

Adverse cardiovascular events in coronary Plaques not undeRgoing pErcutaneous coronary intervention evaluateD with optlcal Coherence Tomography. The PREDICT-AI risk model.

Original

Adverse cardiovascular events in coronary Plaques not undeRgoing pErcutaneous coronary intervention evaluateD with optlcal Coherence Tomography. The PREDICT-AI risk model / Bruno, F., Immobile Molaro, M., Sperti, M., Bianchini, F., Chu, M., Cardaci, C., Waha, W., Gasior, P., Zecchino, S., Pavani, M., Vergallo, R., Biscaglia, S., Cerrato, E., Gabrio Secco, G., Mennuni, M., Mancone, M., De Filippo, O., Mattesini, A., Canova, P., Boi, A., et al.. - In: OPEN HEART. - ISSN 2053-3624. - 12:2(2025), pp. 1-7. [10.1136/openhrt-2025-003389]

Availability:

This version is available at: 11583/3003540 since: 2025-10-01T09:30:44Z

Publisher:

BMJ

Published

DOI:10.1136/openhrt-2025-003389

Terms of use:

This article is made available under terms and conditions as specified in the corresponding bibliographic description in the repository

Publisher copyright

(Article begins on next page)

openheart Adverse cardiovascular events in coronary Plaques not undergoing percutaneous coronary intervention evaluated with optical Coherence Tomography. The PREDICT-AI risk model

Francesco Bruno ¹, Maddalena Immobile Molaro,² Michela Sperti,³ Francesco Bianchini,⁴ Miao Chu,⁵ Camilla Cardaci,³ Wojciech Wańha ⁶, Pawel Gasior,⁷ Simone Zecchino,⁸ Marco Pavani,⁸ Rocco Vergallo,⁹ Simone Biscaglia,¹⁰ Enrico Cerrato,⁸ Gioel Gabrio Secco ¹¹, Marco Mennuni,¹² Massimo Mancone ^{13,14}, Ovidio De Filippo ¹, Alessio Mattesini,¹⁵ Paolo Canova,¹⁶ Alberto Boi,¹⁷ Fabrizio Ugo,¹⁸ Roberto Scarsini,¹⁹ Francesco Costa,²⁰ Enrico Fabris ²¹, Gianluca Campo ¹⁰, Wojtek Wojakowski,⁶ Umberto Morbiducci,³ Marco Deriu,³ Shengxian Tu,⁵ Raffaele Piccolo ², Fabrizio D'Ascenzo,¹ Claudio Chiastra,³ Francesco Burzotta ⁴, PREDICT-AI group

To cite: Bruno F, Immobile Molaro M, Sperti M, *et al.* Adverse cardiovascular events in coronary Plaques not undergoing percutaneous coronary intervention evaluated with optical Coherence Tomography. The PREDICT-AI risk model. *Open Heart* 2025;**12**:e003389. doi:10.1136/openhrt-2025-003389

RP, FD, CC and FB are joint senior authors.

Received 22 April 2025
Accepted 11 August 2025



© Author(s) (or their employer(s)) 2025. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ Group.

For numbered affiliations see end of article.

Correspondence to

Dr Francesco Bruno;
cescobruno@hotmail.it

PREDICT-AI group; cescobruno@hotmail.it

ABSTRACT

Introduction Most acute coronary syndromes (ACS) originate from coronary plaques that are angiographically mild and not flow limiting. These lesions, often characterised by thin-cap fibroatheroma, large lipid cores and macrophage infiltration, are termed 'vulnerable plaques' and are associated with a heightened risk of future major adverse cardiovascular events (MACE). However, current imaging modalities lack robust predictive power, and treatment strategies for such plaques remain controversial.

Methods and analysis The PREDICT-AI study aims to develop and externally validate a machine learning (ML)-based risk score that integrates optical coherence tomography (OCT) plaque features and patient-level clinical data to predict the natural history of non-flow-limiting coronary lesions not treated with percutaneous coronary intervention (PCI). This is a multicentre, prospective, observational study enrolling 500 patients with recent ACS who undergo comprehensive three-vessel OCT imaging. Lesions not treated with PCI will be characterised using artificial intelligence (AI)-based plaque analysis (OctPlus software), including quantification of fibrous cap thickness, lipid arc, macrophage presence and other microstructural features. A three-step ML pipeline will be used to derive and validate a risk score predicting MACE at follow-up. Outcomes will be adjudicated blinded to OCT findings. The primary endpoint is MACE (composite of cardiovascular death, myocardial infarction, urgent revascularisation or target vessel revascularisation). Event prediction will be assessed at both the patient level and plaque level.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Vulnerable coronary plaques not undergoing revascularisation are a major cause of future adverse events. While intracoronary imaging, particularly optical coherence tomography (OCT), can identify high-risk plaque features, no validated model exists to predict outcomes in these patients based on imaging findings.

WHAT THIS STUDY ADDS

⇒ This study introduces the first machine learning-based model integrating high-resolution OCT data to predict future cardiovascular events from untreated coronary plaques with improved accuracy over traditional approaches.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ By leveraging artificial intelligence for risk stratification, this model opens new avenues for personalised management and proactive secondary prevention, setting the stage for data-driven decision support in coronary artery disease.

