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NARRATIVE REVIEW

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Machine learning in cardiovascular risk assessment: Towards a precision medicine approach

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Abstract

Cardiovascular diseases remain the leading cause of global morbidity and mortality. Validated risk scores are the basis of guideline-recommended care, but most scores lack the capacity to integrate complex and multidimensional data. Limitations inherent to traditional risk prediction models and the growing burden of residual cardiovascular risk highlight the need for refined strategies that go beyond conventional paradigms. Artificial intelligence and machine learning (ML) provide unique opportunities to refine cardiovascular risk assessment and surveillance through the integration of diverse data types and sources, including clinical, electrocardiographic, imaging and multi-omics derived data. In fact, ML models, such as deep neural networks, can handle high-dimensional data

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through which phenotyping and cardiovascular risk assessment across diverse patient populations become much more precise, fostering a paradigm shift towards more personalized care. Here, we review the role of ML in advancing cardiovascular risk assessment and discuss its potential to identify novel therapeutic targets and to improve prevention strategies. We also discuss key challenges inherent to ML, such as data quality, standardized reporting, model transparency and validation, and discuss barriers in its clinical translation. We highlight the transformative potential of ML in precision cardiology and advocate for more personalized cardiovascular prevention strategies that go beyond previous notions.

KEYWORDS

artificial intelligence, biomarkers, cardiovascular disease, inflammation, machine learning, omics, precision medicine, residual risk, risk prediction

1 | INTRODUCTION

Cardiovascular diseases (CVDs) caused an estimated 17.9 million deaths, equal to one-third of all fatal events worldwide.[1] Traditional cardiovascular risk prediction models, such as the Framingham, SCORE-2/OP, ASCVD, GRACE 2.0 and CHA_2DS_2-VA scores, rely on unidimensional predictors, perform well in certain populations but are limited in integrating complex, multidimensional data—a necessity to capture the intricacy of overall cardiovascular risk. In an era of improved risk factor control, residual cardiovascular risk (RR) emerges as an important player in the prevention of major adverse cardiovascular events (MACE).[2] For instance, contemporary randomized controlled trials (RCTs) have made remarkable inroads into anti-inflammatory strategies targeting NLRP3-related pathways,[3–5] with low-dose colchicine now entering the clinical arena[6–8] and interleukin antibodies being tested in phase III studies.[9]

Although several approaches for the control of single cardiovascular risk factors exist, actionable tools to significantly reduce RR remain an unmet medical need. Indeed, the inter-individual variability of RR is considerable,[10] to which multiple interrelated factors contribute. Several traditional risk stratification tools for the improvement of secondary prevention exist, including but not limited to the SMART risk score, which estimates 10-year RR in patients with stable atherosclerotic cardiovascular disease (ASCVD),[10] and the EUROASPIRE model, providing a 2-year risk estimate for recurrent events in atherosclerotic patients.[11]

Artificial intelligence (AI) is superior in processing large-scale datasets and is expected to transform cardiovascular research and patient care at large. The relationship between AI, machine learning (ML) and deep learning (DL) is like Russian nesting dolls (Graphical Abstract), with each concept being contained within the next. AI represents the broadest level, enabling decision-making and pattern recognition. ML, a subset of AI, involves algorithms that can learn from data, allowing algorithms to make predictions or classifications without explicit programming with increasing precision over time. Within ML, DL is a specialized field that leverages multi-layered (by definition, exceeding three layers) neural networks, ideally suited to process complex data like image and language recognition. In its core, neural networks consist of interconnected nodes mimicking brain neuron activity, enabling these models to capture intricate data patterns and relationships.[12] As compared to traditional models, ML-based approaches can process multidimensional data, thereby providing a more adaptable and comprehensive framework for personalized risk assessment. Here, we synthesize ML applications in cardiovascular risk assessment and discuss their potential to reduce overall RR.

2 | ML IN CARDIOVASCULAR RISK ASSESSMENT

The integration of ML with clinical, electrocardiographic (ECG), imaging and multi-omics data enhances cardiovascular risk prediction, facilitating tailored clinical decision-making (Figure 1).

2.1 | ML for ECG interpretation

By harnessing DL models, specifically deep neural networks (DNNs) and convolutional neural networks (CNNs) on ECG data, the detection of arrhythmias and the screening for structural heart diseases can be facilitated. For instance, Hannun et al. developed a DNN

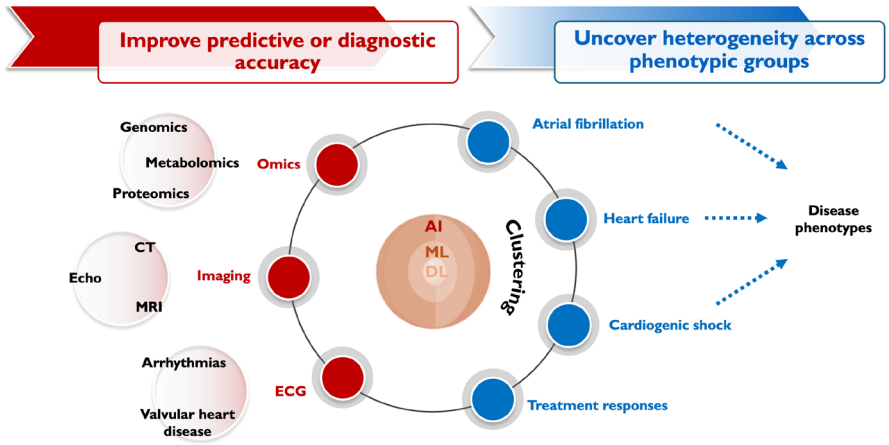

FIGURE 1 Leveraging machine learning on multimodal data can enhance cardiovascular risk prediction and phenotyping. Machine learning, integrating electrocardiogram (ECG), imaging- (such as cardiac MRI, CT and echocardiography) and multi-omics data, may improve the accuracy of cardiovascular disease risk prediction (left panel). Clustering analysis may also uncover distinct phenotypes in heterogeneous cardiovascular diseases (such as heart failure, atrial fibrillation and cardiogenic shock), facilitating the identification of patient subgroups and personalizing cardiovascular care (right panel).

