A systematic review of clinical and biomechanical engineering perspectives on the prediction of restenosis in coronary and peripheral arteries

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ABSTRACT

Objective: Restenosis is a significant complication of revascularization treatments in coronary and peripheral arteries, sometimes necessitating repeated intervention. Establishing when restenosis will happen is extremely difficult due to the interplay of multiple variables and factors. Standard clinical and Doppler ultrasound scans surveillance follow-ups are the only tools clinicians can rely on to monitor intervention outcomes. However, implementing efficient surveillance programs is hindered by health care system limitations, patients' comorbidities, and compliance. Predictive models classifying patients according to their risk of developing restenosis over a specific period will allow the development of tailored surveillance, prevention programs, and efficient clinical workflows. This review aims to: (1) summarize the state-of-the-art in predictive models for restenosis in coronary and peripheral arteries; (2) compare their performance in terms of predictive power; and (3) provide an outlook for potentially improved predictive models.

Methods: We carried out a comprehensive literature review by accessing the PubMed/MEDLINE database according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The search strategy consisted of a combination of keywords and included studies focusing on predictive models of restenosis published between January 1993 and April 2023. One author independently screened titles and abstracts and checked for eligibility. The rest of the authors independently confirmed and discussed in case of any disagreement. The search of published literature identified 22 studies providing two perspectives—clinical and biomechanical engineering—on restenosis and comprising distinct methodologies, predictors, and study designs. We compared predictive models' performance on discrimination and calibration aspects. We reported the performance of models simulating reocclusion progression, evaluated by comparison with clinical images.

Results: Clinical perspective studies consider only routinely collected patient information as restenosis predictors. Our review reveals that clinical models adopting traditional statistics (n = 14) exhibit only modest predictive power. The latter improves when machine learning algorithms (n = 4) are employed. The logistic regression models of the biomechanical engineering perspective (n = 2) show enhanced predictive power when hemodynamic descriptors linked to restenosis are fused with a limited set of clinical risk factors. Biomechanical engineering studies simulating restenosis progression (n = 2) are able to capture its evolution but are computationally expensive and lack risk scoring for individual patients at specific follow-ups.

Conclusions: Restenosis predictive models, based solely on routine clinical risk factors and using classical statistics, inadequately predict the occurrence of restenosis. Risk stratification models with increased predictive power can be potentially built by adopting machine learning techniques and incorporating critical information regarding vessel hemodynamics arising from biomechanical engineering analyses. (JVS—Vascular Science 2023;4:100128.)

Keywords: Coronary artery disease; Peripheral arterial disease; Predictive models; Restenosis; Risk factors

Restenosis is the reoccurrence of stenosis, an abnormal narrowing (≥50%[1]) of blood vessels, causing limited blood flow. Restenosis usually pertains to arteries that have undergone surgical or endovascular procedures to treat the vascular damage from atherosclerosis.[2]

Some of the high-susceptibility sites subjected to clinically significant atherosclerotic diseases are the coronary[3] (coronary artery disease [CAD]) and the peripheral arteries[4] (peripheral artery disease [PAD]). Preliminary, conservative treatment for CAD and PAD includes

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Table I. Common demographic, clinical, angiographic, altered hemodynamics- and morphology-related risk factors identified in the literature as increasing the risk of restenosis

Demographic, clinical, and angiographic risk factors		
Patient-related		**Clinical**: diabetes mellitus, older age, male sex, hypertension, smoking **Biological**: elevated CRP level, elevated levels of specific complement components (C3a, C5a), genetic variation in the vitamin D receptor, higher LDL-C, HDL, TC, TGs levels, inhibition of platelet parameters (PDW, PCT, MPV), history of restenosis, microalbuminuria, neutrophil-lymphocyte ratio **Genetic**: multivessel disease — indicating genetic predisposition and potential identification of genetic markers for restenosis
Lesion-related		Long lesion length, small vessel diameter, minimal lumen diameter after PCI alone/stenting, ACC/AHA type C lesion, chronic total occlusion, tortuous and calcified lesion, restenotic lesion
Procedure-related		Treatment modality (PTA/PCI alone, with or without DCB, BMS or DES implantation), implantation or presence of multiple stents, stent overlapping, smaller stent area
Hemodynamics and vessel morphology risk factors		
Altered hemodynamics-related (WSS-related indices)	Low TAWSS (<0.5 Pa)	TAWSS: WSS averaged over an entire cardiac cycle
	High OSI (>0.2)	OSI: identifies regions on the vessel wall subjected to highly oscillating WSS over the cardiac cycle
	High RRT (<1.5 Pa)	RRT: describes the residence time of a fluid particle near the wall
	Low HOLMES (<0.5 Pa^{-1})	HOLMES: identifies regions on the vessel wall simultaneously subjected to low TAWSS and high OSI
Morphology-related	Native vessel curvature and tortuosity	

ACC/AHA, American College of Cardiology/American Heart Association; *BMS*, bare metal stent; *CRP*, C-reactive protein; *DCB*, drug-coated balloon; *DES*, drug-eluting stent; *HDL*, high density lipoprotein; *HOLMES*, highly oscillatory and low magnitude shear; *LDL-C*, lipoprotein cholesterol; *MPV*, mean platelet volume; *OSI*, oscillatory shear index; *PCT*, platelecrit; *PDW*, platelet distribution width; *PCI*, percutaneous coronary intervention; *PTA*, percutaneous transluminal angioplasty; *RRT*, relative residence time; *TAWSS*, time-averaged WSS; *TC*, total cholesterol; *TGs*, triglycerides; *WSS*, wall shear stress.

risk factor modification combined with antiplatelet, anti-thrombotic, and lipid-lowering medical therapy.[5] Surgical and endovascular approaches might later be adopted to restore blood flow. Surgical treatment consists of bypass procedures, commonly using an autologous healthy blood vessel (ie, saphenous vein, radial, and mammary arteries).[6] Endovascular procedures are increasingly employed in revascularization strategies for either CAD or PAD[7,8] because they are minimally invasive, require local over general anesthesia, and have a quicker recovery period. These include percutaneous transluminal angioplasty (PTA) alone (percutaneous coronary intervention [PCI] for the coronary arteries), with or without drug-coated balloons (DCB), PTA or PCI with balloon-expandable stent, and self-expandable stent implantation. Stenting might involve bare metal stents (BMS), drug-eluting stents (DES), or bioresorbable stents. Despite the advantages of their minimally invasive nature, revascularization treatments can lead to restenosis, sometimes necessitating repeated intervention.[9,10] Restenosis is a complex, multifactorial phenomenon as well as a challenging clinical problem with high prevalence, occurring in up to 60% and 30% of cases at 1-year follow-up for PAD[10] and CAD treatment,[11] respectively.

In some patients, restenosis leads to adverse consequences, such as stable/unstable angina and acute myocardial infarction in case of CAD or gangrene and leg amputation in case of PAD, or—worst-case scenario—death.

Different demographic, clinical, and angiographic risk factors triggering the development of restenosis are identified in the literature.[9,12-16] This information is routinely collected and commonly grouped under three categories (Table I): patient-, lesion-, and procedure-related predictors.[9,15]

In addition, altered hemodynamics in the arterial (mechanical) environment with respect to the healthy

Table II. Definitions of clinical endpoints investigated by the reviewed papers for the development of predictive models

Different endpoints investigated by the reviewed studies
Restenosis: (1) recurrent diameter narrowing >50% at the first site dilated, (2) loss of at least 50% of the gain in the diameter narrowing
Target lesion revascularization: defined as the need for repeated minimally invasive revascularization or bypass graft placement for stenosis in the treated lesion at the index endovascular procedure or occurring within 5 mm of the stent ("edge effect")
Target lesion failure: defined as a composite multiple clinical endpoints such as cardiovascular death, target lesion revascularization, and target vessel myocardial infarction

vessel,[17] caused by balloon inflation and/or stent or bypass implantation, also seems to play a role in restenosis progression (Table I). The vessel lumen is lined with endothelial cells subjected to mechanical forces exerted by the blood flow, determining their function, gene expression, and structure.[18] These mechanical forces typically refer to the wall shear stress (WSS), defined as the tangential force of the flowing blood over the endothelial surface of the blood vessel. Under physiological conditions, values of WSS range from 1 to 7 Pa in the peripheral arteries of the lower limbs[19] and between 1 and 2 Pa in the coronary arteries.[20] However, when the arterial cross-section narrows due to plaque presence (drastically reduced but not entirely removed by endovascular procedures), the blood speed rapidly increases, resulting in significantly increased WSS[21] values. On the other hand, distal to the stenosis, WSS often becomes relatively low (<0.5 Pa) due to flow separation and recirculating vortical structures.[21] Stent implantation also reduces the compliance of the vascular segment, leading to a compliance mismatch with other parts of the blood vessel,[22] which might affect blood flow. Intrusions of the stent struts into the lumen can also cause local flow separation and hence low WSS regions, which may turn pathogenic.[21]

In general, vessel locations undergoing revascularization exhibit disturbed flow and coincide with preferred sites for restenosis to develop.[3] More specifically, in regions where WSS values are lower than 0.5 Pa,[19,23,24] a proatherogenic endothelial phenotype is stimulated, and vascular remodeling or neointimal hyperplasia (NIH) takes place as a compensatory phenomenon to maintain the hemodynamic value within the physiological range.

The native curvature and tortuosity of the vessel might also have a significant role in hemodynamic changes[25,26] and are considered geometric risk factors for vessel reocclusion over time[27] (Table I).

Quantitative information on vessel lumen remodeling and the distribution of WSS and WSS-related indices along the vessel wall can be obtained by fusing medical images and patient-specific computational fluid dynamics (CFD) analyses. CFD is a powerful tool used to study complex, pathophysiological flows by numerically solving the continuity and Navier-Stokes equations governing fluid motion. To be solved, boundary conditions (BCs)—parameters or relationships describing the hemodynamic conditions at the boundaries of the vessel geometry—need to be defined. These calculations allow the computation of WSS and WSS-derived indices linked to restenosis progression (Table I) and cannot be measured or estimated otherwise.

