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Study design and rationale of the angio-based final functional effect of PCI (AFFE PCI) study: A prospective multi-center study of post-PCI vFFR impact on clinical outcomes and residual angina

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Background

The primary invasive modality for diagnosing coronary artery disease (CAD) is coronary angiography (CAG) [1], nevertheless, CAG is limited by its inability of direct evaluation of stenosis hemodynamic relevance [2]. Among the methods developed to improve the diagnostics and management of CAD there are fractional flow reserve (FFR) and non-hyperemic pressure indices (NHPRs), which at present constitute a gold standard for lesion significance assessment and revascularization guidance [3]. FFR is an invasive modality employing pressure wire and adenosine infusion to measure the ratio between the mean pressure distal to the stenosis (Pd) and the mean aortic pressure (Pa) during maximal hyperemia within a specific coronary artery segment. FFR has proven its effectiveness in CAD management, aiding in the decision-making process for percutaneous coronary intervention (PCI) qualification and contributing to the reduction of MACE and mortality [4]. Recent evidence also suggests that FFR can additionally be used to assess the final PCI results [5]. Studies revealed that post-PCI FFR is an independent predictor of future cardiovascular events [6, 7]. Post-PCI FFR has the potential to act as a valuable tool for the assessment of PCI results and might identify cases in need of additional procedural optimization [8].

In everyday clinical practice functional assessment of the final effect of PCI is not routinely used to indicate the hemodynamic efficacy of revascularization due to the need for hyperemia associated with patient discomfort, additional pressure wire instrumentation, and presumed additional time of the procedure [9]. To overcome some of these invasive FFR's limitations, alternative methods using computational fluid dynamics (CFD) techniques have been developed, contributing to avoidance of additional invasive procedures by use of angiography-derived FFR, such as vessel fractional flow reserve (vFFR), among others [10–13]. This method enables functional assessment of coronary

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artery lesions without additional coronary artery instrumentation or adenosine administration [11, 12, 14–17]. vFFR is computed using 3D-QCA (three-dimensional quantitative coronary angiography) and simplified fluid dynamics equations [18]. The inlet conditions are determined by the aortic root pressure, while flow velocity is obtained by applying the measured pressure to the reconstructed three-dimensional coronary geometry. It aims to provide a non-invasive alternative to the traditional method of FFR measurements. In turn, post-PCI vFFR and vFFR parameters can be used to assess the severity of ischemic lesions and may be a significant factor in evaluating the response to revascularization procedures in the follow-up [19, 20]. However, most current data on this topic was derived from retrospective analyses, and insufficient prospective results are available regarding the post-PCI vFFR and vFFR values as clinical prognosticators and indicators of patient health and quality of life [21].

The aim of this study is to address this gap and provide information about post-PCI vFFR, vFFR and quality of life, angina severity and clinical outcomes.

Material and methods

Objectives

The objective of this study is to evaluate the association between the value of post-PCI vFFR, vFFR and adverse clinical outcomes, residual angina and quality of life using the validated Seattle Angina Questionnaire (SAQ) and EuroQol 5-level 5-dimensional questionnaire (EQ-5D-5L) at 6, 12 and 24 months following PCI. It was hypothesized that patients with high post-PCI vFFR and larger vFFR values will have improved quality of life and less frequent residual angina, compared to patients with lower post-PCI vFFR values.

Study design

The AFFE PCI is an ongoing multicenter, prospective registry that aims to enroll 2005 patients undergoing PCI for CCS or ACS. The patients enrolled in the study are evaluated at 5 time points: at the beginning of the angiography, at the end of the angiography, and at 6, 12 and 24 months after the procedure. At each time-point, data regarding medical history, quality of life and clinical outcomes are collected during the follow-up visit or by phone contact if the onsite visit is not possible within the protocol mandated timeframes. The registry scheme is presented in Figure 1. The study was registered in ClinicalTrials.gov (NCT06255678). The study protocol has been approved by the Ethics Committee of the Medical University of Warsaw, the coordinating center.

After detailed explanations describing the study protocol, including the risk and benefits, they will sign a written informed consent to participate in the study. Only patients who voluntarily consent will be included. Patients will be able to withdraw at any time without compromising their medical care. The follow-up data will be collected until January 2027 to ascertain all patients' 6-, 12- and 24-month follow-up points, including the last patient.

Participants will be fully informed about the study protocol, and informed consent obtained from each patient included. The study is conducted in compliance with Good Clinical Practice principles, the Declaration of Helsinki and the requirements of the European Medicines Agency as well as local legal and regulatory requirements. Data storage is conducted in compliance with local data protection laws.