Ethics and dissemination The PREDICT-AI study will generate a clinically applicable, AI-driven risk stratification tool based on high-resolution intracoronary imaging. By identifying high-risk, non-obstructive coronary plaques, this model may enhance personalised management strategies and support the transition towards precision medicine in coronary artery disease.

INTRODUCTION

In the setting of acute coronary syndrome (ACS), most of the lesions triggering an acute ischaemic event, usually defined as ‘culprit lesions’, are not angiographically severe, but present with mild stenosis.^{1–3} However, when evaluated at autopsy or with intracoronary imaging, these lesions often show a prothrombotic pattern, with thin-cap fibroatheroma (TCFA), soft plaques and thrombus, prone to rupture. Typically, at coronary angiography, these coronary artery stenoses appear mild, with non-flow-limiting stenosis, but pathologically contain large plaque burden with an organised lipid-rich necrotic core that is separated from the lumen by a thin fibrous cap. These TCFA place patients at risk for future unstable angina, acute myocardial infarction (MI) and cardiac death, and they have been termed ‘vulnerable plaques’.^{4–6}

Optical coherence tomography (OCT) is the latest advancement in intravascular coronary imaging. In analogy to intravascular ultrasounds (IVUS), OCT provides cross-sectional images of the vessel. However, instead of using ultrasounds, OCT employs near-infrared light for tissue analysis, enabling visualisation of the coronary lesions with a resolution in the order of 10 µm. Over the last years, OCT has been widely employed to evaluate and characterise plaque features in both chronic coronary syndrome and ACS.⁷

Recent studies have used OCT to confirm the dynamic nature of coronary atherosclerotic disease. Specifically, OCT has shown that TCFA are highly prevalent at various stages of coronary atherosclerotic disease. Additionally, plaque ruptures are often found away from the culprit lesions, suggesting that vulnerability is widespread throughout the coronary tree.⁸

Moreover, intravascular imaging has revealed subclinical plaque ruptures in 4–79% of patients with coronary artery disease, with up to 75% of ‘vulnerable plaques’ evolving to stability within 12 months due to cycles of rupture and healing.⁴ As a result, flow-limiting thrombi, which manifest as ACS, may be the exception rather than the rule following plaque disruption. While these pathophysiological findings have led to a shift towards a more holistic concept of the ‘vulnerable patient’, the contribution of a vulnerable plaque profile in contributing to the risk of clinical events—whether from the plaque itself or the patient—remains unclear.⁹ Additionally, it is still unclear whether preventive revascularisation of non-flow-limiting vulnerable plaques could improve patient prognosis.¹⁰

To date, both invasive and non-invasive imaging techniques have shown modest sensitivity and positive predictive value in predicting future major adverse cardiovascular events (MACE) in patients with vulnerable plaques. Additionally, the treatment of non-flow-limiting stenosis with high-risk features remains a subject of intense debate.¹¹ While the presence of high-risk coronary lesion features confers a higher and exponential risk of adverse events, there are currently no imaging or clinical-based

risk scores that can predict the risk of MACE in patients with non-flow-limiting coronary artery stenosis.

In recent years, artificial intelligence (AI) has been extensively developed and integrated into clinical practice, including applications in cardiovascular (CV) medicine for interpreting numerical data, images and videos.^{12–14} AI enables the identification and prediction of specific patterns associated with clinical outcomes that are undetectable by the human eye. It encompasses a broad spectrum of technologies and methods, each with varying levels of complexity, potentials and applications. These technologies empower computers to learn efficient data representations, facilitating the detection and quantification of relationships among variables. This capability has significant implications for CV medicine, ultimately aiming to improve patient care. Risk prediction is a cornerstone of precision medicine, and in the context of AI technologies, machine learning (ML) offers a unique opportunity. ML is progressively being applied across various CV domains, where it has shown superiority over traditional, validated risk stratification tools.^{15 16}

METHODS AND ANALYSIS

Study aims and outcome measures

The goals of this project are as follows:

- ▶ Use ML to predict the natural history of non-flow-limiting coronary artery stenoses that are not undergoing coronary stenting. We aim to estimate the risk of adverse events based on the different characteristics of coronary artery plaques.
- ▶ Develop and validate an ML-based risk score to predict the likelihood of MACE at follow-up. This score will be based on OCT findings from non-culprit lesions and the clinical characteristics of the patients.

Ultimately, we aim to develop a robust and user-friendly tool that cardiologists can easily access and use in the catheterisation laboratory to help guide the treatment of non-flow-limiting, high-risk coronary plaques.

The primary endpoint of the study includes:

- ▶ MACE: defined as a mutually exclusive composite endpoint of CV death, MI, urgent revascularisation (UR) or target vessel revascularisation (TVR).

The secondary endpoint includes:

- ▶ MACCE: defined as a mutually exclusive composite endpoint of all-cause death, MI, UR or TVR.
- ▶ The individual components of the primary endpoint will be analysed as secondary endpoints as well as target lesion revascularisation (TLR).

All the analyses will be conducted first at patient level, and then an exploratory lesion-level analysis including TLR and target lesion MI will be conducted.