However, some patients appear to be at increased risk of developing restenosis than others, although the occlusion's timescale and extent cannot be identified a priori. Determining whether a patient will develop restenosis is currently not possible with available tools and methods.

Current clinical pathways impose standard clinical and Doppler ultrasound (DUS) surveillance follow-ups to check on patients' conditions after revascularization.[28,29] Nevertheless, implementing an efficient surveillance program is not straightforward, especially in an overstretched health system dealing with large numbers of patients with CAD and PAD.

Stratification models could predict post-intervention individual risk of reocclusion within a defined time interval, allowing tailored surveillance and developing more efficient clinical workflows for both CAD and PAD.

Aim of the review. This review provides a critical evaluation of available restenosis prediction models for CAD and PAD. The focus is on studies providing either the risk of restenosis or simulating reocclusion progression over a prescribed period, after intervention. An overview of the key advances in this area is provided by describing how the models work, and also, by assessing their prediction ability, with an outline of future developments regarding their potential improvements in predictive power.

METHODS

The papers reviewed herein were identified by accessing the PubMed/MEDLINE database according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The first author (F.N.) searched published literature up to 2023, combining the following keywords and Medical Subject Headings (MeSH) terms: "prediction," "models," "restenosis," "neointimal hyperplasia," "target lesion revascularization," "target lesion failure," "stent," "angioplasty," "coronary arteries," "peripheral arteries," "clinical variables," "computational fluid dynamics," "hemodynamics."

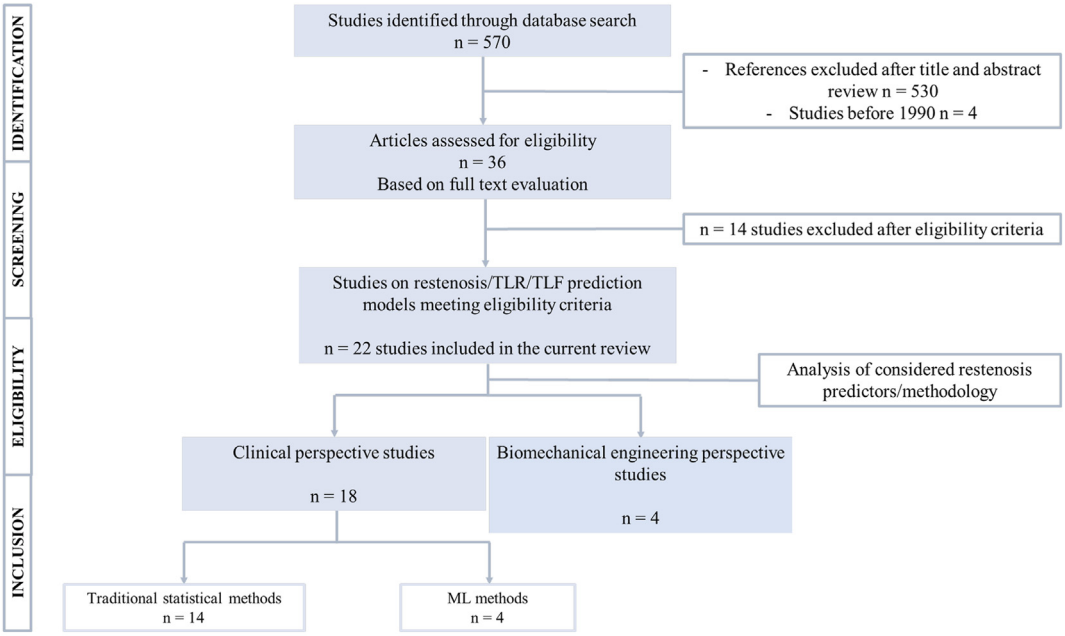

Fig 1. Flow chart showing the process for the literature search and selection of the works. *TLF*, Target lesion failure; *TLR*, target lesion revascularization.

Selection criteria for article inclusion were publications written in the English language addressing prediction models of restenosis or, more widely, target lesion revascularization (TLR)[30] and target lesion failure (TLF)[31] (Table II) for patients undergoing revascularization procedures in the coronary or peripheral arteries.

Both titles and abstracts of the publications identified were reviewed using the aforementioned search strategy. The first author (F.N.) independently checked eligibility and discussed and confirmed with the rest of the authors (J.T., S.B., V.D.Z.) in case of any disagreement. Case reports, articles whose full-text manuscripts could not be accessed, and review papers were excluded. Fig 1 shows the flow chart of the literature search and selection process. Risk of bias analysis for the included studies using the Risk of Bias in Systematic Reviews (ROBIS) tool[32] was conducted to ensure the integrity and reliability of the systematic literature review.

The authors classified the studies meeting eligibility criteria into two groups (encompassing two different perspectives): clinical and biomechanical engineering, based on considered predictors, methodology, and tools used. The clinical perspective studies resulted in another two sub-groups: studies using traditional statistical models and those adopting more advanced predictive tools, such as machine learning (ML) algorithms.

The performance of the prediction models for restenosis was assessed based on discrimination and calibration aspects. For models simulating reocclusion progression, their performance was evaluated by direct comparison with available clinical data acquired at specific time points.

RESULTS

Eighteen clinical perspective studies were identified and summarized in Table III. The common point of all these works is that they consider clinical, demographic, and angiographic variables as the *only* potential predictors of restenosis.

Four biomechanical engineering perspective studies were reported in this review and summarized in Table IV. In this case, the common ground is the use of WSS-related indices (Table I) as predictors of restenosis.

Further details are discussed in the following section, together with a comparison regarding the predictive power of the models identified.

Most clinical studies[1,33-45] appear to rely on traditional statistics, although more advanced ML methods are introduced in recent ones.[46-49] The schemes followed by the models adopting either methodology are illustrated diagrammatically in Fig 2.

Biomechanical engineering models for restenosis prediction that include hemodynamic indices have emerged only recently. This is probably due to the fact that hemodynamic indices cannot be easily retrieved in clinical practice, in contrast with clinical, angiographic, and demographic information. These numerical investigations require expertise in image processing, three-dimensional (3D) vessel reconstruction, and CFD analyses, as shown schematically in Fig 3.

Table III. Clinical perspective studies predicting risk of restenosis, classified into studies using classical statistical models and machine learning (*ML*) techniques respectively

Reference Revascularization procedure Dataset	Aim of the study	Restenosis predictors selection	Predictive model	Model evaluation	Conclusions
Traditional statistical models					
Weintraub et al[33] (1993) Coronary arteries PCI alone (single lesion) 4006 patients from the clinical database at Emory University (single-center study)	Verify whether clinical, angiographic, and procedural variables correlating with restenosis — identified from the dataset — in the learning group could predict restenosis in a validation group	Significant variables from the comparison between restenosis and no restenosis groups in the learning group used as restenosis predictors	Multivariable stepwise logistic regression model	AUC ROC = 0.62 Overlap index = 0.76 ($P < .0001$) Correlation between average predicted and observed restenosis rates confirm the goodness-of-fit of the model	Clinical variables provide limited ability to predict restenosis in a particular patient. Probability of restenosis can be determined with some uncertainty in well-characterized (ie, single lesion) patients who have already undergone angioplasty
de Feyter et al[37] (1999) Coronary arteries PCI with balloon-expandable, self-expanding stents (single lesion) 858 patients from 3 registries and 2 randomized trials on the efficacy of a pharmaceutical agent on restenosis (multi-center study)	Identify post-stent implantation IVUS predictors of stent restenosis to build a reference chart that predicts 6-months restenosis	Univariable logistic regression analysis	Multivariable logistic regression model	Hosmer-Lemeshow goodness-of-fit test ($P = .42$)	Reference chart predicts 6-months restenosis rate. This is only applicable for stent implantation in short lesions in relatively large vessels. Reliability of the reference chart must be confirmed in a prospective study

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Table III. Continued.

Reference Revascularization procedure Dataset	Aim of the study	Restenosis predictors selection	Predictive model	Model evaluation	Conclusions
Singh et al[1] (2004) Coronary arteries PCI alone (single lesion) 1224 patients enrolled in the angiographic substudy of the PRESTO trial (multi-center study)	First approach — Construct a simple risk scoring system to access pre-procedural risk of restenosis including variables (clinical and angiographic) that have been reported in previous studies to be strong predictors of restenosis Second approach — Building a new model including PRESTO dataset-driven variables (clinical and angiographic) that might be predictors of restenosis development. Internal benchmark to compare the predictive power of the first risk score	First approach — Variables frequently reported in the literature to be strong predictors of restenosis Second approach — Significant variables from univariable logistic regression analyses	First approach — Multivariable logistic regression model Second approach — Multivariable stepwise logistic regression model	First approach — AUC ROC = 0.63 Hosmer-Lemeshow goodness-of-fit-test ($P = .18$) Second approach — AUC ROC = 0.63	Pre-procedural clinical and angiographic variables historically correlated with risk of restenosis and those derived from PRESTO trial have only modest predictive ability at predicting restenosis after PCI
Stolker et al[34] (2010) Coronary arteries PCI with DES (single/multiple lesion) 8829 patients from the EVENT registry (multi-center study) undergoing DES implantation	Develop a risk model for TLR and late TLR using demographic, clinical and patient-level angiographic data from the EVENT registry	Significant variables from univariable logistic regression analyses and variables frequently reported in the literature to be strong predictors of restenosis	Multivariable backward stepwise logistic regression model	Hosmer-Lemeshow goodness-of-fit test ($P = .95$)	Risk model incorporating 6 clinical and angiographic variables only identifies individuals at extremely low (<2%) and modestly increased (>7%) risk of TLR

Table III. Continued.