Participants

A total of 2005 adult patients undergoing PCI for chronic coronary syndromes (CCS) or acute coronary syndromes (ACS) with coronary angiographs amenable for vFFR analysis registered during PCI will be included in the study. To be eligible for inclusion in this study, patients must fulfil all inclusion criteria and none of the exclusion criteria presented in Table 1.

Evaluation of coronary physiology in the setting of STEMI carries several limitations and currently is not a guideline-recommended practice [1]. Concurrently, residual angina and long-term risk prediction remain a serious clinical challenge, also in the STEMI population. As such, it was decided not to exclude this patient subset in the present registry. However, prespecified analyses of the study outcomes in STEMI vs. non-STEMI cohort have been planned in the protocol.

Study outcomes

The primary endpoint will be MACE [all-cause death, target-vessel myocardial infarction (TVMI) and target vessel revascularization (TVR)] at 6-, 12- and 24-month follow-ups.

Secondary endpoints will include:

— individual components of the primary endpoint for post-PCI vFFR and vFFR;
— clinically driven invasive coronary angiography due to exacerbation of angina symptoms;
— symptoms of angina assessed by SAQ;

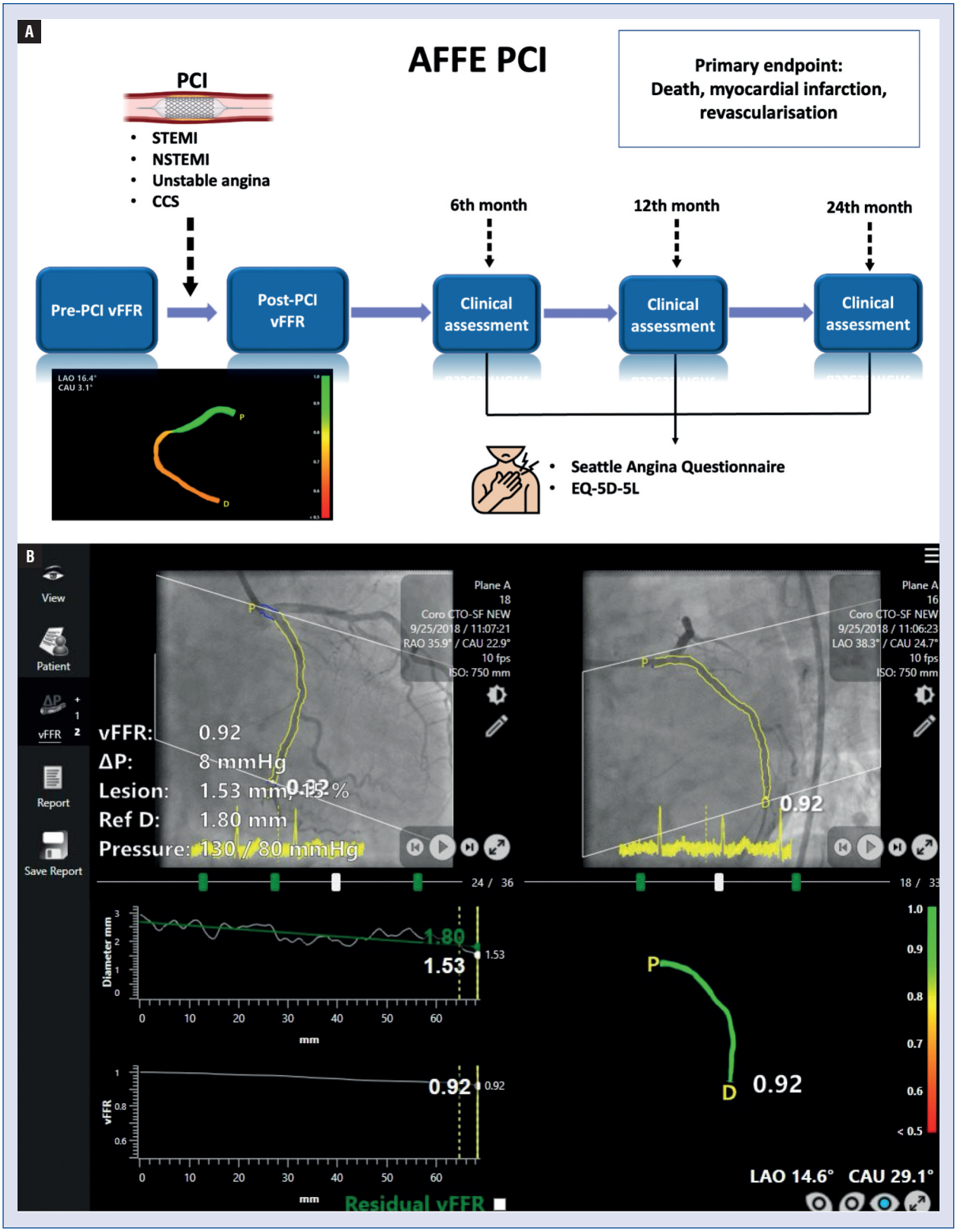

Figure 1. A. Flow chart of the study and example of post-PCI vFFR analysis; **B.** Post-PCI assessment of coronary artery using vFFR. PCI — percutaneous coronary intervention; vFFR — vessel fractional flow reserve; STEMI — ST-segment elevation myocardial infarction); NSTEMI — non-ST-elevation myocardial infarction; LAO — left anterior oblique; CAU — cauda; EQ-5D-5L — EuroQol 5-level 5-dimensional questionnaire.

Table 1. The inclusion and exclusion criteria.

Inclusion criteria
• PCI for CCS or ACS (including STEMI, NSTEMI and UA)
• Angiograms enabling vFFR analysis (available two angiographic views with ≥ 30° differences in rotation/angulation, the possibility of vessel contour selection, proper quality of the images, vessels without severe overlapping, tortuosity, foreshortening and poor vessel opacification
• Over 18 years old
• Patient consent
Exclusion criteria
• cardiogenic shock
• pulmonary oedema
• severe hemodynamical instability
• prior CABG
• severe valvular heart disease
• active bleeding
• acute and chronic inflammatory conditions
