Appraisal of Cardiovascular Risk Factors, Biomarkers, and Ocular Imaging in Cardiovascular Risk Prediction

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"Keeping an Eye on Cardiovascular Disease Risk"

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Abstract

Cardiovascular disease remains a leading cause of death worldwide despite the use of available cardiovascular disease risk prediction tools. Identification of high risk individuals via risk stratification and screening at sub-clinical stages, such as may be offered with ocular screening, is important to prevent major adverse cardiac events. The retinal microvasculature has been widely researched for potential application in both diabetes and cardiovascular disease risk prediction. However, the conjunctival microvasculature as a tool for cardiovascular disease risk prediction remains largely unexplored in comparison. The purpose of this review is to evaluate the current cardiovascular risk assessment methods, identifying gaps in the literature that imaging of the ocular microcirculation may have the potential to fill. This review also explores the themes of machine learning, risk scores, biomarkers and medical imaging and clinical risk factors. Cardiovascular risk classification varies based on the population assessed, the risk factors included and the methods of assessment. A more tailored, standardised and feasible approach of cardiovascular risk prediction, that utilises technological and medical imaging advances, such as may be offered by ocular imaging, is required to support cardiovascular disease prevention strategies and clinical guidelines.

1. Introduction

Currently, an estimated 23% of all deaths in Northern Ireland are attributed to cardiovascular disease [1]. The British Heart Foundation (BHF) estimates that in Northern Ireland alone, cardiovascular disease costs the National Health Service £412 million. The aging population means the burden of cardiovascular disease will only be exacerbated [2]. Prevention is better than cure, and hence critical review of current cardiovascular risk assessments is required. Application or addition of non-invasive vessel measurements of the ocular microcirculation, as demonstrated in the study by Brennan *et al.* (2019), may aid personalisation of a risk score, as well as provide real time data on the microvasculature [3]. Additionally, such advancements in technology and medical imaging should strengthen efforts to reduce morbidity and mortality rates associated with cardiovascular disease.

Cardiovascular risk assessment should support sub-clinical identification, stratification and management of individuals at risk of cardiovascular disease. However, a recent study pinpoints weaknesses such as racial and ethnic disparities within current risk profiling methods despite advances of healthcare [4]. In addition, existing cardiovascular disease risk scores are heterogenous and deficient in vasculature and haemodynamic investigation, with reports of wide variation of risk classification [5]. Inaccuracies of cardiovascular disease risk scores may lead to further burden on an already over-stretched health service, either through over or under-treating patients based on their risk score. Critical review of current cardiovascular risk assessment is required to evaluate areas of improvement and development, and ultimately, help to reduce the burden of cardiovascular disease. The purpose of this review is to appraise current cardiovascular risk prediction methods to include: machine learning, risk scores, biomarkers, medical imaging and clinical risk factors. Moreover, this review aims to highlight the potential of ocular microcirculatory measurements for application in cardiovascular risk stratification.

2. Ocular Measurements in Disease

The eye and the heart share many pathological risk factors such as hypertension, hyperlipidemia, diabetes and aging. Early identification of both eye and cardiovascular pathology is essential as in the example of hypertensive retinopathy (often characterised by cotton wool spots) a progressive loss of vision may occur.

Additionally, age-related macular degeneration and diabetic neuropathy are associated with atherosclerosis of the carotid artery, and hence cerebral ischemia.

The microcirculation of the conjunctiva has been largely unexplored in comparison to that on the retina. Table 1 compares and summarises the advantages and disadvantages of two methods of microvascular examination, retinal and conjunctival. Retinal examination allows for detailed examination of blood vessels and can detect diabetic retinopathy but requires pupil dilation and specialised training for imaging and analysis. In contrast, conjunctival examination allows for easy and non-invasive visualisation of the blood vessels at the front of the eye, can be imaged with simple equipment found in every optician, and does not require the use of ionising radiation or eye drops to dilate the pupil, but may not be able to visualise certain structures such as the optic disc that can help with arteriole and venule classification. The development of an innovative conjunctival microcirculation imaging technique, as we have proposed may also be a promising prognostic tool to sub-clinically assess cardiovascular risk [3, 6, 7].

Table **1**. Advantages and disadvantages of retinal versus microvascular examination in cardiovascular disease risk assessment.