Reference Revascularization procedure Dataset	Aim of the study	Restenosis predictors selection	Predictive model	Model evaluation	Conclusions
Yeh et al[38] (2011) Coronary arteries PCI with DES or BMS (single/multiple lesion) 27,107 patients from Massachusetts Department of Public Health database (multicenter study)	Develop and validate a model to predict the likelihood of TLR after PCI with either DES or BMS implantation, within a large population, using variables commonly collected	Variables identified based on clinical relevance First model — Only clinical variables considered without inclusion of angiographic variables Second model — Including angiographic variables as well	Multivariable backward stepwise logistic regression model	First model — c-index = 0.62 Hosmer-Lemeshow goodness-of-fit test ($P = .65$) Second model — c-index = 0.66 Hosmer-Lemeshow goodness-of-fit test ($P = .90$)	Development and validation of a modest predictive model to predict TLR after PCI, allowing the benefit quantification of PCI with DES compared with BMS. This might support the safer and more cost-effective application of DES technology
Gai et al[35] (2021) Coronary arteries PCI with DES (single/multiple lesion) 968 patients — not specified where data are retrieved but referred to the Xinjiang population	Develop a novel prediction model for restenosis based on platelet parameters, lipid levels, clinical and angiographic characteristics	Significant variables from the comparison between restenosis and no restenosis groups in the learning group used as restenosis predictors and confirmed by univariable, multivariable logistic regression models and ROC analyses (AUC ROC >0.5)	Multivariable forward stepwise logistic regression model	AUC ROC = 0.72 (95% CI: 0.64-0.80) Hosmer-Lemeshow goodness-of-fit test ($P = .655$)	The prediction model based on PDW, TC, LDL-C, SBP and number of lesions is an effective model to predict restenosis and conducting risk stratification in patients with DES implantation
He et al[36] (2021) Coronary arteries PCI with DES (single/multiple lesion) 463 patients from an observational cohort study in a high-volume PCI center in Henan Province, China (single-center study)	Use identified clinical, lesion, procedure characteristics, laboratory tests and use of medications factors correlated to the risk of ISR to develop and validate an easy-to-use clinical risk prediction nomogram to predict the probability of ISR in patients undergoing PCI	LASSO-regression analysis to select restenosis predictors	Multivariable logistic regression model	AUC ROC — validation set = 0.662 Calibration plots — concordance performance compared with an ideal model ($P = .417$)	Development and validation of an easy-to-use individualized prediction nomogram incorporating five simple clinical and angiographic characteristics that should facilitate early identification and improved screening of patients at higher risk of restenosis

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Table III. Continued.

Reference Revascularization procedure Dataset	Aim of the study	Restenosis predictors selection	Predictive model	Model evaluation	Conclusions
Luo et al[39] (2022) Coronary arteries PCI with DES (single/multiple lesions) 477 patients from Enshi Central Hospital (single-center study)	Develop a new preoperative risk factor nomogram considering preoperative blood biochemical parameters for PCI, Gensini (GS) scores and procedural characteristics	LASSO regression analysis	Multivariable logistic regression model	AUC ROC = 0.841 Hosmer-Lemeshow goodness-of-fit test ($P = .609$) Calibration plots — confirm no divergence between predicted and observed probability	Creation of a new prediction model to help clinicians discern high-risk restenosis patients, optimize treatment, and improve prognosis. The model is satisfactory in terms of goodness-of-fit, clinical usefulness and accuracy
Dai et al[40] (2022) Coronary arteries PCI with DES (single/multiple lesions) 1653 patients from Zhongshan Hospital (single-center study)	Develop and validate an easy-to-use predictive model for repeat vascularization after DES implantation in patients with CAD	Significant variables ($P <$ .20) from univariable logistic regression analyses	Multivariable stepwise logistic regression model	c-index = 0.68 (95% CI, 0.619-0.740) Hosmer-Lemeshow goodness-of-fit test ($P = .198$)	Development and validation of a model including 8 accessible variables to modestly predict restenosis after DES implantation. It shows advantages in discriminative ability and clinical usefulness compared with the empirical model including recurrent angina only
Feng et al[41] (2022) Coronary arteries PCI with 2nd generation DES (single/multiple lesions) 235 patients from Handan Central Hospital (single-center study)	Investigate the restenosis occurrence and its predictive factors in patients with CAD who underwent PCI with 2nd generation DES to provide insights for better management of restenosis	Significant variables from univariable logistic regression analyses	Multivariable forward stepwise logistic regression model	AUC ROC = 0.863 (95% CI: 0.779-0.848)	The developed restenosis risk prediction model exhibits the potential as a good marker for restenosis risk in patients with CAD who underwent PCI with 2nd generation DES

Table III. Continued.

Reference Revascularization procedure Dataset	Aim of the study	Restenosis predictors selection	Predictive model	Model evaluation	Conclusions
Wu et al[42] **(2022)** Coronary arteries PCI with DES (single/multiple lesions) 72 patients from Second People's Hospital of Guangdong Province (single-center study)	Construct a prediction model for in-stent restenosis when DESs are implanted	Significant variables from multivariable logistic regression analyses	Multivariable stepwise logistic regression model	AUC ROC = 0.924 (95% CI, 0.880-0.967) Hosmer-Lemeshow goodness-of-fit test (P=.413)	The model has high predictive value for the occurrence of in-stent restenosis. It may be applied to the early prediction of this
Chen et al[43] **(2023)** Peripheral arteries PTA with DCB or BMS (single/multiple lesions) 181 patients from First Affiliated Hospital of Xi'an JiaoTong University (single-center study)	Development and internal validation of nomograms for predicting restenosis after endovascular treatment of PAD	LASSO regression analysis to select restenosis predictors	Cox regression analysis	c-index = 0.864 (95% CI, 0.801-0.927) Calibration plots — predicted value of the model is in good agreement with the real value	This study developed a nomogram to predict restenosis after endovascular procedures in patients with PAD. The nomogram requires external validation to determine the model's applicability
Xi et al[44] **(2023)** Coronary arteries PTA with DES (single/multiple lesions) 414 patients from Fourth Affiliated Hospital of Zhejiang University School (single-center study)	Establish a nomogram model to predict the risk of restenosis	LASSO regression analysis to select restenosis predictors	Multivariable logistic regression analysis	AUC ROC = 0.806 (95% CI, 0.739—0.873) Calibration plots — no significant deviation between the predicted probability and the actual probability	Nomogram model has good accuracy, which can better identify the high-risk patients for restenosis and provide practical decision-making information for the follow-up intervention
Coughlan et al[45] **(2023)** Coronary arteries PCI with DES (single/multiple lesions) 1986 patients from two centers in Germany (multi-center study)	Development and validation of a model to predict repeat PCI for recurrent DES restenosis at 1-year follow-up	LASSO regression analysis to select restenosis predictors	Multivariable logistic regression analysis	c-index = 0.61	Development of the ISAR score, a four-item scoring system that can be used to estimate the risk of repeat PCI for recurrent DES restenosis at 1-year follow-up

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Table III. Continued.

Reference Revascularization procedure Dataset	Aim of the study	Restenosis predictors selection	Predictive model	Model evaluation	Conclusions
ML models					
Sampedro-Gómez et al[46] (2019) Coronary arteries PCI with DES or BMS (single/multiple lesion) 263 patients from (GRACIA)-3 trial (multi-center study) for patients undergoing ST-elevation acute myocardial infarction and consequent PCI	Develop an ML model using daily available demographic, clinical, and angiographic data to predict 12-month follow-up stent restenosis better than the state-of-the-art logistic regression models	Two strategies pursued in parallel: 1) Selection based on ANOVA 2) Random forest (RF) classifier attributing scores to each predictor	Application and comparison of 6 different ML classifiers: RF, ERT, GB, SVM, L2-regularised and non-regularized logistic regression trained with the two different selection techniques for restenosis predictors (12 models in total)	AUC PR (ERT) = 0.46 (95% CI, 0.29-0.63) AUC ROC (ERT) = 0.77 (95% CI, 0.66-0.89)	Development of an ERT model to predict stent restenosis based on variables obtained in routine clinical practice. The model, when compared with the state-of-the-art logistic regression ones, shows increased restenosis prediction power
Pachl et al[47] (2021) Coronary arteries PCI with bioresorbable stent (single lesion) 1975 patients from post-market study Biotronik BIOSOLVE-IV to access clinical performance and long-term safety of the device (multi-center study)	Prediction of TLF after stent implantation using a novel ML approach and an international cohort	86 features used in the study regarding pre-intervention, intra-operation, lesion and stent, medications, discharge information, and follow-up	Application and combination in an "ensemble model" of nine different ML classifiers: ERTs, GB, GP, KNN, L1- and L2-logistic regression, MLP, RF and SVMs	AUC PR ranges from 0.10 and 0.12 for the different pipelines and the "ensemble model". AUC ROC ranges from 0.58 and 0.62 for the different pipelines and the "ensemble model"	Development of a novel ML model to predict TLF based on 86 variables obtained in routine clinical practice. The "ensemble model," being a combination of nine ML classifiers, outperforms all the state-of-the-art logistic regression models in terms of predictive power
Jiang et al[48] (2022) Coronary arteries PCI with 2nd generation DES (single/multiple lesions) 1501 patients from Guizhou Provincial People's Hospital (single-center study)	Test that RF model has better performance than logistic regression model in restenosis prediction due to higher robustness	Stepwise logistic regression model — Stepwise Akaike information criterion RF model — Conditional permutation importance, mean decrease accuracy, mean decrease Gini	1) Multivariable stepwise logistic regression model 2) RF model	RF model has larger AUC ROC and PR than logistic regression model	Development of an ML model using RF to predict restenosis in patients implanted with 2nd DES generation. The RF model shows improved predictive performance as compared with logistic regression model due to its robustness (accuracy less affected by outliers)

Table III. Continued.

