Angiography-derived physiology guidance vs usual care in an All-comers PCI population treated with the healing-targeted supreme stent and Ticagrelor monotherapy: PIONEER IV trial design

Hironori Hara, MD [a,b], Patrick W. Serruys, MD, PhD [b,c], Neil O'Leary, PhD [d], Chao Gao, MD [b,e,f], Alicia Murray, PhD [d], Elaine Breslin, PhD [d], Scot Garg, MD, PhD [g], Christophe Bureau, PhD [h], Johan HC Reiber, PhD [i], Emanuele Barbato, MD, PhD [j], Adel Aminian, MD [k], Luc Janssens, MD [l], Liesbeth Rosseel, MD [m], Edouard Benit, MD [n], Gianluca Campo, MD [o], Vincenzo Guiducci, MD [p], Gianni Casella, MD [q], Andrea Santarelli, MD [r], Alfonso Franzè, MD [s], Victor Alfonso Jimenez Diaz, MD [t], Andrés Iñiguez, MD, PhD [t,u], Salvatore Brugaletta, MD, PhD [v], Manel Sabate, MD, PhD [v], Ignacio J. Amat-Santos, MD, PhD [w], Giovanni Amoroso, MD [x], Joanna Wykrzykowska, MD, PhD [y], Clemens von Birgelen, MD, PhD [z,aa], Samer Somi, MD, PhD [ab], Tommy Liu, MD [ab], Sjoerd H. Hofma, MD, PhD [ac], Nick Curzen, BM(hons), PhD [ad], Ramiro Trillo, MD [ae], Raymundo Ocaranza, MD [af], Anthony Mathur, MD, PhD [ag,ah], Pieter C. Smits, MD, PhD [ai], Javier Escaned, MD, PhD [aj], Andreas Baumbach, MD, PhD [ak,ah,al], William Wijns, MD, PhD [am], Faisal Sharif, MD, PhD [b,an], and Yoshinobu Onuma, MD, PhD [b], On behalf of the PIONEER IV trial investigator *Amsterdam, The Netherlands; Galway, Ireland*

Background Current ESC guidelines recommend the use of intra-coronary pressure guidewires for functional assessment of intermediate-grade coronary stenoses. Angiography-derived quantitative flow ratio (QFR) is a novel method of assessing these stenoses, and guiding percutaneous coronary intervention (PCI).

Methods/Design The PIONEER IV trial is a prospective, all-comers, multi-center trial, which will randomize 2,540 patients in a 1:1 ratio to PCI guided by angiography-derived physiology or usual care, with unrestricted use in both arms of the Healing-Targeted Supreme sirolimus-eluting stent (HT Supreme). The stent's fast, biologically healthy, and robust endothelial coverage allows for short dual-antiplatelet therapy (DAPT); hence the antiplatelet regimen of choice is 1-month DAPT, followed by ticagrelor monotherapy. In the angiography-derived physiology guided arm, lesions will be functionally assessed using

From the [a]Department of Cardiology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands, [b]Department of Cardiology, National University of Ireland, Galway (NUIG), Galway, Ireland, [c]NHLI, Imperial College London, London, United Kingdom, [d]CORRIB Research Centre, College of Medicine, Nursing and Health Sciences, National University of Ireland, Galway, [e]Deparment of Cardiology. Radboudumc, Nijmegen, The Netherlands, [f]Department of Cardiology, Xijing Hospital, Xi'an, China, [g]Department of Cardiology, Royal Blackburn Hospital, Blackburn, United Kingdom, [h]AlchiMedics S.A.S, Paris, France, [i]Department of Radiology, Leiden University Medical Center, Leiden, The Netherlands, [j]Cardiovascular Research Center Aalst, OLV-Clinic, Aalst, Belgium and Department of Advanced Biomedical Sciences, University Federico II, Naples, Italy, [k]Department of Cardiology, Centre Hospitalier Universitaire de Charleroi, Charleroi, Belgium, [l]Department of Cardiology, Imeldaziekenhuis, Bonheiden, Belgium, [m]Department of Cardiology, Algemeen stedelijk ziekenhuis, Aalst, Belgium, [n]Hartcentrum Jessa Ziekenhuis, Campus Virga Jesse, Hasselt, Belgium, [o]Cardiology Unit, Azienda Ospedaliera Universitaria di Ferrara, Cona, Italy, [p]Azienda USL-IRCCS Reggio Emilia, Reggio Emilia, Italy, [q]U.O.C. Cardiologia, Ospedale Maggiore, Bologna, Italy, [r]Cardiology Unit, Infermi Hospital, Rimini, Italy, [s]Interventional Cardiology Unit, San Luigi Gonzaga University Hospital (Orbassano) and Rivoli Infermi Hospital (Rivoli), Turin, Italy, [t]Department of Cardiology, Hospital Universitario de Vigo, Vigo, Spain, [u]Department of Cardiology, Hospital Universitario Álvaro Cunqueiro, Vigo, Spain, [v]Cardiology Department, Clinic Cardiovascular Institute, Hospital Clinic, Institut d'Investigacions Biomèdiques August Pi i Sunyer, IDIBAPS, Barcelona, Spain, [w]CIBERCV, Cardiology Department, Hospital Clínico de Valladolid, Spain, [x]OLVG, Amsterdam, the Netherlands, [y]Department of Cardiology, University Medical Center Groningen, Groningen, the Netherlands, [z]Department of Cardiology, Medisch Spectrum Twente, Thoraxcentrum Twente, Enschede, the Netherlands, [aa]Department of Health Technology and Services Research, Faculty BMS, Technical Medical Centre, University of Twente, [ab]Department of Cardiology, Haga Hospital, The Hague, the Netherlands, [ac]Department of Cardiology, Medical Centre Leeuwarden, Leeuwarden, the Netherlands, [ad]Faculty of Medicine, University of Southampton, and University Hospital Southampton NHS Trust, Southampton, United Kingdom, [ae]Department of Cardiology, University Clinic Hospital, CIBERCV, Santiago de Compostela, Spain, [af]Interventional Cardiology Section, Lucus Augusti University Hospital, Lugo, Spain, [ag]Barts Interventional Group, Barts Heart Centre, Barts Health NHS Trust, London, UK, [ah]Centre for Cardiovascular Medicine and Devices, William Harvey Research Institute, Queen Mary University of London, [ai]Maasstad Ziekenhuis, Rotterdam, The Netherlands, [aj]Hospital Clinico San Carlos IDISCC, Complutense University of Madrid, Madrid, Spain, [ak]Barts Heart Centre, London, United Kingdom, [al]Yale University School of Medicine, New Haven, USA, [am]The Lambe Institute for Translational Medicine and Curam, NUIG, Galway, Ireland, [an]SFI infrastructure funding, NUIG, Galway, Ireland