All patients will attend scheduled clinical visits with a trained physician at 12 months and then during follow-up according to each centre protocol. Follow-up is conducted through a combination of structured outpatient visits, telephone interviews and hospital record

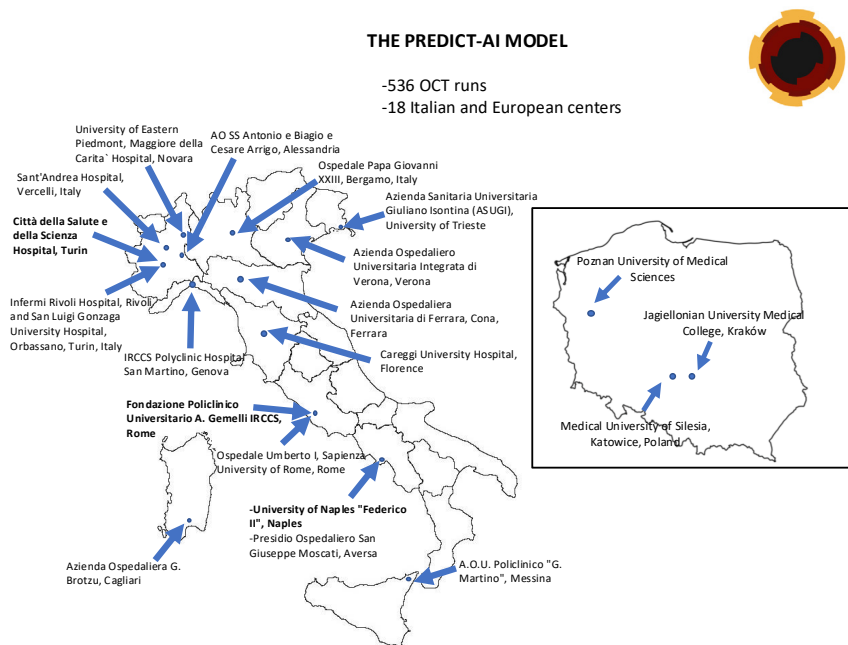


Figure 1 Participating centres in the PREDICT-AI study. OCT, optical coherence tomography.

reviews. Endpoints will be assessed at the longest available follow-up, with a minimum of 12 months of follow-up. Clinical events will be adjudicated by an independent Clinical Event Committee, blinded to OCT and AI-derived imaging data. A central committee composed of principal investigators (PIs blinded to patient and OCT data will review all the adjudicated outcomes and, where necessary, endpoints will be readjudicated. Outcomes will be defined according to the Academic Research Consortium guidelines.¹⁷ Participating centres are reported in [figure 1](#).

Study design

Patient characteristics

Clinical variables (such as the burden of CV risk factors and clinical presentation) will be collected, along with angiographic data (including the site of lesions, number of diseased vessels/lesions and whether revascularisation is complete or incomplete), as well as OCT features.

The following methodologies and definitions will be employed:

1. Type of presentation: Presentations will be classified according to the European Society of Cardiology guidelines,¹ including ST-elevation myocardial infarction, non-ST-elevation myocardial infarction and unstable angina.
2. Plaque analysis: Each plaque identified by OCT and enclosed by at least 5 mm of healthy vessel surrounding it will be analysed individually. The mandatory inclusion criterion is that the OCT assessment must cover at least 30 mm of an untreated proximal coronary segment. Definitions and cut-offs for OCT parameters will be based on available consensus documents and major IVUS/OCT studies.^{18–22} High-risk plaque markers will include: minimum lumen area $<3.5 \text{ mm}^2$ measured along the entire assessed segment (this threshold is derived from the 4.0 mm^2 cut-off used in the PROSPECT clinical study²³ and adjusted for IVUS overestimation); minimum fibrous cap thickness $<75 \mu\text{m}$, defined as a signal-rich, homogeneous band overlying a lipid core, measured at its thinnest portion; lipid plaque with lipid arc extension $>180^\circ$, defined as a signal-poor region diffusely bordered by overlying signal-rich bands corresponding to a fibrous cap; and presence of macrophage clusters, identified visually as signal-rich, distinct or confluent punctate regions exceeding background speckle noise intensity. Additional OCT features will include: intimal vasculature, defined as sharply delineated signal-poor voids visible in multiple contiguous frames; intraplaque layered tissue, defined as deeper tissue layers with a clearly layered structure; cholesterol crystals, defined as thin, linear regions of high intensity; and calcified nodules, defined as an accumulation of nodular calcification with fibrous cap disruption on the calcified plate.
3. Medications and laboratory data: Data on medications (such as dual antiplatelet therapy and lipid-lowering drugs) at baseline and discharge will be collected, along with inflammatory markers and baseline laboratory examinations.²⁴