that classifies 12 ECG rhythm classes, achieving an area under the curve (AUC) of .97 and an F1 score of .84, far outperforming cardiologists' average performance.[13] Another CNN model trained on 180,112 ECGs achieved a diagnostic accuracy of 80% for arrhythmias on a test set of 828 ECGs, superseding physicians with an accuracy ranging from 67% to 75%.[14] Attia et al. used a CNN model to detect atrial fibrillation (AF) during normal sinus rhythm, achieving an AUC of .87 and an accuracy of 79.4%, again outperforming Holter monitoring and manual ECG interpretation.[15] The integration of ML for ECG interpretation is now being practically applied in clinical settings. This is exemplified by PMcardio, a smartphone app that leverages AI to analyse 12-lead ECGs, demonstrating 86% sensitivity and 92% specificity for detecting major abnormalities, and 97% sensitivity with 99% specificity for AF across both Android and iOS platforms.[16]

Beyond arrhythmia detection, a recently developed CNN model shows promise to identify moderate-to-severe aortic stenosis on ECG, achieving an AUC of .85, indicating a potential utility for aortic stenosis screening.[17] Similarly, Elias P et al. introduced *ValveNet*, a novel CNN model, to detect aortic stenosis, aortic regurgitation and mitral regurgitation based on deep learning analysis of ECGs, with AUCs of .88, .77 and .83, respectively.[18] Another CNN model trained on paired ECG and transthoracic echocardiogram data identified asymptomatic left ventricular dysfunction with an AUC of .93, with those having a positive screening result being at a 4-fold increased risk of future dysfunction, demonstrating DL's potential to enhance ECG as a cost-effective screening tool for asymptomatic left ventricular dysfunction.[19]

2.2 | ML in cardiac imaging

DL models for magnetic resonance imaging (MRI), echocardiography and CT-derived data interpretation have consistently matched or even surpassed expert skills (Table 1). For instance, Wang YRJ et al. utilized video-based DL on cardiac MRI for anomaly and CVD detection. Using a dataset of 8,066 patients and 1,653 healthy individuals, their models achieved AUCs of .988 and .991, superseding cardiologists' performance.[20] Similarly, a CNN demonstrated comparable diagnostic accuracy to cardiologists, achieving an AUC of .90 for regional wall motion abnormality identification in conventional 2D echocardiography.[21] Beyond 2D data, a novel 3D-based CNN identifies left ventricular wall motion abnormalities with a Dice coefficient (a measure of the similarity between the computer's segmented regions and the actual regions) of .756 and an AUC of .891 across 1,756 exams.[22] Hence, DNNs can automate peak velocity measurement in mitral Doppler inflow in 2D echocardiography, with performance comparable to human experts.

Coronary computed tomography angiography (CCTA) is likely to become the future gatekeeper for coronary interventions, thereby guiding patient referral for invasive procedures. In this regard, a DL-based coronary artery calcium (CAC) scoring system has demonstrated expert-level accuracy in predicting cardiovascular risk,[32] with calcification >400 Agatston units—especially in the left-main or anterior descending coronary artery—being strongly linked to increased cardiovascular risk.[33] Similarly, a recently published DL-based model enables fully automated quantification of CAC using ECG-gated noncontrast cardiac computed tomography (gated CCT) images. This

TABLE 1 Integration of multi-omics and imaging data with machine learning in cardiovascular risk prediction.

Domain	Predictors	Data type	ML algorithms	Population	Endpoint	Clinical application	Ref
Genomics	72 significant genetic loci linked to LVRWT traits	GWAS	DL	Participants from UK Biobank	HCM	Identifying high-risk individuals for HCM based on LVRWT and genetic markers	23
Proteomics	Two complementary protein signatures	Proteomics data	Gradient Boosting Classifier	Patients with suspected CAD	Presence of high-risk plaques or absence of CAD	Predicting presence of high-risk plaque or absence of coronary atherosclerosis	24
Metabolomics	13 differential metabolites (e.g. arginine, proline and glutathione)	Metabolomics data	SVM, RF, KNN, Logistic Regression	Plasma samples from patients with metabolic syndrome and healthy controls.	Metabolic syndrome	Predictive diagnosis and targeted prevention of metabolic syndrome	25
	Plasma miRNAs, plasma catechol O-methylated metabolites, plasma steroids, urinary steroid metabolites, plasma small metabolites	Multi-omics (plasma and urine)	Decision Trees, Naive Bayes, K-nearest neighbours, LogitBoost, Logistic Model Tree, Simple Logistic, Random Forest, Sequential Minimal Optimisation	Hypertensive patients	Identification of subtypes of secondary hypertension (PA, PPGL, Cushing's Syndrome) versus PHT	Diagnostic and stratification tool for secondary hypertension.	26
Imaging data	EAT volume and attenuation	Noncontrast cardiac computed tomography	DL	Asymptomatic subjects	MACE (MI, late [>180 days] revascularization and cardiac death)	Prognostic assessment for MACE risk prediction in asymptomatic patients	27
	Epicardial adipose volume	CCTA	DNN	1. ORFAN study: patients undergoing CCTA 2. AdipoRedOx study: cardiac surgery patients; 3. SCOT-HEART trial: patients with suspected angina	All-cause mortality, myocardial infarction, stroke, in-hospital and post-surgery atrial fibrillation	Cardiovascular risk stratification	28
	Perivascular fat attenuation index, fat radiomic profile and radiomic texture features (e.g. wavelet-transformed mean attenuation)	CCTA	RF	1. Study 1: Patients who underwent cardiac surgery 2. Study 2: Patients with major adverse cardiac events (MACE) and matched controls 3. Study 3: Acute myocardial infarction (MI) patients and matched controls	MACE (cardiac mortality and nonfatal MI)	Improving cardiac risk prediction beyond traditional methods; identifies persistent PVAT changes linked to CAD.	29
	7 Radiomics features (including similarity of dependence, randomness in the distribution of zone sizes and grey levels, 90th percentile CT values of ROI, variability of size zone volumes, joint distribution of small dependence with higher grey-level values, local intensity variation, and variance in dependence size)	CCTA	XGboost	Patients with coronary lesions	Rapid plaque progression	Predicting and identifying rapid plaque progression in coronary arteries	30
	Lumen area, plaque area, EEM area, stent diameter, stent length, inflation pressure, balloon diameter and maximal balloon pressure	IVUS	CNN, XGBoost	Patients with coronary lesions	Post-stenting stent area; binary classification for stent underexpansion (stent area $<5.5\,mm^2$)	Assists clinicians in pre-procedural planning to predict and avoid stent underexpansion as a preventable cause of stent failure	31