Reference Revascularization procedure Dataset	Aim of the study	Restenosis predictors selection	Predictive model	Model evaluation	Conclusions
Güldener et al[49] (2023) Coronary arteries PCI with BMS or DES (single/ multiple lesion) 10,004 patients from two centers in Germany (multi-center study)	Application of SOMs to detect patterns with the aim of better predicting in-stent restenosis at surveillance angiography 6 to 8 months after PCI with stenting	Two strategies pursued in parallel: 1) Conventional multivariable logistic regression analyses 2) SOM-based approach	1) Conventional model based on multivariable logistic regression 2) SOM-based model	AUC ROC = 0.726 (P=.3) — logistic regression AUC ROC = 0.728 (P=.3) — SOM-based model	SOMs approach identified several novel predictors of restenosis after PCI. However, ML methods did not improve identification of patients at high risk for restenosis after PCI

ANOVA, Analysis of variance; *AUC ROC*, area under the receiver operating characteristic curve; *BMS*, bare metal stent; *CAD*, coronary artery disease; *CI*, confidence interval; *DCB*, drug-coated balloon; *DES*, drug-eluting stent; *ERT*, extremely randomized tree; *GB*, gradient boosting; *GP*, Gaussian process; ISR, in-stent restenosis; *IVUS*, intravascular ultrasound; *KNN*, K-nearest neighbors; *LASSO*, least absolute shrinkage and selection operator; *LDL-C*, low-density lipoprotein cholesterol; *MLP*, multi-layer perceptron; *PAD*, peripheral artery disease; *PCI*, percutaneous coronary intervention; *PDW*, platelet distribution width; *PR*, precision recall; *PTA*, percutaneous transluminal angioplasty; *RF*, random forest; *SBP*, systolic blood pressure; *SOM*, self-organizing map; *SVM*, support vector machine; *TC*, total cholesterol; *TLF*, target lesion failure; *TLR*, target lesion revascularization.

Preliminary steps. Clinical perspective studies, independently from traditional statistical or ML models, entail—as a first step—data screening by applying inclusion and exclusion criteria to reduce the available dataset to one suitable for analysis. Due to the applied criteria but also to the lack of consistent data, a smaller subset of data can be used for analysis. This highlights one of the most significant limitations in using clinical data: data collection is not standardized, potentially leading to inadequate sample size for analyses and preventing direct comparisons between models.

Once the dataset is identified, some initial data preprocessing is required when using ML algorithms, to make it amenable to these and to reduce bias in the findings. For example, Sampedro-Gómez et al[46] preprocessed their data by 1-hot encoding in binary variables multicategory variables (ie, by representing every variable as a sequence of 0 and 1 only) and filling missing values with the median and the mode for each continuous and categorical variable, respectively. Pachl et al[47] corrected for differences in variable scales and outliers, performed data normalization and oversampled (undersampled) for the underrepresented (overrepresented) category of patients (not) presenting TLF.

Once the data are finalized, they are randomly split into the so-called "learning" or "training" and "test" sets (Fig 2). The "learning" set is usually larger since it is used to build the model. The "test" set is used to evaluate the model's performance. In a few studies, no splitting is performed and the whole dataset is used for "learning."[1,35,37,39,41,42] This leads to overly optimistic results in model performance (overfitting), which might be corrected by bootstrapping techniques (Table V). Bootstrapping has emerged as a popular solution to correct optimistic performance estimates of predictive models[1,35,38-40,43-45] enhancing model reliability.

In ML approaches, the split into "training" and "test" sets is performed by k-fold cross-validation[46-48] (Table V). This process can be replicated multiple times[46,48] to counteract highly unbalanced datasets, potentially biasing the final model's predictive results. This ensures that a minimum number of minority cases (ie, patients presenting restenosis) is represented in both model training and evaluation phases.

Moving to the biomechanical engineering perspective, the first step consists of the acquisition of clinical images (Fig 3), providing different information according to the diagnostic technique. Two-dimensional (2D) X ray angiography[17] and computed tomography (CT)[50-52] scans allow 3D vessel reconstruction, giving information about vessel geometry. DUS images provide information about blood velocity waveforms and are used to define patient-specific BCs, as explained in the Introduction.

Published biomechanical engineering studies often deal with a considerably lower number of patients when compared with clinical ones (Tables III and IV). This is not surprising considering the data requirements and computational costs involved in simulating patient-specific hemodynamics or modeling restenosis progression, making them complex and time-consuming to model and analyze, and thus effectively computationally intractable for very large datasets.

As a second step, vessel geometry reconstruction from clinical images is crucial for CFD analyses and the computation of the hemodynamic indices linked to restenosis progression (Fig 3). CFD results are sensitive

Table IV. Biomechanical engineering perspective studies on restenosis detailing patient datasets, model details, and findings

Reference Revascularization procedure Dataset	Aim of the study	Predictive model	Restenosis predictors	Model evaluation	Conclusions
Gökgől et al[17] (2019) Peripheral arteries (Femoro-popliteal artery) PTA alone or with self-expandable (Nitinol) stents (single/multiple lesions) 20 patients (10 undergoing balloon angioplasty alone and the rest Nitinol stent implantation) (not known if single-or multi-center study) Angiographic data acquired at baseline and instances of restenosis at 6-months follow-up	Test if patient-specific CFD simulations performed on femoro-popliteal arteries can provide hemodynamic markers that are able to predict the risk of restenosis in 6-months time	3 different logistic regression models: 1) Including only non-flow related patients' characteristics; 2) Including only patient-specific CFD-calculated parameters; 3) Incorporating both non-flow and CFD-calculated parameters	*First model*: presence of kinking, lesion length, age, level of calcification, treatment method *Second model*: low TAWSS in straight and flexed positions, high TAWSS and OSI in the straight configuration *Third model*: low TAWSS in straight and flexed positions, high TAWSS and OSI in the straight configuration, treatment method	Paired *t*-tests between predicted values and clinical data to assess whether the model produces statistically significant differences between restenosed and non-restenosed arteries. Accuracy estimated from leave-out analyses. The Mc Fadden pseudo R^2 to compare the predictive strength between models. Cessie-van Houwelingen-Copas-Hosmer unweighted sum of squares test to determine the goodness of fit of the models	Logistic regression analysis based solely on hemodynamical markers has an accuracy of 80% and shows a statistically significant difference between restenosed and non-restenosed arteries ($P = .02$). If treatment method is included, the difference between the two groups becomes strongly statistically significant ($P = .002$) and the goodness of fit increases (from 0.29 to 0.38)
Donadoni et al[50] (2020) Peripheral arteries (Femoro-popliteal artery) Autogenous sapheneous bypass graft 3 patientsundergoing femoral-popliteal saphenous bypass (single-center study) CT scans acquired at 8, 19, 24 months (for patients 1-3, respectively), Doppler ultrasound scans acquired immediately after surgery	Simulation of NIH progression using a multiscale computational framework and comparison of results with a patient-specific clinical dataset	Multiscale computational framework informed by patient-specific imaging data and hemodynamic markers (TAWSS and HOLMES) having as output the predicted value of NIH growth along the graft	Low TAWSS, high OSI and HOLMES indices	Analysis of cross-sectional areas of the lumen where restenosis is most severe and comparison with the available CT scans	The simulation model correctly predicts areas of NIH growth, with values similar to the stenosis observed in the CT scans with the use of the HOLMES index (max discrepancy 8% between stenosis values observed in patients 1-3 compared with the CT scan)
Colombo et al[51] (2021) Peripheral arteries (Superficial femoral artery) PTA with self-expandable (Nitinol) stents (single/multiple lesions) 7 patients from Malcom Randall VAMC (Gainesville, FL, USA) — total of 10 stented lesions (single-center study) CT and Doppler ultrasound images at 1-week (baseline) and 1-year post-intervention follow-up	Analysis of the relationships between the local hemodynamics computed at the baseline and the lumen remodeling occurring at 1-year follow-up, taking into consideration also some demographic and clinical information	Logistic regression models: 1) Simple logistic regression between stent length and success-failure at 2-year follow-up; 2) Simple and multiple logistic regressions between the hemodynamics descriptors and success-failure at 2-year follow-up; 3) Simple logistic regression between age and success-failure at 2-years follow-up. Two-sided Fisher exact test to compare the dichotomous variables stent overlapping and success-failure at 2-years follow-up	Low TAWSS (below 33th percentile of the distribution), high OSI and RRT (above 66th percentile of the distributions) *First model*: stent length *Second model*: TAWSS, OSI, and RRT singularly (in simple logistic regression model) and all together (in multiple logistic regression model) *Third model*: age and stent overlapping for Fisher exact test	Tjur's pseudo R^2 to indicate the ability of the model to clearly separate between success-failure groups	No significant relationship between patients' age and treatment failure at 2-years follow-up. Stent length and stent overlapping are predictors of restenosis

Table IV. Continued.

Reference Revascularization procedure Dataset	Aim of the study	Predictive model	Restenosis predictors	Model evaluation	Conclusions
Corti et al[52] (2022) Peripheral arteries (Superficial femoral artery) PTA with self-expandable (Nitinol) stents (single/multiple lesions) 1 patient (single-center study) — to access framework feasibility 14 patients — to measure monocyte gene expression (single-center study) CT scans and Doppler ultrasound images acquired at baseline (1-week post-intervention) and at 1-month follow-up for the one-patient pilot-study Blood samples of 14 patients to perform monocyte gene expression analysis	Development of a novel multiscale framework to emulate patient-specific cellular behaviours and arterial wall remodeling (leading to restenosis) in response to local hemodynamic indices input and markers of systemic inflammation triggered by stenting	Patient-specific multiscale framework of restenosis consisting of CFD simulations coupled with an ABM of cellular dynamics. The inputs are the patient-specific superficial femoral artery geometry, the blood velocity waveform (derived from Doppler) and the longitudinal data of the patient's monocyte gene expression. The output is the 1-month follow-up 3D lumen geometry	Low WSS, systemic inflammatory response	The simulated lumen area reduction for the stented region at 1-month follow-up is compared to the patient's 1-month follow-up data	Predicted 1-month lumen contours of the stented region show no significant differences when compared with the patient's lumen area at 1-month. In both simulated and actual patient cases, a significant lumen area reduction is found at 1-month with respect to the condition immediately after intervention ($P < .05$). Model not fully able to capture local lumen geometrical variability (especially at stented portion proximal region)

ABM, Agent-based model; *CFD*, computational fluid dynamics; *CT*, computed tomography; *HOLMES*, highly oscillatory and low magnitude shear; *NIH*, neointimal hyperplasia; *OSI*, oscillatory shear index; *PTA*, percutaneous transluminal angioplasty; *RRT*, relative residence time; *TAWSS*, time-averaged WSS; *WSS*, wall shear stress.

to both the geometry and applied BCs, thus an accurate reconstruction of the vessel *and* patient-specific BCs are required to compute reliable patient hemodynamics.