The PREDICT-AI machine-learning risk model

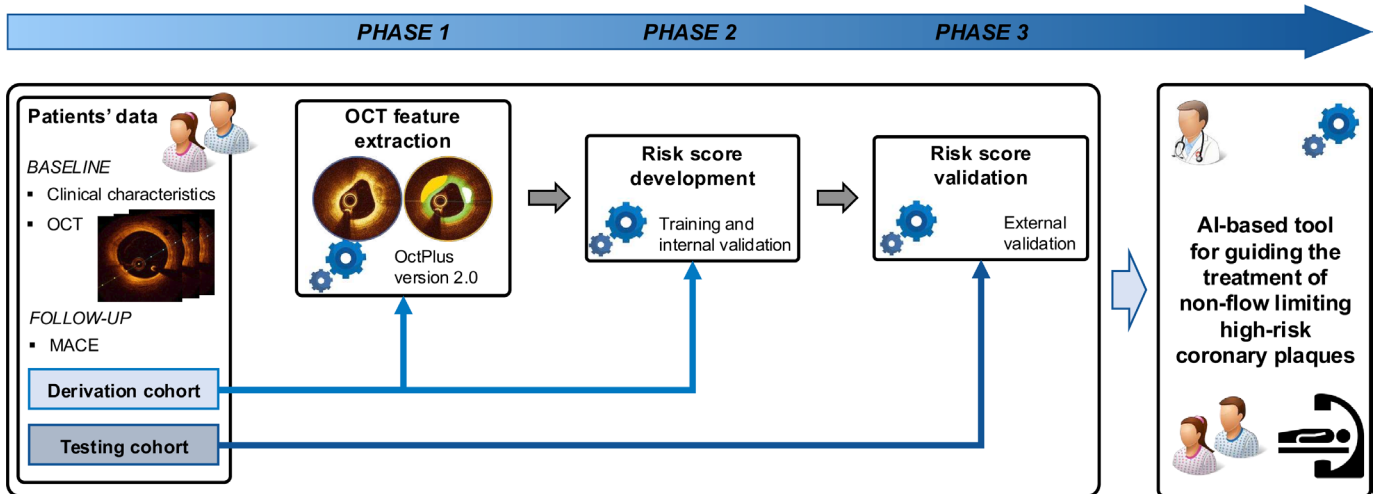


Figure 2 Three-phase machine learning approach to define the risk score for stratification of patients presenting with non-flow-limiting coronary plaques from OCT images. AI, artificial intelligence; MACE, major adverse cardiovascular events; OCT, optical coherence tomography.

4. Angiographic and physiology analysis: All the angiographies will be centrally reviewed by a core laboratory and fraction flow reserve (FFR) and instantaneous wave-free ratio (iFR) values for each stenosis will be calculated using ML with the STARFLOW system.²⁵

ML-based analysis

A three-step ML-based strategy will be implemented to develop a risk score for stratifying patients presenting with non-flow-limiting coronary plaques based on OCT images (figure 1). The strategy will be implemented using a dataset split into a derivation cohort and a testing (external validation) cohort (eg, 80–20% split). Separate analyses will be conducted at both patient level and plaque level. The three ML-based approach steps of the proposed approach are described below.

Step 1: extraction of OCT features

The OCT features identified as markers of high-risk plaques will be automatically extracted using the OctPlus software (V.2.0, Pulse Medical, Shanghai, China) by an independent and blinded central core laboratory.²⁶ The software includes an AI-based model for automatic and standardised plaque characterisation, which has been previously described and validated.²⁶ Briefly, the AI-based model consists of a convolutional neural network with an encoder-decoder structure (designed and fed with consecutive OCT cross sections), incorporating the information extracted from adjacent cross sections of the vessel. The AI-based model automatically delineates the lumen and media contours, classifying the tissue in between as fibrous, lipidic or calcified plaque (figures 2 and 3).

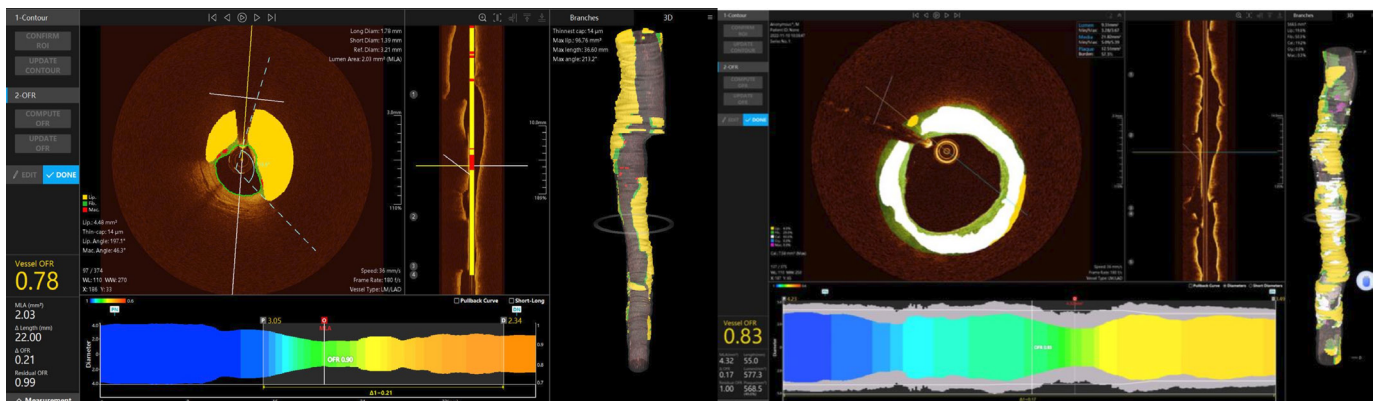


Figure 3 OCT image analysis with OctPlus software (V.2.0) with plaque characterisation. LAD, left anterior descending; LM, left main; MLA, minimum lumen area; OCT, optical coherence tomography; OFR, OCT-based FFR; ROI, region of interest.

