Intravascular ultrasound guidance for complex high-risk indicated procedures: The IVUS CHIP trial study design

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Abstract

Background Intravascular ultrasound (IVUS) guidance for percutaneous coronary intervention (PCI) has been associated with a reduction in clinical events. Whereas most evidence is generated in Asian-Pacific populations, its global adoption remains low.

Methods The IVUS complex high-risk indicated procedures (CHIP) trial is a multicenter, international, event-driven, randomized superiority trial comparing IVUS-guided PCI with angio-guided PCI during complex high-risk indicated procedures. The primary endpoint is target vessel failure, defined as a composite of cardiac death, target vessel myocardial infarction, or clinically indicated target vessel revascularization. The IVUS CHIP trial utilizes an event-driven approach. The outcomes for the primary endpoint are first reported when at least 169 patients with a primary endpoint have been confirmed. A total of 2020 patients will be enrolled in 37 European sites.

Conclusions The aim of the IVUS CHIP trial is to assess the superiority of an IVUS-guided approach vs an angio-guided approach in patients undergoing complex high-risk indicated procedures in terms of the study primary endpoint of target vessel failure.

Trial Registration The IVUS CHIP trial is registered at ClinicalTrial.gov and assigned the identifier NCT04854070. (Am Heart J 2026;294:107339.)

Background

Intravascular ultrasound (IVUS) guidance has been reported to improve clinical outcomes after percutaneous coronary intervention (PCI).[1-6] Most of the evidence

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has been obtained in Asian-Pacific populations, where IVUS-guided PCI is more commonly used. Conversely, its adoption in Western countries remains low.[7] Data suggest that IVUS-guidance plays a critical role both before stenting, allowing lesion assessment and plaque preparation, as well as poststenting for optimization of results.[8-10] The latter proved to be of particular relevance in patients with complex coronary lesions.[1,2,11] In August 2024, updated European guidelines for the management of chronic coronary syndromes upgraded the use of intracoronary imaging guidance when performing PCI in anatomically complex lesions, in particular left main (LM) lesions, true bifurcations and long lesions to a class I, level of evidence A recommendation. Of note, specific guideline recommendations for the use of intracoronary imaging in moderate to heavily calcified coronary lesions are lacking.[12]

American guidelines for coronary artery revascularization recommend considering the use of IVUS in LM disease and in in-stent restenosis (ISR). However, these guidelines do not support the use of intracoronary imaging during routine PCI.[13] More recently, the updated American guidelines for the management of patients with acute coronary syndromes (ACSs) have promoted the use of imaging-guided PCI in LM disease and in complex lesions.[14]

The intravascular ultrasound guidance for complex high-risk indicated procedures (IVUS CHIP) randomized trial was designed to investigate whether IVUS-guided PCI is associated with a reduction in clinical events compared to an angio-guided PCI, in patients undergoing CHIP.

Methods

Study design

The IVUS CHIP trial is a multicenter, international, event-driven, randomized trial designed to investigate the superiority of IVUS-guided PCI compared with angiography-guided PCI (Figure 1) in terms of target vessel failure (TVF), a composite of cardiac death, target vessel myocardial infarction, and clinically-driven target vessel revascularization.[15]

The study is currently undertaken at 37 high-volume interventional centers in seven European countries, including Belgium, France, Germany, Italy, Spain, the Netherlands, and the United Kingdom. All centers were selected on the basis of established IVUS-guidance experience within their routine care. The authors take responsibility for the design and conduct of this study, all study analyses, the drafting and editing of the paper, and its final contents.

Study population

This study enrolls patients presenting with silent ischemia, stable angina, unstable angina, or non-ST-elevation ACS, planned to undergo percutaneous revascularization of complex coronary lesions, or in patients with an indication for elective mechanical circulatory support-assisted PCI. Complex lesions include angiographic heavy calcification, ostial lesions, true bifurcation lesions involving side-branches >2.5 mm, LM lesions, chronic total occlusion (CTO), ISR, and long lesions (estimated stent length >28 mm). Full eligibility criteria are available in Table 1.

