonymized. It is imperative that all documents submitted to NHCS or Boston Scientific is labelled with study index number and that participants personal details cannot be retrieved from the documents.

12. Publications

National Heart Centre Singapore (NHCS), as the primary site, will hold exclusive rights to this study. All study site investigators will be involved in the drafting of manuscripts related to this study. As this is a multicenter study, investigators are not allowed to write/ submit a manuscript until the final analysis from the multicenter study is completed, unless it is approved by NHCS. With regards to manuscripts and publications, NHCS reserves the right to determine the final outcome.

13. Data archiving

In accordance to regulations, study investigators should properly preserve the original records of the research. All clinical research data must be kept for at least 5 years from the start of data collection. It is the responsibility of the primary site to inform the study investigators when such information is no longer required to be saved.

14. References

1. Popma JJ BT. Qualitative and Quantitative Angiography. In: E. T, ed. *Textbook of Interventional Cardiology*. WB Saunders, Philaedelphia, PA; 1994:1052-1068.

2. Moussa ID, Klein LW, Shah B, et al. Consideration of a new definition of clinically relevant myocardial infarction after coronary revascularization: An expert consensus document from the society for cardiovascular angiography and interventions (SCAI). *J Am Coll Cardiol*. Published online 2013. doi:10.1016/j.jacc.2013.08.720

3. Thygesen K, Alpert JS, Jaffe AS, et al. Fourth Universal Definition of Myocardial Infarction (2018). *J Am Coll Cardiol*. Published online 2018. doi:10.1016/j.jacc.2018.08.1038

4. Ellis SG, Ajluni S, Arnold AZ, et al. Increased coronary perforation in the new device era: Incidence, classification, management, and outcome. *Circulation*. Published online 1994. doi:10.1161/01.cir.90.6.2725

5. Généreux P, Madhavan M V., Mintz GS, et al. Ischemic outcomes after coronary intervention of calcified vessels in acute coronary syndromes: Pooled analysis from the HORIZONS-AMI (Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction) and ACUITY (Acute Catheterization. *J Am Coll Cardiol*. Published online 2014. doi:10.1016/j.jacc.2014.01.034

6. Hansen DD, Auth DC, Vracko R, Ritchie JL. Rotational atherectomy in atherosclerotic rabbit iliac arteries. *Am Heart J*. Published online 1988. doi:10.1016/0002-8703(88)90532-7

7. Reifart N, Vandormael M, Krajcar M, et al. Randomized comparison of angioplasty of complex coronary lesions at a single center: Excimer laser, rotational atherectomy, and balloon angioplasty comparison (ERBAC) study. *Circulation*. Published online 1997. doi:10.1161/01.CIR.96.1.91

8. Dill T, Dietz U, Hamm CW, et al. A randomized comparison of balloon angioplasty versus rotational atherectomy in complex coronary lesions (COBRA study). *Eur Heart J*. Published online 2000. doi:10.1053/euhj.2000.2242

9. Sharma SK, Tomey MI, Teirstein PS, et al. North American Expert Review of Rotational Atherectomy. *Circ Cardiovasc Interv*. Published online 2019. doi:10.1161/CIRCINTERVENTIONS.118.007448

10. Whitlow PL, Bass TA, Kipperman RM, et al. Results of the study to determine rotablator and transluminal angioplasty strategy (STRATAS). *Am J Cardiol*. Published online 2001. doi:10.1016/S0002-9149(00)01486-7

11. Safian RD, Feldman T, Muller DWM, et al. Coronary Angioplasty and Rotablator Atherectomy Trial (CARAT): Immediate and late results of a prospective multicenter randomized trial. *Catheter Cardiovasc Interv*. Published online 2001. doi:10.1002/ccd.1151