	Advantages	Disadvantages
Retinal microvascular examination	-Blood vessels examined for diabetic retinopathy -Age-related macular degeneration may be assessed	-Requires dilation of the pupil -Specialised training is often required for imaging and analysis (e.g., optical coherence tomography training)
Conjunctival microvascular examination	-Blood vessels can be easily and non-invasively seen at the front of the eye in contrast with the white background of the sclera -Can be imaged inexpensively with minimal training using simple equipment	-Inability to visualise certain structures within the eye such as the optic disc that can help arteriole and venule classification

3. Machine Learning

The advances and applications of technology, such as with electronic healthcare records, as well as approaches to big data have led to automated and machine-learning based techniques. Machine learning techniques are now front-runners in the search for earlier and more accurate cardiovascular risk stratification tools. Suri *et al.* (2022) report a reduced risk of bias with machine learning compared to non-machine learning techniques for the risk estimation of cardiovascular disease [8]. Machine learning methods, such as neural networks may enhance and help to personalise current risk scores [9, 10]. The area under the curve (AUC) for the studies that evaluated the use of machine learning for cardiovascular risk classification in this review ranged from 0.55 [11] with a Cox regression model to 0.92 [12] with a support vector machine approach. Table S1 summarises the literature on

the role of machine learning in cardiovascular disease risk prediction. Table S1 also identifies the cardiovascular risk factors assessed throughout the literature. Age appeared to be the most commonly assessed risk factor, followed by gender, smoking status, total cholesterol, high density lipoprotein, diabetes status and blood pressure. The studies within Table S1 include prospective studies and case-control studies [13, 14, 15, 16, 17, 18, 19]. Machine learning approaches are typically unbiased and more reproducible in comparison to more manual and subjective assessments. The machine learning models evaluated, particularly the Autoprognosis [13] and deep learning models such as Deepsurv [15] were able to augment risk prediction compared to the traditional risk factors and conventional models such as the Framingham Risk Score.

A similar binary logistic regression approach has now been implemented with an algorithm based on conjunctival haemodynamic parameters (blood velocity) to support coronary artery disease screening [20]. The study by Awuah *et al.* demonstrates how assessment of the conjunctival microcirculation may be easily integrated into machine learning. Currently, there is no widely used risk score that utilises ocular measurements such as that of the conjunctival microcirculation.

4. Current Cardiovascular Risk Scores; Strengths and Weaknesses

Awuah *et al*. [20] assessed ocular parameters to include conjunctival vessel diameter, cross sectional velocity, axial velocity, blood flow rate and wall shear rate, alongside clinical/lifestyle characteristics and blood biomarkers to include lipids and markers of inflammation and endothelial dysfunction as listed; haemoglobin A1c, sodium, potassium, urea, creatinine, creatinine clearance, haemoglobin, haematocrit, white cell count, platelet count, mean corpuscular volume, C-reactive protein, N-terminal pro-brain natriuretic peptide, total cholesterol, triglyceride, high density lipoprotein (HDL), low density lipoprotein, non-HDL, cholesterol HDL ratio, prothrombin time, activated partial thromboplastin clotting time, fibrinogen, urate, apolipoprotein A, apolipoprotein B, methylenetetrahydrofolate reductase, folic acid, homocysteine, vitamin B12, adiponectin, heart-type fatty acid binding protein, HDL3, interleukin (IL) -α, IL-β, IL-2, IL-4, IL-6, IL-8, IL-10, monocyte chemoattractant protein-1, tumor necrosis factor-α, vascular endothelial growth factor, interferon-γ, epidermal growth factor, asymmetric dimethylarginine and leucine-rich α-2-glycoprotein-1. Consequently, the best classification variables as identified through binary logistic regression analysis for high risk cardiovascular disease patients versus controls were conjunctival cross sectional velocity, N-terminal pro-brain natriuretic peptide and adiponectin. The variables were employed within the algorithm-derived patient score and performed better than QRISK3 score for the classification of high risk cardiovascular disease patients compared to controls (Wilcoxon test $p<2.2e^{-16}$ for the algorithm-derived patient score versus $p=0.00031$ for QRISK3). The application or addition of ocular measurements such as conjunctival blood velocity to existing cardiovascular risk scores may positively impact cardiovascular risk assessment.