Abbreviations: CAD, coronary artery disease; CCTA, coronary computed tomography angiography; CNN, convolutional neural network; DL, deep learning; DNN, deep neural network; EAT, epicardial adipose tissue; EEM, external elastic membrane; GWAS, genome-wide association studies; HCM, hypertrophic cardiomyopathy; IVUS, intravascular ultrasound; KNN, K-nearest neighbours; LVRWT, left ventricular regional wall thickness; MACE, major adverse cardiovascular events; MI, myocardial infarction; ORFAN, The Oxford Risk Factors And Non-invasive Imaging Study; PA, primary aldosteronism; PHT, primary hypertension; PPGL, pheochromocytoma and paraganglioma; PVAT, perivascular adipose tissue; RF, random forest; ROI, region of interest; SVM, support vector machine; XGBoost, extreme gradient boosting.

model, trained on 560 gated CCT images, showed high accuracy in total and vessel-specific CAC score classification, surpassing previous techniques with Cohen's kappa values of .95 for testing and .89 for validation.[34] Beyond CAC scoring, a CNN model has been used to quantify atherosclerotic plaque volumes from CCTA images, with plaque volumes ≥238.5 mm^3 being linked to a 5.4-fold myocardial infarction risk.[35] Going forward, ML-based models for CAC scoring and the simultaneous assessment of quantitative and qualitative plaque characteristics have the potential to improve the identification of high-risk patients and thus guide the need for invasive procedures, thus optimizing workflows and reducing unnecessary interventions.

ML, combined with various cardiovascular imaging techniques, has significantly enhanced cardiovascular risk assessment and the prediction of MACE. DL models quantified epicardial adipose tissue (EAT) volume and attenuation, revealing increased EAT volume and decreased attenuation independently associated with MACE.[27] Another deep learning model for EAT segmentation from CCTA predicted mortality and postoperative AF, underscoring EAT as a biomarker for visceral obesity and cardiovascular risk.[28] Additionally, Oikonomou et al. applied random forest to develop a perivascular adipose tissue radiomic profile, the so-called fat attenuation index (FAI), analysing 1,391 features and achieving a C-statistic of .77, which enhanced MACE prediction beyond traditional risk stratification methods.[29] Moreover, a CCTA-based radiomics score identified plaques at risk for rapid progression using seven radiomic features, independently predicting rapid plaque progression and outperforming conventional plaque parameters.[30] Similarly, a study utilizing dual-energy computed tomography (DECT) radiomics for pulmonary embolism (PE) severity classification showed that ML models could accurately stratify patients using 107 radiomic features, achieving 90% classification accuracy for high-risk PE patients.[36] Hence, AI, by integrating radiomics, significantly enhances clinical decision-making, improving risk stratification and enabling personalized interventions in the management of cardiovascular diseases, pulmonary embolism, and venous thromboembolism (VTE).[37]

2.3 | ML and its integration with multi-omics data

The integration of ML with multi-omics data holds transformative potential for CVD prediction (Table 1). For instance, *DLANet*, a DL model applied to genome-wide association studies (GWAS) data from 42,194 participants in the UK Biobank undergoing cardiac MRI, successfully identified 72 genetic loci linked to left ventricular regional wall thickness phenotypes, crucial markers for hypertrophic cardiomyopathy and signifying individuals at high risk.[23] Moreover, *NeuralCVD* adeptly integrates polygenic and clinical data to predict a 10-year risk of MACE, demonstrating superior performance over traditional models like QRISK3 and linear Cox regression, especially for low-to-intermediate risk patients.[38]

Similarly, the lipidomic-enhanced risk score, developed through a ML workflow, improves risk stratification by enhancing discrimination and reclassification in intermediate-risk individuals in which traditional tools like the Framingham Risk Score (FRS) fall short.[39] Reel PS et al. utilized ML algorithms to classify subtypes of secondary hypertension by analysing 409 plasma- and urine-borne biomarkers. Their random forest classifier achieved a 92% accuracy and 96% specificity, outperforming traditional methods and providing better classification performance across different subtypes of secondary hypertension.[26] Wang H et al. utilized multiple ML algorithms to analyse metabolomics data. These analyses yielded 13 metabolites linked to metabolic syndrome, revealing disruptions in pathways such as arginine, proline and glutathione metabolism.[25]

ML has also revolutionized the landscape of cardiovascular diagnosis. The Collaboration for the Diagnosis and Evaluation of Acute Coronary Syndrome (CoDE-ACS) model utilizes serial cardiac troponin measurements and clinical data, thereby identifying 56% of patients as low risk for myocardial infarction at initial presentation, achieving a 99.7% negative predictive value, partly outperforming the European Society of Cardiology (ESC) and High-STEACS pathways, identifying more patients for safe discharge than guideline-based methods while minimizing observation times.[40] Matthias Unterhuber et al. developed eXtreme Gradient Boosting (XGBoost) and a neural network-based model to predict all-cause mortality in cardiovascular patients by analyzing 92 proteins, with both models achieving a higher AUC than FRS.[41] Rajat Deo et al. developed a proteomics-based model to predict incident cardiovascular events in chronic kidney disease patients, achieving AUCs of .84–.89, compared to .70–.73 for the ACC/AHA Pooled Cohort Equation.[42]

2.4 | ML-driven phenotypic classification

Clustering, a key unsupervised learning technique, organizes data into similar groups, revealing hidden patterns. Methods like K-means, hierarchical clustering, and

DBSCAN assess similarity differently to uncover natural groupings.[43] Clustering is crucial in phenotypic classification, enabling clinicians to identify patients with distinct characteristics and varying treatment responses.

A Japanese study using hierarchical cluster analysis on 4304 AF patients identified six clusters with different mortality and adverse event outcomes, underscoring the need for tailored management strategies for the very elderly group.[44] Similarly, a study from a European multicenter observational registry identified three AF phenotypic groups, each associated with distinctly different healthcare resource utilization and MACE risk.[45] Compared to Europe, Japan faces a more pronounced aging population issue, making the 'very elderly' cluster distinctive in their cohort, which aligns with their greater emphasis on managing very elderly AF patients.