Once the CFD simulation is performed, providing as output WSS, post-processing allows the calculation of WSS-related indices.

Models' development/training. Almost all the clinical perspective studies using traditional statistical methods employed a multivariable logistic regression model (Table V) to predict restenosis occurrence. This statistical model is the preferred method to analyze prognostic studies[53] when the goal is to quantify the risk of a future event. This is probably because the model returns probabilities as outputs and allows the classification of new patients using both continuous and discrete measurements, which is the case when dealing with clinical, demographic, and angiographic predictors. Cox regression analysis (Table V), adopted by Chen et al,[43] is a valid alternative providing as output the probability for that event to occur at a defined time point.

When ML approaches are adopted, several models (Table V) are usually built in parallel and eventually compared in terms of performance.[46-49]

To select the potential restenosis predictors to develop/train the model, different strategies were followed by the clinical perspective studies adopting traditional statistical models and ML approaches.

Some statistical-based studies[33,35] considered as restenosis predictors the variables proved to be statistically significantly different between the patients' groups (Table III), presenting and not presenting with restenosis.

Other studies considered variables either based on clinical relevance[38] or frequently reported in the literature as restenosis markers.[1] In some others, variables that resulted as significant from univariable[1,34,40,41] and/or multivariable logistic regression analyses[35,42] (Table V) and satisfied a specific criterion for receiver operator characteristic (ROC) curve analyses[35] (Table VI) were selected as predictors. The latter alternatives are more data-driven and use logistic regression models to test whether they are linked to restenosis (ie, variable considered as a predictor when P-value $\leq .05$).

An alternative approach to select restenosis predictors is the least absolute shrinkage and selection operator (LASSO) regression analysis[36,39,43-45] (Table V). This reduces the number of potential predictors to a limited set, improving model interpretability.

In ML-based studies, Sampedro-Gómez et al[46] based predictors' selection following two parallel strategies: (1) by performing univariate analysis of variance (ANOVA) (ie, test whether the mean differences of variables between patients presenting/not presenting with restenosis were statistically significantly different) to consider only the variables having the strongest relationship with restenosis; (2) by considering variable (feature) importance; through a random forest (RF) classifier (Table V), a score

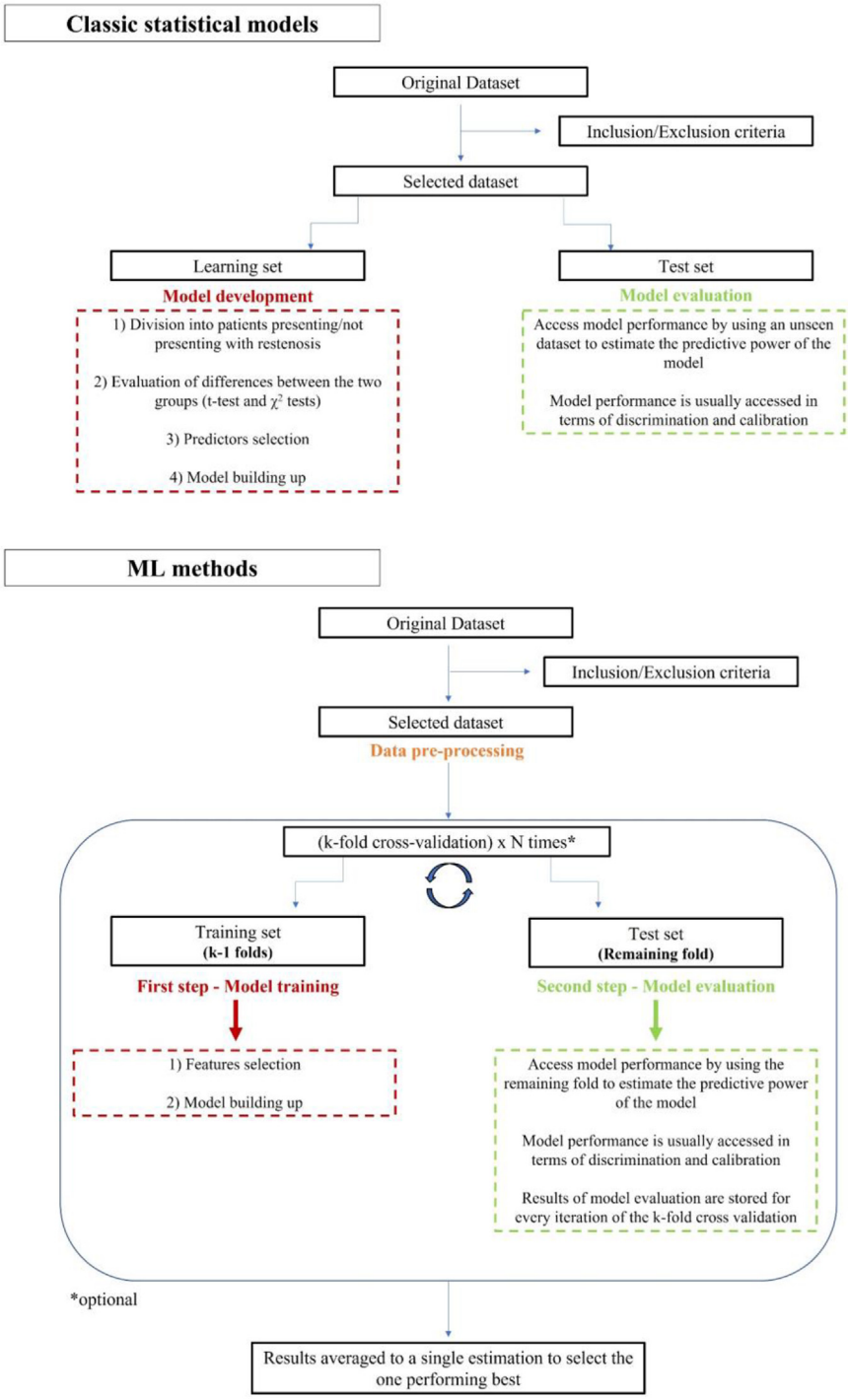

Fig 2. Methodological framework followed by clinical perspective studies to build restenosis predictive models for classic statistical models and machine-learning (*ML*) methods.

for each predictor was assigned, signifying its contribution towards restenosis occurrence. Pachl et al[47] did not explicitly mention any feature selection strategy, implying that all identified variables were employed in their model development. Jiang et al[48] relied on the stepwise Akaike information criterion (Table V) to assess the quality of a set of multivariable stepwise logistic regression models given a set of predictors, in order to pick the one performing best. For the RF model that they built in parallel, they computed the conditional permutation importance, mean decrease accuracy, and mean decrease Gini (Table V) for predictors' selection.

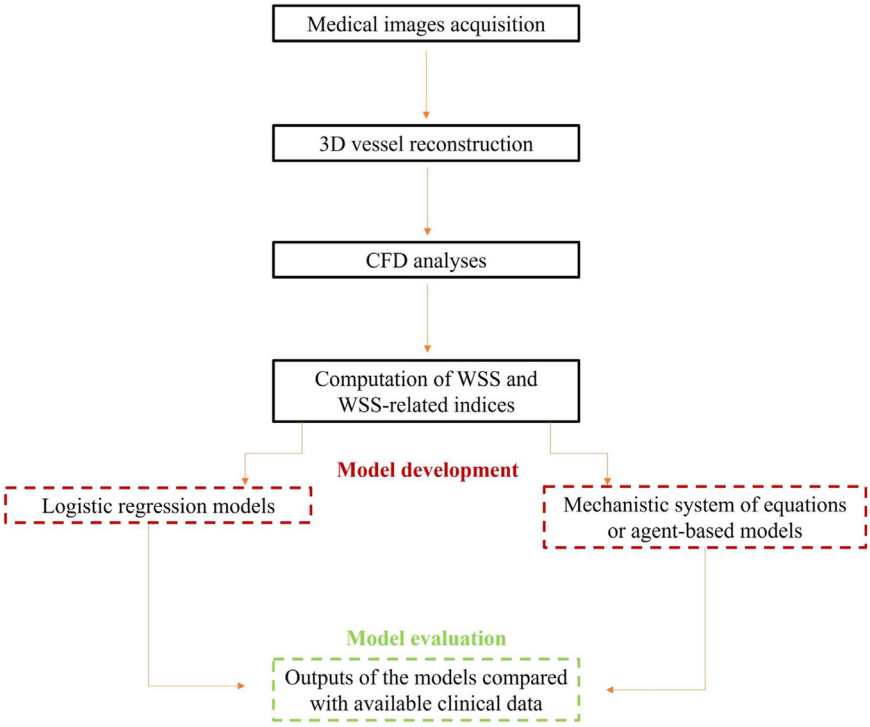

Fig 3. Computational pipeline followed by biomechanical engineering perspective studies to build predictive models for restenosis. *CFD*, Computational fluid dynamics; *WSS*, wall shear stress.

Güldener et al[49] introduced the use of a novel self-organizing-maps (SOMs)-based approach for restenosis predictors selection (Table V).

As for the biomechanical engineering studies, three types of prediction models have been developed (Fig 3): logistic regression, mechanistic, and models having a stochastic component (ie, agent-based models).

Studies adopting logistic regression models[17,51] (Table IV) consider different sets of restenosis predictors to test whether the introduction of hemodynamic indices result in enhanced predictive power and identify which variables contribute the most to restenosis. As reported in Table IV, Gőkgől et al[17] implemented three different multivariable logistic regression models: the first excluding all hemodynamic indices as predictors; the second, including only hemodynamic indices; and the third one, combining clinical, demographic, angiographic, and hemodynamics. Colombo et al[51] implemented two univariable logistic regression analyses as part of a study investigating the impact of local hemodynamics on restenosis in femoral arteries. These studies were set to investigate if stent length and age correlated with absence/presence of restenosis at 2-year follow-up. In addition, univariable and multivariable logistic regressions were also implemented, considering hemodynamic predictors only. A two-sided Fisher exact test (Table VII) was also conducted to assess whether stent overlapping correlated with the absence or presence of restenosis after 2 years from baseline.