Exclusion criteria include PCI for ST-elevation myocardial infarction, cardiogenic shock, IVUS strictly required for pre-PCI lesion assessment, complex lesion located in a diseased aorto-coronary bypass, absolute contraindications, or allergy that cannot be premedicated to iodinated contrast or to antiplatelet drugs, including both aspirin and P2Y12 inhibitors. The IVUS CHIP trial is not an all-comers trial, but enrolls a selected high-risk study population, at a recommended rate of 2 to 3 patients per site per month.

Informed consent

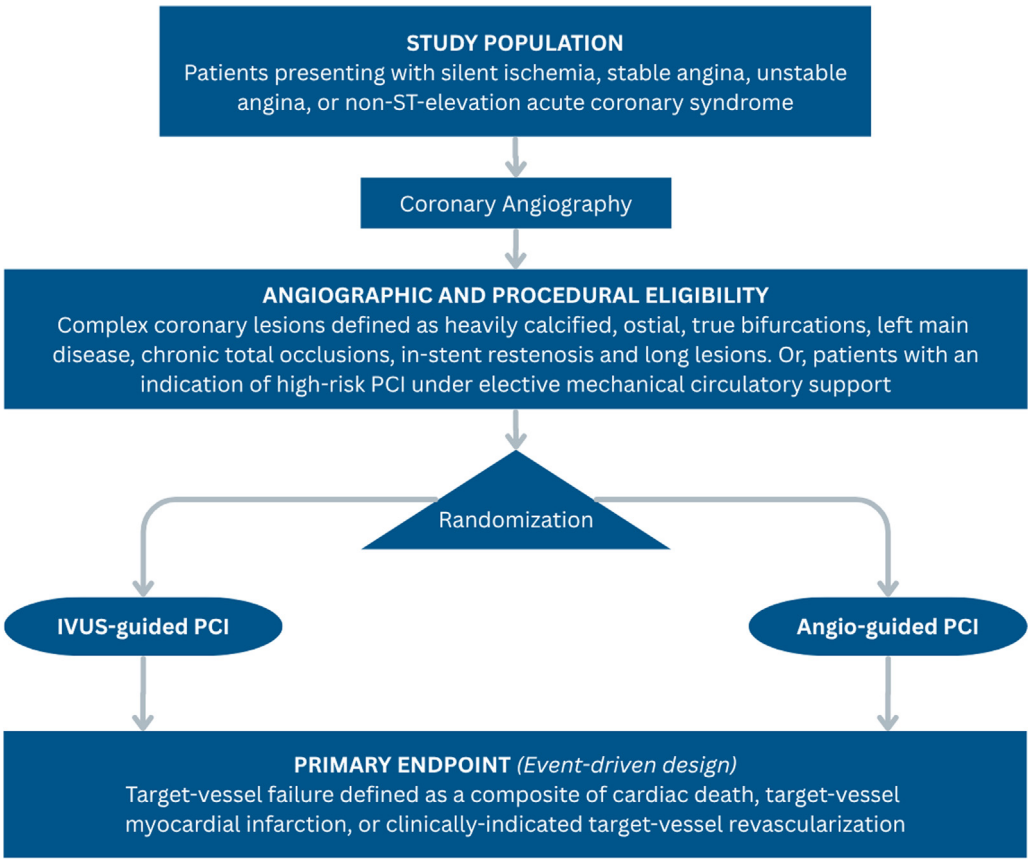
After the investigator or a designee has screened the routinely available items and determines the patient eligible, the patient is informed about the study and asked to participate.

In patients undergoing ad-hoc revascularization, a staged informed consent process is implemented. In this scenario, patients are orally informed about the nature of the study by one of the investigators, in the presence of an independent witness. Consenting patients provide oral informed consent, which is then signed by both the investigator and an independent witness. After the procedure, and within a maximum of 24 hours, the patient is fully informed of the study details through the complete written informed consent. Both the investigator and the patient, or designee, sign the complete informed consent.