Cardiogenic shock (CS) is a highly heterogeneous syndrome with variations in aetiology, clinical presentation and lab parameters. This heterogeneity complicates diagnosis and treatment and is a major challenge for clinical trial design.[46,47] Elric Zweck et al. analysed data from 1,959 CS patients using the consensus k-means clustering, identifying three phenotypes—noncongested, cardiorenal, and cardiometabolic, with the cardiometabolic group having the highest in-hospital mortality.[48] These findings were further validated in an additional cohort of 1,890 CS patients.[49] Heterogeneity also exists in heart failure (HF), particularly in HF with preserved ejection fraction (HFpEF), possibly explaining the poor results of clinical trials of pharmacologic agents in HFpEF.[50,51,52] Sanjiv J. Shah et al. utilized hierarchical clustering on 397 HFpEF patients, identifying three distinct pheno-groups with varied characteristics and outcomes, and a particularly high hospitalization risk in older patients with chronic kidney disease and right ventricular dysfunction.[53] Additionally, Lancaster M et al. employed hierarchical clustering to identify two phenotypes of diastolic dysfunction in patients with HFpEF. Their clustering model outperformed traditional algorithms in predicting adverse events, enhancing risk stratification and potentially redefining diastolic dysfunction diagnostics.[54]

Different phenotypic clusters also exhibit unique treatment responses. A meta-analysis of RCTs using iterative hierarchical clustering identified treatment response clusters for β-blockers in heart failure with reduced ejection fraction (HFrEF) patients, revealing that a young-aged AF cluster showed significant improvement, while a less symptomatic, older-aged group did not benefit.[55] In the SPRINT trial, Da-Ya Yang et al. identified four subgroups, with intensive antihypertensive treatment only improving outcomes for the highest-risk group.[56] Maja Cikes et al. studied 1,106 HF patients, identifying four phenogroups, with two demonstrating significant treatment benefits from cardiac resynchronization therapy.[57]

Clustering aids in disease subtype identification, enabling tailored treatments and improving clinical trial design by refining patient selection. However, results can be influenced by the subjectivity in selecting cluster numbers and inherent characteristics within different cohorts, which may limit generalizability across different populations. As mentioned, clustering results from a Japanese AF cohort may differ significantly from those of a European cohort due to population traits. Consequently, findings from the Japanese cohort are primarily applicable to Japan and may not extend to European contexts.

2.5 | ML-driven versus traditional risk scores

Most ML-driven models demonstrate enhanced predictive performance compared to traditional models and/or physicians across various cardiovascular outcomes by leveraging complex algorithms on multidimensional data (Table 2). Conversely, traditional models remain valuable for their simplicity and interpretability. ML methods are deployed across crucial stages of model development, including data preprocessing, feature selection, model training and optimization. Feature selection, an essential step in model construction, benefits significantly from ML, enabling precise identification of key predictors. For instance, Ambale-Venkatesh B et al. used random forest to develop models identifying the top 20 predictors, including TNF-α. Of note, these models outperformed the FRS and Multi-Ethnic Study of Atherosclerosis (MESA) scores in identifying asymptomatic cases.[58] In terms of modelling approaches, unlike conventional models, ML techniques can process high-dimensional, nonlinear data, thereby capturing intricate patterns within the dataset. Developed with XGBoost, GRACE 3.0 addresses GRACE 2.0's underestimation of mortality risk in women and better stratification by reclassifying more women as high-risk.[59] Moreover, XGBoost and *DeepHit* neural networks have shown superior performance over Cox regression, logistic regression (LR) and traditional risk scores (SCORE and FRS) in predicting mortality.[41]

In some cases, ML models are notably superior to traditional models. Segar M et al. developed random forest-based predictive models for in-hospital mortality in acute decompensated HF patients, achieving high discrimination and significantly surpassing the traditional GWTG-HF risk score model and other rederived LR models.[62] A support vector machine (SVM)-based risk

calculator significantly outperformed the ACC/AHA risk calculator, while the ACC/AHA model recommended statins for 46.0% of participants and identified only 76.2% of 'Hard CVD' events, the SVM-based model advised only 11.4% for statins and captured 85.6% of events.[64] Additionally, a LogitBoost model, integrating clinical and CT imaging data, surpassed ASCVD and CAC scores in predicting CVD and cardiac deaths[60]; similarly, XGBoost, using quantitative CT biomarkers like CAC and EAT volume, outperformed these scores in predicting MI and cardiac death.[61] Moreover, extreme gradient boosting models applied to TAVI data from multiple centers yielded an AUC of .82 for predicting 1-year all-cause mortality, outperforming traditional clinical scoring systems such as EuroSCORE II (AUC = .57).[65]

However, ML is not always superior to traditional models. Gradient Boosting Decision Trees (GBDT) and random forest-based models show only marginal improvements over LR in predicting in-hospital mortality after cardiac surgery.[66] Indeed, Frizzell J et al. found that tree-augmented naive Bayesian networks, random forest and gradient-boosted models did not improve 30-day HF readmission predictions compared to traditional LR.[67] Additionally, gradient-boosted modelling demonstrated only marginal improvements over traditional LR in predicting HF outcomes. While adding electronic medical record-derived predictors enhanced mortality and home time loss predictions, results for other outcomes were similar, indicating no absolute advantage.[68] Similarly, in predicting TAVI outcomes, a study found that despite using various ML models, such as Artificial Neural Networks (ANN), Naive Bayes (NB) and Random Forest (RF), the Logistic Regression model achieved the highest predictive accuracy for in-hospital mortality, with an AUC of .92.[69] Moreover, ML models for TAVR outcomes show a range of predictive abilities, from inadequate (C-statistic <.60) to excellent (C-statistic >.80).[70] These findings suggest that, while ML has potential, traditional models may still provide competitive or superior performance for certain clinical outcomes.

Combining ML with traditional modelling methods can enhance model performance. Wang Y et al. used random forest and multilayer perceptron algorithms to identify four novel variables associated with CS. These previously overlooked variables, combined with the LR model, proved to outperform the ORBI score.[63] Likewise, Vistisen D et al. developed a prediction model for CVD risk in patients with type 1 diabetes mellitus (DM), utilizing random forest for variable selection and Poisson regression to build the model, demonstrating excellent discrimination and calibration.[71]

While ML excels at processing high-dimensional, nonlinear data and often captures complex patterns better than traditional models, traditional models may be better for certain tasks due to their interpretability, simplicity and reliability, especially with smaller datasets and clear variable relationships. Given the limited dimensionality of clinical variables, balancing practicality and computational cost is crucial. Embracing the *K.I.S.S.* principle (Keep It Simple, Stupid), opting for simplicity is sometimes the smartest choice instead.