• acute mechanical complications of myocardial infarction
• congenital heart disease
• heart transplantation
• non-cardiac comorbidities with a life expectancy of less than 1 year

CCS — chronic coronary syndromes; NST-ACS — non-ST-segment elevation acute coronary syndromes; STEMI — ST-elevation elevation myocardial infarction; UA — unstable angina; CABG — coronary artery bypass grafting; vFFR — vessel fractional flow reserve

— quality of life assessed by EQ-5D-5L;
— correlation of post-PCI vFFR, vFFR with angina symptoms as assessed using the SAQ in all follow-up points;
— correlation of post-PCI vFFR, vFFR with components of the primary endpoint;
— assessment of the accuracy of post-PCI vFFR, vFFR in predicting all-cause death, TVMI and TVR;
— correlation of pressure gradient index (PPG) calculated using prePCI angiograms with post-PCI vFFR, vFFR and with the components of the primary endpoint;
— determination of the optimal cutoff point of post-PCI vFFR, vFFR and PPG values by analysis of the receiver operating characteristic (ROC) curves and area under curve (AUC) for detecting future MACE;
— determination of the optimal cutoff point of post-PCI vFFR, vFFR, and PPG values by analysis of the ROC curves and AUC for prediction of the high severity of angina symptoms described using the Seattle Angina Questionnaire;
— assessment of the value of post-PCI vFFR, vFFR and PPG in predicting the aggravation of anginal symptoms over time;
— assessment of the value of post-PCI vFFR, vFFR and PPG in predicting the rate of definite and probable stent thrombosis;
— assessment of the value of in-stent vFFR gradient in predicting the rate of MACE;
— assessment of the value of 3-vessel post-PCI vFFR burden (sum of the vFFR estimated in the three main epicardial arteries) in predicting the rate of MACE.

The primary and secondary endpoints' analyses will be stratified according to the presence of ACS (*vs.* CCS), STEMI vs NSTEMI, UA, CCS), diabetes, renal dysfunction with the cut-off of < 60 mL/min./1.73 m^2], focal/diffuse disease pattern and multivessel/single-vessel disease.

The primary and secondary endpoints will be analyzed using vFFR as a continuous variable as well as stratifying vFFR value according to:
— median value,
— tertile values,
— value identified in the ROC curve analysis.

All endpoint evaluations will be performed at 6, 12 and 24 months.