Additionally, inflammatory markers of macrophages and cholesterol crystals are also identified. This analysis will be conducted on the entire dataset.

In addition to the previous analysis, a subgroup of OCT pullbacks will be manually annotated by two expert readers from our clinical centres. These annotations will serve as labels for developing new ML-based approaches to automatically classify atherosclerotic plaques into subcategories (eg, lipid, fibrous, calcium or mixed) and identify other key arterial wall characteristics, such as thin fibrous caps and macrophage accumulation.

Step 2: risk score definition based on patient characteristics and OCT features

An ML-based risk score for MACE at follow-up for each patient will be developed. The input for this risk score will include the patient's baseline characteristics and OCT features related to plaque vulnerability (as listed above), which are obtained through the OctPlus software analysis. Various ML algorithms will be tested, including naïve Bayes, logistic regression, linear discriminant analysis, feedforward neural networks, random forests, support vector machines and K-nearest neighbour.²⁷ To mitigate potential issues with irrelevant or noisy data, dimensionality reduction techniques will be applied, such as principal component analysis or feature selection methods (eg, genetic algorithms, random forest feature importance, L1 penalty in logistic regression, forward search). These techniques will help filter key predictors, improving both predictive accuracy and training efficiency.²⁸ Simultaneously, the models' hyperparameters (eg, K for K-nearest neighbour, the number of neurons and layers for feedforward neural networks) will be optimised. The different ML algorithms will be applied to a derivation cohort of OCT images and corresponding patient's characteristics, which will be subdivided into a training dataset and an internal validation dataset (eg, 80–20% split). To ensure the ML model robustness, the training and internal validation dataset split will be repeated at least 50 times. Alternatively, techniques such as K-fold cross-validation or nested K-fold cross-validation may be considered.^{29 30} The performance of the ML algorithms will be assessed using various metrics, including the area under the curve (AUC) of the receiver operating characteristic (ROC) curve, accuracy, sensitivity, specificity and F1 score with two-sided 95% CIs.

Step 3: external validation of the risk score

The best performing ML model from step 2 will be applied to an external cohort of OCT images and corresponding patient's characteristics from a separate cohort from two additional centres (University Hospital in Cracow and Poznan University of Medical Sciences), which will serve as testing dataset (ie, external validation dataset, also referred to as holdout dataset). The probability threshold, selected by calculating the AUC of the ROC curve for the internal validation dataset, will be applied to the testing dataset. On the testing dataset, the performance of the best performing ML model will be evaluated in terms of AUC, accuracy, sensitivity, specificity and

F1 score with two-sided 95% CIs (eg, obtained through a bootstrap analysis of the external validation dataset).³¹

Power calculation

In the PROSPECT II study,²³ the primary endpoint MACE, which was a composite of CV death, MI, unstable angina or progressive angina during follow-up, was observed in approximately 12% of patients. To develop and validate a robust ML model, we aim to enrol 500 patients to have 60 recurrent events of the primary endpoint in the derivation cohort. External validation will be performed using an independent cohort.

DISCUSSION

The goal of this project is to predict the natural history of non-flow-limiting coronary artery stenosis using an AI-based risk evaluation. In detail, we aim to develop and validate an ML-based risk score that estimates the likelihood of adverse events at follow-up, based on the OCT appearance of coronary plaques. The development of this PREDICT-AI-based risk score is expected to mark a step forward in personalised CV care.

This model will be the first AI-based model designed to assess the risk of adverse cardiac events by analysing OCT images of untreated coronary artery plaques, which are known to correlate with the risk of MACE. By incorporating these features into a data-driven algorithm, the model provides an objective, reproducible and quantitative risk assessment, potentially reducing the interobserver variability affecting the single operator interpretation.

The rupture of a lipid-rich atherosclerotic coronary artery lesion is the most common cause of ACS and sudden cardiac death. Vulnerable plaques often appear mild on angiography and may not be flow limiting on haemodynamic assessment. However, intravascular imaging can identify these plaques, which have a large plaque burden and a lipid-rich necrotic core, separated from the lumen by a thin fibrous cap.^{32 33} Prospective studies have shown that vulnerable plaques detected by imaging are associated with an increased risk of adverse cardiac events compared with plaques without these features.^{46 23} Despite this, all available invasive and non-invasive imaging techniques have demonstrated only modest accuracy in predicting which vulnerable plaques will rupture and lead to MI.¹¹

Current clinical guidelines recommend revascularisation via percutaneous coronary intervention only for coronary lesions that are haemodynamically flow limiting or have caused an ACS.¹ The safety and effectiveness of revascularising non-flow-limiting vulnerable plaques remains a topic of debate.¹⁰ Recently, the PREVENT trial demonstrated that in patients with non-flow-limiting coronary plaques, preventive percutaneous coronary intervention could reduce MACE arising from high-risk vulnerable plaques, compared with optimal medical therapy alone.³⁴ However, the reduction in events was modest, and the number needed to treat to prevent one event was very high, highlighting the ongoing challenge of accurately identifying the vulnerable plaques most likely to cause an adverse event.

