Rationale and design of the pullback pressure gradient (PPG) global registry

Daniel Munhoz, MD, PhD[a,b], Carlos Collet, MD, PhD[a], Takuya Mizukami, MD, PhD[a,c], Andy Yong, MD, PhD[d], Antonio Maria Leone, MD, PhD[e,f], Ashkan Eftekhari, MD, PhD[g], Brian Ko, MD, PhD[h], Bruno R. da Costa, MSc, PhD[i,j], Colin Berry, MD, PhD[k], Damien Collison, MBBCh, MD[k], Divaka Perera, FRCP, MD[l], Evald Høj Christiansen, MD, PhD[m], Fernando Rivero, MD, PhD[n], Frederik M. Zimmermann, MD, PhD[o], Hirohiko Ando, MD, PhD[p], Hitoshi Matsuo, MD, PhD[q], Masafumi Nakayama, MD, PhD[r], Javier Escaned, MD, PhD[s], Jeroen Sonck, MD, PhD[a], Koshiro Sakai, MD, PhD[a,t], Julien Adjedj, MD, PhD[u], Liyew Desta, MD, PhD[v], Lokien X. van Nunen, MD, PhD[w], Nick E.J. West, MD[x], Stephane Fournier, MD, PhD[y], Tatyana Storozhenko, MD[a,z], Tetsuya Amano, MD, PhD[p], Thomas Engstrøm, MD PhD[aa], Thomas Johnson, MBBS, MD[bb], Toshiro Shinke, MD, PhD[t], Simone Biscaglia, MD, PhD[cc], William F. Fearon, MD[dd], Ziad Ali, MD, PhD[ee], Bernard De Bruyne, MD, PhD[a,y], and Nils P. Johnson, MD, MS[ff] *Aalst, Belgium; Naples, Italy; Tokyo, Japan; New South Wales, Australia; Rome, Italy; Aalborg, Denmark; Victoria, Australia; Oxford, England; Ontorio, Canada; Glasgow, UK; London, UK; Aarhus, Denmark; Madrid, Spain; Eindhoven, The Netherlands; Aichi, Japan; Gifu, Japan; Stockholm, Sweden; Nijmegen, The Netherlands; Santa Clara, CA; Lausanne, Switzerland; Kharkiv, Ukraine; Copenhagen, Denmark; Bristol, United Kingdom; Ferrara, Italy; Palo Alto, CA; Roslyn, NY; Houston, TX*

Introduction Diffuse disease has been identified as one of the main reasons leading to low post-PCI fractional flow reserve (FFR) and residual angina after PCI. Coronary pressure pullbacks allow for the evaluation of hemodynamic coronary artery disease (CAD) patterns. The pullback pressure gradient (PPG) is a novel metric that quantifies the distribution and magnitude of pressure losses along the coronary artery in a focal-to-diffuse continuum.

Aim The primary objective is to determine the predictive capacity of the PPG for post-PCI FFR.

Methods This prospective, large-scale, controlled, investigator-initiated, multicenter study is enrolling patients with at least 1 lesion in a major epicardial vessel with a distal FFR $\leq$ 0.80 intended to be treated by PCI. The study will include 982 subjects. A standardized physiological assessment will be performed pre-PCI, including the online calculation of PPG from FFR pullbacks performed manually. PPG quantifies the CAD pattern by combining several parameters from the FFR pullback curve. Post-PCI physiology will be recorded using a standardized protocol with FFR pullbacks. We hypothesize that PPG will predict optimal PCI results (post-PCI FFR $\geq$ 0.88) with an area under the ROC curve (AUC) $\geq$ 0.80. Secondary objectives include patient-reported and clinical outcomes in patients with focal vs. diffuse CAD defined by the PPG. Clinical follow-up will be collected for up to 36 months, and an independent clinical event committee will adjudicate events.

Results Recruitment is ongoing and is expected to be completed in the second half of 2023.

From the [a]Cardiovascular Center Aalst, OLV Clinic, Aalst, Belgium, [b]Department of Advanced Biomedical Sciences, University Federico II, Naples, Italy, [c]Division of Clinical Pharmacology, Department of Pharmacology, Showa University, Tokyo, Japan, [d]Concord Repatriation General Hospital, University of Sydney, New South Wales, Australia, [e]Department of Cardiovascular Sciences, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Catholic University School of Medicine, Rome, Italy, [f]Center of Excellence in Cardiovascular Diagnostics and Therapeutic, Ospedale Fabenefratelli Isola Tiberina Gemelli Isola, Rome, Italy, [g]Department of Cardiology, Aalborg University Hospital, Aalborg, Denmark, [h]Monash Cardiovascular Research Centre, Monash University and Monash Heart, Monash Health, Clayton, Victoria, Australia, [i]Clinical Trial Service Unit and Epidemiological Studies Unit (CTSU), Nuffield Department of Population Health, University of Oxford, Oxford, England, [j]Clinical Epidemiology and Health Care Research, Institute of Health Policy and Management Evaluation (IHPME), University of Toronto, Toronto, Ontorio, Canada, [k]School Cardiovascular and Metabolic Health, University of Glasgow, Glasgow, UK, [l]School of Cardiovascular Medicine and Sciences, St Thomas' Hospital Campus, King's College London, London, UK, [m]Department of Cardiology, Aarhus University Hospital, Aarhus, Denmark, [n]Cardiac Department, Hospital Universitario de La Princesa, Madrid, Spain, [o]Department of Cardiology, Catharina Hospital Eindhoven, Eindhoven, The Netherlands, [p]Department of Cardiology, Aichi Medical University, Aichi, Japan, [q]Department of Cardiovascular Medicine, Gifu Heart Center, Gifu, Japan, [r]Department of Cardiology, Tokyo D Tower Hospital, Tokyo, Japan, [s]Instituto de Investigacion Sanitaria del Hospital Clinico San Carlos and Complutense University, Madrid, Spain, [t]Department of Medicine, Division of Cardiology, Showa University School of Medicine, Tokyo, Japan, [u]Department of Cardiology, Arnault Tzanck Institute Saint Laurent du Var, France, [v]Department of Cardiology, Karolinska University Hospital, Solna, Stockholm, Sweden, [w]Department of Cardiology, Radboud University Medical Center, Nijmegen, The Netherlands, [x]Abbott Vascular, Santa Clara, CA, [y]Department of Cardiology, University Hospital of Lausanne, Lausanne, Switzerland, [z]Department of Prevention and Treatment of Emergency Conditions, L.T. Malaya Therapy National Institute NAMSU, Kharkiv, Ukraine, [aa]Rigshospitalet, University of Copenhagen, Copenhagen, Denmark, [bb]University Hospitals Bristol & Weston NHS Foundation Trust, Bristol, United Kingdom, [cc]Cardiology Unit, Azienda Ospedaliera Universitaria di Ferrara, Ferrara, Italy, [dd]Division of Cardiovascular Medicine and Stanford Cardiovascular Institute, Stanford University School of Medicine and VA Palo Alto Health Care System, Palo Alto, CA, [ee]St Francis Hospital and Heart Center, Roslyn, NY, [ff]Weatherhead PET Center, Division of Cardiology, Department of Medicine, McGovern Medical School at UTHealth and Memorial Hermann Hospital, Houston, TX