Abbreviations: CAD, coronary artery disease; CEC, Clinical Event Committee; DAPT, dual antiplatelet therapy; DSMB, Data Safety and Monitoring Board; DOCE, device-oriented composite endpoint; FFR, fractional flow reserve; HR, hazard ratio; iFR, instantaneous wave-free ratio; IVUS, intravascular ultrasound; MI, myocardial infarction; NOAC, novel oral anticoagulants; OCT, optical coherence tomography; PCI, percutaneous coronary intervention; POCE, patient-oriented composite endpoint; QCA, quantitative coronary analysis; QFR, quantitative flow ratio; SES, sirolimus-eluting stent; STEMI, ST-elevation myocardial infarction; TVF, target vessel failure; VOCE, vessel-oriented composite endpoint.

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Reprint requests: Patrick W. Serruys, MD, PhD, Department of cardiology, National University of Ireland, Galway (NUIG), 46 University Road, Galway H91 TK33, Ireland

E-mail address: patrick.w.j.c.serruys@gmail.com.

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on-line QFR, with stenting indicated in lesions with a QFR ≤0.80. Post-stenting, QFR will be repeated in the stented vessel(s), with post-dilatation or additional stenting recommended if the QFR<0.91 distal to the stent, or if the delta QFR (across the stent) is >0.05. Usual care PCI is performed according to standard clinical practice. The primary endpoint is a non–inferiority comparison of the patient-oriented composite endpoint (POCE) of all-cause death, any stroke, any myocardial infarction, or any clinically, and physiologically driven revascularization with a non–inferiority risk-difference margin of 3.2%, at 1-year post-procedure. Clinical follow-up will be up to 3 years.

Summary The PIONEER IV trial aims to demonstrate non–inferiority of QFR-guided PCI to usual care PCI with respect to POCE at 1-year in patients treated with HT Supreme stents and ticagrelor monotherapy.

Clinical Trial Registration ClinicalTrials.gov

Unique Identifier NCT04923191

Classifications Interventional Cardiology (Am Heart J 2022;246:32–43.)

The objective of percutaneous coronary intervention (PCI) is the removal of flow-limiting coronary stenoses, thereby improving prognosis, and/or anginal symptoms. Based on extensive supporting evidence, ESC guidelines recommend intracoronary pressure indices to assess a lesion's functional severity in order to justify coronary revascularization.[1] Over the years these guideline recommendations have expanded from using such indices in only intermediate-grade stenoses with no evidence of ischemia in non–invasive testing, to a richer palette of clinical and anatomic scenarios, reflecting the supportive evidence gathered in the FAME I, FAME II, and SYNTAX II trials, in which coronary revascularization in high-risk patient subsets was based on a lesion's functional significance.[1-7]

Despite the inception of fractional flow reserve (FFR) more than 25 years ago, and the wealth of accumulated evidence supporting its use, its adoption has been disappointingly poor, with many operators not perceiving the need to gather physiological data to supplement clinical and angiographic data, in order to make the most appropriate informed decision regarding revascularization.[8,9] Recently the introduction of instantaneous wave-free ratio (iFR) has contributed to an increased utilization of functional stenosis assessment, as compared to FFR, iFR avoids the need to administer hyperemic agents which sometimes cause chest discomfort and dyspnea. Nevertheless, pressure-based indices are invariably bound to a more complex diagnostic procedure than stand-alone angiography, as they require use of guiding catheters and pressure guidewires, intra-coronary instrumentation and adapted heparinization, all contributing to an increase in the length, costs, and risk of the diagnostic procedure.

