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%) 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.

Some of the high-susceptibility sites subjected to clinically significant atherosclerotic diseases are the coronary (coronary artery disease [CAD]) and the peripheral arteries (peripheral artery disease [PAD]). Preliminary, conservative treatment for CAD and PAD includes...
risk factor modification combined with antiplatelet, anti-thrombotic, and lipid-lowering medical therapy. 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 (i.e., saphenous vein, radial, and mammary arteries). Endovascular procedures are increasingly employed in revascularization strategies for either CAD or PAD because they are minimally invasive, require local or 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. 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 and CAD treatment, 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. This information is routinely collected and commonly grouped under three categories (Table I): patient-, lesion-, and procedure-related predictors.

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

| Demographic, clinical, and angiographic risk factors | 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 | Low TAWSS (<0.5 Pa) | TAWSS: WSS averaged over an entire cardiac cycle |
| deted (WSS-related indices) | 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 Pa¹) | 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, plateletcrit; 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.
Table II. Definitions of clinical endpoints investigated by the reviewed papers for the development of predictive models

<table>
<thead>
<tr>
<th>Different endpoints investigated by the reviewed studies</th>
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<tr>
<td>Restenosis: (1) recurrent diameter narrowing &gt;50% at the first site dilated, (2) loss of at least 50% of the gain in the diameter narrowing</td>
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<tr>
<td>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”)</td>
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<tr>
<td>Target lesion failure: defined as a composite multiple clinical endpoints such as cardiovascular death, target lesion revascularization, and target vessel myocardial infarction</td>
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vessel 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. 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 and between 1 and 2 Pa in the coronary arteries. 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 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. Stent implantation also reduces the compliance of the vascular segment, leading to a compliance mismatch with other parts of the blood vessel, 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.

In general, vessel locations undergoing revascularization exhibit disturbed flow and coincide with preferred sites for restenosis to develop. More specifically, in regions where WSS values are lower than 0.5 Pa, a proathero-genetic 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 and are considered geometric risk factors for vessel reocclusion over time (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. 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.”
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

<table>
<thead>
<tr>
<th>Reference Procedure</th>
<th>Dataset Aim of the study</th>
<th>Restenosis predictors selection</th>
<th>Predictive model</th>
<th>Model evaluation</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Traditional statistical models</strong></td>
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<tr>
<td>Weintraub et al (^{13}) (1993) Coronary arteries PCI alone (single lesion) 4006 patients from the clinical database at Emory University (single-center study)</td>
<td>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</td>
<td>Significant variables from the comparison between restenosis and no restenosis groups in the learning group used as restenosis predictors</td>
<td>Multivariable stepwise logistic regression model</td>
<td>AUC ROC = 0.62 Overlap index = 0.76 ( (P &lt; .0001) ) Correlation between average predicted and observed restenosis rates confirm the goodness-of-fit of the model</td>
<td>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</td>
</tr>
<tr>
<td>de Feyter et al (^{17}) (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)</td>
<td>Identify post-stent implantation IVUS predictors of stent restenosis to build a reference chart that predicts 6-months restenosis</td>
<td>Univariable logistic regression analysis</td>
<td>Multivariable logistic regression model</td>
<td>Hosmer-Lemeshow goodness-of-fit test ( (P = .42) )</td>
<td>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</td>
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Table III. Continued.