Enrolment and randomization

After informed consent and final eligibility are established, the study participant is randomized in a 1:1 ratio to IVUS-guided PCI or angio-guided PCI using the randomization module of the electronic data capture system. The types of qualifying lesions are captured at randomization. For patients with CTO lesions, randomization occurs after initial successful crossing of the lesion(s). Stratification by site and by presentation (ACS vs non-ACS) is performed to ensure balance across potential local differences in treatment practices. It is strongly recommended that the PCI procedure is scheduled within 24 hours after informed consent for ACS patients, or within 72 hours for stable patients. Relevant baseline characteristics are collected to ensure adequate clinical characterization, including standard modifiable risk factors, cardiovascular medical history,

Figure 1. Study flow-chart.



angina status, left ventricular ejection fraction, and valve pathologies.

Study device

The OptiCross High Definition (60 MHz) IVUS catheter (Boston Scientific Corporation, Marlborough, MA) is CE-marked and will be used in this trial. No support by artificial intelligence is anticipated. All study lesions must be treated with the Synergy everolimus-eluting stent or any next generation of the Synergy stent family (Boston Scientific Corporation). The Synergy stent family has received CE-mark and is not under investigation in this study.

Treatment

For patients randomized to IVUS-guided PCI, the protocol highly recommends performing a baseline pre-PCI IVUS for lesion assessment and preparation. IVUS after PCI and post-PCI optimization are mandatory. Only motorized pullbacks are allowed, and the use of the complete pullback length is recommended (Figure 2).

Criteria for optimal stenting comprise: (1) A final minimal stent area (MSA) >5 mm^2 or MSA >90% of distal reference lumen; (2) a plaque burden <50% within 5 mm from the proximal or distal stent edge; (3) no edge dissection involving the media and >3 mm in length.

During the study, a stent sizing algorithm was implemented. Stent landing zones are defined as: (1) 3 mm distal and proximal to plaque with <30% area stenosis. (2) No large lipid pools. (3) Plaque burden <50%. (4) Proximal landing zone at least 5 mm proximal to bifurcation of side branches >2.5 mm in order to allow proximal optimization technique. In addition, the study protocol recommends avoiding stent overlap at the site of bifurcations with side-branches >2.5 mm and selecting the stent diameter based on distal reference lumen area or external elastic membrane, and upsize proximally with a postdilatation balloon in case of significant tapering.

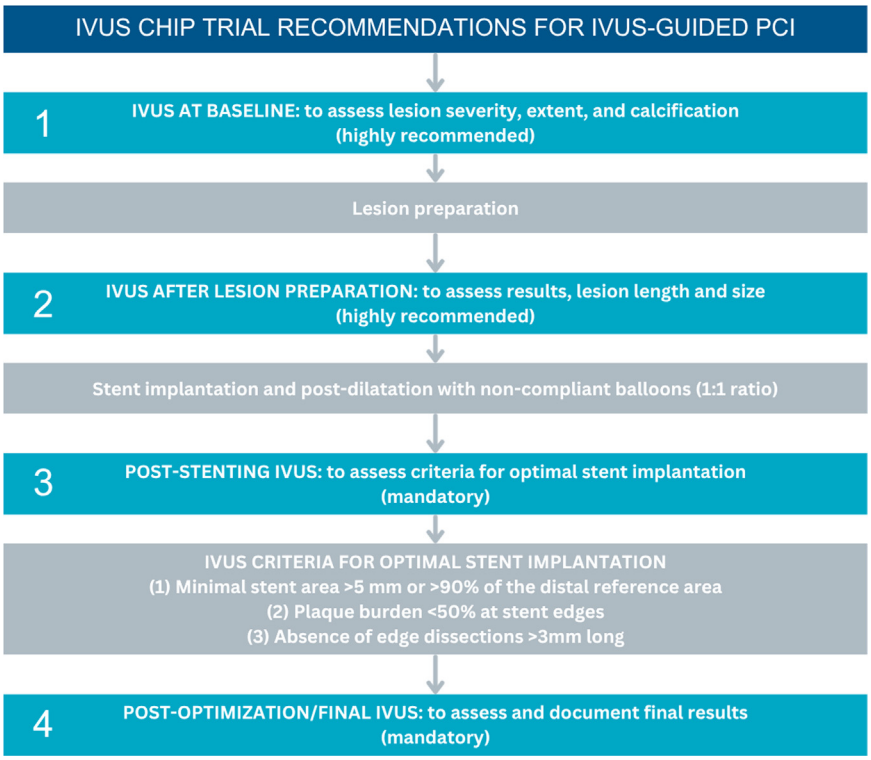
In the angiography-guided arm, treatment is performed according to standard clinical practice without IVUS-guidance unless strictly medically indicated, such as in the presence of luminal haziness or doubtful dissection.