3 | LEVERAGING ML TO REDUCE RESIDUAL CARDIOVASCULAR RISK

RR is determined by the interplay of residual inflammatory, residual thrombotic, residual lipid and residual diabetes risk, with ML providing novel avenues to address these hazards effectively.[2]

3.1 | Residual inflammatory risk

According to an analysis of the Cardiovascular Inflammation Reduction Trial, residual lipid and inflammatory risk, as depicted by hs-CRP, IL-6 and LDL-C, remain high.[72] Indeed, despite the optimization of pharmacological therapy for CVD management, residual inflammatory risk accounts for many adverse outcomes in patients with or at high risk of CVD.[73–76] Certain biomarkers are related to residual inflammatory risk, including hs-CRP, IL-18, IL-6, IL-1β, neutrophil-derived indicators and core body temperature.[75–78] For instance, among patients undergoing PCI, those with hs-CRP ≥2 mg/L show higher all-cause mortality and incident MI.[76] Similarly, increased IL-1β levels in the setting of acute MI have been linked to increased mortality and recurrent MACE risk.[75] Further, there is higher inflammatory proteome expression in patients with a rupture of the fibrous cap of the culprit plaque, which was associated with an increased MACE rate compared to those with an intact fibrous cap. Notably, a recent analysis of RCTs comprising a total of 31,245 patients suggests that residual inflammatory risk is more strongly linked to MACE than lipid risk assessed by LDL-C.[79] The IL-1β pathway inhibiting antibody canakinumab provides a potential avenue to reduce residual inflammatory risk and thus MACE; however, it was associated with an increased number of fatal infections.[3] Conversely, low-dose colchicine combines excellent efficacy in secondary CVD prevention in stabilized patients with a safe risk profile.[7]

ML may provide novel avenues to address residual inflammatory risk. For instance, by leveraging Boruta and LASSO regression analyses, 15 inflammatory proteins

TABLE 2 ML-driven models versus traditional models or physicians.

Endpoint	Population	Traditional models/ physicians	ML-driven models		Metrics		Key modification (vs. traditional models)	Ref
			Names	Algorithms	Traditional models/physicians	ML-driven models		
CVD events and CAC scoring-based outcomes	Participants from AusDiab, Busselton and BioHEART cohorts	Framingham Risk Score	Lipidomic-enhanced risk score (LRS)	Ridge regression	.74 (BioHEART)	AusDiab: +.114, Busselton: +.077, BioHEART: +.02	Incorporation of lipidomic data	39
MACE within 10years	Participants from UK Biobank	SCORE, ASCVD, QRISK3 and Cox Model	NeuralCVD	Neural network	QRISK3: C-index Δ + .01 (95% CI .009–.011); NRI +.0488 (95% CI .0442–.0534); Cox Model: C-index Δ + .003 (95% CI .002–.004); NRI +.0469 (95% CI .0429–.0511)		Integration of polygenic scores with clinical predictors	38
CVD death and CHD death	Asymptomatic subjects	ASCVD Risk Calculator and CAC Risk Score	/	LogitBoost	CVD death: ASCVD: AUC .821; CAC: AUC .781 CHD death: ASCVD: AUC .835; CAC: AUC .816	CVD death: AUC .845 CHD death: AUC .860	Integrated CAC score with additional CT features (plaque number, volume, density) and extracoronary scores	60
MI and cardiac death	Asymptomatic subjects		/	XGBoost	ASCVD: AUC .77 (95% CI: .72–.82) CAC: AUC .77 (95% CI: .72–.83)	AUC .82 (95% CI: .78–.87)	Integrated EAT volume, aortic calcium, clinical co-variates and lipid panel measurements	61
In-hospital mortality	Patients with acute decompensated heart failure	GWTG-HF Risk Score	/	RF	AUC .69	Black: AUC .79 Non-Black: AUC .80	Incorporation of social determinants of health (SDOH)	62
All-cause mortality	Patients with heart disease symptoms (e.g. dyspnea and angina) and at increased cardiovascular risk	Framingham Risk Score, Cox regression, Logistic regression	Protein-based mortality prediction models	XGBoost classifier, XGBoost survival estimator, Neural network	1. Framingham Risk Score: AUC .64 (95% CI: .59–.68); 2. Logistic regression: AUC .65 (95% CI: .57–.73); 3. Cox regression: AUC .55 (95% CI: .51–.59)	1. XGBoost AUC .83 (95% CI: .79–.87); 2. Neural Network AUC .87 (95% CI: .83–.91)	Incorporates proteomics data with 92 proteins	41
In-hospital mortality	NSTE-ACS	GRACE 2.0	GRACE 3.0	XGBoost	Female: AUC .82 (95% CI: .81–.82) Male: AUC 0·86 (95% CI: 0·86–0·86)	Female: AUC 0·87 (95% CI: 0·84–0·89) Male: AUC 0·91 (95% CI: 0·89–0·92)	Sex-stratified analyses	59
In-hospital cardiogenic shock	ACS patients undergoing PCI	ORBI Risk Score	SEX-SHOCK Risk Score	MLP, RF	Female: AUC .78 (95% CI: .76–.81) Male: AUC .81 (95% CI: .79–.83)	Female: AUC .82 (95% CI: .79–.85)[a] Male: AUC .88 (95% CI: .86–.89)[a]	LVEF, ST-segment elevation, creatinine and CRP replaced previous stroke/TIA, anterior myocardial infarction, First medical contact-to-PCI delay >90 min, and Killip class II	63
Incident cardiovascular risk	CKD patients with no history of CVD	ACC/AHA Pooled Cohort Equation	Proteomics-Based Cardiovascular Risk	Elastic net regression	AUC: .70–.73	AUC: .84–.89	Addition of 32 proteins as key predictors	42

TABLE 2 (Continued)

Endpoint	Population	Traditional models/ physicians	ML-driven models		Metrics		Key modification (vs. traditional models)	Ref
			Names	Algorithms	Traditional models/physicians	ML-driven models		
Hard CVD events (including MI, fatal CHD, stroke and stroke death)	Participants who were atherosclerotic CVD-free at baseline.		/	SVM	AUC .71	AUC .92	/	64
21 distinct rhythm classes (including most types of heart rhythm or conduction abnormalities)	Adult patients (≥18 years old)	ECG physicians working in cardiology departments	/	CNN	F1 Score: .789 (0–6 years), .815 (7–12 years) and .831 (>12 years experience)	AUC .983 (95% CI: .980–.986); F1 Score: .887	/	14
Classification of 12 rhythm classes	Patients with single-lead ECGs	Cardiologist	/	DNN	F1 score = .780	F1 score = .837	/	13
Fatal or non-fatal MI		Expert readers	/	CNN	1. Plaque volume ICC: .964. 2. Diameter stenosis ICC: .879. 3. Plaque volume (IVUS): ICC .949. 4. Minimal luminal area (IVUS): ICC .904		/	35
Regional wall motion abnormalities	300 MI patients and 100 control patients	Cardiologists, sonographer readers and resident readers	/	CNN	Cardiologist readers: AUC .99; Sonographer readers: AUC .98; Resident readers: AUC .90	AUC .99	/	21

Note: The absence of AUC values with 95% CI indicates that they were not reported in the referenced study.