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<tr>
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<tr>
<td>Singh et al (2004)</td>
<td>Coronary arteries PCI alone (single lesion)</td>
<td>1224 patients enrolled in the angiographic substudy of the PRESTO trial (multi-center study)</td>
<td>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</td>
<td>First approach — Variables frequently reported in the literature to be strong predictors of restenosis</td>
<td>First approach — Multivariable logistic regression model</td>
<td>First approach — AUC ROC = 0.63 Hosmer-Lemeshow goodness-of-fit test (P = .18)</td>
<td>Second approach — Multivariable stepwise logistic regression model</td>
</tr>
<tr>
<td>Stolker et al (2010)</td>
<td>Coronary arteries PCI with DES (single/multiple lesion)</td>
<td>8829 patients from the EVENT registry (multi-center study) undergoing DES implantation</td>
<td>Develop a risk model for TLR and late TLR using demographic, clinical and patient-level angiographic data from the EVENT registry</td>
<td>Significant variables from univariable logistic regression analyses and variables frequently reported in the literature to be strong predictors of restenosis</td>
<td>Multivariable backward stepwise logistic regression model</td>
<td>Hosmer-Lemeshow goodness-of-fit test (P = .95)</td>
<td>Risk model incorporating 6 clinical and angiographic variables only identifies individuals at extremely low (&lt;2%) and modestly increased (&gt;7%) risk of TLR</td>
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<td><strong>Yeh et al. (2011)</strong></td>
<td>Coronary arteries PCI with DES or BMS (single/multiple lesion)</td>
<td>27,107 patients from Massachusetts Department of Public Health database (multi-center study)</td>
<td>Variables identified based on clinical relevance</td>
<td>Multivariable backward stepwise logistic regression model</td>
<td>First model – c-index = 0.62 Hosmer-Lemeshow goodness-of-fit test (P = .65)</td>
<td>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</td>
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<tr>
<td><strong>Gai et al. (2021)</strong></td>
<td>Coronary arteries PCI with DES (single/multiple lesion)</td>
<td>968 patients – not specified where data are retrieved but referred to the Xinjiang population</td>
<td>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 &gt;0.5)</td>
<td>Multivariable forward stepwise logistic regression model</td>
<td>AUC ROC = 0.72 (95% CI: 0.64-0.80) Hosmer-Lemeshow goodness-of-fit test (P = .655)</td>
<td>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</td>
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<tr>
<td><strong>He et al. (2021)</strong></td>
<td>Coronary arteries PCI with DES (single/multiple lesion)</td>
<td>463 patients from an observational cohort study in a high-volume PCI center in Henan Province, China (single-center study)</td>
<td>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</td>
<td>Multivariable logistic regression model</td>
<td>AUC ROC – validation set = 0.662 Calibration plots – concordance performance compared with an ideal model (P = .417)</td>
<td>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</td>
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<td>Luo et al. (2022)</td>
<td>Coronary arteries PCI with DES (single/multiple lesions)</td>
<td>477 patients from Enshi Central Hospital (single-center study)</td>
<td>Develop a new preoperative risk factor nomogram considering preoperative blood biochemical parameters for PCI, Gensini (GS) scores and procedural characteristics</td>
<td>LASSO regression analysis</td>
<td>Multivariable logistic regression model</td>
<td>AUC ROC = 0.841 Hosmer-Lemeshow goodness-of-fit test (P = .609) Calibration plots confirm no divergence between predicted and observed probability</td>
<td>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</td>
</tr>
<tr>
<td>Dai et al. (2022)</td>
<td>Coronary arteries PCI with DES (single/multiple lesions)</td>
<td>1653 patients from Zhongshan Hospital (single-center study)</td>
<td>Develop and validate an easy-to-use predictive model for repeat vascularization after DES implantation in patients with CAD</td>
<td>Significant variables (P &lt; .20) from univariable logistic regression analyses</td>
<td>Multivariable stepwise logistic regression model</td>
<td>c-index = 0.68 (95% CI: 0.619-0.740) Hosmer-Lemeshow goodness-of-fit test (P = .198)</td>
<td>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</td>
</tr>
<tr>
<td>Feng et al. (2022)</td>
<td>Coronary arteries PCI with 2nd generation DES (single/multiple lesions)</td>
<td>235 patients from Handan Central Hospital (single-center study)</td>
<td>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</td>
<td>Significant variables from univariable logistic regression analyses</td>