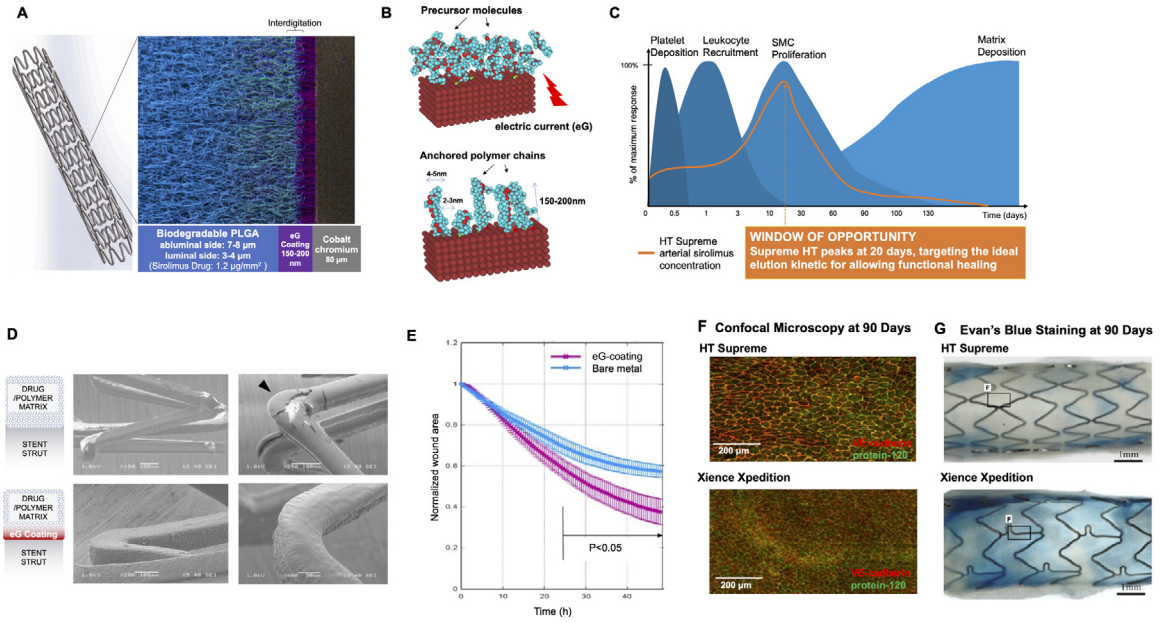
Consequently, in routine clinical practice most operators use pressure guidewires selectively, and on a subjective basis, favoring functional assessment of intermediate severity stenoses and relying on visual estimation or non–invasive tests for angiographically mild or severe lesions. Available studies demonstrate that this approach may lead to inaccurate assessments of a lesion's true functional significance, and therefore to incorrect revascularization plans.

Recently, novel physiological methods have been developed to functionally assess coronary stenoses without requiring wire-based interrogation. Quantitative flow ratio (QFR) is an angiography-derived physiological assessment[10-12] which does not require use of an intra-coronary pressure wire, and therefore is very favorable in terms of time saving and safety, compared to using a conventional pressure wire. Importantly, a very high level of agreement between QFR® and FFR has been seen with respect to assessing the functional significance of coronary stenoses in the FAVOR I, FAVOR II China and FAVOR II Europe-Japan studies, and in a Bayesian meta-analysis.[13-17] However, clinical outcome data from randomized control trials are still lacking.

Notably, the arrival of QFR coincides with a growing interest in the use of physiology, not only to justify PCI, but also to plan the PCI procedure and to functionally assess the result. Post-PCI QFR in the SYNTAX II and HAWKEYE trials have demonstrated the frequent occurrence of residual flow-limiting coronary narrowings, resulting in a poorer prognosis, even though the PCI procedures were deemed "successful" by the operator.[18,19] Therefore, it is plausible that clinical outcomes following PCI could be improved by monitoring, and optimizing the functional results of the intervention using QFR guidance.

The evolution of physiological assessment has run in parallel to the developments in the field of PCI. Among some of these developments are new generation thin strut stents with programmed short drug elution aimed to facilitate vascular healing and minimize thrombogenicity.[20,21] Recent studies have demonstrated that the use of new stent technologies combined with an antiplatelet treatment regimen based on dual antiplatelet therapy (DAPT) for 1 month only, followed by monotherapy with a P2Y12 inhibitor, could improve clinical outcomes, compared to conventional DAPT for 1-year.[22,23]

Figure 1



Healing-targeted (HT) supreme stent. (A) Stent design of HT supreme stent. (B) Electro-grafting (*eG*) coating technology. *eG*-coating is a passive coating where precursor molecules are electroplated, which generate polymer chains to grow perpendicularly in a helical shape on the surface of the stent. (C) Mean values of normalized wound area for bare metal stents and *eG*-coating stents over time in *in vitro* simulated arterial model. Bare metal stents provided a lower healing rate compared to the *eG*-coating stents[20]. (D) Pharmacokinetics designed to suppress smooth muscle cell (SMC) without limiting functional healing. PLGA, polylactic co-glycolic acid. (E) Images taken following a tortuous-path track test and balloon expansion. *eG* coating prevents fractures, delamination and peeling. (F-G) Evaluation of endothelial barrier function by VE-cadherin and protein-120 (F) and endothelial impermeability by Evan's blue (G) at 90 days[21].

The PIONEER IV trial aims to demonstrate non-inferiority of QFR-guided PCI to usual care PCI with respect to the patient oriented composite endpoint (POCE) at 1 year in patients treated with the healing-targeted HT Supreme Drug Eluting Stent (SINOMED, Tianjin, China) and ticagrelor monotherapy. In this trial, usual care PCI will be performed according to the local, and usual clinical practice.

Methods

Device used: healing-targeted supreme stent (HT Supreme)

The HT Supreme stent struts are made of a L605 cobalt chromium (CoCr) alloy with a strut thickness of 80 μm coated with a thin layer (150-200 nm) grown directly from the metallic surface by electro-grafted (*eG*) and co-valently bound to the stent surface (Figure 1A, B).[24] This is interdigitated with a conformal coating of a biodegradable polymer (polylactic co-glycolic acid [PLGA]) (Figure 1A).

By reason of device name change, the experimental device is referred as HT Supreme, regardless of the name (BuMA Supreme) used in previous publications.

The HT Supreme represents a new type of drug eluting stent which focuses on maximizing the ability for early natural restoration of endothelial function. The device ensures that the peak sirolimus drug concentration coincides with the smooth muscle cell (SMC)-proliferation phase (Figure 1C). The *eG* base layer functions as a protective layer to ensure superior polymer integrity and attachment that prevents fractures, delamination and peeling (Figure 1D), and has the effect of promoting endothelial wound healing, although the biological mechanism involved in this enhanced endothelialization is not elucidated (Figure 1E).[20] The HT Supreme showed rapid good endothelial cell binding in a rabbit model (Figure 1F, G).[21] The abundant presence of VE-cadherin and protein-120, visualized by immunostaining, demonstrated the quality and robustness of the endothelial interconnection, and the low level of staining by Evans Blue dye when a vessel stented with HT Supreme was compared to Xience Expedition, indicates less permeability, and a better endothelial barrier.