By identifying key factors for risk stratification, the PREDICT-AI-based risk score will provide actionable insights to guide personalised therapeutic strategies. It will be a valuable tool for interventional cardiologists, helping optimise treatment plans and identify high-risk patients who may benefit from closer follow-up and optimised medical therapy.

The potential applications of this project are vast, with impacts extending across multiple fields.

From both scientific and social perspectives, predicting the risk of adverse events for individual coronary plaques during follow-up will support clinicians in patient management. This approach will help identify patients with plaques at higher risk of adverse events, enabling more aggressive treatment strategies, both pharmacological and interventional. This approach will contribute to the shift towards precision medicine, moving away from a 'one size fits all' approach to a more tailored and holistic strategy for each patient.¹²

The 'PREDICT AI' risk score enhances these assessments by focusing on the microstructural characteristics of plaques and the patient's clinical profile, providing a more comprehensive risk evaluation. Patients identified at high risk by the 'PREDICT AI' risk score could benefit from closer monitoring, lifestyle changes or pre-emptive pharmacological interventions. Conversely, those classified at low risk may avoid unnecessary procedures, thereby reducing healthcare costs and potential complications.

From an economic perspective, we aim to reduce adverse events at follow-up, including MI, hospitalisation and improvements in patients' quality of life, ultimately lowering CV and overall mortality. In this framework, AI-based predictive risk scores show promise in addressing these challenges by enhancing healthcare delivery and improving cost-effectiveness, while assisting clinicians in diagnosing disease and making treatment decisions. Reducing MI and hospitalisations related to cardiac symptoms through the implementation of our risk score could result in significant cost savings for national healthcare systems and governments.

CONCLUSIONS

The 'PREDICT AI' risk score represents a transformative approach to risk stratification in coronary artery disease, bridging the gap between advanced imaging and precision medicine. By providing accurate, individualised predictions of MACE risk, it has the potential to revolutionise the management of non-flow-limiting coronary artery stenosis, ultimately improving patient outcomes.

Author affiliations

¹Azienda Ospedaliero–Universitaria Città della Salute e della Scienza di Torino, Turin, Italy

²Department of Advanced Biomedical Sciences, University of Naples Federico II, Naples, Italy

³Dipartimento di Ingegneria Meccanica e Aerospaziale, Politecnico di Torino, Turin, Italy

⁴Fondazione Policlinico Universitario A Gemelli IRCCS, Rome, Italy

⁵School of Biomedical Engineering, Shanghai Jiao Tong University, Shanghai, China

⁶Department of Cardiology and Structural Heart Diseases, Medical University of Silesia, Katowice, Poland

⁷Medical University of Silesia, Katowice, UK

⁸Rivoli Hospital, Rivoli, Italy

⁹Dipartimento Cardio-Toraco-Vascolare, IRCCS Ospedale Policlinico San Martino, Genova, Italy

¹⁰UO Cardiologia, Azienda Ospedaliero–Universitaria di Ferrara Arcispedale Sant'Anna, Cona, Italy

¹¹Interventional Cardiology, Univ Piemonte Orientale, Alessandria, Italy

¹²University Hospital Maggiore della Carità, Novara, Italy

¹³Department of Cardiovascular, Respiratory, Nephrological and Geriatric Sciences, University of Rome La Sapienza, Roma, Italy

¹⁴University of Rome La Sapienza, Rome, Italy

¹⁵AOU Careggi, Florence, Italy

¹⁶Azienda Ospedaliera Papa Giovanni XXIII, Bergamo, Italy

¹⁷Azienda Ospedaliera Brotzu, Cagliari, Italy

¹⁸Interventional Cardiology, PO S Andrea di Vercelli, Vercelli, Italy

¹⁹Azienda Ospedaliera Universitaria Integrata Verona, Verona, Italy

²⁰Faculty of Medicine and Surgery, University of Messina, Messina, Italy

²¹Cardiology Department, Azienda Sanitaria Universitaria Giuliano Isontina Dipartimento ad Attività Integrata Cardioracovascolare, Trieste, Italy

Collaborators PREDICT-AI group: Pawel Pawlus, MD; Edoardo Elia, MD; Maria Federica Crociani, MD; Carlo Carbone, MD; Gianluca Caiazza, MD; Vincenzo Castaldo Tuccillo, MD; Federico Giacobbe, MD; Stefano Siliano, MD; Elodi Bacci, MD; Gianluca Di Pietro, MD; Riccardo Improta, MD; Marco Licciardi, MD; Giustina Iuvara, MD; Sylwia Iwańczyk, MD; Maciej Lesiak, MD; Stanisław Bartuś, MD; Shah Syed Taimoor Hussain, MSc; Giulia Di Marcantonio, MSc; Konstantinos Panagiotopoulos, MSc; Karim Kassem, MSc; Giuseppe De Nisco, PhD; Sylwia Iwańczyk, MD; Maciej Lesiak, MD; Stanisław Bartuś, MD; Jan Rocznik, MD.