ClinicalTrials.gov Identifier: NCT04789317.

Submitted April 6, 2023; accepted July 8, 2023

Reprint requests: *Nils P. Johnson, MD, MS, Weatherhead PET Center, McGovern Medical School at UTHealth, 6431 Fannin Street, Room MSB 4.256, Houston, TX 77030.*

E-mail address: nils.johnson@uth.tmc.edu.

0002-8703

https://doi.org/10.1016/j.ahj.2023.07.016

Conclusion This international, large-scale, prospective study with pre-specified powered hypotheses will determine the ability of the preprocedural PPG index to predict optimal revascularization assessed by post-PCI FFR. In addition, it will evaluate the impact of PPG on treatment decisions and the predictive performance of PPG for angina relief and clinical outcomes. (Am Heart J 2023;265:170–179.)

Assessing the distribution of flow-limiting atherosclerosis along a coronary artery adds a second dimension to evaluating lesion significance. Ascertainment of the hemodynamic pattern of coronary artery disease (CAD)—either as focal or diffuse—carries therapeutic implications. Coronary angiography has historically been used to assess CAD patterns. However, insights from intracoronary pressure pullbacks and intravascular imaging have underlined that coronary angiography underestimates the burden of atherosclerosis and can misjudge the distribution of disease.[1,2] Moreover, CAD patterns have been shown to influence treatment decisions concerning myocardial revascularization; diffuse CAD has been identified as 1 mechanism associated with persistent angina after percutaneous coronary intervention (PCI).[3,4]

Fractional flow reserve (FFR) is a hyperemic intracoronary pressure measurement that correlates with myocardial ischemia by providing a metric of peak flow reduction.[5] It has proven superior to an angiographic-based strategy when selecting lesions for PCI for predicting death, myocardial infarction or urgent revascularization[6] as well as for cost effectiveness[7]. Nevertheless, the distal FFR value (also referred to as spot or single point FFR) results from cumulative pressure loss along the entire vessel due to focal or diffuse atherosclerotic disease and, frequently, a combination of both.[1,8] Diffuse CAD is associated with a lower FFR after PCI[9,10] and a higher incidence of clinical events.[11] Currently, definitions of diffuse CAD are heterogenous, commonly based on visual assessment, and therefore subject to high interobserver variability.[8,12]

Intracoronary pressure losses along the vessel reflect the interplay between epicardial atherosclerotic burden and coronary flow. A pullback maneuver reveals the distribution and magnitude of these pressure losses. This pattern can be quantified along a focal-to-diffuse continuum using a novel metric: the pullback pressure gradient (PPG).[8] PPG quantifies the CAD pattern by combining 2 parameters: the maximal pressure gradient in the pullback and the amount of functional disease along the vessel.

A preintervention evaluation of the pressure pullback pattern may help predict the post-PCI FFR and thus individualize revascularization decisions. [13] When measured immediately after PCI, a low residual FFR has been identified as an independent predictor of future vessel-related adverse events.[14-16] Likewise, the magnitude of improvement in FFR after PCI has been associated with angina relief, linking the clinical benefit of PCI to a reduction of pressure gradients and improvements in epicardial conductance.[10,17-19]

The PPG Global study will determine the capacity of PPG to predict optimal functional revascularization assessed by FFR after PCI. It will also explore the implications for clinical decision-making, its association with angina improvement at one year, and clinical outcomes up to 3 years.