12. Abdel-Wahab M, Richardt G, Joachim Büttner H, et al. High-speed rotational atherectomy before paclitaxel-eluting stent implantation in complex calcified coronary lesions: The randomized ROTAXUS (Rotational Atherectomy Prior to Taxus Stent Treatment for Complex Native Coronary Artery Disease) trial. *JACC Cardiovasc Interv*. Published online 2013. doi:10.1016/j.jcin.2012.07.017

13. Levine GN, Bates ER, Blankenship JC, et al. 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention. *J Am Coll Cardiol*. Published online 2011. doi:10.1016/j.jacc.2011.08.007

14. Barbato E, Carrié D, Dardas P, et al. European expert consensus on rotational atherectomy. *EuroIntervention*. Published online 2015. doi:10.4244/EIJV11I1A6

15. Wong ND, Kouwabunpat D, Vo AN, et al. Coronary calcium and atherosclerosis by ultrafast computed tomography in asymptomatic men and women: Relation to age and risk factors. *Am Heart J*. Published online 1994. doi:10.1016/0002-8703(94)90133-3

16. Goel M, Wong ND, Eisenberg H, Hagar J, Kelly K, Tobis JM. Risk factor correlates of coronary calcium as evaluated by ultrafast computed tomography. *Am J Cardiol*. Published online 1992. doi:10.1016/0002-9149(92)90346-Z

17. M.V. M, M. T, G.S. M, A. M, G.W. S, P. G. Coronary artery calcification: Pathogenesis and prognostic implications. *J Am Coll Cardiol*. Published online 2014.

18. Bild DE, Detrano R, Peterson D, et al. Ethnic differences in coronary calcification: The Multi-Ethnic Study of Atherosclerosis (MESA). In: *Circulation*. ; 2005. doi:10.1161/01.CIR.0000157730.94423.4B

19. Abedin M, Tintut Y, Demer LL. Vascular calcification: Mechanisms and clinical ramifications. *Arterioscler Thromb Vasc Biol*. Published online 2004. doi:10.1161/01.ATV.0000133194.94939.42

20. Demer LL, Tintut Y. Vascular calcification: Pathobiology of a multifaceted disease. *Circulation*. Published online 2008. doi:10.1161/CIRCULATIONAHA.107.743161

21. Wang X, Matsumura M, Mintz GS, et al. In Vivo Calcium Detection by Comparing Optical Coherence Tomography, Intravascular Ultrasound, and Angiography. *JACC Cardiovasc Imaging*. Published online 2017. doi:10.1016/j.jcmg.2017.05.014

22. Vavuranakis M, Toutouzas K, Stefanadis C, Chrisohou C, Markou D, Toutouzas P. Stent deployment in calcified lesions: Can we overcome calcific restraint with high-pressure balloon inflations? *Catheter Cardiovasc Interv*. Published online 2001. doi:10.1002/1522-726X(200102)52:2<164::AID-CCD1041>3.0.CO;2-S

23. Kume T, Okura H, Kawamoto T, et al. Assessment of the coronary calcification by optical coherence tomography. *EuroIntervention*. Published online 2011. doi:10.4244/EIJV6I6A130

24. Tomey MI, Kini AS, Sharma SK. Current status of rotational atherectomy. *JACC Cardiovasc Interv*. Published online 2014. doi:10.1016/j.jcin.2013.12.196

25. Tamura H, Miyauchi K, Dohi T, et al. Comparison of clinical and angiographic outcomes after bare metal stents and drug-eluting stents following rotational atherectomy. *Int Heart J*. Published online 2016. doi:10.1536/ihj.15-222

26. De Waha S, Allali A, Büttner HJ, et al. Rotational atherectomy before paclitaxel-eluting stent implantation in complex calcified coronary lesions: Two-year clinical outcome of the randomized ROTAXUS trial. *Catheter Cardiovasc Interv*. Published online 2016. doi:10.1002/ccd.26290

27. Kawamoto H, Latib A, Ruparelia N, et al. Planned versus provisional rotational atherectomy for severe calcified coronary lesions: Insights From the ROTATE multi-center registry. *Catheter Cardiovasc Interv*. Published online 2016. doi:10.1002/ccd.26411