Guidelines such as those proposed by the National Institute of Clinical Excellence (NICE) in 2016 [21], or the European Society of Cardiology (ESC) [22], largely advocate the application of risk scores such as QRISK3 for patient management. However, risk scores must evolve over time in response to trends in populations and for various risk factors. The long-term Framingham risk study demonstrates this concept as it now comprises of three generations of participants with the Framingham off-spring study [23]. Although the Framingham risk study is widely published and evaluated, it focuses on a specific population of people from the United States. It may not comprehensively account for factors such as ethnicity or socioeconomic status.

Ko *et al.* (2020) studied a cohort of 84,617 multi-ethnic Canadian participants with a maximum follow-up period of 5 years [24]. The predicted event rate was overestimated by 101% with the Framingham risk score. Similarly, Rospleszcz *et al.* (2019) also found the Framingham risk score overestimated cardiovascular disease risk [25]. However, van Kempen *et al.* (2014) found that this risk score performed well in the low-intermediate risk groups but poorly for the high-risk group [26]. Using data from the Framingham heart study, Zhang and Pincus (2015) found a 10% variation in future lifespan of 28-38-year old's, with blood pressure, blood glucose, weight and body mass index (BMI) being the most relevant factors in determining lifespan [27]. Various risk factors have been disputed in subsequent studies such as in the example of the study by Esteghamati *et al.* (2013) that suggests the waist to hip ratio is a superior predictor variable compared to BMI [28].

The prospective study by Maas *et al.* (2017) investigated plasma nitrate levels within the Framingham Off-spring study [29]. The study found that whilst elevated plasma nitrate concentrations were associated with all-cause mortality it was not associated with incident cardiovascular disease. Puurunen *et al.* (2018) also assessed the Framingham Heart Study participants and found the blood biomarker of platelet function increased risk of thrombosis associated with hyperplatelet aggregability to adenosine diphosphate (ADP) [30]. Lastly, two further biomarkers were assessed in the study by Lyngbæk *et al.* (2013), soluble urokinase plasminogen activator receptor (suPAR) and C-reactive protein (CRP) [31]. Lyngbæk *et al.* found suPAR and CRP were significantly increased in participants who experienced a cardiovascular disease event compared to those who experienced no event (suPAR; 3.93 ng/mL (95% confidence intervals= 2.61-6.48) vs 4.53 ng/mL (2.86-7.86), CRP; 1.61 mg/L (0.31-11.1) vs 2.63 mg/L (0.40-13.8), respectively, $p<0.0001$).

The ESC introduced the SCORE cardiovascular risk assessment. Graversen *et al.* (2016) found the SCORE algorithm predicted the risk of cardiovascular disease with an area under the curve (AUC) of 0.837, whereas in the original SCORE population the AUC was 0.81 for the high-risk population and 0.74 for the low-risk population [32]. Improvements of SCORE have been suggested such as through the addition of education level [33]. The study by Woźnicka-Leśkiewicz *et al.* (2015) concluded that the ankle-brachial index (ABI) and pulse wave velocity (PWV) in predicting cardiovascular disease risk according to the SCORE scale was more precise than that of the Framingham [34]. Contrastingly, to aforementioned studies, Woźnicka-Leśkiewicz *et al.* suggests that the Framingham scale underestimates those at high risk of cardiovascular disease.

The European Heart Journal (2021) introduced the SCORE2 and SCORE2-OP algorithms [35]. Compared to the SCORE algorithm, SCORE2 significantly improved the overall risk discrimination ($p<0.001$). Following the development of the SCORE2 algorithm, the SCORE2-OP model was established. The Harrell's C-statistic (similar to AUC) performed better for SCORE-OP when compared to the atherosclerotic cardiovascular disease (ASCVD) score for all cohorts to include Atherosclerosis Risk in Communities (ARIC) (0.644 vs 0.668), MESA (0.645 vs 0.654) and pooled trial populations (0.612 vs 0.632), except for the CPRD cohort (0.663 vs 0.657).

The concept of modifying and updating risk scores may enable a more accurate, as well as a more tailored risk score to be developed. This concept was demonstrated in the study by Argyridou *et al.* (2020) that modifies SCORE to include walking pace, and the results show improved performance metrics [36]. Correspondingly, the exercise capacity assessed via metabolic equivalents (METS) of a task were reported to be a valuable cardiovascular disease risk factor in the study by Salokari *et al.* (2019) [37], and as walking pace would increase, it would also be expected that METS would increase [38].