Methods

Study design

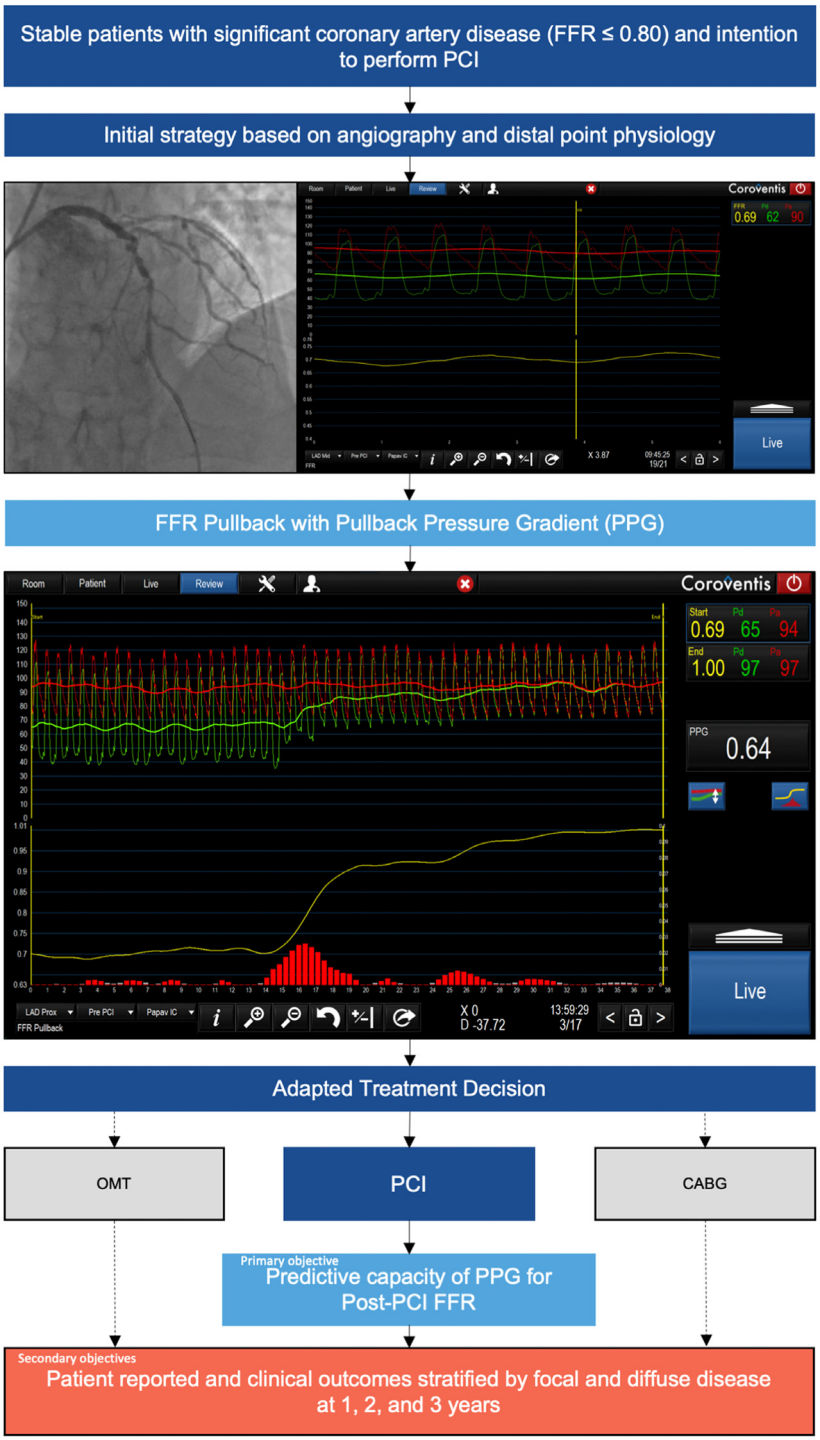
This prospective, investigator-initiated, multicenter, international, large-scale study with prespecified powered hypotheses, registered at clinicaltrials.gov as NCT04789317, is enrolling subjects with at least 1 lesion in a major epicardial vessel with a distal FFR $\leq$ 0.80 intended to be treated with PCI. Table 1 provides inclusion and exclusion criteria. Briefly, subjects must be 18 years or older at the time of inclusion with stable CAD or a nonculprit vessel after an acute coronary syndrome (ACS). Aorto-ostial lesions are excluded, given the challenges of maintaining a suitable guide catheter position during pressure wire pullback. A total of 25 centers with experience in coronary physiology are recruiting patients in Europe, the United Kingdom, Japan, the USA, and Australia (Table S1). The trial follows the Declaration of Helsinki and all applicable local regulations. Every subject must give written informed consent before enrollment, and every site must receive approval from its local institutional review board before recruitment begins. Figure 1 details the flow of patients included in the PPG Global registry.

Primary and secondary endpoints

The primary endpoint is the predictive capacity of the PPG index for post-PCI FFR evaluated by area under the curve (AUC) from receiver operating characteristic (ROC) analysis. Secondary endpoints include the following:

1. Impact of the PPG on treatment decisions assessed by the rate of deferral from planned PCI to either coronary artery bypass grafting (CABG) or medical therapy;

Figure 1



Study Flowchart. Detailed flow of the study, with first and second clinical decisions registered in dedicated questionnaires. The second (or adapted) clinical decision is registered after FFR pullback with PPG calculation. PCI or deferral is at the operator's discretion. Patients will be followed up to 3 years. ACS, Acute coronary syndrome; FFR, Fractional flow reserve; SAQ-7, 7-point Seattle Angina Questionnaire; PCI, Percutaneous coronary intervention; PPG, Pullback pressure gradient.; OMT, Optimized Medical Therapy; CABG, Coronary artery bypass graft.

Table 1. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
1. Age >18 y 2. Provide written informed consent (IC) 3. Angiographic lesion amenable to PCI 4. Invasive FFR ≤0.80	**Angiographic exclusion criteria:** 1. Aorto-ostial lesions. 2. Severe vessel tortuosity*. 3. Vessel rewiring is deemed "difficult" by the operator. 4. Bifurcation with planned 2-stent strategy. **Concomitant contra-indications** 1. NYHA class III or IV, or last known left ventricular ejection fraction <30% 2. Acute STEMI 3. NSTEMI culprit vessels 4. Uncontrolled or recurrent ventricular tachycardia 5. Prior myocardial infarction in the treated vessel 6. History of any haemorrhagic stroke 7. Active liver disease or hepatic dysfunction, defined as AST or ALT > 3 times the upper limit of normal 8. Severe renal dysfunction, defined as an eGFR <30 mL/min/1.73 m^2 **Other exclusion criteria** 1. Known pregnancy or breastfeeding at the time of randomization.

*Tortuosity is defined as 1 or more bends of 90° or more, or 3 or more bends of 45° to 90° proximal of the diseased segment.

2. Relationship between the baseline PPG and improvement in angina symptoms 1 year after PCI assessed by the Seattle Angina Questionnaire (SAQ-7) both in the overall population and in patients with symptoms at baseline;
3. Relationship between baseline PPG and health-related quality of life improvement assessed by the SAQ-7;
4. Proportion of patients with focal and diffuse disease free from angina after PCI (defined by the SAQ-7 angina frequency domain) both in the overall population and in patients with symptoms at baseline;
5. Proportion of patients with focal and diffuse disease with post-PCI FFR ≥ 0.90 or > 0.80;
6. Rates of TVF defined as a composite of cardiac death, target-vessel myocardial infarction, and ischemia-driven target vessel revascularization between patients with focal and diffuse disease at 1, 2 and 3 years;
7. Rates of the individual components of TVF, including periprocedural MI, in patients with focal and diffuse disease defined by PPG;
8. Impact of intracoronary imaging guidance during PCI on TVF stratified by focal and diffuse disease defined by the PPG index.