28. Kovach JA, Mintz GS, Pichard AD, et al. Sequential intravascular ultrasound of the mechanisms of rotational atherectomy and adjunct balloon angioplasty. *J Am Coll Cardiol*. Published online 1993. doi:10.1016/0735-1097(93)90412-T

29. Kotowycz MA, Khan SQ, Freixa X, et al. Rotational atherectomy through the radial artery is associated with similar procedural success when compared with the transfemoral route. *Coron Artery Dis*. Published online 2015. doi:10.1097/MCA.0000000000000198

30. Watt J, Oldroyd KG. Radial versus femoral approach for high-speed rotational atherectomy. *Catheter Cardiovasc Interv*. Published online 2009. doi:10.1002/ccd.22066

31. Gupta T, Weinreich M, Greenberg M, Colombo A, Latib A. Rotational atherectomy: A contemporary appraisal. *Interv Cardiol Rev*. Published online 2019. doi:10.15420/icr.2019.17.R1

15. Appendix

15.1 Appendix 1: Contemporary data on RA-related complication rates

Table 3: Complications of Rotational Atherectomy in the Drug-eluting Stent Era

Study	n	Death (%)	MI (%)	Dissection (%)	Perforation (%)	Slow Flow/No Reflow (%)
PREPARE-CALC, 2018 [53]	100	0.0	2.0	3.0	4.0	2.0
Kawamoto et al, 2016[68]	1176	0.6	7.4	7.0	1.0	1.1
Sakakura et al, 2016[83]	13,335	0.6	–	–	–	–
Eftychiou et al, 2016[82]	518	0.6	–	–	1.4	0.6
ROTAXUS, 2013[11]	120	1.7	1.7	3.3	1.7	0.0
Abdel-Wahab et al, 2013[46]	205	1.5	2.4	4.4	0.5	2.0
Naito et al, 2012[74]	233	0.0	1.3	1.7	0.4	–
Benezet et al, 2011[47]	102	1.0	1.0	2.9	0.0	–
Garcia de Lara et al, 2010[73]	50	4.0	14.0	2.0	2.0	0.0
Rathore et al, 2010[48]	391	1.0	6.9	5.9	2.0	2.6
Vaquerizo et al, 2010[49]	63	0.0	3.2	–	–	–
Furuichi et al, 2009[50]	95	0.0	3.2	2.1	1.1	1.1
Clavijo et al, 2006[51]	81	0.0	19.8	1.9	–	–

Source: Tomey et al. 2014.[5] Adapted with permission from Elsevier © The American College of Cardiology Foundation.

15.2 Appendix 2: Definition and breakdown of RA-related complications

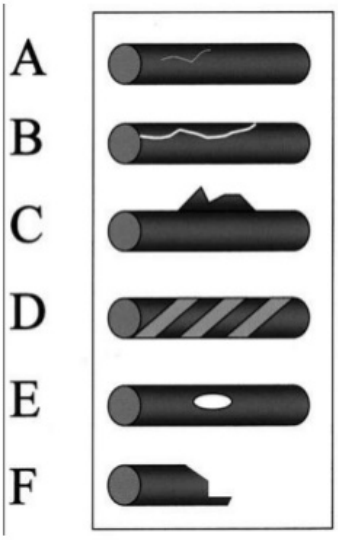
Paper	Study	Modality	Definition	Outcomes in RA
Safian et. al CARAT trial CCI 2001	Prospective, randomised, multicenter	RA (large vs small burr)	Any of (i) severe dissection (ii) no reflow (iii) side branch occlusion	Total 12.1%; severe dissection 6.3%, no reflow (2.3%), sidebranch occlusion (3.5%) Breakdown by burr size: large (12.7%) vs small (5.1%), $p < 0.05$
Abdel-Wahab et. al PREPARE CALC trial CCI 2018	Prospective, randomised, multicenter	RA vs modified balloon (MB)	Any of (i) large dissection (>5mm) (ii) perforations (iii) no/slow reflow (iv) side branch occlusion	Large dissection (3%), Perforation (4%), No/slow reflow (2%), side branch occlusion (6%)
Lee et. al AJC 2017	Retrospective, single center	RA vs OA	Any of (i) perforation (ii) dissection leading to less than TIMI 3 flow (iii) no reflow	Perforation/ dissection (0%), no- reflow (7%)
Chen et. al. J Interven Cardiol 2018	Retrospective, single center	RA of main vessel (MV) vs side branch +/- main vessel (SB-MV)	Any of (i) No flow (ii) SB perforation (iii) Wire transection	No flow in SB (4.2%) vs SB-MV (2.9%), perforation in SB (6.3%) vs SB-MV (0.8%), wire transection SB (0%) vs SB-MV (0.8%)