Abbreviations: AUC, area under the curve; CAC, coronary artery calcium; CHD, coronary heart disease; CI, confidence interval; CKD, chronic kidney disease; CNN, convolutional neural network; CVD, cardiovascular disease; DNN, deep neural network; EAT, epicardial adipose tissue; GWTG-HF, get with the guidelines–heart failure; ICC, intraclass correlation coefficient; IVUS, intravascular ultrasound; LASSO, least absolute shrinkage and selection operator; LVEF, left ventricular ejection fraction; MACE, major adverse cardiovascular events; MI, myocardial infarction; ML, machine learning; NRI, net reclassification improvement; NSTE-ACS, non-ST elevation acute coronary syndrome; PCI, percutaneous coronary intervention; RF, random forest; SDOH, social determinants of health; SVM, support vector machine; TIA, transient ischemic attack; XGBoost, extreme gradient boosting.

[a]Results pertain to the RICO cohort.

independently associated with increased MI risk were recently identified. Specifically, CDCP1, CD6, IL1–8R1, IL-6 and CXCL1 have emerged as independent biomarkers associated with the highest MI risk,[80] underscoring their potential as targets for therapeutic intervention. Recently, ML was used on proteome data from two independent secondary prevention cohorts; notably, CVD risk was predicted more accurately utilizing the proteome model than a clinical model in both the derivation and validation cohorts.[81] Despite proteome models appearing promising, they involve the risk of missing significant predictors affecting the outcome. *Cari-Heart*® is an AI-based software using CCTA images to assess inflammation and atherosclerosis in coronary arteries and clinical information to predict cardiac mortality.[82] The perivascular fat attenuation index measures coronary inflammation by identifying changes in the perivascular fat of coronary arteries, which can be assessed using *Cari-Heart*®. High fat attenuation index values around LAD and RCA predict all-cause and cardiac mortality on top of traditional clinical risk scores and optimal interpretation of CCTA images but without AI algorithms.[83,84] Chan et al. recently introduced an AI-risk algorithm, integrating coronary inflammation measured by fat attenuation index in CCTA, clinical risk factors and plaque burden in CCTA to predict MACE. The novel AI-risk algorithm is estimated using *Cari-Heart*® and reclassified patients, including those without obstructive CAD, for MACE and cardiac death risk better than the traditional prediction tool QRISK3.[84] In aggregate, ML can be used to explore unknown pathophysiological pathways, identify potential treatment targets and interpret complex radiology images to reduce residual inflammatory risk.

3.2 | Residual thrombotic risk

Patients with ASCVD face a significant residual thrombotic risk following major cardiovascular events, which has become a focal point of current research.[85] Although antiplatelet therapy is the accepted standard for secondary prevention, this approach may not sufficiently mitigate residual thrombotic risk in certain high-risk patients. Two studies indicate that a low-dose rivaroxaban combined with aspirin can further reduce the incidence of cardiovascular events in specific patients, though it also elevates the risk of bleeding.[86,87] Similarly, the PEGASUS-TIMI 54 study demonstrates that long-term DAPT with ticagrelor and aspirin significantly reduces MACE and coronary events in high-risk post-MI patients, including those with multivessel disease, regardless of prior stenting. These findings underscore the necessity of enhanced management of residual thrombotic risk in selected populations.[88,89]

Current ML applications in thrombosis management focus mainly on optimizing venous thrombosis diagnosis and treatment. For instance, neural networks analyse radiology reports to accurately identify and classify thrombosis cases, achieving high accuracy in detecting deep vein thrombosis and pulmonary embolism.[90] Additionally, neural networks use clinical and lab data—such as age, D-dimer levels, and genetic mutations—to predict thrombosis recurrence.[91,92] However, ML applications for assessing residual thrombosis risk in ASCVD patients are limited and mainly diagnostic. For example, ML models predicting stent restenosis using GRACIA-3 trial data outperformed existing scores,[93] while another neural network diagnosed antiphospholipid syndrome with 92% accuracy using thrombin generation parameters, independent of anticoagulation.[94] The LAT-AI machine learning model was developed to predict left atrial appendage thrombus in patients on chronic oral anticoagulation using clinical and transthoracic echocardiography features. It achieved an AUC of .85, outperforming left ventricular ejection fraction and CHA2DS2-VASc score.This model could potentially reduce unnecessary transoesophageal echocardiography by 40% in these patients.[95]

3.3 | Residual lipid risk

While the addition of newer drugs to statin treatment (e.g. ezetimibe, PCSK9 inhibitors) leads to MACE reduction, a substantial residual risk persists, as found in IMPROVE-IT and FOURIER trials, respectively.[96,97] A 1 mmol/L increase in time-weighted average exposure to LDL-C links to a 2-fold higher risk of recurrent MACE over a 3-year period, highlighting the need to address lipid risk early and aggressively.[98] The interindividual variation in the statin-mediated reduction of LDL-C, non-HDL-C and apoB is high, with >40% not achieving LDL-C target goals, which is directly linked to higher MACE risk.[99] Lipoprotein(a) is another established risk factor for CVD, mainly genetically determined, and it cannot be directly therapeutically targeted with currently available medications.[100]

A novel ML tool using boosted regression tree analysis intergrated anthropometric, laboratory, demographic, and lifestyle variables. Itfound that a non-HDL-C/apoB ratio of 1.4 or less was linked to a higher CAC score, an important feature of coronary atherosclerosis.[101] Recently, Zhu et al. have built a lipid risk score combining advanced lipid measurements and clinical data. Of note, among BioHEART-CT study participants, the ML score predicted subclinical CAD better than FRS.[102] Similar results were obtained in two large cohorts from the Australian Diabetes, Obesity and Lifestyle and the Busselton Health Studies, with a novel score significantly improving the

stratification of the intermediate-risk group for MACE over FRS (AUC .635 vs. .558).[39] Another ML model based on electronic health record (EHR) data identified patients with familial hypercholesterolaemia with good positive predictive value and sensitivity in both internal and external validation datasets. Importantly, this ML algorithm uses complex data, such as text from clinical notes, that could not be incorporated into traditional scores.[103] ML models outperformed LDL-C cutoffs (AUROC .711 vs. .642) and showed improved performance in low-prevalence cohorts (AUROC .801–.856).[104,105] Implementing AI-guided analysis for familial hypercholesterolaemia patients may drive clinical decisions for treatment initiation, possibly facilitating lipid management and improving patient outcomes.