Mechanistic and agent-based models simulate restenosis progression. Donadoni et al[50] developed a mechanistic model based on mathematical descriptions of the biological mechanisms leading to NIH growth. The four mechanisms triggering NIH progression, namely smooth muscle cell and collagen turnover, growth factors, and nitric oxide production, were described by ordinary differential equations and linked to computed WSS values. Corti et al[52] developed a framework coupling WSS computation with a 2D agent-based model (ABM) simulating cellular dynamics. This emulated cellular behavior and vessel remodeling based on WSS computation and systemic inflammatory response, triggered by the endovascular intervention. Both models[50,52] were intrinsically designed so that low values of WSS enhanced smooth muscle cells' proliferative and synthetic activity, responsible for vessel reocclusion due to NIH. The output of both models[82,84] was the 'altered' vessel geometry due to restenosis progression. Donadoni et al[50] returned a 3D geometry (ie, the new vessel coordinates in the 3D space), whereas Corti et al[52] returned the new lumen cross-sections on which the disease was simulated and from which the 3D geometry could be reconstructed.

Table V. Definitions of the technical terms related to clinical perspective predictive models development/training

Technical terms used for predictive models development/training
Bootstrapping: resampling of the available dataset. One patient's information is sampled with replacement (ie, randomly and allowing for its duplicate) from the selected dataset to obtain a new dataset (bootstrap sample) of the same dimensions as the original one. This might be performed multiple times, allowing the building of new prediction models for every bootstrap sample. Then, the model's performances on the bootstrap sample and on the original "learning" set are computed, together with the model's optimism (ie, the difference between the two performances). These steps are repeated for each bootstrap sample to obtain a stable averaged estimate of the optimism, which is later subtracted from the initial overly estimated performance
K-fold cross-validation: it consists of randomly splitting the dataset into k-equally sized parts: k-1 folds act as the "training" folds, whereas the remaining one is the "test" set. This is repeated so that every fold is used once for model evaluation and k-1 times for training
Logistic regression: statistical model modeling the probability of a dichotomous event taking place by having the logarithm of the odds (ratio of the number of events producing the outcome to the number that do not) for the event be a linear combination of one (*univariable*) or more (*multivariable*) independent variables (predictors). A reduced number of predictive variables can be selected automatically to build the best performing model (*stepwise logistic regression*) by adding (*forward stepwise logistic regression*) or removing (*backward stepwise logistic regression*) the most or least significant ones one after the other by imposing some criteria in terms of *P*-value (normally variable considered as a predictor when *P*-value $\leq$ .05)
Cox regression analysis: statistical model that produces a function predicting the probability that the event of interest (ie, restenosis) has occurred at a given time t for given values of the predictor variables
Least absolute shrinkage and selection operator (LASSO) regression analysis: regression analysis method that imposes a regression penalty on all variable coefficients, such that relatively unimportant ones are excluded from the model
Stepwise Akaike information criterion: criterion comparing the quality of a set of statistical models to each other for a given set of predictors. This allows ranking different models having different predictors from best to worst
Conditional permutation importance: measure of the decrease in a model score when a single predictor value is randomly shuffled. A drop in the model score is indicative of how much the model depends on that predictor
Mean decrease accuracy: measure of how much accuracy the model loses by excluding each variable. The higher the value, the higher the importance of the variable in the model
Mean decrease Gini: measure of how each variable contributes to the model. The higher the value, the higher the importance of the variable in the model
ML models adopted:
Random forest (RF): classification algorithm consisting of many decision trees built during the training. Each tree spits a class prediction and the class with the most votes becomes the model's prediction
Extremely randomized tree (ERT): similar to RF with the difference that the decision rule during tree construction is randomly selected
Gradient boosting (GB): prediction model in the form of an ensemble of weak prediction models, typically decision trees
Support vector machine (SVM): linear classification model. The algorithm can create a line or a hyperplane separating the data into classes
Gaussian process (GP): generalization of the Gaussian probability distribution which can be used as the basis for sophisticated non-parametric machine learning algorithms for classification
K-nearest neighbours (KNN): the algorithm estimates how likely a data is to be a member of one group or the other, depending on what group the data closest to it are in
L1- and L2- regularised logistic regression: logistic regression as explained above introducing regularisation terms to the equation to reduce overfitting
Non-regularised logistic regression: normal logistic regression as explained above
Multi-layer perceptron (MLP): deep, artificial neural network composed of an input layer receiving data, an output layer making the predictions and an arbitrary number of hidden layers in between capable to model the correlations between the inputs and the outputs
Self-organizing maps (SOMs): a specific application of ML techniques helping to understand relationships in complex data. This can be seen as a non-parametric regression technique that generates a non-linear representation of the data distribution and orders the considered lesions by the overall similarity of their attribute vector (ie measured parameters related to restenosis severity)

Models' performance evaluation. Prediction models' performance is normally evaluated regarding two key aspects: discrimination and calibration.[54]

Discrimination refers to the model's ability to distinguish between patients who will have restenosis and those who will not. Computing the area under (AUC) the ROC curve (also called "c-index") (Table VI) is a popular choice to do this.[53]

As for the clinical perspective, Table III shows that the values for the AUC ROC obtained with statistical-based models ranged from 0.61 to 0.706 in most studies,[1,33,36,38,40,45] showing modest model discrimination ability. However, a few statistical-based studies show high AUC ROC values,[35,39,41,42] up to 0.924. Nevertheless, this should be interpreted with caution, because these last set of models were tested using the same dataset used

Table VI. Technical terms used in the evaluation of clinical perspective predictive models

Technical terms used for predictive models evaluation
Evaluation in terms of discrimination:
Receiver operator characteristic (ROC) curve: plot of sensitivity (true positive (restenosis) rate of observations) against one minus specificity (false positive rate of observations) for different varieties of probability thresholds above which the observation (the patient) would be labelled as positive (presenting restenosis)
Area under (AUC) the ROC curve (also called "c-index"): area under the plot of sensitivity against one minus specificity for all possible cut-offs of probability thresholds. If AUC ROC = 1, the classifier is able to perfectly distinguish between all the positive and the negative (patients presenting and not presenting restenosis, respectively) class points correctly. If AUC ROC = 0.5 predictions are no better than chance, whereas AUC ROC between 0.5 and 1 shows some predictive ability
Precision-recall (PR) curve: plot of the precision (aka positive predictive value, ie fraction of positive predictions that actually belong to the positive (restenosis) class) against the recall (aka sensitivity) for a single classifier at a variety of thresholds, helping to visualize how the choice of thresholds affects classifier performance and select the best threshold for a specific problem
Area under (AUC) the PR curve: area under the plot of precision against the recall for a single classifier at a variety of thresholds. This is judged in the range of the value corresponding to a "baseline" classifier (determined by looking at the fraction of patients belonging to the positive class, ie patients presenting restenosis) and 1. A classifier that provides some predictive value falls between the "baseline" (meaning that predictions that are no better than chance) and the perfect classifier, having AUC PR = 1
Overlap index: overlap between the distributions of the probability of the outcome (ie restenosis) in patients belonging to the positive (ie presenting restenosis) and negative (ie patients not presenting restenosis) classes. An overlap equal to 1 means that the median predicted probability of the outcome is the same for those belonging to positive and negative classes (no discrimination). An overlap equal to 0 means no overlap in the predicted probability of the outcome between those belonging to the positive and negative class (perfect discrimination)
Evaluation in terms of calibration:
Calibration plots: linear regression of the plotted average predicted and observed positive (restenosis) rates of identified risk subgroups and comparison (in terms of statistically significant difference) with the linear line of an ideal model in which the observed probability exactly matches the predicted probability. *P*-values > .05 refer to strong concordance, whereas *P*-values < .05 account for poor concordance
Hosmer-Lemeshow goodness-of-fit test: test for logistic regression models telling how well the data fit the model, ie if the observed event rates match the predicted event rates in populations subgroups (patients presenting or not presenting restenosis). *P*-values > .05 refer to good fit, whereas *P*-values < .05 account for poor fit

for model development/training. Models' performance on an unseen dataset cannot be assessed.

Despite not being widely used in logistic regression models, an alternative measure for model discrimination is the overlap index (Table VI) between the predicted probability distributions of restenosis for patients with or without restenosis in the "test" set. The work of Weintraub et al[33] is the only one to use this index, reporting a value of 0.76, which confirms the model's modest discrimination power.

As for the ML-based models, their discrimination ability is evaluated on each "test" set of the k-fold cross-validation (Fig 2 and Table V). The results are then averaged for every "test" set to ascertain the performance on unseen data. This allows either selecting the best model[46] when developing them in parallel (as explained in the "*Models' development/training*" section) or combining all individual predictions by the various models into an "ensemble model."[47] The latter strategy can integrate predictions from two or more models, potentially reducing misclassification between patients presenting or not presenting with restenosis. Then, both the AUC ROC and the AUC under the precision-recall (PR) curve (see Table VI) are computed. The AUC PR value is more informative in classification problems involving unbalanced datasets.[55,56] In the work of Sampedro-Gómez et al,[46] the average value of AUC PR for the best classifier was 0.46, whereas in Pachl et al,[47] it ranged from 0.10 to 0.12 for the nine different ML models and the "ensemble model," showing a good predictive capacity in the first study, while only a modest predictive power in the second one. This was also confirmed by the AUC ROC values, equal to 0.77[46] and ranging from 0.58-0.62,[47] respectively.

The prediction results from ML models were also compared with some of state-of-the-art logistic regression models.[1,34] The results showed that the extremely randomized tree (ERT) model (Table V) developed by Sampedro-Gómez et al[46] outperformed the multivariable logistic regression models implemented by Singh et al[1] and Stolker et al,[34] both in terms of AUC ROC and PR. The "ensemble model" of Pachl et al,[47] performed better than the models from Singh et al[1] and Stolker et al.[34] The RF model developed by Jiang et al[48] showed larger AUC ROC and PR values with respect to a developed logistic regression model considering the same restenosis predictors. In contrast, Güldener et al[49] reported that the model developed using ML techniques did not improve the identification of patients at high risk of restenosis compared with a conventional multivariable logistic regression one.