<td>Multivariable forward stepwise logistic regression model</td>
<td>AUC ROC = 0.863 (95% CI: 0.779-0.848)</td>
<td>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</td>
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<td>Wu et al (2022)</td>
<td>Coronary arteries PCI with DES (single/multiple lesions)</td>
<td>Construct a prediction model for in-stent restenosis when DESs are implanted</td>
<td>Significant variables from multivariable logistic regression analyses</td>
<td>Multivariable stepwise logistic regression model</td>
<td>AUC ROC = 0.924 (95% CI, 0.880-0.967) Hosmer-Lemeshow goodness-of-fit test (P=0.413)</td>
<td>The model has high predictive value for the occurrence of in-stent restenosis. It may be applied to the early prediction of this</td>
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<tr>
<td>Chen et al (2023)</td>
<td>Peripheral arteries PTA with DCB or BMS (single/multiple lesions)</td>
<td>Development and internal validation of nomograms for predicting restenosis after endovascular treatment of PAD</td>
<td>LASSO regression analysis to select restenosis predictors</td>
<td>Cox regression analysis</td>
<td>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</td>
<td>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</td>
</tr>
<tr>
<td>Xi et al (2023)</td>
<td>Coronary arteries PTA with DES (single/multiple lesions)</td>
<td>Establish a nomogram model to predict the risk of restenosis</td>
<td>LASSO regression analysis to select restenosis predictors</td>
<td>Multivariable logistic regression analysis</td>
<td>AUC ROC = 0.806 (95% CI, 0.739-0.873) Calibration plots – no significant deviation between the predicted probability and the actual probability</td>
<td>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</td>
</tr>
<tr>
<td>Coughlan et al (2023)</td>
<td>Coronary arteries PCI with DES (single/multiple lesions)</td>
<td>Development and validation of a model to predict repeat PCI for recurrent DES restenosis at 1-year follow-up</td>
<td>LASSO regression analysis to select restenosis predictors</td>
<td>Multivariable logistic regression analysis</td>
<td>c-index = 0.61</td>
<td>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</td>
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<td><strong>ML models</strong></td>
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<tr>
<td><strong>Sampedro-Gómez et al (2019)</strong></td>
<td>Coronary arteries PCI with DES or BMS (single/multiple lesion)</td>
<td>263 patients from (GRACIA)-3 trial (multi-center study) for patients undergoing ST-elevation acute myocardial infarction and consequent PCI</td>
<td>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</td>
<td>Two strategies pursued in parallel: 1) Selection based on ANOVA 2) Random forest (RF) classifier attributing scores to each predictor</td>
<td>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)</td>
<td>AUC PR (ERT) = 0.46 (95% CI, 0.29-0.63) AUC ROC (ERT) = 0.77 (95% CI, 0.66-0.89)</td>
</tr>
<tr>
<td><strong>Pachl et al (2021)</strong></td>
<td>Coronary arteries PCI with bioresorbable stent (single lesion)</td>
<td>1975 patients from post-market study Biotronik BIOSOLVE-IV to access clinical performance and long-term safety of the device (multi-center study)</td>
<td>Prediction of TLF after stent implantation using a novel ML approach and an international cohort</td>
<td>86 features used in the study regarding pre-intervention, intra-operation, lesion and stent, medications, discharge information, and follow-up</td>
<td>Application and combination in an &quot;ensemble model&quot; of nine different ML classifiers: ERTs, GB, GP, KNN, L1- and L2-logistic regression, MLP, RF and SVMs</td>
<td>AUC PR ranges from 0.10 and 0.12 for the different pipelines and the &quot;ensemble model&quot;. AUC ROC ranges from 0.58 and 0.62 for the different pipelines and the &quot;ensemble model&quot;</td>
</tr>
<tr>
<td><strong>Jiang et al (2022)</strong></td>
<td>Coronary arteries PCI with 2nd generation DES (single/multiple lesions)</td>
<td>1501 patients from Guizhou Provincial People’s Hospital (single-center study)</td>
<td>Test that RF model has better performance than logistic regression model in restenosis prediction due to higher robustness</td>
<td>Stepwise logistic regression model — Stepwise Akaike information criterion RF model — Conditional permutation importance, mean decrease accuracy, mean decrease Gini</td>
<td>1) Multivariable stepwise logistic regression model 2) RF model</td>
<td>RF model has larger AUC ROC and PR than logistic regression model</td>
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</tbody>
</table>
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.66 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.67 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’.68,39,41,42