Hippisley-Cox *et al.* (2017) first proposed QRISK3, the succeeding algorithm to the QRISK2 calculator [39]. This QRISK3 model considered the additional factors of chronic kidney disease (CKD), systolic blood pressure variability, migraine, corticosteroids, systemic lupus erythematosus (SLE), atypical antipsychotics, severe mental illness and erectile dysfunction. The QRISK3 model with systolic blood pressure variability included (R^2 (%) = 59.6 (59.3 to 60.0) for women and 55.0 (54.6 to 55.3) for men) performed better than without the systolic blood pressure variability (59.5 (59.2 to 59.9) for women vs 54.8 (54.5 to 55.2) for men), as well as performing better than the QRISK2 model (59.6 (59.2 to 60.0) for women vs 54.8 (54.4 to 55.1) for men). However, in a more recent population cohort study by Livingstone *et al.* (2022), both CRISK and CRISK-CCI outperformed QRISK3 [40].

QRISK3 provides a 10-year risk score, yet the study by Wickramasinghe *et al.* (2014) indicates the 10-year risk assessments may not comprehensively assess the cardiovascular disease burden of younger individuals; and instead considers a long-term risk prediction tool of 30 years [41]. The study conducted by Chiuve *et al.* (2014) again focuses on minimising long-term cardiovascular disease risk through a Bayes information criterion-derived 'Healthy Heart Risk Score', proposed for use as a public health tool [42]. This risk score had a Harrell's C-index of 0.72, demonstrating good discrimination. The risk score incorporated the familiar factors of age, smoking status, body mass index, physical activity levels, alcohol intake as well as diet through a composite diet score. Baik *et al.* (2012) and Georgousopoulou *et al.* (2020) suggest a similar incorporation of dietary evaluation for cardiovascular disease risk prediction [43, 44]. A summary of the commonly used risk scores described above along with the risk factors they assess are detailed in Table 2.

Table 2. Risk scores.

Risk Score	**Summary**
Framingham	Long-term multigenerational study of over 15,000 individuals spanning over 70 years. Risk factors include: • Blood pressure • Blood lipid levels • Age • Gender • Anthropometrics • Psychosocial factors • Smoking status
SCORE	ESC recommended risk score. Risk factors include: • Gender • Age • Cholesterol • Smoking status • Blood pressure
QRISK3	NICE recommended risk score. Risk factors include: • Age • Gender • Ethnicity • Postcode • Family history of cardiovascular disease • CKD, atrial fibrillation, migraine, rheumatoid arthritis, SLE, severe mental illness • Medications • Cholesterol/High Density Lipoprotein (HDL) ratio • Blood pressure and systolic blood pressure variability • BMI

The above risk scores do not fully consider measurements of the vasculature. A major advantage of the conjunctival vessel measurements is the ability to objectively assess the conjunctival vessels and

haemodynamics non-invasively, serially and without ionising radiation or the need for expensive equipment. Large longitudinal studies of the population would be required, particularly, to assess the ability of these measurements, alongside other risk factors, for indicating long-term risk.

5. Biomarkers

Corbacho-Alonso *et al.* (2020), Racis *et al.* (2020) and Xuan *et al.* (2018) suggest blood or urine markers of oxidative stress as an addition to cardiovascular risk prediction models [45, 46, 47]. Other studies suggest blood biomarkers of inflammation [48, 49] or subclinical myocardial injury [50]. Repeat measurements of some biomarkers, such as high-sensitivity cardiac troponins have been independently associated with cardiovascular events [51], whilst Ohm *et al.* [52] report that recurrent cardiovascular events to include myocardial infarction or stroke cannot be predicted by blood lipid levels. Despite the findings presented by Ohm *et al*., Willeit *et al.* [53] suggest that lipoprotein(a) may be a valuable addition to cardiovascular risk scores such as the Framingham or Reynolds Risk Score. Conversely, Kouvari *et al.* (2019) imply that lipoprotein(a) testing may have less utility for women compared to men [54]. The literature largely agrees on the addition of such biomarker testing to cardiovascular risk prediction. Often the feasibility of adding clinical or laboratory-based measures may inhibit such cardiovascular risk assessments in individual or resource-limited settings within areas of deprivation, where often cardiovascular disease is most prevalent [55, 56]. Contrastingly, examination of the ocular microcirculation, as proposed within this review, would be inexpensive and require minimal training.