In the PIONEER II OCT study, OCT follow-up at 1 month demonstrated a higher coverage rate of the HT Supreme (83.8%, n = 18 lesions) compared to the

XIENCE stent (73.0%, n = 17 lesions, $P = .037$), presumably due to faster, and shorter drug elution.[25]

As supported by histologic and OCT findings, the HT Supreme stent allows the vessel to heal and return to its natural protective defenses against thrombosis, restenosis, and possibly neoatherosclerosis, and enables shorter DAPT followed by P2Y12 inhibitor monotherapy.

Recently, the PIONEER III trial randomized 1632 patients in a 2:1 fashion to the HT Supreme or a Xience/Promus DES.[24] At 12 months, target lesion failure (cardiac death, target-vessel myocardial infarction [MI], ischemia-driven target lesion revascularization [TLR]) occurred in 5.4% of the HT-DES patients and 5.1% of the durable-polymer DES patients, a non–significant difference that met the trial criteria for non–inferiority (*P* for non–inferiority = .002).

Study design

The PIONEER IV trial (ClinicalTrials.gov, NCT04923191) is a prospective, multi-center, all-comers study randomising approximately 2,540 patients, from 30 European sites, in a 1:1 ratio, to PCI guided by angiography-derived physiology (QFR) or usual care, with unrestricted use of the HT Supreme sirolimus-eluting stent (SES) (SINOMED, Tianjin, China), and 1-month of dual-antiplatelet therapy (DAPT) followed by 11-months of ticagrelor monotherapy. Inclusion and exclusion criteria are listed in Table I. Randomization will be performed via web-based software, stratified by centre and in blocks of randomly permuted lengths of 2, 4 and 6 (Figure 2).

1. Angio-based physiology guidance PCI

Pre-procedural guidance

On-line QFR assessment will be performed to evaluate a lesion's functional severity, with PCI performed using the HT Supreme stent if the QFR is ≤0.80, and deferred if the QFR is >0.80.

Post-stenting assessment

After stenting, QFR will be remeasured in the stented vessel(s) with post-dilatation of the stented segment and/or additional stenting recommended if the distal QFR is <0.91 or the delta QFR (across the stent) is >0.05. Post-stent intra-vascular ultrasound (IVUS) or OCT can be used at the discretion of the investigator for the assessment and guidance of further treatment, however they are highly recommended if the distal QFR, or the delta QFR (across the stent), post-procedure indicates a residual flow limitation.

2. Local routine diagnostic procedure and usual care

The HT Supreme stent will be implanted in stenotic lesions (with a visual diameter stenosis [DS] ≥50%). Non–invasive and/or invasive assessment of a lesion's physiological severity, prior to, or during, treatment is left to the operator's discretion in accordance with their usual practice; the number, type, and timing of these tests, however will be carefully documented, and recorded in the electronic case report form (eCRF).

Table I. Inclusion and exclusion criteria.

(A) Inclusion criteria

1. Male or female patient ≥18 y of age.
2. Patient has chronic stable angina, acute coronary syndromes or silent ischemia.
3. Presence of one or more coronary artery stenoses of ≥50% (by visual assessment) in a native coronary artery or in a saphenous venous or arterial bypass conduit suitable for coronary stent implantation.
4. The vessel should have a reference vessel diameter of at least 2.25 mm by visual assessment (no limitation on the number of treated lesions, vessels, or lesion length).
5. Patient has been informed of the nature of the study and agrees to its provisions and has provided written informed consent as approved by the Ethical Committee and is willing to comply with all protocol-required (follow-up) evaluations.

(B) Exclusion criteria

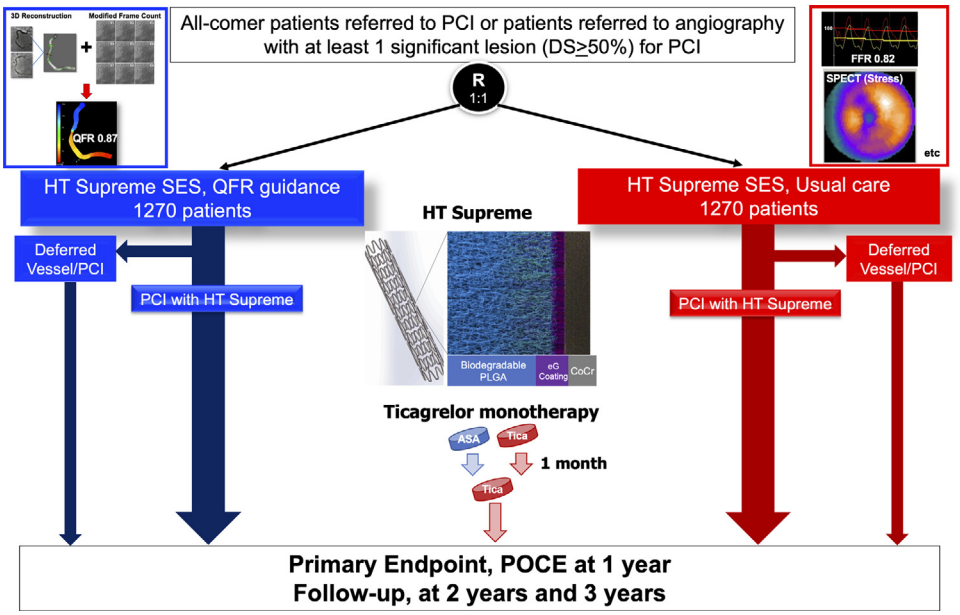
1. Patient is a woman who is pregnant or nursing (a pregnancy test must be performed within 7 d prior to the index procedure in women of child-bearing potential according to local practice).
2. Known contraindication to cobalt chromium, and medications such as sirolimus, aspirin, heparin, bivalirudin or P2Y12 inhibitors.
3. Planned major elective major surgery requiring discontinuation of (D)APT within 12 mo of procedure.
4. Concurrent medical condition with a life expectancy of less than 3 y.
5. Currently participating in another trial and not yet at its primary endpoint.
6. Active pathologic bleeding,
7. History of intracranial hemorrhage.