Contributors FBr, FDA, CCh, RP and FBU conceived and designed the study. FBr, MIM, FBI, SZ, WWa, PG, MP, RV, SB, EC, GGS, MME, MMa, AM, PC, AB, FU, RS, FC, EF and GC contributed to patient enrolment, OCT image acquisition and clinical data collection. MS, CCa, CCh, UM and MD developed the computational framework and performed the machine learning analyses in collaboration with MC and ST. Data curation and imaging annotation were coordinated by FBr, MIM, FBI, MS, CCa and collaborators from the PREDICT-AI group. FDA and RP supervised the statistical analysis and model validation. FBr, MS, FDA and CCh drafted the manuscript. All the authors critically revised the manuscript for intellectual content. All authors reviewed and approved the final version of the manuscript and agree to be accountable for all aspects of the work. FDA is the guarantor of the manuscript and is responsible for the overall content. RP, FDA, CCh and FBU are joint last authors.

Funding This study was carried out within the project 'Adverse cardiovascular events in coronary Plaques not undergoing percutaneous coronary intervention evaluated with optical Coherence Tomography. The PREDICT machine-learning risk score', funded by the European Union–NextGenerationEU, Italian Ministry of University and Research, Italy, within the PRIN 2022 programme (DD104 dated 2 February 2022).

Competing interests FBr has received speaker honoraria from Abbott and Boston Scientific. FDA has received personal and institutional grants from Abbott. FBU has received speaker honoraria from Abbott, Abiomed, Edwards, Medtronic and Terumo.

Patient consent for publication Not applicable.

Ethics approval The study is carried out in accordance with the Declaration of Helsinki and in keeping with the Good Clinical Practice guidelines. The protocol of the study was approved by the ethical committees of the participating centres, and when indicated patients were asked to provide informed consent. Trial results will be published in peer-reviewed scientific journals and presented at national and international conferences relevant to cardiovascular care and internal academic seminars.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. The data that support the findings of this study are available from the corresponding author (FBr) upon reasonable request.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

ORCID iDs

Francesco Bruno <http://orcid.org/0000-0003-0019-0273>
 Wojciech Wańha <http://orcid.org/0000-0003-1220-9496>
 Gioel Gabrio Secco <http://orcid.org/0000-0002-9998-7049>
 Massimo Mancone <http://orcid.org/0000-0002-0881-7299>
 Ovidio De Filippo <http://orcid.org/0000-0002-4915-9501>
 Enrico Fabris <http://orcid.org/0000-0001-9458-0736>
 Gianluca Campo <http://orcid.org/0000-0002-5150-188X>
 Raffaele Piccolo <http://orcid.org/0000-0002-3124-9912>
 Francesco Burzotta <http://orcid.org/0000-0002-6569-9401>