Breakdown by each complication:

(i) Severe dissection: 1.7 – 5.9%
   a. Lee et. al AJC 2017: any dissection that resulted in < TIMI 3 flow
   b. Safian et. al CARAT trial 2001: any dissection that requires stenting
   c. Abdel-Wahab et al. PREPARE-CALC 2018: large dissection > 5mm
   d. Ali et. al DISRUPT CAD II 2019: any dissection Type D-F that impaired flow
   e. NHLBI (based on depth and breadth of dissection + presence of intimal flap)

The National Heart, Lung and Blood Institute (NHLBI) classification system for intimal tears

Type A dissections represent minor radiolucent areas within the coronary lumen during contrast injection with little or no persistence of contrast after the dye has cleared
Type B dissections are parallel tracts or a double lumen separated by a radiolucent area during contrast injection, with minimal or no persistence after dye clearance
Type C dissections appear as contrast outside the coronary lumen ("extraluminal cap") with persistence of contrast after dye has cleared from the lumen
Type D dissections represent spiral ("barber shop pole") luminal filling defects, frequently with excessive contrast staining of the dissected false lumen
Type E dissections appear as new, persistent filling defects within the coronary lumen
Type F dissections represent those that lead to total occlusion of the coronary lumen without distal antegrade flow



(ii) Slow flow/ no reflow: 2.5%
(iii) Perforation: 2%
   a. All papers did not define/ classify perforation type. They included all types of perforation in analysis for complications

15.3 Appendix 3: List of study sites/ institutions involved in ROVUS Asia Registry

Country	Hospital/Institutions	PI name	Last Name	PI E-mail
Singapore	National Heart Centre Singapore (Co-PI)	Khung Keong	Yeo	yeo.khung.keong@singhealth.com.sg
	Tan Tock Seng Hospital	Deanna	Khoo	deanna_zl_khoo@ttsh.com.sg
	National University Hospital	Hui Wen	Sim	hui_wen_sim@nuhs.edu.sg
Japan	Kokura Memorial Hospital (Co-PI)	Kuramitsu	Shoichi	kuramitsu@circulation.jp
	Sapporo Cardiovascular Clinic	Kashima	Yoshifumi	rotamonster@gmail.com
		Sugie	Takuro	t.sugie@scvc.jp
	Sendai Kousei Hospital	Horie	Kazunori	horihori1015@gmail.com
Vietnam	Bach Mai Hospital	Ngoc Quang	Nguyen	quangtm@gmail.com
	Cho Ray University Hospital	Minh Hung	Ngo	drngominhhung@gmail.com
		Ich Trung	Ly	lyichtrung@yahoo.com
Thailand	Central Chest Hospital	Wirash	Kehasukcharoen	kwirash@yahoo.com
	King Chulalongkorn Hospital	Wacin	Buddhari	wacin_buddhari@yahoo.com
Malaysia	Serdang Hospital	Dato Kahar	Abdul Ghapar	drabdkahar@moh.gov.my
	Cardiac Vascular Sentral Kuala Lumpur	Dato Dr Tamil	Selvan	selvan63@gmail.com