As for calibration (also called "goodness of fit"), this is defined as finding a unique set of model parameters to provide an accurate restenosis prediction. This is usually

Table VII. Definition of the technical terms used in evaluating biomechanical engineering perspective predictive models

Technical terms used for biomechanical engineering perspective predictive models
Two-sided Fisher exact test: statistical test used when two categorical variables are present and it is necessary to find out if proportions for one categorical variable are different among values of the other one
Evaluation in terms of discrimination:
Tjur's pseudo R^2: difference between the mean predicted probability of the positive group (patients presenting restenosis) and the negative group (patients not presenting restenosis). It ranges from 0 to 1, where 1 corresponds to a model which absolutely separates patients presenting and not presenting restenosis
Evaluation in terms of calibration:
The McFadden pseudo R^2: metric providing the predictive strength of logistic regression models. It can range from 0 to 1, with values ranging from 0.2 and 0.4 to account for good model fit
Cessie-van Houwelingen-Copas-Hosmer unweighted sum of squares test: test for logistic regression models telling how well the data fit the model, ie if the observed event rates match the predicted event rates in populations subgroups (patients presenting or not presenting restenosis). *P*-values $> .05$ refer to good fit, whereas *P*-values $< .05$ account for poor fit

done by analyzing the discrepancy between the model predictions for restenosis and the actual occurrence rates. A significant difference between the two implies poor model calibration, potentially producing misleading predictions. Calibration for logistic regression models in clinical perspective studies was assessed using calibration plots[33,36,43,44] or Hosmer-Lemeshow goodness-of-fit test[1,34,35] (Table VI). As shown in Table III, all models evaluated in terms of calibration aspects showed *P*-values $> .05$, indicating a good fit.

Moving to biomechanical engineering studies, Gőkgől et al[17] evaluated their models' discrimination by: (1) performing paired *t*-tests between predicted values and medical data to access statistical significant differences between the two; (2) computing the prediction accuracy with leave-one-out analyses (ie, by testing the model on a held-out number of patients); and (3) computing AUC ROC. Calibration was assessed by computing the McFadden pseudo R^2 (see Table VII) and the Houwlingen-Copas-Hosmer unweighted sum of squares test (see Table VII). The model including only WSS-related indices showed promising results, which were further enhanced by adding the treatment method (ie, PTA alone or with Nitinol stent). Indeed, the multivariable logistic regression model including the treatment method and the WSS-related indices as predictors showed the strongest statistical significance, the highest accuracy, highest AUC ROC, and the best optimal fit to the model (Table IV). The one including only non-related-hemodynamic markers did not show any statistically significant difference between the patients presenting and not presenting restenosis, had a lower accuracy, lower AUC ROC, and a weaker predictive power.

In the work of Colombo et al,[51] the models were only evaluated in terms of discrimination using Tjur's pseudo R^2 (see Table VII). There was no explicit testing of the models on a held-out number of patients, but the variables contributing to restenosis were identified. More specifically, the univariate logistic regression model including only the stent length as a predictor was able to perfectly discriminate between patients having (or not) restenosis. The two-sided Fisher test also demonstrated the statistically significant association between stent overlapping and 2-year follow-up restenosis, meaning that both stent length and overlapping are good predictors of disease occurrence. In contrast, only the univariable logistic regression model using the total area of the vessel subjected to low time-adjusted WSS (TAWSS) (Table I) as a predictor, produced a nearly statistically significant correlation, suggesting that low TAWSS could be linked to restenosis development.

In studies,[50,57] model accuracy was evaluated by comparing the simulated results of reocclusion progression with actual medical images. In Donadoni et al,[50] the simulations were found to be able to capture the vessel restenosis shown in the medical images. In particular, CFD analyses showed that the better-performing hemodynamic index was HOLMES (Table I); all locations showing severe restenosis exhibited altered values of the HOLMES index compared with the baseline, suggesting that this hemodynamic index could be a stronger predictor of restenosis than other indices. In Corti et al,[52] the predicted lumen contours for a single patient matched those in medical images, although the local lumen geometric variability, especially in the proximal region of the stented portion, was not fully captured.

DISCUSSION

Clinical and biomechanical engineering models on restenosis prediction are relatively narrow, each type focused on only *part* of the evidence linked to restenosis development. Traditional statistical models—used in both clinical and biomechanical engineering approaches—rely on predictions performed with relatively easy-to-develop and interpretable models. These normally consider a limited number of predictors, selected by either traditional statistical methods or literature. However, these models are usually based on strong assumptions and exhibit *modest* predictive

power. In contrast, ML methods do not require a priori assumptions and can include all available variables as predictors, although this is achieved by somewhat sacrificing model interpretability. The drawback of such a promising approach is that ML models need large datasets for accurate predictions, which is a challenge given the lack of standardized data collection. Nevertheless, ML-based clinical perspective studies show *enhanced* predictive power compared with those using only traditional statistical models.

From a biomechanical engineering perspective, when patient-specific clinical, demographic, and angiographic information is combined with hemodynamics in traditional statistical models, the highest predictive performance is reported. However, the computation of hemodynamic variables/indices requires a great deal of expertise, is time-consuming, and is highly dependent on the quality of the imaging data and available BCs. Additionally, models simulating disease progression are computationally expensive and complex and difficult to calibrate and validate. Despite these challenges, an undeniably strong advantage is that their nature allows for interpretation of the underlying mechanisms of restenosis progression. That been said, they do not provide clinicians with a risk score for any given patient undergoing vessel reocclusion at a defined follow-up.

The holy grail would be to ideally fuse clinical and hemodynamic information in an ML-based model, running on high-quality and large datasets. Currently, predictive models do not consider all the retrievable information for the complex, multifactorial phenomenon that is restenosis, resulting in models with a modest ability to risk-stratify patients.

In a fast-developing landscape, prediction models for restenosis would coexist in a pipeline relying on artificial intelligence and data-driven approaches. In this scenario, 3D vessel reconstruction on large datasets would be automatically obtained,[58,59] and the blood flow and computation of the hemodynamic indices would be performed in real-time, with high accuracy,[60,61] by means of deep-learning (ie, a subset of artificial intelligence, more specifically of machine learning methods) and reduced order modeling methods.[62] These fast hemodynamic computations, combined with the daily retrieved clinical, demographic, and angiographic information, would then be the input of a ML-based risk prediction model able to stratify patients with PAD and CAD, targeting and tailoring surveillance programs.

CONCLUSIONS

In both clinical and biomechanical approaches, the resulting predictive power of models for restenosis is modest at best. The literature reveals that restenosis predictors are usually considered in silos—always sacrificing essential information contributing to what is undeniably a complex and multivariable phenomenon—resulting in models with limited predicted power.

A more holistic approach integrating hemodynamic indices and routinely collected variables into ML algorithms would offer a first step towards the development of innovative tools able to classify patients' risk of restenosis development in a defined time interval. This information will help clinicians predict treatment outcomes to better inform patients, enable the implementation of tailored surveillance programs, and create more efficient clinical workflows for both CAD and PAD.

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AUTHOR CONTRIBUTIONS

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Analysis and interpretation: FN, JT, SB, VDZ
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REFERENCES

1. Singh M, Gersh BJ, McClelland RL, et al. Clinical and angiographic predictors of restenosis after percutaneous coronary intervention: insights from the Prevention of Restenosis with Tranilast and its Outcomes (PRESTO) trial. Circulation 2004;109:2727-31.
2. Schillinger M, Minar E. Restenosis after percutaneous angioplasty: the role of vascular inflammation. Vasc Health Risk Manag 2005;1:73-8.
3. VanderLaan PA, Reardon CA, Getz GS. Site specificity of atherosclerosis: site-selective responses to atherosclerotic modulators. Arterioscler Thromb Vasc Biol 2004;24:12-22.
4. Poredoš P, Jug B. The prevalence of peripheral arterial disease in high risk subjects and coronary or cerebrovascular patients. Angiology 2007;58:309-15.
5. Wee I, Tan G, Ng S, et al. Endovascular versus open surgical endarterectomy for atherosclerotic lesions of the common femoral artery (CFA). Cochrane Database Syst Rev 2020:2020.
6. Mishall PL, Matakas JD, English K, et al. Axillobifemoral bypass: a brief surgical and historical review. Einstein J Biol Med 2016;31:6-10.
7. Bisdas T, Borowski M, Stavroulakis K, Torsello G; CRITISCH Collaborators. Endovascular therapy versus bypass surgery as first-line treatment strategies for critical limb ischemia: results of the interim analysis of the CRITISCH registry. JACC Cardiovasc Interv 2016;9:2557-65.
8. Nakashima T, Tahara Y. Achieving the earliest possible reperfusion in patients with acute coronary syndrome: a current overview. J Intensive Care 2018;6:20.