In addition, subanalyses are planned to address the association between microvascular assessment and PPG, comparison of PPG derived in resting and hyperemic conditions, impact of serial lesions on the post-PCI FFR prediction, and a comparison between stable and ACS patients.

Clinical event definitions

Cardiovascular death represents a death resulting from cardiovascular or undetermined causes. Myocardial infarction (MI) includes both spontaneous and periprocedural. Spontaneous MI represents an infarct after the first 48 hours following PCI or CABG and unrelated to the revascularization procedure.[20] Periprocedural MI occurs within the first 48 hours following PCI or CABG. The criteria for periprocedural MI are shown in Supplemental material Table S2.[20,21] Target-vessel MI is defined as an MI in the vessel that underwent FFR and PPG measurement during the index procedure. Target vessel revascularization (TVR) is defined as repeat PCI or CABG of any segment of a target vessel, including the target lesion. Target lesion revascularization is defined as a reintervention up to 5 mm proximally or distally to the index lesion. Revascularization is considered ischemia-driven if associated with any of the following: (1) positive noninvasive stress test or invasive FFR ≤ 0.80; (2) angiographic diameter stenosis ≥50% by core laboratory quantitative coronary angiography (QCA) with ischemic clinical symptoms or angiography-derived FFR ≤ 0.80; or (3) angiographic diameter stenosis ≥70% by core laboratory QCA without angina. Completeness of revascularization will be quantified by the residual SYNTAX score (rSS) with complete revascularization indicating an rSS of 0.[22]

Catheterization laboratory protocol

Vascular access and size of the guiding catheter are left to the operator's discretion. All subjects will receive 100 to 200 μg of intracoronary nitroglycerin at the beginning of the procedure. An 0.014″ coronary wire with a distal pressure sensor (PressureWire X, Abbott Vascular, Santa Clara, CA) will be introduced into the target vessel after pressure equalization at the tip of the guiding catheter.[23] The pressure wire will be positioned in the distal coronary artery in a segment ≥ 2 mm and at least 15 mm beyond the most distal stenosis by visual estimation and

its position recorded by contrast angiography. Resting full cycle ratio (RFR) and FFR will be measured at the distal wire position. Hyperemia can be induced by various pharmacologic agents (eg, Adenosine, Papaverine, Nicorandil, ATP, etc.) according to local practice. The most commonly used hyperemic agents are intracoronary (IC) Papaverine, Adenosine IV, and Nicorandil IC. It is important to note that IC Adenosine cannot be used for PPG assessment because the hyperemic time is not long enough to perform a pullback maneuver. The operator will then record 3 items of the initial strategy in a dedicated pre-PPG questionnaire: (1) the segment to be treated, (2) the number of stents, and (3) the total stent length. Subsequently and during maximal hyperemia, a manual pullback will be performed at a steady speed over 20 to 30 seconds. All operators will be trained via movies on how to perform the manual pullback maneuver.[13] PPG will be calculated online using CoroFlow software (version 3.5.1, Coroventis Research, Uppsala, Sweden). After the calculation of the PPG, the operator will answer a dedicated post-PPG questionnaire with the same 3 questions regarding the treatment plan. After the calculation of PPG, deferral of PCI to either CABG or medical therapy is permitted. Measurement of microvascular function (coronary flow reserve [CFR] and index of microvascular resistance [IMR]) pre- and post-PCI will be performed optionally in selected centers. PCI will be performed at the operator's discretion; the use of intravascular imaging for PCI guidance will be encouraged. After PCI, RFR and distal FFR will again be assessed with the pressure wire in the same position as before the PCI. Finally, an FFR pullback will be repeated, with markers placed at the distal and proximal stent edges to allow for coregistration with residual pressure gradients and stent position. The quality of the pressure pullback tracings and compliance with the physiology protocol will be controlled by the core laboratory, providing feedback to the investigators on the adequacy of the tracings during the first ten cases at every site.

Calculation of the PPG

The formula for PPG has been described and modified previously.[13] Its equation combines 2 equally-weighted parameters:

$$\textbf{PPG} = \frac{\frac{\text{Maximal Pressure Gradient over 20\% pullback duration}}{\text{Vessel FFR gradient}} + \left(1 - \text{proportion of pullback time with FFR deterioration}\right)}{2}$$

The *maximal pressure gradient over 20% of the pullback duration* calculates the pressure drop over a fixed time window lasting 20% of the total pullback duration. Likewise, the *proportion of pullback time with FFR deterioration* uses an FFR threshold of 0.0015 units per time. The adapted formula has been incorporated into a commercial console and allows for calculation of the PPG after a manual pullback manuever (CoroFlow, Coroventis Research, Uppsala, Sweden). Figure 2 shows the diffuse to focal functional CAD spectrum.

The 7 items Seattle angina questionnaire

The 7-items Seattle Angina Questionnaire (SAQ-7) is a shortened version of a commonly-used tool to measure health status by quantifying anginal symptoms, functional limitations due to angina, and the impact of angina on quality of life. The SAQ-7 summary score and scores from its individual domains will be used to quantify angina frequency, physical limitation, and quality of life. In addition, angina frequency scores will be categorized into daily or weekly ($\leq$ 60), monthly (>60, < 100), or none (= 100), and for the domains of physical limitation and quality into poor or fair (< 50), good ($\geq$50, < 75), or excellent ($\geq$75) categories.[24]

Clinical decision and treatment

While an FFR $\leq$ 0.80 is considered abnormal and revascularization deemed appropriate, there is no guidance on a PPG threshold; therefore, no threshold was provided to operators regarding the PPG value. As the first clinical decision is registered before the pullback, this clinical decision resembles a strategy without access to the PPG value or the pullback curve pattern, as is common in clinical practice. Based on prior work, we hypothesize that PCI of lesions in vessels with low PPG (representing more diffuse disease) will lead to low post-PCI FFR, less angina relief, and more frequent target vessel failure (TVF).