Clinical endpoint definitions

MACE will include all-cause death, TVMI and TVR. Myocardial infarction (MI) will include both spontaneous and periprocedural. Spontaneous MI represents an infarct after the first 48 hours following PCI and unrelated to the revascularization procedure [22]. Periprocedural MI occurs within the first 48 hours following PCI. TV MI is defined as an MI in the vessel that underwent post-PCI vFFR during the index procedure. TVR is defined as repeat PCI or coronary artery bypass grafting (CABG) of any segment of a target vessel, including the target lesion. Completeness of revascularization will be evaluated in the enrolled patients using the residual SYNTAX Score (rSS) [23, 24].

vFFR analysis

The computation of vFFR will be performed offline by experienced analysts blinded to patient clinical and angiographic data. A total of two two-dimensional angiograms will be exported to the CAAS workstation 8.3 (Pie Medical Imaging, Maastricht, the Netherlands). Temporal alignment

of the two orthogonal view phases in the cardiac cycle will be performed automatically by electrocardiogram (ECG) triggering. Contour detecting will be performed semiautomatically. The manual correction will be allowed in case of suboptimal automatic contour detection following a standard operating procedure. The calculations are based on the computational fluid dynamics (CFD) equations [10]. Thus, the software creates a 3D reconstruction of the vessels. Percent diameter stenosis, minimal lumen diameter, reference lumen diameter, minimal lumen area, and lesion length will be derived from the same 3D-QCA model from which the vFFR is derived. vFFR will be calculated as a difference between the post-PCI vFFR and the pre-PCI vFFR.

Preprocedural angiogram-based disease pattern

The recently validated pressure gradient index (PPG) index will be computed post-hoc from the pre-PCI angiogram-based vFFR pullback [25]. The PPG incorporates two parameters derived from vFFR pullback curves: the maximum pressure gradient over 20% of the pullback duration and the length of functional disease. This combination yields a value ranging from 0 to 1, where PPG values close to 1.0 indicate focal disease and values approaching 0 suggest diffuse CAD [26]. The median PPG value will differentiate between focal and diffuse CAD.

Questionnaires

The questionnaires will be collected during follow-up visits, or by phone in case the patient is not able to attend the ambulatory follow-up visit onsite within the per protocol time-frames of assessment. The anonymized results will be stored on the Scientific Platform of the Polish Cardiac Society.

The SAQ-7 evaluates three areas (angina frequency, physical limitation, and quality of life), and the results are combined into an overall score. A higher score indicates better health. For instance, a score of 100 in the angina frequency domain means that the person is free from angina [25]. The EQ-5D-5L comprises five dimensions (mobility, self-care, usual activities, pain and discomfort, anxiety and depression), each with five severity levels. Level 1 suggests no problem, while level 5 indicates severe difficulties. The EQ-5D-5L is then transformed into a country-specific weighted health index ranging from 0 to 1, where higher values correspond to poorer health status [25].

Data collection and study management

The registry has been launched under the patronage of the scientific platform of the Polish Cardiac Society. Site investigators enter the required data into the Polish Cardiac Society's password-protected, web-based electronic scientific platform. This platform is designed and maintained by a dedicated IT specialist. The following data are collected from the included patients: demographical data, medical history and comorbidities, baseline laboratory parameters, baseline additional examinations data (echocardiography, angiography, biomarkers), questionnaire results (SAQ, EQ-5D-5L), angiography images, vFFR values and derivatives, procedural details, medical therapy at baseline and during hospitalization, PCI results and complications. An independent Study Steering Committee monitors the quality of the collected data.

Statistical analysis and sample size

The study sample size was calculated based on the previous preliminary data on the post-PCI physiology values and clinical outcomes [5, 21]. Under the assumptions of power of 80%, 5.0% 2-sided alpha, a sample size of 1790 patients will be required to demonstrate 30% relative risk reduction between the patients with higher post-PCI vFFR group and lower post-PCI vFFR group. Assuming that up to 12% of patients may be potentially lost to follow-up it was decided to enroll 2005 patients in this investigation.

Data will be expressed as mean ± standard deviation or median and interquartile range. The Kolmogorov-Smirnov test will be used to test the normality of distribution. Continuous variables with normal and non-normal distributions will be compared using the Student t-test and the Mann–Whitney U test, respectively, whereas categorical variables will be compared using Pearson's chi-square test or the Fischer exact test, as appropriate. To determine the association between group results and PPG, vFFR and post-PCI vFFR results, linear or logistic regression will be applied as appropriate. Patients lost to follow-up will be censored on the date of the last follow-up. Rates of primary endpoints will be estimated as the cumulative incidence from the date of angiography to 730 days after it by Kaplan-Meier methods. Kaplan-Meier analysis with the log-rank test will be conducted to compare the endpoint between the groups at 6-, 12-, and 24-month follow-ups. The potential influence of baseline risk factors on observed results will be assessed using the Cox proportional hazards regression model. Alternative

statistical models will be used when hypotheses regarding risks cannot be suitably analyzed with the Cox model. The optimal cut-off points for continuous physiological indices will be defined using ROC curve analysis with the derivation of AUC. Statistical analyses will be performed using the SPSS version 28.0 (IBM Corp, Armonk, NY, USA) and Prism GraphPad 5.0 (GraphPad Software, Inc, CA). The results will be considered significant for $p < 0.05$.