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 enhancing model reliability.

In ML approaches, the split into “training” and “test” sets is performed by k-fold cross-validation66–69 (Table V). This process can be replicated multiple times66,48 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 angiography17 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

<table>
<thead>
<tr>
<th>Reference</th>
<th>Dataset</th>
<th>Aim of the study</th>
<th>Predictive model</th>
<th>Restenosis predictors</th>
<th>Model evaluation</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gökgöl et al (2019)</td>
<td>Peripheral arteries (Femoral-popliteal artery)</td>
<td>Test if patient-specific CFD simulations performed on femoral-popliteal arteries can provide hemodynamic markers that are able to predict the risk of restenosis in 6-months time</td>
<td>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</td>
<td>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.</td>
<td>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 R² to compare the predictive strength between models.</td>
<td>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 = 0.02). If treatment method is included, the difference between the two groups becomes strongly statistically significant (P = 0.002) and the goodness of fit increases (from 0.29 to 0.38).</td>
</tr>
<tr>
<td>Donadoni et al (2020)</td>
<td>Peripheral arteries (Femoral-popliteal artery)</td>
<td>Simulation of NIH progression using a multiscale computational framework and comparison of results with a patient-specific clinical dataset</td>
<td>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</td>
<td>Low TAWSS, high OSI and HOLMES indices</td>
<td>Analysis of cross-sectional areas of the lumen where restenosis is most severe and comparison with the available CT scans</td>
<td>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).</td>
</tr>
<tr>
<td>Colombo et al (2021)</td>
<td>Peripheral arteries (Superficial femoral artery)</td>
<td>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</td>
<td>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</td>
<td>Low TAWSS (below 33rd 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.</td>
<td>Tjur’s pseudo R² to indicate the ability of the model to clearly separate between success-failure groups.</td>
<td>No significant relationship between patients' age and treatment failure at 2-years follow-up. Stent length and stent overlapping are predictors of restenosis.</td>
</tr>
</tbody>
</table>
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 abilities 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., 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.

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 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 or frequently reported in the literature as restenosis markers. In some others, variables that resulted as significantly different between the patients’ groups (Table V), a score

**Table IV.** Continued.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Revascularization procedure</th>
<th>Dataset</th>
<th>Aim of the study</th>
<th>Predictive model</th>
<th>Restenosis predictors</th>
<th>Model evaluation</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corti et al (2022)</td>
<td>Peripheral arteries (Superficial femoral artery)</td>
<td>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</td>
<td>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</td>
<td>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</td>
<td>Low WSS, systemic inflammatory response</td>
<td>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</td>
<td>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 &lt; .05). Model not fully able to capture local lumen geometrical variability (especially at stented portion proximal region)</td>
</tr>
</tbody>
</table>

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.
for each predictor was assigned, signifying its contribution towards restenosis occurrence. Pachl et al. did not explicitly mention any feature selection strategy, implying that all identified variables were employed in their model development. Jiang et al. 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.
Güldener et al. 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 (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, Gökgöl et al. 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. 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. 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. 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 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 was the ‘altered’ vessel geometry due to restenosis progression. Donadoni et al. returned a 3D geometry (ie, the new vessel coordinates in the 3D space), whereas Corti et al. 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

<table>
<thead>
<tr>
<th>Technical terms used for predictive models development/training</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bootstrapping</strong>: 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.</td>
</tr>
<tr>
<td><strong>K-fold cross-validation</strong>: 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.</td>
</tr>
<tr>
<td><strong>Logistic regression</strong>: 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 ≤ .05).</td>
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<tr>
<td><strong>Cox regression analysis</strong>: 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.</td>
</tr>
<tr>
<td><strong>Least absolute shrinkage and selection operator (LASSO) regression analysis</strong>: regression analysis method that imposes a regression penalty on all variable coefficients, such that relatively unimportant ones are excluded from the model.</td>
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<tr>
<td><strong>Stepwise Akaike information criterion</strong>: 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.</td>
</tr>
<tr>
<td><strong>Conditional permutation importance</strong>: 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.</td>
</tr>
<tr>
<td><strong>Mean decrease accuracy</strong>: 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.</td>
</tr>
<tr>
<td><strong>Mean decrease Gini</strong>: measure of how each variable contributes to the model. The higher the value, the higher the importance of the variable in the model.</td>
</tr>
<tr>
<td><strong>ML models adopted</strong>:</td>
</tr>
<tr>
<td><strong>Random forest (RF)</strong>: classification algorithm consisting of many decision trees built during the training. Each tree splits a class prediction and the class with the most votes becomes the model’s prediction.</td>
</tr>
<tr>
<td><strong>Extremely randomized tree (ERT)</strong>: similar to RF with the difference that the decision rule during tree construction is randomly selected.</td>
</tr>
<tr>
<td><strong>Gradient boosting (GB)</strong>: prediction model in the form of an ensemble of weak prediction models, typically decision trees.</td>
</tr>
<tr>
<td><strong>Support vector machine (SVM)</strong>: linear classification model. The algorithm can create a line or a hyperplane separating the data into classes.</td>
</tr>
<tr>
<td><strong>Gaussian process (GP)</strong>: generalization of the Gaussian probability distribution which can be used as the basis for sophisticated non-parametric machine learning algorithms for classification.</td>
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<tr>
<td><strong>K-nearest neighbours (KNN)</strong>: 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.</td>
</tr>
<tr>
<td><strong>L1- and L2- regularised logistic regression</strong>: logistic regression as explained above introducing regularisation terms to the equation to reduce overfitting.</td>
</tr>
<tr>
<td><strong>Non-regularised logistic regression</strong>: normal logistic regression as explained above.</td>
</tr>
<tr>
<td><strong>Multi-layer perceptron (MLP)</strong>: 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.</td>
</tr>
<tr>
<td><strong>Self-organizing maps (SOMs)</strong>: 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).</td>
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</table>