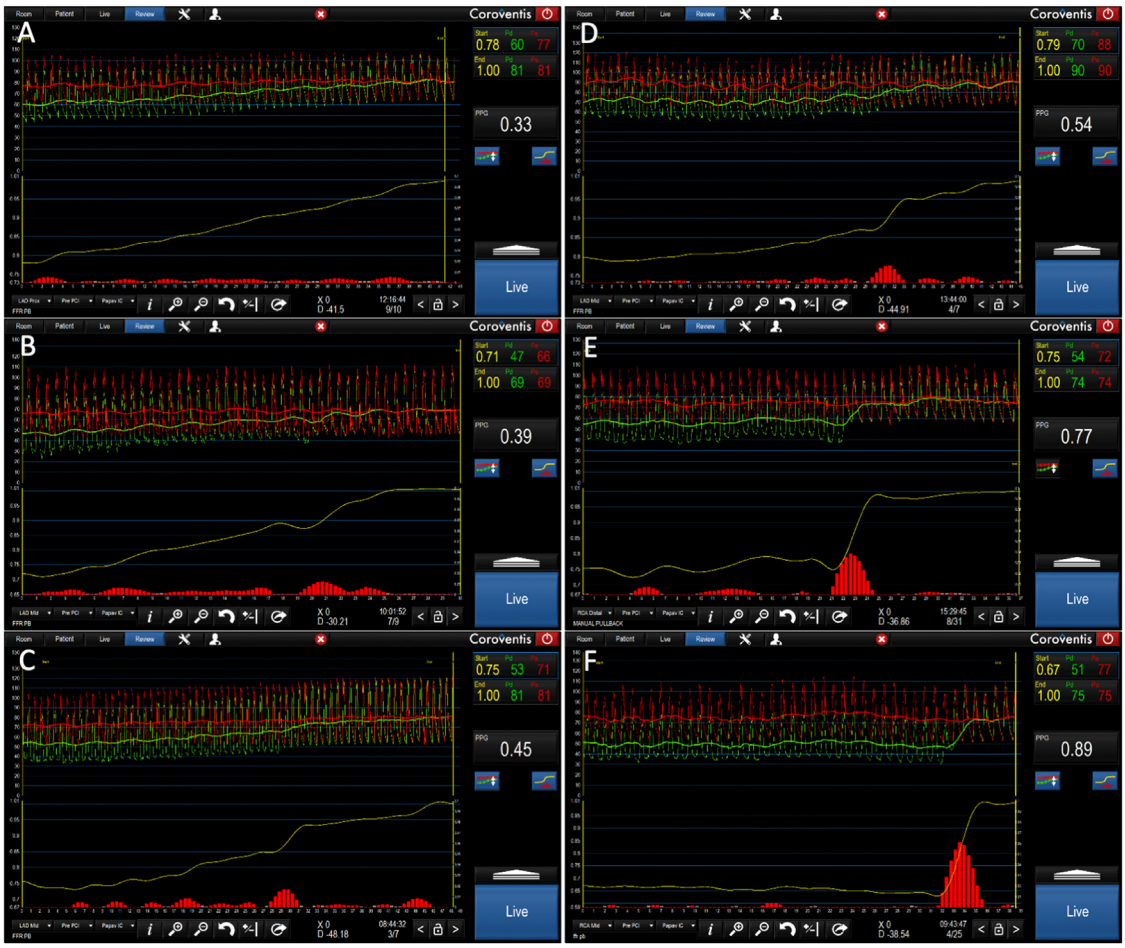
Clinical follow-up

Patients will be followed up to 36 months. Follow-up can occur either by a clinical visit or by telephone contact. During the first-year follow-up interview, an SAQ-7 will be readministered, and clinical status will be collected at 12, 24, and 36 months. Documentation of hospital records will be reviewed for all subjects admitted for major adverse coronary events (cardiac death, periprocedural and spontaneous myocardial infarction, target vessel revascularization, and stent thrombosis). Based on the documentation provided by the local site, clinical endpoints will be adjudicated by an independent clinical events committee (CEC).

Statistical analysis and sample size

We hypothesize that PPG will predict optimal revascularization defined as post-PCI FFR $\geq$ 0.88 with an expected area under the ROC curve (AUC) of 0.80.[14] Under the assumptions of power of 90%, 2.5% 2-sided alpha, a sample size of 128 patients will be required. The study