Patients will be followed up for 3 years after their index procedure. All patients will be (at minimum) contacted at 30 days, 6 months, 12 months, 24 months, and 36 months post procedure to assess clinical status and adverse events. All clinical events occurring from randomization up to the end-of-study visit will be collected and adjudicated by an independent Clinical Event Committee (CEC). An independent Data Safety and Monitoring Board (DSMB) will monitor the individual and collective safety of patients in the study during the enrolment phase and follow-up period.

Informed consent

Patients must sign the consent form prior to any study-specific assessment being performed in accordance with ISO14155, local Ethics Committee requirements, and

Figure 2



Study flowchart. DS, diameter stenosis; PCI, percutaneous coronary intervention; POCE, patient-oriented composite endpoint; QFR, quantitative flow ratio; SES, sirolimus-eluting stent.

country specific regulations. In patients with acute MI who are "transiently incapacitated," a provisory informed consent prior to primary PCI will be obtained, and signed by a third party, which will need to be confirmed by the patient in writing after recovery from their incapacity.[26]

The trial authorizes ad-hoc PCI; therefore, it is imperative that patients are informed and sign a (provisory) informed consent prior to diagnostic angiography. If PCI is subsequently not indicated following diagnostic angiography due to the absence of significant coronary artery disease (CAD) or the presence of extensive CAD amenable only to surgical revascularization, the patients will not be included in the trial.

Of note, amongst patients with ST-elevation MI (STEMI) only those who have bystander disease, in addition to the culprit lesion, will be included. Patients with STEMI who have no bystander disease will not be randomized but will be included in a nested registry.

Study endpoints

The primary endpoint is a non–inferiority comparison at 1 year of POCE in patients randomized to angiography-derived physiology-guided PCI or to usual care (Table II). POCE[27] is a composite clinical endpoint of all cause death, any stroke, any MI, or any clinically, and physiologically driven revascularization. MI will be defined using the SCAI consensus for peri-procedure MI

Table II. Endpoints.

Primary endpoint
• Non-inferiority comparison of POCE at 1 y
Secondary endpoints
1. POCE at 2 and 3 y
2. DOCE/ VOCE /TVF at 1, 2, 3 y
3. Rates of individual components of POCE/DOCE/VOCE /TVF
4. Peri-procedural MI according to 4th universal definition of MI[29]
5. Device success rate[65]
6. Definite/Probable Stent thrombosis rates according to ARC-II[27] classification
7. Bleeding Academic Research Consortium (BARC) type 2, 3, or 5 bleeding [66]

POCE[27,67] is a composite clinical endpoint of (i) all cause death, (ii) any stroke (modified Rankin scale ≥1), (iii) any MI, or (iv) any clinically, and physiologically driven revascularization.
DOCE[27,67] is a composite clinical endpoint of (i) cardiovascular death, (ii) target-vessel-related MI, or (iii) clinically, and physiologically driven target lesion revascularization.
VOCE[18] is a composite of (i) vessel-related cardiovascular death, (ii) target-vessel-related MI, or (iii) clinically, and physiologically driven target vessel revascularization.
TVF[27,67] is a composite clinical endpoint of (i) cardiovascular death, (ii) target-vessel-related MI, or (iii) clinically and physiologically driven target vessel revascularization.
Definition of MI will follow the SCAI consensus for peri-procedure MI ≤48 hours,[28] and Fourth Universal Definition (FUD) for MI >48 hours after index procedure.[29]

within 48 hours of the index procedure,[28] and the Fourth Universal Definition of MI >48 hours after the index procedure.[29] Secondary endpoints are described in Table II.

QFR computation

QFR will be computed using the CE-marked QAngio XA 3D/QFR solution software (Medis Medical Imaging Systems bv., Leiden, the Netherlands), and will be analyzed on-line and in real-time by well-trained and certified technicians/investigators in the Cathlab.[30] The computation of QFR requires 2 angiographic projections for each lesion of interest, acquired at least 25° apart and after the administration of intracoronary nitroglycerin (Supplemental Table I). An end-diastolic frame is selected in each projection and used for the 3-dimensional reconstruction of the segmented vessel. The reference vessel is constructed by fitting to non–stenotic segments preferably proximal and distal to the lesion of interest. The contrast frame count is performed in an angiographic run with contrast movement clearly visualized and preferably within frames from the same cardiac cycle. Frame count-based contrast QFR is used for all analyses. If QFR is unavailable, or if the investigator questions its validity or accuracy, then the investigator will be required to perform an iFR/FFR with the results collected in the electronic case report form. Post-hoc analysis of the index of microcirculatory resistance (IMR) will be performed in a central core lab (CORRIB Core Lab, Galway, Ireland).[31,32]

Index and staged procedures

Stenting with HT Supreme stents should be attempted for all functionally significant lesions with a vessel diameter of ≥2.25 mm by visual assessment. The choice of stent size (length and diameter) will be left to the operator's discretion, but should cover the entire lesion. If additional stenting is needed, HT Supreme stents should be used. The use of IVUS/OCT is left to the discretion of the investigator.