Models’ performance evaluation. Prediction models’ performance is normally evaluated regarding two key aspects: discrimination and calibration. 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. 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, showing modest model discrimination ability. However, a few statistical-based studies show high AUC ROC values, 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 predictive models

<table>
<thead>
<tr>
<th>Technical terms used for predictive models evaluation</th>
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<tbody>
<tr>
<td><strong>Evaluation in terms of discrimination:</strong></td>
</tr>
<tr>
<td>Receiver operator characteristic (ROC) curve:</td>
</tr>
<tr>
<td>Area under (AUC) the ROC curve (also called &quot;c-index&quot;):</td>
</tr>
<tr>
<td>Precision-recall (PR) curve:</td>
</tr>
<tr>
<td>Area under (AUC) the PR curve:</td>
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<tr>
<td>Overlap index:</td>
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<tr>
<td><strong>Evaluation in terms of calibration:</strong></td>
</tr>
<tr>
<td>Calibration plots:</td>
</tr>
<tr>
<td>Hosmer-Lemeshow goodness-of-fit test:</td>
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</tbody>
</table>

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 al33 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 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.” 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 0.7746 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.134 The results showed that the extremely randomized tree (ERT) model (Table V) developed by Sampedro-Gómez et al46 outperformed the multivariable logistic regression models implemented by Singh et al1 and Stolker et al,34 both in terms of AUC ROC and PR. The “ensemble model” of Pachl et al47 performed better than the models from Singh et al1 and Stolker et al.34 The RF model developed by Jiang et al48 showed larger AUC ROC and PR values with respect to a developed logistic regression model considering the same restenosis predictors. In contrast, Güldener et al49 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

<table>
<thead>
<tr>
<th>Technical terms used for biomechanical engineering perspective predictive models</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Two-sided Fisher exact test:</strong> 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</td>
</tr>
<tr>
<td><strong>Evaluation in terms of discrimination:</strong></td>
</tr>
<tr>
<td>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</td>
</tr>
<tr>
<td><strong>Evaluation in terms of calibration:</strong></td>
</tr>
<tr>
<td>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</td>
</tr>
<tr>
<td>Cessie-van Houwelingen-Copas-Hosmer unweighted sum of squares test: test for logistic regression models telling how well the data fit the model, i.e., if the observed event rates match the predicted event rates in populations subgroups (patients presenting or not presenting restenosis). $P$-values $&gt; .05$ refer to good fit, whereas $P$-values $&lt; .05$ account for poor fit</td>
</tr>
</tbody>
</table>

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 or Hosmer-Lemeshow goodness-of-fit test (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, Gökgöl et al 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 (i.e., 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 (i.e., 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., 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, model accuracy was evaluated by comparing the simulated results of reocclusion progression with actual medical images. In Donadoni et al., 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., 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 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,\(^\text{58,59}\) and the blood flow and computation of the hemodynamic indices would be performed in real-time, with high accuracy.\(^\text{50,61}\) by means of deep-learning (ie, a subset of artificial intelligence, more specifically of machine learning methods) and reduced order modeling methods.\(^\text{62}\) 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 isundeniably 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**

Conception and design: FN
Analysis and interpretation: FN, JT, SB, VDZ
Data collection: Not applicable
Writing the article: FN
Critical revision of the article: FN, JT, SB, VDZ
Final approval of the article: FN, JT, SB, VDZ
Statistical analysis: Not applicable
Obtained funding: Not applicable
Overall responsibility: VDZ

**DISCLOSURES**

None.

**REFERENCES**


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