Figure 2

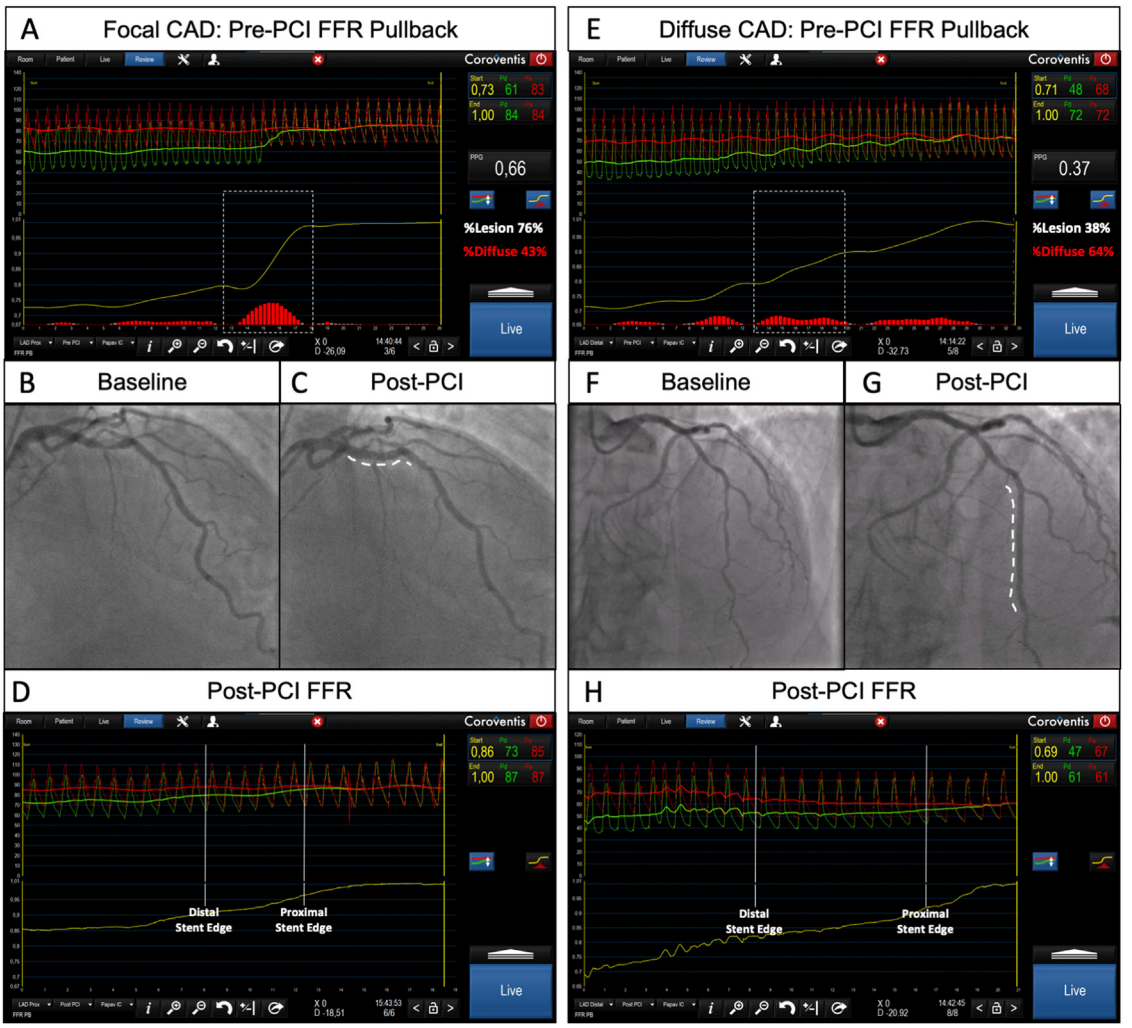


Diffuse to Focal functional CAD spectrum. Fractional flow reserve (FFR) pullbacks with a pullback pressure gradient (PPG) ordered from panel A showing diffuse (low PPG) to panel F depicting focal disease (high PPG).

will also be powered for the key major secondary objective of the impact of PPG on treatment decisions expecting a 20% change in revascularization decisions from the initial intention to perform PCI to either CABG or medical therapy. Considering a width of the 95% confidence interval of 5%, a sample size of 982 patients will be required to detect this change.

The analysis cohort for the primary outcome will consist only of patients who received PCI. For the primary objective, we will calculate the area under the receiver operating characteristic (AUC) curve, adjusted by vessel type and pre-PCI FFR, and its 95% bias-corrected bootstrapped confidence interval (CI) as a measure of PPG discrimination of patients achieving optimal revascularization (post-PCI FFR $\geq$ 0.88). If this interval excludes 0.60 and contains $\geq$ 0.80, the study will have met its primary endpoint. We will then calculate sensitivity, specificity, positive and negative likelihood ratios to identify the most appropriate baseline PPG cut-off(s) to identify patients who will likely achieve optimal revascularization. We will use 2 different linear regression models to predict post-PCI FFR: one using baseline PPG dichotomized according to the selected cut-off, and the other using baseline PPG on a continuous scale as predictor, with both models including vessel type and pre-PCI FFR as additional predictors. Discrimination based on AUC, likelihood ratios associated with identified cut-off(s) of baseline PPG, calibration of predicted post-PCI FFR from dichotomized baseline PPG, and calibration of predicted post-PCI FFR from baseline PPG will be internally validated in the temporally defined derivation cohort based on 500 bootstrap samples with replacement (primary validation), and then validated in the temporally defined validation cohort (secondary valida-

Figure 3



Case examples. Panel A shows the pre-PCI FFR pullback of a mid LAD lesion with a distal FFR of 0.73 and a PPG of 0.66 (calculated with the average of 2 components of a maximal pressure gradient within 20% of the pullback length of 76% and 43% of disease length). The dashed box, for illustration purposes, shows the location of the maximal pressure gradient detected in the pullback curve. Panel B shows the baseline angiography, and panel C shows the post-PCI angiographic results (the white dashed line indicates the position of the stent). Panel D shows the post-PCI FFR pullback with a distal FFR of 0.86. Panel E shows another case with diffuse disease; the pre-PCI FFR was 0.71 with a PPG 0.37. Panel F and G show the pre- and post-PCI angiography (the white dashed line indicates the position of the stent). Panel H shows a post-PCI FFR of 0.69 with residual diffuse disease. LAD, Left anterior descending artery; FFR, Fractional flow reserve; PG, Pressure gradient; PPG, Pullback pressure gradient.

tion).[25] Calibration is defined as the agreement between observed and predicted values and will be assessed using calibration plots, ratio of predicted to observed post-PCI FFR, and calibration-in-the-large.[26] Therefore, this analysis will provide a PPG threshold for the prediction of optimal revascularization based on post-PCI FFR. For the secondary endpoints, the definition of focal and diffuse coronary artery disease will be based on the baseline PPG threshold derived from the AUC analysis.[4] Patients reported-outcomes will be evaluated by comparing focal and diffuse disease using linear regression models adjusted by baseline values and medication use. Clinical outcomes between patients with focal and diffuse disease will be assessed using adjusted multivariable logistic regression and Cox regression analyses.

Study limitations

Because of the nonrandomized, observational, and nonblinded design, certain limitations apply. The primary objective will be assessed using the AUC method

and a post-PCI FFR cut-off of 0.88.[14] However, after starting this study a large pooled analysis indicated an optimal post-PCI FFR threshold of 0.86 to predict target vessel failure, very similar to the 0.88 prospectively chosen in this registry.[27] Clinical thresholds for PPG have not yet been fully determined; therefore, there is no guidance regarding treatment decisions based on the PPG value at the current stage.