In case of multivessel disease, all lesions are to be treated according to the allocated strategy. For intermediate lesions (50%-70% diameter stenosis by angiographic visual estimate), coronary physiology testing (FFR or iFR)

Table 1. Inclusion and exclusion criteria

Inclusion criteria
The patient must be ≥18 years of age
Patients with an indication for PCI of at least one lesion satisfying any of the following criteria:
Angiographic heavy calcification
Ostial lesions
True bifurcation lesions involving side-branches >2.5 mm
Left main lesions
Chronic total occlusion
In-stent restenosis
Long lesions (estimated stent length >28 mm)
Patient with an indication for PCI for any lesion and in need for elective mechanical circulatory support assisted PCI
Presenting with silent ischemia, stable angina, unstable angina, or non-ST-elevation acute coronary syndrome (NSTE-ACS)
All lesions must be suitable for treatment with the Synergy stent system, Synergy Megatron system, or other Synergy platform iteration
The patient is willing and able to cooperate with study procedures and follow-up until study completion
Subject is able to confirm understanding of risks, benefits, and treatment alternatives, and he/she provides informed consent prior to any protocol-related procedure, as approved by the appropriate Ethics Committee
Exclusion criteria
ST-elevation myocardial infarction
Cardiogenic shock
Known untreated severe valvular heart disease
IVUS is strictly required for pre-PCI lesion severity assessment
Requiring PCI in a diseased aorto-coronary bypass
Known contraindication or hypersensitivity to everolimus, platinum-chromium, or to anticoagulants
Absolute contraindications or allergy that cannot be premedicated to iodinated contrast or to antiplatelet drugs, including both aspirin and P2Y12 inhibitors

Figure 2. IVUS imaging protocol. Recommended use of IVUS in patients randomized to the IVUS-guided PCI.



is recommended. Lesion preparation is per operator's discretion. Complete revascularization was strongly encouraged. If the treatment of multivessel disease requires a staged procedure, planned staged procedures are to be completed within 45 days, as defined in previous clinical trials.[16-18] The intent to stage has to be documented at the end of the first procedure. Staging of multiple lesions in a single vessel is not allowed.

Follow-up

The enrolment period was anticipated to be approximately 24 months. Follow-up of all participants has been planned to continue up to 2 years after randomization or until 169 primary endpoints have occurred, whichever comes last.

Telephone follow-up contacts may be discontinued at the participant's explicit request. Gathering of clinical follow-up via treating cardiologists, general practitioners, or the civic registries is continued unless the participant objects. In that case, the participant is considered lost to follow-up as of the date of the last clinical contact. Participants are followed for at least 2 years after randomization, with a yearly telephone call starting at 1-year postrandomization, for all listed clinical endpoints, including the occurrence of death, myocardial infarction, repeat revascularization, stent thrombosis, and stroke.

Study endpoints

The primary endpoint of IVUS CHIP is TVF, defined as a composite of cardiac death, target vessel myocardial infarction, or clinically indicated target vessel revascularization.