Staged procedures are permitted and will be encouraged for more complex cases in order to increase the likelihood of complete revascularisation and to decrease the risk of contrast induced nephropathy.[33,34] In patients with chronic coronary syndrome (CCS), "retouch" of the vessel treated during the index procedure is not allowed. However, in patients with acute MI, staged treatment of a narrowing proximal or distal (upstream/downstream) to the culprit lesion is permitted provided the QFR is positive. Planned staged elective PCI procedures are required to be performed within 8 weeks of the index procedure. If the staged procedure is performed beyond 8 weeks, such procedures will be evaluated by the Core Lab, and following its assessment a decision will be made regarding whether to send the procedure to the CEC for further adjudication. The patient should receive the same treatment strategy as during the original index procedure. Physiological assessment for staged lesions will be performed at the time of the index PCI, and if performed, does not need to be repeated at the time of the staged PCI.[35]

Antiplatelet and anticoagulation therapy

Peri-procedure. Preloading with aspirin 300 to 325 mg pre-PCI is mandatory unless the patient already receives chronic aspirin. Pre-loading with ticagrelor 180 mg is also mandatory. For patients already receiving ticagrelor, preloading is recommended, but left to the investigator's discretion. Anticoagulation during the procedure is mandatory, though the type, and dose will be left to operator's discretion.

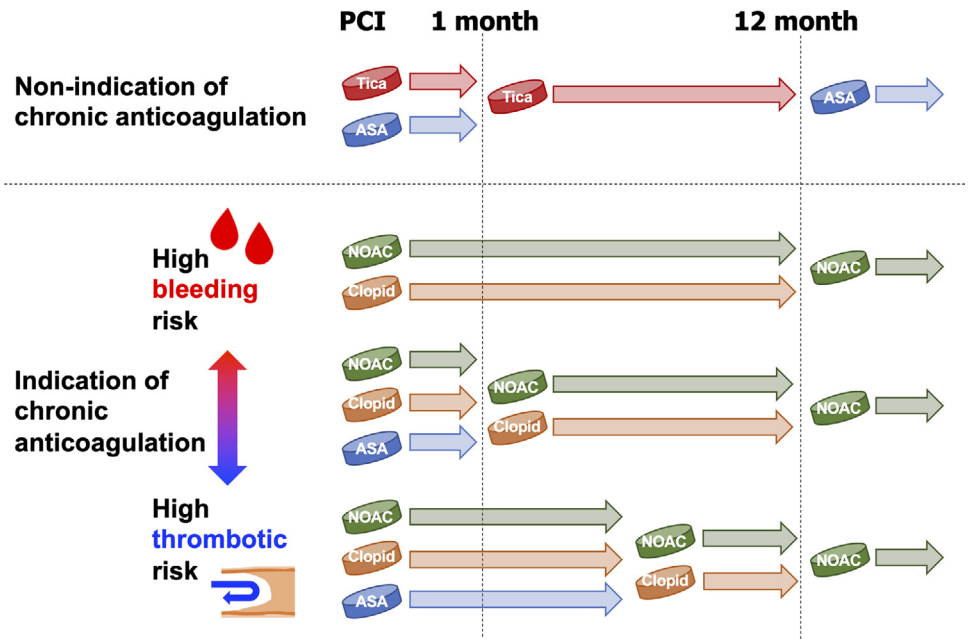
Post-procedure. Patients treated with PCI must receive DAPT, in the form of aspirin and ticagrelor for 1 month, followed by 11 months of ticagrelor monotherapy.[22] At 1 year, ticagrelor monotherapy may be replaced by aspirin monotherapy at the discretion of the investigator (Figure 3). The dose of aspirin and ticagrelor will be 75 to 100 mg and 180 mg per day, respectively. If the patient experiences incapacitating dyspnea (a transient side-effect) with ticagrelor, it should be replaced by prasugrel, with interruption in the P2Y12 inhibitor therapy of <24 hours considering ticagrelor's short half-life. In patients with an indication for chronic anticoagulation (eg, atrial fibrillation), dual therapy with novel oral anticoagulants (NOAC) and clopidogrel is preferred, although use of triple therapy (NOAC, aspirin, and clopidogrel or ticagrelor/prasugrel) is left to the discretion of the investigator, who should consider the treatment strategy most appropriate for whether thrombotic or bleeding events predominate[36] (Figure 3). Probabilistic formulas to determine whether thrombotic ischemia or bleeding events pose the greatest risk post stenting are available and can guide the decision.[36] Antiplatelet medication for patients who do not undergo stent implantation is left to physician's discretion.

Statistics analysis

The primary endpoint (POCE at 1-year) will be analyzed by estimating the difference in POCE event rates between (1) the angiography-derived physiology-guided PCI group and (2) the usual care group (difference = a-b). The upper bound of the 1-sided 95% confidence interval for this estimate will be compared to the pre-specified non–inferiority margin of 3.2% to assess non–inferiority of angiography-derived physiology-guided PCI compared to usual care. Secondary endpoints will be analyzed as appropriate and pre-specified according to a detailed statistical analysis plan, and inference for the treatment effect estimate of these endpoints will focus on the point estimate and confidence interval.

For the primary analysis of the primary endpoint and all secondary endpoints, the intention-to-treat population will be used. The per-protocol population will consist of all patients who have been randomized to a treatment strategy group, and been treated according to

Figure 3



Management of antiplatelet and anticoagulation therapy. ASA, aspirin; Clopid, clopidogrel; NOAC, novel oral anticoagulants; Tica, ticagrelor.

this assigned group, using a study stent in the intended target lesion during the index procedure. Patients who do not receive the treatment strategy to which they were randomized and/or receive any stent other than the study stent will be excluded from the per-protocol population (Supplemental Table II). A secondary analysis of the primary endpoint and all secondary clinical endpoints will also be conducted in the per-protocol population. Missing data for the primary endpoint is anticipated to be low for the primary endpoint (<3%) and the statistical analysis plan will detail handling of censored and missing data in analyses, including the use of the Kaplan Meier estimator and inverse probability weighting.