Role of the funding source and study oversight

The PPG Global Registry is an investigator-initiated trial sponsored by the Cardiac Research Institute Aalst with an unrestricted grant from Abbott Vascular. The grant giver will not be involved in the study design, data collection, and data analysis. A core laboratory (CoreAalst BV, Aalst, Belgium) will analyze imaging and physiological data. An independent CEC will adjudicate all endpoints, blinded to the physiological data.

Results

Recruitment is ongoing, and the primary endpoint is anticipated in the second half of 2023. Figure 3 shows 2 case examples from the PPG global registry with FFR pullback before and after PCI in focal and diffuse CAD.

Discussion

Studies in which the indication of PCI has been set on the grounds of intracoronary physiology have shown that, after an angiographically successful procedure, approximately one-fourth of patients show residual flow-limiting epicardial vessel disease.[15,28,29] The main reasons for low FFR after PCI relate to residual atherosclerotic disease or suboptimal stent deployment.[30] By anticipating the impact of residual disease after PCI, PPG provides a tool to predict post-PCI FFR and angina improvement, thereby allowing personalized revascularization decisions. PPG pullback augments the single value distal FFR evaluation by quantifying the CAD pattern and identifying focal pressure gradients amenable to PCI. The present study will determine PPG's predictive capacity for post-PCI physiology. In addition, the change in treatment decision after systematic longitudinal vessel investigation with hyperemic manual pullbacks will be defined. Furthermore, the impact of focal and diffuse disease quantified based on intracoronary hemodynamics on patient-reported and clinical outcomes will be assessed at mid-term follow-up.

The field of coronary physiology continues to evolve, and longitudinal pressure evaluation obtained by manual pullback manuevers has been shown to have clinical implications and predict the interventions' results.[4] Pullback maneuvers can be performed in resting or hyperemic conditions to define the disease as focal or diffuse. In addition to PPG Global, a randomized clinical trial, Distal Evaluation of Functional Performance With Intravascular Sensors to Assess the Narrowing Effect: Guided Physiologic Stenting (DEFINE-GPS NCT04451044), which uses coregistration of instantaneous wave-free ratio (iFR) with angiography, is also utilizing systematic pullback evaluations to plan and guide PCI. These trials will shed light of the effects of PCI in focal vs. diffuse CAD.

Conclusion

This international, large-scale, controlled, prospective study with pre-specified powered hypotheses will determine the ability of the PPG index to predict post-PCI FFR. In addition, it will evaluate the impact of PPG on treatment decision-making and the predictive performance of PPG for angina relief and clinical outcomes. A subsequent randomized clinical trial will be required to assess the clinical benefit of a PPG-guided PCI strategy.

Disclosures

AML reports receiving consultancy fees from Abbott and honoraria for sponsored symposiums from Abbott, Medtronic and Abiomed. DM report a research grant provided by the Cardiopath PhD program and speaker fees from Abbott Vascular. BDB reports receiving consultancy fees from Boston Scientific and Abbott and research grants from Coroventis Research, Pie Medical Imaging, Cathworks, Boston Scientific, Siemens, HeartFlow Inc. and Abbott Vascular. CC reports receiving research grants from Biosensor, Coroventis Research, Medis Medical Imaging, Pie Medical Imaging, Cathworks, Boston Scientific, Siemens, HeartFlow Inc. and Abbott Vascular; and consultancy fees from Heart Flow Inc, Opsens, Abbott Vascular and Philips Volcano. BK has received consulting fees from Canon Medical, Abbott and Medtronic. AI has received consulting fees from Canon, Artrya Medical and Boston Scientific. TWJ has received consultancy/speaker fees from Abbott Vascular, Boston Scientific, Medtronic, Shockwave, Terumo and research grants from Abbott Vascular. NPJ received internal funding from the Weatherhead PET Center for Preventing and Reversing Atherosclerosis; has received significant institutional research support from St. Jude Medical (CONTRAST, NCT02184117) and Philips Volcano Corporation (DEFINE-FLOW, NCT02328820) for other studies using intracoronary pressure and flow sensors; has an institutional licensing agreement with Boston Scientific for the smart-minimum FFR algorithm (now commercialized under 510(k) K191008); and has patents pending on diagnostic methods for quantifying aortic stenosis and TAVI physiology, and on methods to correct pressure tracings from fluid-filled catheters. SB received research grants provided by Sahajanand Medical Technologies Ltd (SMT), Medis Medical Imaging Systems, Eukon S.r.l., Siemens

Healthineers, General Electric (GE) Healthcare, and Insight Lifetech. EHC has received consulting fees from Abbott Medical Denmark A/S. CB receives research funding from the British Heart Foundation (RE/18/6134217, BHF/FS/17/26/32744, PG/19/28/34310). Colin Berry is employed by the University of Glasgow which holds consultancy and research agreements for his work with Abbott Vascular, AstraZeneca, Boehringer Ingelheim, Coroventis, GSK, HeartFlow, Menarini, Novartis, Servier, Siemens Healthcare, and Valo Health. WFF receives institutional research support from Abbot, Boston, and Medtronic and has consulting relationships with CathWorks and Siemens and stock options with HeartFlow. TE reports speakers and advisory board fees from Abbott, Boston and Novo Nordisk. AY has received minor honoraria from Abbott Vascular, and research grants from Abbott Vascular and Philips. DC has received consulting fees from Abbott. TS reports a grant provided by the EAPCI Fellowship Programme.

Data availability

This rationale and design paper contains no primary data.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ahj.2023.07.016.