Additional secondary endpoints are listed in Table 2. All deaths and major cardiovascular events, including the individual components of primary and secondary endpoints are adjudicated by an independent CEC using standardized definitions.[15,19] Furthermore, the Fourth Universal MI definition is adopted to define all spontaneous MI events occurring beyond 48 hours of the procedure, while the Academic Research Consortium-2 MI definition is used for peri-procedural MI.[20] Source documents, including discharge letters, laboratory values, electrocardiograms, and angiographic materials, were available during event adjudication.

Core laboratory

Pseudonymized IVUS images are collected centrally for standardized analysis. Final post-PCI images will be analyzed by an IVUS core laboratory (Cardialysis, Rotterdam, the Netherlands), unaware of clinical outcomes, on the basis of previously reported methods.[21] Similarly, pseudonymized angiographic materials are collected centrally for determination of the anatomical SYNTAX score at baseline by the SYNTAX Score core laboratory (Cardialysis).

Statistical considerations

The IVUS CHIP trial utilizes an event-driven approach and defines the analysis cut-off (ACO) date as the time for the primary analysis. More specifically, the outcomes for the primary endpoint are first reported up to the ACO date, which is defined by the executive committee when the CEC has confirmed at least 169 patients with a primary endpoint. In the event of a higher incidence of the primary endpoint, patient enrolment can be terminated ahead of schedule. In case of an extremely low incidence of the primary endpoint, the executive committee will determine the final duration of minimal follow-up, in agreement with the sponsor.

Data analysis

The data analysis will be performed according to the Intention-to-Treat principle, which includes all randomized participants. This population is equivalent to the "Full Analysis Set" as defined in the International Conference on Harmonization E9 guidelines. For the primary endpoint, the null hypothesis of no treatment benefit with IVUS-guided PCI is tested against the alternative hypothesis of treatment benefit using a 2-sided log-rank test with an alpha level of 0.05. The corresponding 2-sided *P*-value (for superiority) is calculated as two times the 1-sided *P*-value for superiority of IVUS-guided vis-a-vis angio-guided PCI. For all other endpoints, statistical significance will be declared if the two-sided *P*-value is $\leq .05$, unless otherwise specified. All analyses will be performed using SAS version 9.4 or higher. Prespecified subgroup analyses include clinical presentation (ACS vs non-ACS), lesions type, age, sex, use of mechanical circulatory support, achievement of optimal IVUS criteria, and the use of prestenting IVUS.

Sample size calculation

The sample size determination is driven by requirements for testing superiority of IVUS-guided PCI over angiography-guided PCI. Based on observations of the RESOLUTE all-comers trial, the expected incidence of the primary endpoint is 9.8% at 12 months and 12% to 15% at 18 months. The target hazard ratio is 0.65, corresponding to a reduction in the incidence of the primary endpoint from approximately 12% to 8%. The assumed treatment benefit (hazard ratio of 0.65) was based on available evidence at the time of producing the first version of the clinical protocol. Using a hazard ratio of 0.65 in Cox PH analysis, the accrual of 169 primary endpoints provides the study with 80% power to show superiority of IVUS-guided over angiography-guided PCI. Using a conservative approach, and expected cross-over of approximately 3% of patients and attrition rate of 8% due

Table 2. Primary and secondary endpoints

Primary endpoint
Target vessel failure defined as a composite of cardiac death, target vessel myocardial infarction*, or clinically indicated target vessel revascularization†
Ranked key secondary endpoints
Composite of target vessel myocardial infarction* and clinically indicated target vessel revascularization†
Clinically-indicated target vessel revascularization†
Composite of cardiac death and target vessel myocardial infarction*
Target-Lesion Failure (TLF) defined as a composite of cardiac death, target vessel myocardial infarction*, or clinically indicated target-lesion revascularization†
Target-lesion revascularization†
Cardiac death
Other clinical endpoints
Patient-oriented Composite Endpoint (POCE) defined as a composite of all-cause death, any stroke, any myocardial infarction*, and any revascularization†
Device-oriented Composite Endpoint (DOCE) defined as the composite of cardiovascular death, target vessel MI*, clinically indicated repeat revascularization† of the target lesion
Target vessel revascularization†
Study vessel revascularization†
Any stroke
Definite and probable stent thrombosis
Procedural endpoints
Procedural time
Total contrast volume
Device usage
Additional clinical/procedural endpoints
Acute kidney injury
Vascular access site complications
Bleeding
Major intraprocedural complications, including Type C-F dissection, any perforation, persistent slow- or persistent no-reflow, abrupt closure, distal embolization, thrombus, and major (≥2 mm vessel diameter) side branch occlusion
Perforations by Ellis criteria
Core lab reported endpoints
Achievement of optimal IVUS criteria