Sample size calculation

The primary endpoint of POCE will be analyzed for non-inferiority of angiography-based physiology-guided PCI compared to usual care. The assumptions for the sample size calculation are as follows: a 1:1 treatment allocation ratio, a 1-sided significance level (alpha) of 0.05, 90% power to show non-inferiority of angiography-based physiology-guided PCI compared to usual care, a non-inferiority margin of 3.2% (Hazard ratio [HR], 1.4), a POCE event rate for usual care of 8.0% (Supplemental Figure 1) at 1 year, and no difference in event rate between the 2 groups. Hence, in each arm, 1232 patients are required, however taking into account an attrition rate (loss to follow-up or withdrawal) of approximately 3%, these numbers increase to 1270 in each group, giving a total randomized sample of 2,540 patients.

Prespecified subgroup analyses

Prespecified subgroup analyses are listed in Supplemental method. For these analyses, the study does not have significant power to demonstrate non-inferiority/superiority, meaning the results are only considered as exploratory (hypothesis-generating).

Discussion

The PIONEER IV trial compares clinical outcomes between angiography-derived physiology-guided PCI and usual care PCI in an all-comers population treated with the HT Supreme stent and ticagrelor monotherapy.

The efficacy of QFR

The efficacy and safety of FFR and iFR as a decision-making tool in coronary revascularization has been demonstrated in numerous randomized control trials,[3-6,37-41] however similar evidence for QFR is currently lacking. National Institute for Health and Care Excellence (NICE) organization in United Kingdom has requested more clinical outcome data before endorsing publicly this diagnostic method of investigation. Following confirmation of the diagnostic accuracy of QFR compared to FFR and iFR,[13-16] the results from one large ongoing randomized clinical outcome trial, the FAVOR III China

has been recently published and has confirmed the clinical superiority of the QFR guided PCI over the visually guided PCI (NCT03656848)[42] and the results of the FAVOR III Europe-Japan trial (NCT03729739), which is currently assessing the clinical efficacy of QFR in patients with stable and unstable angina, are eagerly awaited. The PIONEER IV trial may also contribute to the endorsement of the diagnostic modality by national regulatory bodies.

The FAVOR III China trial randomized 3825 patients to QFR-guided PCI (n = 1,913) or angiography-guided PCI (n = 1,912), in which pressure wire-based physiological assessment were not permitted.[42] The composite primary endpoint of major adverse cardiac events, defined as all-cause death, MI, or ischemia-driven revascularization, occurred within 1 year in 110 patients (5.8%) in the QFR-guided group and in 167 patients (8.8%) in the angiography-guided group ($P = .0004$). The FAVOR III China trial demonstrated the superiority of QFR-guided PCI in terms of clinical outcome, compared to angiography-guided PCI, however, the trial could not answer the question whether QFR-guided PCI is non–inferior to the current and contemporary European strategy of heterogeneous, and sometimes redundant, invasive, and non–invasive tests that are requested by the ESC guidelines.[1,2,43] The objective of the FAVOR III Europe-Japan study is to investigate whether a QFR-based diagnostic strategy will result in non–inferior clinical outcomes after 12 months compared to an FFR-based diagnostic strategy. The study should answer the question whether QFR, as a tool for physiological assessment, is non–inferior to FFR in terms of clinical outcomes.

In daily clinical practice, wire-derived FFR is still used in <20% of patients with intermediate lesions according to data from the VA CART Program in the United States.[44] Public reports including the data from Europe also demonstrated the low performance rate of wire-derived FFR (5%-31%), although the performance rate is increasing.[45] In daily clinical practice, noninvasive functional test is probably the dominant diagnostic approach whilst invasive functional test is performed incidentally or in a minority of case. In the 2019 ESC guidelines, CTA along with noninvasive functional imaging was given a Class I, Level of Evidence B recommendation as the initial test to diagnose CAD in symptomatic patients in whom obstructive CAD could not be excluded by clinical assessment alone.[2] NICE also recommends selective use of FFR_{CT}.[46] In the new USA guidelines on assessment of chest pain, FFR_{CT} has also receive a prominent position.[47]

The rate of non–invasive and/or wire-derived physiological assessment in current clinical practice is not presumed to be low, and whether routine QFR-guided PCI can be a diagnostic approach non–inferior to the usual diagnostic work out practiced in Europe remains an important unanswered question. In the PIONEER IV trial, usual care PCI will be performed based on routine clinical practice, and this trial investigates the non–inferiority of QFR-guided PCI to usual care PCI. In addition, the comparison between QFR-guided PCI in the QFR guidance arm and the incidental use of FFR/iFR-guided PCI in the usual care arm will be analyzed as sensitivity analysis although the results are considered exploratory only.

Post-PCI QFR guidance

Post-PCI physiological assessment has been shown to be useful for stent optimization. Multiple large observational studies and post hoc analyses of randomized controlled trials have demonstrated that the post-PCI FFR value is an independent predictor of long-term clinical outcomes, although best cut off value has varied from 0.86 to 0.92.[48-51] In the DEFINE-PCI trial, adverse events defined as cardiac death, spontaneous MI, or clinically driven target vessel revascularization occurred in 1.8% of patients with a post-PCI iFR ≥0.95 compared to 5.7% in patients with a lower post-PCI iFR (HR, 3.38 [0.99-11.6]; $P = .04$). In addition, in highly symptomatic patients at baseline, a post-PCI iFR ≥0.95 was associated with greater improvements in anginal symptoms at 12 months compared with a post-PCI iFR <0.95.