References

1 De Bruyne B, Hersbach F, Pijls NH, et al. Abnormal epicardial coronary resistance in patients with diffuse atherosclerosis but "Normal" coronary angiography. Circulation 2001;104:2401–6.
2 Mintz GS, Painter JA, Pichard AD, et al. Atherosclerosis in angiographically "normal" coronary artery reference segments: an intravascular ultrasound study with clinical correlations. J Am Coll Cardiol 1995;25:1479–85.
3 Crea F, Bairey Merz CN, Beltrame JF, et al. Mechanisms and diagnostic evaluation of persistent or recurrent angina following percutaneous coronary revascularization. Eur Heart J 2019;40:2455–62.
4 Collet C, Collison D, Mizukami T, et al. Differential improvement in angina and health-related quality of life after PCI in focal and diffuse coronary artery disease. JACC Cardiovasc Interv 2022;15:2506–18.
5 Pijls NH, De Bruyne B, Peels K, et al. Measurement of fractional flow reserve to assess the functional severity of coronary-artery stenoses. New Engl J Med 1996;334:1703–8.
6 Tonino PA, De Bruyne B, Pijls NH, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. N Engl J Med 2009;360:213–24.
7 Fearon WF, Shilane D, Pijls NH, et al. Cost-effectiveness of percutaneous coronary intervention in patients with stable coronary artery disease and abnormal fractional flow reserve. Circulation 2013;128:1335–40.
8 Collet C, Sonck J, Vandeloo B, et al. Measurement of hyperemic pullback pressure gradients to characterize patterns of coronary atherosclerosis. J Am Coll Cardiol 2019;74:1772–84.
9 Baranauskas A, Peace A, Kibarskis A, et al. FFR result post PCI is suboptimal in long diffuse coronary artery disease. EuroIntervention 2016;12:1473–80.
10 Mizukami T, Sonck J, Sakai K, et al. Procedural outcomes after percutaneous coronary interventions in focal and diffuse coronary artery disease. J Am Heart Assoc 2022;11:e026960.
11 Di Sciascio G, Patti G, Nasso G, et al. Early and long-term results of stenting of diffuse coronary artery disease. Am J Cardiol 2000;86:1166–70.
12 Sianos G, Morel MA, Kappetein AP, et al. The SYNTAX score: an angiographic tool grading the complexity of coronary artery disease. EuroIntervention 2005;1:219–27.
13 Sonck J, Mizukami T, Johnson NP, et al. Development, validation, and reproducibility of the pullback pressure gradient (PPG) derived from manual fractional flow reserve pullbacks. Catheter Cardiovasc Interv 2022;99:1518–25.
14 Piroth Z, Toth GG, Tonino PAL, et al. Prognostic value of fractional flow reserve measured immediately after drug-eluting stent implantation. Circ Cardiovasc Interv 2017;10.
15 Pijls NH, Klauss V, Siebert U, et al. Coronary pressure measurement after stenting predicts adverse events at follow-up: a multicenter registry. Circulation 2002;105:2950–4.
16 Li SJ, Ge Z, Kan J, et al. Cutoff value and long-term prediction of clinical events by FFR measured immediately after implantation of a drug-eluting stent in patients with coronary artery disease: 1- to 3-year results from the DKCRUSH VII registry study. JACC Cardiovasc Interv 2017;10:986–95.
17 Fournier S, Ciccarelli G, Toth GG, et al. Association of Improvement in Fractional Flow Reserve With Outcomes, Including Symptomatic Relief, After Percutaneous Coronary Intervention. JAMA Cardiol 2019;4:370–4.
18 Nishi T, Piroth Z, De Bruyne B, et al. Fractional flow reserve and quality-of-life improvement after percutaneous coronary intervention in patients with stable coronary artery disease. Circulation 2018;138:1797–804.
19 Collison D, Didagelos M, Aetesam-Ur-Rahman M, et al. Post-stenting fractional flow reserve vs coronary angiography for optimisation of percutaneous coronary intervention: TARGET-FFR trial. Eur Heart J 2021;42:4656–68.
20 Thygesen K, Alpert JS, Jaffe AS, et al. Fourth universal definition of myocardial infarction (2018). J Am Coll Cardiol 2018;72:2231–64.
21 Garcia-Garcia HM, McFadden EP, Farb A, et al. Standardized end point definitions for coronary intervention trials: the academic research consortium-2 consensus document. Eur Heart J 2018;39:2192–207.
22 Généreux P, Palmerini T, Caixeta A, et al. Quantification and impact of untreated coronary artery disease after percutaneous coronary intervention: the residual SYNTAX (Synergy Between PCI with Taxus and Cardiac Surgery) score. J Am Coll Cardiol 2012;59:2165–74.
23 Toth GG, Johnson NP, Jeremias A, et al. Standardization of fractional flow reserve measurements. J Am Coll Cardiol 2016;68:742–53.
24 Chan PS, Jones PG, Arnold SA, Spertus JA. Development and validation of a short version of the Seattle angina questionnaire. Circ Cardiovasc Qual Outcomes 2014;7:640–7.
25 Leligdowicz A, Conroy AL, Hawkes M, et al. Risk-stratification of

febrile African children at risk of sepsis using sTREM-1 as basis for a rapid triage test. Nat Commun 2021;12:6832.
26 Steyerberg EW, Vergouwe Y. Towards better clinical prediction models: seven steps for development and an ABCD for validation. Eur Heart J 2014;35:1925–31.
27 Hwang D, Koo BK, Zhang J, et al. Prognostic implications of fractional flow reserve after coronary stenting: a systematic review and meta-analysis. JAMA Netw Open 2022;5:e2232842.
28 Jeremias A, Davies JE, Maehara A, et al. Blinded physiological assessment of residual ischemia after successful angiographic percutaneous coronary intervention: the DEFINE PCI study. JACC Cardiovasc Interv 2019;12:1991–2001.
29 Agarwal SK, Kasula S, Hacioglu Y, et al. Utilizing Post-Intervention Fractional Flow Reserve to Optimize Acute Results and the Relationship to Long-Term Outcomes. JACC Cardiovasc Interv 2016;9:1022–31.
30 Samady H, McDaniel M, Veledar E, et al. Baseline fractional flow reserve and stent diameter predict optimal post-stent fractional flow reserve and major adverse cardiac events after bare-metal stent deployment. JACC Cardiovasc Interv 2009;2:357–63.