All clinical endpoints will be reported at ACO, and with a study extension annually up to 5 years.

* ARC-2; 4th universal definition for spontaneous (>48 hours) MI.

† Revascularizations will be assessed according to ARC-2.

to noncardiovascular death, loss to follow-up, or withdrawal of informed consent, a total of 2020 participants were targeted.

Study organization, timelines, and ethical concerns

The IVUS CHIP study is an investigator-initiated study sponsored by and conducted with oversight from the European Cardiovascular Research Institute (ECRI, Rotterdam, The Netherlands). The IVUS CHIP study is performed in accordance with the Declaration of Helsinki, Good Clinical Practice, ISO 14155:2020 (Clinical investigation of medical devices for human subjects—Good clinical practice), and institutional review board requirements. The protocol, informed consent, and other study-related documents are submitted to the institutional review boards and any other regulatory bodies as required per local regulations.

The executive committee is responsible for the overall design, conduct, and supervision of the study, including the development of any protocol amendments. The executive committee also reviews the study progress at regular intervals to ensure participant safety and study integrity. The steering committee is composed by members of the executive committee and national lead investigators.

An independent data safety and monitoring board, appointed by the sponsor, plays a critical role in ensuring participant safety and study integrity. Comprising independent experts, the data safety and monitoring board is tasked with periodically reviewing accumulating data on safety, efficacy, and protocol adherence, maintaining confidentiality to avoid bias. This independent oversight ensures ethical conduct and safeguards participants while supporting the trial's scientific objectives.

Project management, electronic data capturing development, data management, imaging data coordination, site management and monitoring, CEC coordination, safety reporting activities, and statistical analysis are conducted by a European contract research organization (Cardialysis).

Estimated study duration and first reporting of main findings

The first reporting of the main findings is event-driven and is scheduled according to the power calculation, after at least 169 subjects have experienced an event adjudicated as qualifying for the primary endpoint of TVF. After the ACO date has been determined, participants are scheduled for an additional intermediary telephonic study visit, which should occur on or after the ACO date. At the time of submission, the inclusion and follow-up for the primary endpoint have been completed.

Discussion

Angiography-guided PCI is limited in its ability to accurately define atherosclerotic burden, particularly as it relates to detailed plaque and calcium morphology. Moreover, angiography-guided PCI hampers precise assessment of stent expansion and geographic miss, resulting in a significant risk for future TVF in up to 12% of patients at 5 years.[22] In contrast, intravascular imaging provides detailed information on plaque morphology, amount, and distribution of coronary calcification, and vessel caliber. As such, it represents a valid tool to guide lesion preparation and stent sizing. In addition, poststenting imaging interrogation has the ability to identify underexpansion, malapposition, geographical miss, and residual dissections.[9,10] Therefore, the potential beneficial impact of imaging guidance has been investigated and subsequently demonstrated in several studies.[5]

In the IVUS-XPL Trial, IVUS guidance for treatment of long lesions resulted in a significantly lower rate of the composite of major adverse cardiac events at 1 year.[2]

The ULTIMATE Trial showed that IVUS-guided DES implantation was associated with significantly lower rates of TVF and stent thrombosis during 3-year follow-up among all comers[23] and particularly in long lesions.[24]