3.4 | Residual diabetes risk

Patients with diabetes are at particularly high ischaemic risk despite ongoing efforts to identify novel antidiabetic drugs.[106,107] In parallel, GLP-1 agonists and SGLT2 inhibitors have proven high efficacy to reduce MACE not only in patients with diabetes but also in those with heart failure and CKD.[108–110] A variety of ML models have been introduced more recently. For example, among 32,611 patients with type 1 DM, ML significantly contributed to the assessment of MACE risk, increasing accuracy, improving robustness, and reducing the variance of predictions, with glycated haemoglobin, albuminuria, DM duration, systolic blood pressure and LDL-C representing the most potent predictors.[111] The Risk Equations for Complications Of type 2 Diabetes (RECODe) used an ML model to identify predictors and incorporate them into a Cox proportional hazard model for each outcome, showing better discrimination and calibration than UK Prospective Diabetes Study Outcomes Model 2 (UKPDS OM2) and American College of Cardiology/American Heart Association pooled cohort equations (ACC/AHA) risk scores.[112] Numerous ML models have been proposed to improve MACE prediction beyond existing risk scores in patients with DM or impaired glucose tolerance, both in primary and secondary prevention settings. For example, plasma protein N-glycan profiling and a model combining numerous factors with top three statin treatment, NT-proBNP, and albumin levels have shown promising results.[113,114] As noted earlier, an increasing number of studies now utilize phenomapping in DM cohorts to identify DM phenogroups with distinct MACE risk and treatment response.[115–117]

Predicting harm or benefit induced by intensive glycaemic therapy in DM patients can guide personalized therapy, as exemplified by the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial.[118] Additional ML-based algorithms have been tested in DM populations with the scope to guide clinical decision-making for diabetes treatment. Canagliflozin, personalized postprandial-targeting diet, and insulin initiation are examples of interventions that could be selected based on a personalized and not average benefit following results from studies using ML models.[119–121] Overall, ML offers numerous opportunities in diabetes, such as predicting cardiovascular and other complications, determining glycaemic targets, and selecting drug or lifestyle treatments on a personalized approach.

4 | FUTURE CHALLENGES AND DIRECTIONS

The rapid evolution of AI and its branches has led to the expansion of AI-based tools in the cardiovascular field. However, implementing these innovative applications in clinical practice comes along with potential issues related to their safety, reliability and validity. Indeed, algorithms that have not been properly validated may cause harm to patients; thus, quality standards are crucial for the use of these novel tools.

4.1 | Data quality and model explainability

While the number of available ML tools is increasing exponentially, standardized and transparent data reporting remains scarce, with a limited number of studies reporting performance metrics in external validation data sets. Further, the underrepresentation of certain patient groups (e.g. different ethnicities, across socioeconomic status and sexes) hampers the generalizability of many ML models.[122–125] Data quality may also be affected by interobserver variability, for example, in diagnostic procedures in which human intervention has a role.[124] Therefore, appropriate guidance by international societies in close collaboration with authorities (e.g. European Medical Agency, Food and Drug Administration) is a necessity. Moreover, we need to overcome the 'black box' issue of ML algorithms when applied in healthcare settings.[126] Indeed, the process through which novel algorithms provide predictions should be reported transparently to ensure advances in clinical decision-making. To simplify the complexity of AI, explainable AI (XAI) has been introduced,[127] with gradient-weighted class activation mapping (GradCAM) and Shapley additive explanations (SHAP) being the most frequently used. For instance, the HARD MACE-DL model, a DL model using single photon emission CT myocardial perfusion imaging to estimate risk for MI and death, incorporates the GradCAM and the

SHAP approaches, which may guide physicians and allow better data interpretation.[128]

4.2 | Bias

Bias in AI applications for cardiovascular care stems from underrepresentation in digital datasets and data selection challenges, including sampling, annotation and measurement bias, disproportionately affecting underrepresented patient populations. For example, Elias et al. reported reduced accuracy in AI-based tools for detecting valvular heart disease in elderly and non-Caucasian patients,[18] while Cheema et al. identified lower accuracy for female and non-white patients in HF detection.[129] These biases are exacerbated through algorithm development and application, resulting in disparities such as missed diagnoses, misclassification and inappropriate recommendations. Jabbour et al. further noted that systematically biased AI models can significantly decrease diagnostic accuracy among clinicians.[130] These findings underscore the need for diverse data integration, comprehensive validation and meticulous deployment to ensure AI models support equitable cardiovascular care.

AI applications in cardiovascular care are closely linked to EHR, leveraging EHR data for digitization and analysis to understand treatment effect variability,[131] assess the comparative effectiveness of tests and interventions,[132] and more recently, to develop prediction,[133] classification,[134] and optimization models[135] that inform clinical decision-making. However, EHR introduces inherent biases from three main sources: missing data, limited sample sizes and misclassification errors. Missing data often exclude patients from underrepresented groups, limiting their identification by algorithms. Small sample sizes fail to capture nuances within minority groups. Misclassification occurs when patient records reflect provider biases, inaccurately labeling or diagnosing individuals based on socioeconomic or demographic factors. Together, these biases risk distorting ML predictions, potentially amplifying health disparities rather than reducing them.[136]

Effective mitigation requires a diverse research team, robust validation across demographic categories, and ongoing bias audits. Regulatory oversight, like the FDA's guidelines, emphasizes transparency and equity to minimize AI bias and promote health justice.[137]

4.3 | Integration with clinical workflows

Achieving more precise cardiovascular risk assessment by AI depends on its successful clinical translation and integration of available ML models into clinical practice. First, as many published AI algorithms lack external validation, their clinical implementation is hampered.[138] Second, legal issues arise from the lack of clear assignment of responsibilities, for example, to the physician or the constructor of an AI model in case of harmful clinical decision-making after implementing an AI tool.[122] Third, as many ML models are not run locally, data protection may become an issue.[139,140] Finally, the effectiveness of ML models not only depends on their inherent characteristics but also on human perception of their results and arising clinical implications. While ML applications using next-generation sequencing data can be integrated into oncology diagnostics and pharmacogenomics,[141,142] the use of genomic data in cardiovascular medicine is still in its infancy, possibly due to the multifactorial aetiologies of most CVDs, including both environmental and genetic factors. Leveraging AI by combining GWAS and EHR data may transform risk prediction and cardiovascular care at large in the near future.[125] Continuously updated legislation regarding medical AI by the EU and US FDA will facilitate the rapid expansion of AI tools in medicine.