Post-PCI physiological assessment using QFR has also been validated.[18,19] The HAWKEYE trial demonstrated that a post-PCI QFR cut-off of ≤0.89 had the best predictive accuracy for the vessel-oriented clinical endpoint in an all-comers population (VOCE: a composite of vessel-related cardiovascular death, vessel-related MI, and ischemia-driven target vessel revascularization) at 2 years (AUC, 0.77 [0.74-0.80]).[19] Similarly, a sub-study of the SYNTAX II trial showed that a post-PCI QFR ≥0.91 was associated with improved VOCE at 2 years amongst patients receiving state-of-the-art PCI for de novo 3-vessel disease (12.0% vs 3.7%; HR, 3.37 [1.91-5.97]; $P < .001$).[18] Whilst the cut off value is still a matter of debate, the use of post-PCI physiological assessment appears to improve clinical outcomes. In accordance with the aforementioned sub-study of the SYNTAX II trial, the PIONEER IV trial will also use <0.91 as the cut off for post-PCI QFR.[18]

Antiplatelet and anticoagulation treatment post PCI

The GLOBAL LEADERS trial demonstrated that ticagrelor monotherapy following 1-month DAPT with aspirin (n = 7,980) reduced the occurrence of all-cause death and new Q-wave MI at 1 year, when compared with standard 1-year DAPT (n = 7,988) (1.95% vs 2.47%; risk ratio, 0.79 [0.64-0.98]).[22] One-month DAPT was also investigated in the STOP-DAPT 2 randomized trial, which was conducted in Japan, and compared P2Y12 inhibitor (clopidogrel) monotherapy after 1-month of DAPT (n = 1,523), with a conventional DAPT strategy (n = 1,509) in patients with CCS or acute coronary syndrome (ACS).[23] The primary endpoint, a composite of cardiac death, MI, and TIMI major bleeding, was significantly lower in patients receiving clopidogrel

monotherapy, compared to conventional DAPT (2.4% vs 3.7%; HR: 0.64 [0.42-0.98]; *P* for non–inferiority <.001; *P* for superiority = .04). Notably, there was no significant difference in the risk of adverse ischemic events, a composite of cardiac death, MI, stent thrombosis, or stroke (2.0% vs 2.5%; HR, 0.79 [0.49-1.29]; *P* for non–inferiority = .005; *P* for superiority = .34). A novel aspirin-free strategy after PCI was investigated in the Acetyl Salicylic Elimination Trial (ASET),[52] which enrolled 200 patients with CCS and a SYNTAX score <23, who all received a loading dose of prasugrel just after successful PCI with optimal acute stent implantation, and continued with prasugrel monotherapy for 3 months. One patient death, adjudicated as a cardiac death, occurred following a hemorrhagic stroke a few hours after PCI. The ASET study demonstrated the feasibility and safety of P2Y12 inhibitor (prasugrel) monotherapy immediately after optimal stent implantation. In the ongoing Multivessel TALENT trial (NCT04390672), 1-month DAPT followed by prasugrel monotherapy is being used as one component of the so-called "best practice PCI."[53] Therefore, very short DAPT followed by P2Y12 inhibitor monotherapy (aspirin-free strategy) should be promoted (Figure 3). The HT Supreme SES has rapid endothelial recovery, due to the short and timely elution of the cytostatic agent, and this is an additional reason to test a strategy of 1-month DAPT. The 1-year landmark analysis in the GLOBAL LEADERS trial showed no difference in clinical outcomes between patients receiving ticagrelor or aspirin monotherapy during the second year, therefore there is no argument to prolong ticagrelor monotherapy beyond 1 year.[54] Hence, at 1 year, ticagrelor monotherapy should be replaced by aspirin monotherapy considering the wealth of evidence in favor of its long-term use for secondary prevention (Figure 3).[55]

In patients with atrial fibrillation, 4 large trials, WOEST, PIONEER AF-PCI, RE-DUAL PCI, and AUGUSTUS, and their network meta-analysis, have demonstrated that treatment with a NOAC and P2Y12 inhibitor reduces bleeding risk without an increased risk of ischemic events up to 1 year after PCI, compared to vitamin K antagonists plus DAPT.[56-60] In these 4 trials, clopidogrel was used as the P2Y12 inhibitor in more than 90% of patients. Therefore, in patients with atrial fibrillation undergoing PCI, it is recommended to use 1-year of combination therapy with a NOAC and P2Y12 inhibitor (clopidogrel), followed by NOAC monotherapy. The AFIRE trial demonstrated that NOAC monotherapy was noninferior to combination therapy with a NOAC and single antiplatelet agent for efficacy (stroke, systemic embolism, MI, unstable angina requiring revascularization, or all-cause death; HR, 0.72 [0.55-0.95]) and was superior for safety (major bleeding; HR, 0.59 [0.39-0.89]) in patients with atrial fibrillation and stable CAD, including those with prior PCI more than 1 year earlier.[61] Recently, a novel algorithm for the management of antithrombotic therapy in atrial fibrillation patients undergoing PCI was proposed, and dual therapy with a NOAC and P2Y12 inhibitor (clopidogrel) or triple therapy with NOAC, clopidogrel, and aspirin were recommended according to the patient's thrombotic and bleeding risk in the first 6 months after PCI.[62] In the PIONEER IV trial, dual- or triple-therapy after PCI in patients requiring anti–coagulation is left to the discretion of the investigator, however NOAC monotherapy beyond 1 year is highly recommended in patients who need chronic anticoagulation (Figure 3). Probabilistic formulas to assess what is more prevailing, -the risk of bleeding or the risk of ischemia-, have been published and may guide the investigator in choosing between double or triple therapy, and a short or long duration.[36,63]

Limitation

Measurements of QFR are sometimes challenging because of overlap with surrounding vessels or foreshortening of the target vessel. Notably however, the analyzability of on-line QFR was 96%, 99% and 94% in FAVOR II Europe-Japan, FAVOR II China and WIFI-II studies, respectively.[14,15,64] The use of QFR in aorto-ostial lesions and bypass grafts has not been validated, and iFR/FFR will be a substitute whenever QFR assessment is not available or reliable.

Conclusions

The PIONEER IV trial will establish whether QFR is non–inferior to the usual diagnostic approach practiced in Europe and subsidiarily whether novel approach can improve clinical outcomes in daily practice. Additionally, the study may provide a better understanding of the clinical performance of HT Supreme stent in an unselected patient cohort receiving 1-month DAPT, followed by 11-month ticagrelor monotherapy.

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Supplementary materials

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