REFERENCES

- Byrne RA, Rossello X, Coughlan JJ, et al. ESC Guidelines for the management of acute coronary syndromes. *Eur Heart J* 2023;3720–826.
- Ino Y, Kubo T, Tanaka A, et al. Difference of culprit lesion morphologies between ST-segment elevation myocardial infarction and non-ST-segment elevation acute coronary syndrome: an optical coherence tomography study. *JACC Cardiovasc Interv* 2011;4:76–82.
- D'Ascenzo F, Agostoni P, Abbate A, et al. Atherosclerotic coronary plaque regression and the risk of adverse cardiovascular events: a meta-regression of randomized clinical trials. *Atherosclerosis* 2013;226:178–85.
- Stone GW, Maehara A, Lansky AJ, et al. A prospective natural-history study of coronary atherosclerosis. *N Engl J Med* 2011;364:226–35.
- Iannaccone M, Quadri G, Taha S, et al. Prevalence and predictors of culprit plaque rupture at OCT in patients with coronary artery disease: a meta-analysis. *Eur Heart J Cardiovasc Imaging* 2016;17:1128–37.
- Prati F, Romagnoli E, Gatto L, et al. Relationship between coronary plaque morphology of the left anterior descending artery and 12 months clinical outcome: the CLIMA study. *Eur Heart J* 2020;41:383–91.
- Kubo T, Ino Y, Mintz GS, et al. Optical coherence tomography detection of vulnerable plaques at high risk of developing acute coronary syndrome. *Eur Heart J Cardiovasc Imaging* 2021;33619524.
- Vergallo R, Porto I, D'Amario D, et al. Coronary Atherosclerotic Phenotype and Plaque Healing in Patients With Recurrent Acute Coronary Syndromes Compared With Patients With Long-term Clinical Stability: An In Vivo Optical Coherence Tomography Study. *JAMA Cardiol* 2019;4:321–9.
- Vergallo R, Park S-J, Stone GW, et al. Vulnerable or High-Risk Plaque: A JACC: Cardiovascular Imaging Position Statement. *JACC Cardiovasc Imaging* 2025;18:709–40.
- Stone GW, Maehara A, Ali ZA, et al. Percutaneous Coronary Intervention for Vulnerable Coronary Atherosclerotic Plaque. *J Am Coll Cardiol* 2020;76:2289–301.
- Gallone G, Bellettini M, Gatti M, et al. Coronary Plaque Characteristics Associated With Major Adverse Cardiovascular Events in Atherosclerotic Patients and Lesions: A Systematic Review and Meta-Analysis. *JACC Cardiovasc Imaging* 2023;16:1584–604.
- Gallone G, Bruno F, D'Ascenzo F, et al. What will we ask to artificial intelligence for cardiovascular medicine in the next decade? *Minerva Cardiol Angiol* 2022;70:92–101.
- Schalwe N, Wahl B. Artificial intelligence and the future of global health. *Lancet* 2020;395:1579–86.
- Samant S, Bakhos JJ, Wu W, et al. Artificial Intelligence, Computational Simulations, and Extended Reality in Cardiovascular Interventions. *JACC Cardiovasc Interv* 2023;16:2479–97.
- Quer G, Arnaout R, Henne M, et al. Machine Learning and the Future of Cardiovascular Care: JACC State-of-the-Art Review. *J Am Coll Cardiol* 2021;77:300–13.
- D'Ascenzo F, De Filippo O, Gallone G, et al. Machine learning-based prediction of adverse events following an acute coronary syndrome (PRAISE): a modelling study of pooled datasets. *Lancet* 2021;397:199–207.
- Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation* 2007;115:2344–51.
- Paraggio L, Burzotta F, Aurigemma C, et al. Trends and outcomes of optical coherence tomography use: 877 patients single-center experience. *Cardiovasc Revasc Med* 2019;20:303–10.
- Burzotta F, Leone AM, Aurigemma C, et al. Fractional Flow Reserve or Optical Coherence Tomography to Guide Management of Angiographically Intermediate Coronary Stenosis: A Single-Center Trial. *JACC Cardiovasc Interv* 2020;13:49–58.
- Tobis J, Azarbal B, Slavin L. Assessment of intermediate severity coronary lesions in the catheterization laboratory. *J Am Coll Cardiol* 2007;49:839–48.
- Prati F, Regar E, Mintz GS, et al. Expert review document on methodology, terminology, and clinical applications of optical coherence tomography: physical principles, methodology of image acquisition, and clinical application for assessment of coronary arteries and atherosclerosis. *Eur Heart J* 2010;31:401–15.
- Tearney GJ, Regar E, Akasaka T, et al. Consensus standards for acquisition, measurement, and reporting of intravascular optical coherence tomography studies: a report from the International Working Group for Intravascular Optical Coherence Tomography Standardization and Validation. *J Am Coll Cardiol* 2012;59:1058–72.
- Erlinge D, Maehara A, Ben-Yehuda O, et al. Identification of vulnerable plaques and patients by intracoronary near-infrared spectroscopy and ultrasound (PROSPECT II): a prospective natural history study. *The Lancet* 2021;397:33714389:985–95.
- Vrijens B, De Geest S, Hughes DA, et al. A new taxonomy for describing and defining adherence to medications. *Br J Clin Pharmacol* 2012;73:691–705.
- De Filippo O, Mineo R, Millesimo M, et al. Non-invasive physiological assessment of intermediate coronary stenoses from plain angiography through artificial intelligence: the STARFLOW system. *Eur Heart J Qual Care Clin Outcomes* 2025;11:343–52.
- Chu M, Jia H, Gutiérrez-Chico JL, et al. Artificial intelligence and optical coherence tomography for the automatic characterisation of human atherosclerotic plaques. *EuroIntervention* 2021;17:41–50.
- Sperti M, Malavolta M, Staunovo Polacco F, et al. Cardiovascular risk prediction: from classical statistical methods to machine learning approaches. *Minerva Cardiol Angiol* 2022;70:102–22.
- Velliangiri S, Alagumuthukrishnan SJPCS. A review of dimensionality reduction techniques for efficient computation. *Procedia Comput Sci* 2019;165:104–11.
- Stone M. Cross-Validatory Choice and Assessment of Statistical Predictions. *Journal of the Royal Statistical Society Series B* 1974;36:111–33.
- Cawley GC, Talbot NL. On over-fitting in model selection and subsequent selection bias in performance evaluation. *J Mach Learn Res* 2010;11:2079–107.
- Efron B, Tibshirani RJ. *An Introduction to the Bootstrap*. Chapman and Hall/CRC, 1994.
- Kristensen TS, Kofoed KF, Kühl JT, et al. Prognostic implications of nonobstructive coronary plaques in patients with non-ST-segment elevation myocardial infarction: a multidetector computed tomography study. *J Am Coll Cardiol* 2011;58:502–9.
- Kedhi E, Berta B, Roleder T, et al. Thin-cap fibroatheroma predicts clinical events in diabetic patients with normal fractional flow reserve: the COMBINE OCT-FFR trial. *Eur Heart J* 2021;42:4671–9.
- Park SJ, Ahn JM, Kang DY, et al. Preventive percutaneous coronary intervention versus optimal medical therapy alone for the treatment of vulnerable atherosclerotic coronary plaques (PREVENT): a multicentre, open-label, randomised controlled trial. *Lancet* 2024;403:1753–65.