For example, certain ML-based applications, such as *PM cardio*, a mobile app aiding in ECG interpretation,[16] as mentioned above, can be easily incorporated into clinical workflows. Conversely, more complex, potentially expensive ML tools such as *CaRi-Heart*® for the quantification of spatial changes in perivascular fat composition and thus coronary inflammation have not been broadly implemented yet,[83,84] with interventional studies pending publication. Considering the global shortage of limited health resources (both in personnel and finances), particularly in regions with low socioeconomic development, AI offers unprecedented opportunities to address these challenges. Indeed, leveraging ML-based models for the management of patients may ultimately offer more cost-effective prevention, diagnosis and treatment opportunities, reducing both personal and financial needs.

4.4 | Primary prevention

Going forward, AI may also prove useful in real-world practice for the primary prevention of CVDs. Indeed, as noted earlier, most ML models supersede the performance of traditional models.[64] For instance, an AI-guided CCTA interpretation algorithm improves 10-year cardiovascular risk stratification among individuals without clinically overt CVD.[143] Along similar lines, the potential of AI-guided CCTA in primary prevention settings is currently being studied in the TRANSFORM trial, in which individuals without known symptoms of ASCVD but who are at increased risk for ASCVD will be recruited (ClinicalTrials.gov identifier: NCT06112418). The trial will test the

hypothesis that a CAD staging system-based care strategy (including an imaging-based evaluation for coronary atherosclerosis, algorithm-supported pharmacotherapy and personalized education) reduces cardiovascular events compared with risk factor-based care. The results of this innovative trial will add high-level evidence on the efficacy and safety of AI-guided CCTA on personalized CVD prevention. While ML models using demographic data and medical history to predict CVD risk are likely to be incorporated into clinical practice and applied to the general population in the future, ML models using more complex data, such as CCTA imaging, may be broadly implemented only in specific high-risk individuals, possibly limited to high-income regions. For instance, the AI-driven CardioSight dashboard and CHAMP program now integrate real-time cardiovascular risk assessment, socioeconomic data and preventive care coordination in Singapore, bridging gaps in primary prevention and CVD management.[144] Accumulating evidence supports the great potential of AI in primary prevention,[145] though, pending external validation, its safety and efficacy to improve hard cardiovascular endpoints need to be rigorously assessed in well-designed interventional trials.

5 | CONCLUSIONS

The introduction of ML has transformed cardiovascular risk assessment and patient management at large. Indeed, ML allows for more precise and objective risk assessment, with data-driven clinical decision-making representing an essential building block of future patient management. By integrating multidimensional data (e.g. multi-omics, imaging and nonstructured data such as EHR), ML models can learn from complex and diverse data types and thus provide the basis for future clinical decision-making in both primary and secondary prevention settings. Harnessing externally validated ML-assisted tools may foster global efforts to mitigate cardiovascular risk early and in a more personalized fashion. Through the identification and targeting of specific residual risk factors—such as inflammation, dyslipidemias, diabetes and pro-thrombotic states—ML models can individualize risk management across the heterogeneous spectrum of CVDs. With the global shortage of physicians (driven by reduced working hours and more part-time roles), ML will play a key role in facilitating the delegation of routine monitoring for chronic conditions to advanced nurse practitioners. On the other hand, however, overreliance on ML and AI-assisted tools should currently be avoided, as most models have neither undergone external validation in independent settings nor have their efficacy and safety been rigorously assessed in interventional trials. Moving forward, beyond the conduct of well-designed RCTs, we will need to continue our efforts to address barriers that hamper the implementation of ML in routine clinical care, including those related to data quality, ethics, legal frameworks and system integration. In this context, the FUTURE-AI framework provides a structured approach to developing and deploying trustworthy AI tools in healthcare, emphasizing key principles such as fairness, universality, traceability, usability, robustness and explainability.[146] Adopting these best practices will be critical in ensuring that ML models are not only clinically effective but also ethically sound and widely applicable across diverse populations. Achieving this vision will require coordinated efforts across multiple disciplines, including researchers, clinicians, data scientists, stakeholders and—eventually—individual patients.

AUTHOR CONTRIBUTIONS

S.K, Y.W. and T.F.L. designed and wrote the first version of this article. All co-authors revised the work critically for important intellectual content and approved the version to be published, and agreed to be accountable for all aspects of the work in ensuring that questions related to the integrity of any part of the work presented are appropriately investigated and resolved.

CONFLICT OF INTEREST STATEMENT

L.L. is co-inventor on the international patent WO/2020/226993 filed in April 2020. The patent relates to the use of antibodies which specifically bind IL-1α to reduce various sequelae of ischaemia–reperfusion injury to the central nervous system. L.L. is counsellor of the European Society for Clinical Investigation and has received funding from the Novartis Foundation for Medical-biological Research, the Swiss Heart Foundation and the Italian Ministry of Health (unrelated to this work). M.Z. declares research grants from Amarin Corp and lecture fees from Pfizer, Organon and Amgen. T.F.L. has no conflicts of interest related to the present manuscript but has received research and educational grants from Abbott, Amgen, AstraZeneca, BAYER, Boehringer Ingelheim, Cytokinetics, Daichi-Sankyo, Eli Lilly, Novartis, Novo Nordisk, Sanofi and Vifor. S.K. declares outside this work speaker fees from Roche Diagnostics and the Foundation for Cardiovascular Research – Zurich Heart House. Further, he has received research grants to the institution from the Jubiläumsstiftung SwissLife, the Lindenhof Foundation, the Novartis Foundation for Medical-biological Research, the Swiss Heart Foundation, the Swiss Society of Cardiology and the Theodor-Ida-Herzog-Egli Foundation, and equipment and materials from Roche Diagnostics outside the submitted work. Travel support, again unrelated to this work, was

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DATA AVAILABILITY STATEMENT

This state-of-the-art review article does not contain any original data. All data analysed and discussed in this study were obtained from previously published sources cited in the manuscript.

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