The RENOVATE-COMPLEX PCI demonstrated the superiority of imaging guidance in truly complex coronary-artery lesions compared with angio-guidance adopting a mixed strategy of optical coherence tomography and IVUS imaging modalities.[11] While in various Asian countries, the use of intracoronary imaging exceeds 80%, its use in the United States (US) and Europe is below 25%.[4,25-28] In Western countries, clinical evidence in terms of large randomized trials is limited to use of OCT in the OCTOBER trial, showing superior clinical outcomes in OCT—as compared to angiography-guided PCI for bifurcation lesions[29] and the ILUMIEN IV trial that showed significantly larger MSAs following OCT-guided PCI but failed to demonstrate the clinical superiority of OCT-guided PCI compared with angiography-guided PCI on the basis of TVF.[30]

Of note, whereas a dedicated ILUMIEN IV subgroup analyses on patients with complex coronary anatomy also failed to show a significant difference in TVF at 2 years, a significant difference was found in the occurrence of cardiac death, target vessel MI, or stent thrombosis. The latter illustrates the concept that imaging could be particularly beneficial when treating complex lesions, but also highlights the need for large-scale randomized trials performed in Europe supporting contemporary guideline recommendations.[30]

The IVUS-CHIP trial builds on this evidence, addressing a broader European population with high-risk anatomical and clinical features, including patients with calcified lesions, LM, CTO, and those requiring mechanical circulatory support. To address the heterogeneity of this population, prespecified subgroup analyses and stratification by clinical presentation have been incorporated. Recognizing variability in procedural technique, particularly in calcium management, lesion preparation strategies were left to operator discretion to reflect real-world practice, while IVUS optimization criteria were standardized.

The IVUS CHIP trial represents the first and largest European randomized trial evaluating the potential impact of high definition IVUS guidance for treatment of the full spectrum of complex and high-risk PCI, including patients with heavily calcified lesions, CTOs, ostial lesions, LM disease, ISR, true bifurcation, long lesions, and also evaluating patients in need for mechanical circulatory support. Another adequately powered randomized trial is currently enrolling patients in the United States of America, and results are expected in 2027 (NCT04221815).

Summary

The IVUS CHIP Trial is the first randomized controlled trial to assess the superiority of IVUS-guided vs angiography-guided PCI for the primary endpoint of target vessel failure in patients undergoing complex and high-risk indicated procedures.

Funding

This is an investigator-initiated study sponsored by the European Cardiovascular Research Institute (ECRI, Rotterdam, The Netherlands). An unrestricted research grant is awarded by Boston Scientific Corporation (Marlborough, Massachusetts) to fund this study, which includes provision of IVUS catheters. The funder of the study has no role in the study design, collection or management of the data, statistical analysis, writing of manuscripts, or decisions to submit manuscripts for publication.

Conflict of interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Roberto Diletti declares speaker fees from ACIST Medical Systems, Biotronik, Boston Scientific and Medtronic;

institutional research grants from ACIST Medical Systems, Biotronik, Boston Scientific and Medtronic; is member of an advisory board at Boston Scientific.

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Benjamin Faurie declares consultancy fees from Asahi, Boston Scientific, Terumo, Vascular Therapy; speaker fees from Terumo; an executive role at Eletroducer; is shareholder at 4C Medical and Electroducer.

Didier Tchetche declares speaker fees from Abbott, Boston Scientific, Caranx Medcial, Edwards Lifesciences, Medtronic and Meril; is member of an advisory board at Caranx Medical and T-Heart. Thomas Hovasse declares speaker fees from Abbott, Boston Scientific and Edwards Lifesciences.

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CRediT authorship contribution statement

Roberto Diletti: Writing – review & editing, Writing – original draft, Validation, Supervision, Methodology, Investigation, Data curation, Conceptualization. **Joost Daemen:** Writing – review & editing, Validation, Methodology, Investigation, Data curation, Conceptualization. **Benjamin Faurie:** Writing – review & editing, Investigation. **Marco Barbierato:** Writing – review & editing, Investigation. **Didier Tchetche:** Writing – review & editing, Investigation. **Thomas Hovasse:** Writ-

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