9. Jukema JW, Verschuren JJW, Ahmed TAN, Quax PHA. Restenosis after PCI. Part 1: pathophysiology and risk factors. Nat Rev Cardiol 2012;9:53-62.
10. Sherif M. Angioplasty and stenting for peripheral arterial disease of the lower limbs. E-J Cardiol Prac 2018;16.
11. Madanchi M, Cioffi GM, Attinger-Toller A, et al. Long-term outcomes after treatment of in-stent restenosis using the Absorb everolimus-eluting bioresorbable scaffold. Open Heart 2021;8:e001776.
12. Ota H, Takehara N, Aonuma T, et al. Association between microalbuminuria predicting in-stent restenosis after myocardial infarction and cellular senescence of endothelial progenitor cells. PLoS One 2015;10:e0123733.
13. Song HG, Kang SJ, Ahn JM, et al. Intravascular ultrasound assessment of optimal stent area to prevent in-stent restenosis after zotarolimus-, everolimus-, and sirolimus-eluting stent implantation. Catheter Cardiovasc Interv 2014;83:873-8.
14. Yang Y, Ge F, Shen J, et al. The relationship between neutrophil-lymphocyte ratio and in-stent restenosis in superficial femoral artery. Biosci Rep 2020;40:BSR20193448.
15. Buccheri D, Piraino D, Andolina G, Cortese B. Understanding and managing in-stent restenosis: a review of clinical data, from pathogenesis to treatment. J Thorac Dis 2016;8:E1150.
16. Pan T, Tian SY, Liu Z, et al. Relationship between neutrophil—lymphocyte ratio and drug-coated balloon restenosis in patients with femoropopliteal arterial disease. Angiology 2023;74:252-8.
17. Gökgöl C, Diehm N, Räber L, Büchler P. Prediction of restenosis based on hemodynamical markers in revascularized femoropopliteal arteries during leg flexion. Biomech Model Mechanobiol 2019;18:1883-93.
18. Reneman RS, Arts T, Hoeks APG. Wall shear stress–an important determinant of endothelial cell function and structure–in the arterial system in vivo. Discrepancies with theory. J Vasc Res 2006;43:251-69.
19. Malek AM, Alper SL, Izumo S. Hemodynamic shear stress and its role in atherosclerosis. J Am Med Assoc 1999;282:2035-42.
20. Gijsen F, Katagiri Y, Barlis P, et al. Expert recommendations on the assessment of wall shear stress in human coronary arteries: existing methodologies, technical considerations, and clinical applications. Eur Heart J 2019;40:3421-33.
21. Davies PF. Hemodynamic shear stress and the endothelium in cardiovascular pathophysiology. Nat Clin Pract Cardiovasc Med 2009;6:16-26.
22. Wang J, Jin X, Huang Y, et al. Endovascular stent-induced alterations in host artery mechanical environments and their roles in stent restenosis and late thrombosis. Regen Biomater 2018;5:177-87.
23. Nordgaard H, Swillens A, Nordhaug D, et al. Impact of competitive flow on wall shear stress in coronary surgery: computational fluid dynamics of a LIMA-LAD model. Cardiovasc Res 2010;88:512-9.
24. Dolan JM, Kolega J, Meng H. High wall shear stress and spatial gradients in vascular pathology: a review. Ann Biomed Eng 2013;41:1411-27.
25. Wood NB, Zhao SZ, Zambanini A, et al. Curvature and tortuosity of the superficial femoral artery: a possible risk factor for peripheral arterial disease. J Appl Physiol 2006;101:1412-8.
26. Kim YH, Kim JE, Ito Y, Shih AM, Brott B, Anayiotos A. Hemodynamic analysis of a compliant femoral artery bifurcation model using a fluid structure interaction framework. Ann Biomed Eng 2008;36:1753-63.
27. Friedman MH, Deters OJ, Mark FF, Bargeron C, Hutchins GM. Arterial geometry affects hemodynamics. A potential risk factor for atherosclerosis. Atherosclerosis 1983;46:225-31.
28. Romero-Farina G, Aguadé-Bruix S. Planning the follow-up of patients with stable chronic coronary artery disease. Diagnostics (Basel) 2021;11:1762.
29. Zubair A, Lotfollahzadeh S. Peripheral Arterial Duplex Assessment, Protocols, And Interpretation. StatPearls; 2022, . Accessed July 20, 2023.
30. Fiorella DJ, Levy EI, Turk AS, et al. Target lesion revascularization after wingspan: assessment of safety and durability. Stroke 2009;40:106-10.
31. Garcia-Garcia HM, McFadden EP, Farb A, et al. Standardized End Point Definitions for Coronary Intervention Trials: The Academic Research Consortium-2 Consensus Document. Circulation 2018;137:2635-50.
32. Whiting P, Savović J, Higgins JPT, et al; ROBIS group. ROBIS: A new tool to assess risk of bias in systematic reviews was developed. J Clin Epidemiol 2016;69:225-34.
33. Weintraub WS, Kosinski AS, Brown CL, King SB. Can restenosis after coronary angioplasty be predicted from clinical variables? J Am Coll Cardiol 1993;21:6-14.
34. Stolker JM, Kennedy KF, Lindsey JB, et al. Predicting restenosis of drug-eluting stents placed in real-world clinical practice: derivation and validation of a risk model from the EVENT registry. Circ Cardiovasc Interv 2010;3:327-34.
35. Gai MT, Zhu B, Chen XC, et al. A prediction model based on platelet parameters, lipid levels, and angiographic characteristics to predict in-stent restenosis in coronary artery disease patients implanted with drug-eluting stents. Lipids Health Dis 2021;20:118.
36. He W, Xu C, Wang X, et al. Development and validation of a risk prediction nomogram for in-stent restenosis in patients undergoing percutaneous coronary intervention. BMC Cardiovasc Disord 2021;21:435.
37. de Feyter PJ, Kay P, Disco C, Serruys PW. Reference chart derived from post-stent-implantation intravascular ultrasound predictors of 6-month expected restenosis on quantitative coronary angiography. Circulation 1999;100:1777-83, http://www.circulationaha.org.
38. Yeh RW, Normand SLT, Wolf RE, et al. Interventional cardiology predicting the restenosis benefit of drug-eluting versus bare metal stents in percutaneous coronary intervention. Circulation 2011;124:1557-64.
39. Luo Y, Tan N, Zhao J, Li Y. A nomogram for predicting in-stent restenosis risk in patients undergoing percutaneous coronary intervention: a population-based analysis. Ijgm 2022;15:2451-61.
40. Dai C, Yao Z, Chen Z, Qian J, Ge J. A simple model to predict repeat revascularization after drug-eluting stent implantation in patients with stable coronary artery disease. Angiology 2022;73:557-64.
41. Feng Q, Zhao Y, Wang H, Zhao J, Wang X, Shi J. A predictive model involving serum uric acid, C-reactive protein, diabetes, hypercholesteremia, multiple lesions for restenosis risk in everolimus-eluting stent-treated coronary heart disease patients. Front. Cardiovasc. Med 2022;9:857922.
42. Wu H, Yu T, Fan T, Liao W. Efficacy and prediction model construction of drug-coated balloon combined with cutting balloon angioplasty in the treatment of drug-eluting stent in-stent restenosis. Computational and Mathematical Methods in Medicine 2022;2022:1-8.
43. Chen J, Tang Y, Shen Z, et al. Predicting and analyzing restenosis risk after endovascular treatment in lower extremity arterial disease: development and assessment of a predictive nomogram. J Endovasc Ther 2023:15266028231158294.
44. Xi H, Liu J, Xu T, et al. Risk investigation of in-stent restenosis after initial implantation of intracoronary drug-eluting stent in patients with coronary heart disease. Front Cardiovasc Med 2023;10:1117915.
45. Coughlan JJ, Aytekin A, Lahu S, et al. Derivation and validation of the ISAR score to predict the risk of repeat percutaneous coronary intervention for recurrent drug-eluting stent restenosis. EuroIntervention 2023;18:e1328-38.
46. Sampedro-Gómez J, Dorado-Díaz PI, Vicente-Palacios V, et al. Machine learning to predict stent restenosis based on daily demographic, clinical, and angiographic characteristics. Can J Cardiol 2020;36:1624-32.
47. Pachl E, Zamanian A, Stieler M, Bahr C, Ahmidi N. Early-, Late-, and Very Late-Term Prediction of Target Lesion Failure in Coronary Artery Stent Patients: An International Multi-Site Study. Applied Sciences 2021;11:6986.
48. Jiang Z, Tian L, Liu W, et al. Random forest vs. logistic regression: predicting angiographic in-stent restenosis after second-generation drug-eluting stent implantation. PLoS One 2022;17:e0268757.
49. Güldener U, Kessler T, von Scheidt M, et al. Machine learning identifies new predictors on restenosis risk after coronary artery stenting in 10,004 patients with surveillance angiography. Jcm 2023;12:2941.
50. Donadoni F, Pichardo-Almarza C, Homer-Vanniasinkam S, Dardik A, Díaz-Zuccarini V. Multiscale, patient-specific computational fluid dynamics models predict formation of neointimal hyperplasia in saphenous vein grafts. J Vasc Surg Cases Innov Tech 2020;6:292-306.
51. Colombo M, He Y, Corti A, et al. Baseline local hemodynamics as predictor of lumen remodeling at 1-year follow-up in stented superficial femoral arteries. Sci Rep 2021;11:1613.

52. Corti A, Colombo M, Rozowsky JM, et al. A predictive multiscale model of in-stent restenosis in femoral arteries: linking haemodynamics and gene expression with an agent-based model of cellular dynamics. J R Soc Interface 2022;19:20210871.
53. Royston P, Altman DG. Visualizing and assessing discrimination in the logistic regression model. Stat Med 2010;29:2508-20.
54. Royston P, Moons KGM, Altman DG, Vergouwe Y. Prognosis and prognostic research: developing a prognostic model. BMJ 2009;338:b604.
55. Davis J, Goadrich M. In: . The relationship between precision-recall and ROC curves, Vol 148. ACM International Conference Proceeding Series; 2006.
56. Saito T, Rehmsmeier M. The precision-recall plot is more informative than the ROC plot when evaluating binary classifiers on imbalanced datasets. PLoS One 2015;10:e0118432.
57. Colombo M, Corti A, Luraghi G, Rodriguez JF. Femoral artery hemodynamics : state of the art of computational analyses and future trends 2019, https://re.public.polimi.it/handle/11311/1126154. Accessed October 17, 2019.
58. Hwang M, Hwang S bin, Yu H, et al. A simple method for automatic 3D reconstruction of coronary arteries from X-ray angiography. Front Physiol 2021;12:724216.
59. Gao Z, Wang L, Soroushmehr R, et al. Vessel segmentation for X-ray coronary angiography using ensemble methods with deep learning and filter-based features. BMC Med Imaging 2022;22:10.
60. Arzani A, Wang JX, D'Souza RM. Uncovering near-wall blood flow from sparse data with physics-informed neural networks. Phys Fluids 2021;33.
61. Arzani A, Dawson STM. Data-driven cardiovascular flow modelling: examples and opportunities. J R Soc Interface 2021;18:20200802.
62. Buoso S, Manzoni A, Alkadhi H, Plass A, Quarteroni A, Kurtcuoglu V. Reduced-order modeling of blood flow for noninvasive functional evaluation of coronary artery disease. Biomech Model Mechanobiol 2019;18:1867-81.

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