Discussion

The AFFE PCI registry is a first prospective registry specifically providing insights into post-PCI angiography-based FFR values and adverse clinical outcomes. The angiography derived FFR is a rapidly evolving technique for assessing the PCI effects without additional instrumentation. On top of the diagnostic role in evaluation of hemodynamical significance of stenosis, pre-procedural and final PCI effect physiological assessment may become a useful factor in the evaluation of PCI results and future risk stratification, especially with the use of the non-invasive angiography-derived FFR methods [27–29]. This is a rapidly evolving field, offering faster, precise, and easier-to-use software that have recently been validated against invasive indices [3, 11]. Consequently, these modalities, including vFFR may be a crucial adjunct to intravascular imaging in the PCI guidance and evaluation of the risk of future complications in the initially treated coronary artery. Such an approach could be helpful to adjust the frequency of the follow-up and to optimize the potency of secondary prevention pharmacotherapy. Preliminary analyses indicate that individuals those with a post-PCI vFFR < 0.88 in the revascularized artery have a 1.8-fold increased risk of cardiovascular death, spontaneous myocardial infarction in the intervened vessel, or repeat revascularization in that vessel within 5 years after the procedure, while those with a post-PCI vFFR in the revascularized artery in the range of 0.88–0.93 have almost a 1.6 times higher risk of these complications, compared to patients with high post-PCI vFFR (vFFR ≥ 0.94) [21]. However, these preliminary results are derived from a retrospective single-center study including patients with older stent platforms; according to available literature no larger studies currently address this issue.

In recent AQVA trial it was shown that pre-PCI PPG ratios characterized for diffuse disease were an independent factor for predicting suboptimal hemodynamic results after PCI [30]. Patients exhibiting a high PPG frequently experience freedom from angina following the procedure, while those with a low PPG have an increased likelihood of recurrent angina post-PCI. To date, it has been shown that higher PPG at baseline results in higher post-PCI FFR than patients with low PPG index. However, the correlation between preprocedural angiogram-based PPG values and post-PCI vFFR and vFFR has yet to be evaluated. Such prespecified analyses planned in the present investigation may be informative for future clinical trials regarding aggressive medical therapy based on these indicators.

There is also a paucity of studies on the association of post-PCI vFFR or vFFR with the quality of the patients' life following PCI as assessed by objective, standardized tools, such as the SAQ or EQ-5D-5L questionnaires. The results of the presented study are expected to provide, for the first time, information on the relationship between the objectively quantified final functional effect of angioplasty and the risk of clinical events and patient-reported outcomes of angina and health-related quality of life characterized using dedicated questionnaires in a prospectively evaluated population of patients undergoing PCI for CCS or ACS.

The above information may lead to more personalized management and patient-tailored frequency of follow-up visits. It is hypothesized herein, that groups of patients with lower post-PCI vFFR values might significantly benefit from a more frequent follow-up. In addition, the study paves the way for image-based therapy escalation (i.e. hypolipemic agent dose increase) among patients with ischemic or suboptimal post PCI vFFR values, which would warrant investigation in the dedicated randomized clinical trial.

Ethics statement: The Ethics committee approved the design of the study.

Author contributions: Mariusz Tomaniak — conception of the study, study design and rationale, writing of the first draft of the manuscript., writing and editing of the manuscript, critical revision of the manuscript for relevant content, obtaining study funds, obtaining ethics committee approval, study oversight and coordination, approving the final version of the manuscript Karol Sadowski — participation in study design, writing and editing of the manuscript, approving the final version of the manuscript Adrian Bednarek — participation in study design, writing and editing of the manuscript, ap-

proving the final version of the manuscript Zenon Huczek — participation in study design, critical revision of the manuscript for relevant content, approving the final version of the manuscript Marek Gierlotka — participation in study design, critical revision of the manuscript for relevant content, approving the final version of the manuscript Michał Hawranek — participation in study design, critical revision of the manuscript for relevant content, approving the final version of the manuscript Marcin Grabowski — participation in study design, critical revision of the manuscript for relevant content, approving the final version of the manuscript Wojciech Wojakowski — participation in study design, critical revision of the manuscript for relevant content, approving the final version of the manuscript Krzysztof Milewski — participation in study design, critical revision of the manuscript for relevant content, approving the final version of the manuscript Janusz Kochman — participation in study design, critical revision of the manuscript for relevant content, approving the final version of the manuscript

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Conflict of interest: None declared.

Supplementary material: None.

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