The conjunctival imaging system utilised by Brennan *et al.* [3] and the potential clinical applications of the imaging system are shown in Figure 1 below. Brennan *et al*. describe how ocular imaging can be performed with a slit-lamp and a smartphone to record videos of the conjunctival haemodynamics. The videos are then processed using a bespoke application and ocular biomarkers measured include vessel diameter, cross sectional velocity, axial velocity, blood flow rate and wall shear rate. Brennan *et al.* later assessed these values for different patient cohorts to include myocardial infarction [6] and cyanotic congenital heart disease patients [7], reporting reductions in conjunctival vessel parameters to include axial velocity and wall shear rate when compared to control subjects.

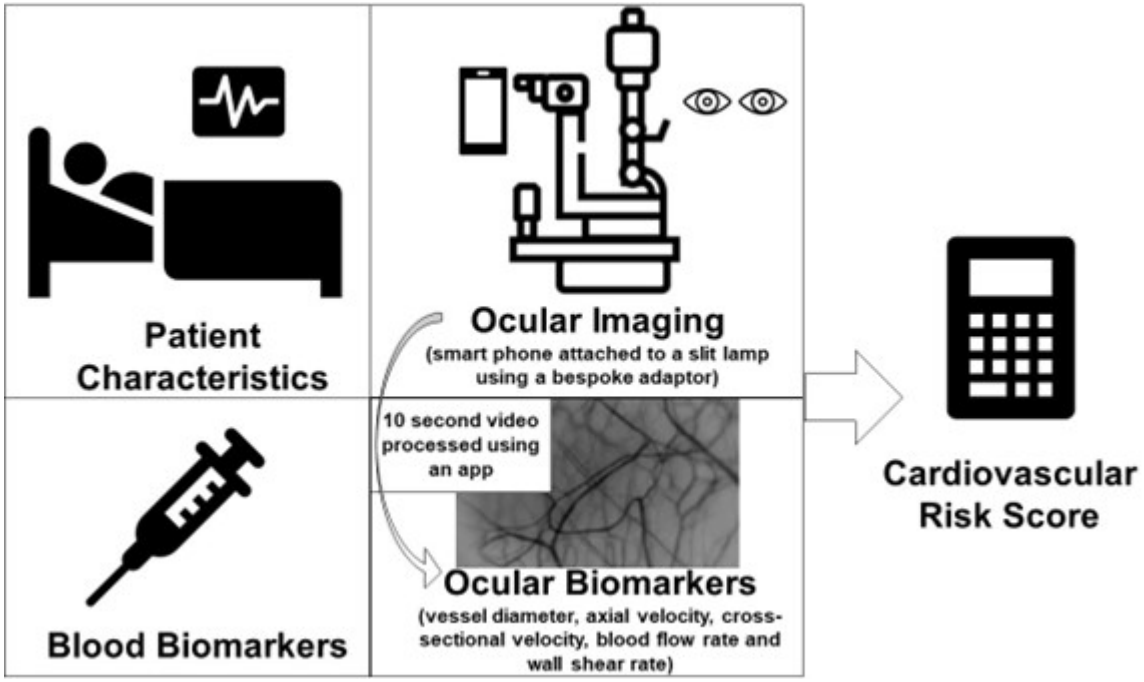

Figure 1. The conjunctival imaging system and its potential clinical applications.

Further alternatives to the traditional and clinical risk scores described in this review have been suggested through applications of multi-omics. Proteomics was shown to enrich cardiovascular disease risk stratification in multiple studies [45, 57, 58]. The study by Würtz *et al.* (2015) promotes the application of metabolomics through metabolic profiling for cardiovascular disease risk prevention [59]. Assessment of risk scores is dependent upon the population studied, and hence methods to advance detection of individuals at high-risk of cardiovascular disease may include epigenomics [60]. A genetic risk score based on 3 single-nucleotide polymorphisms was introduced in a study by Verbeek *et al.* (2019), and showed a positive association with plasma triglyceride levels, as well as an increased risk of cardiovascular disease [61]. Figure 2 illustrates a selection of biomarkers associated with cardiovascular disease.

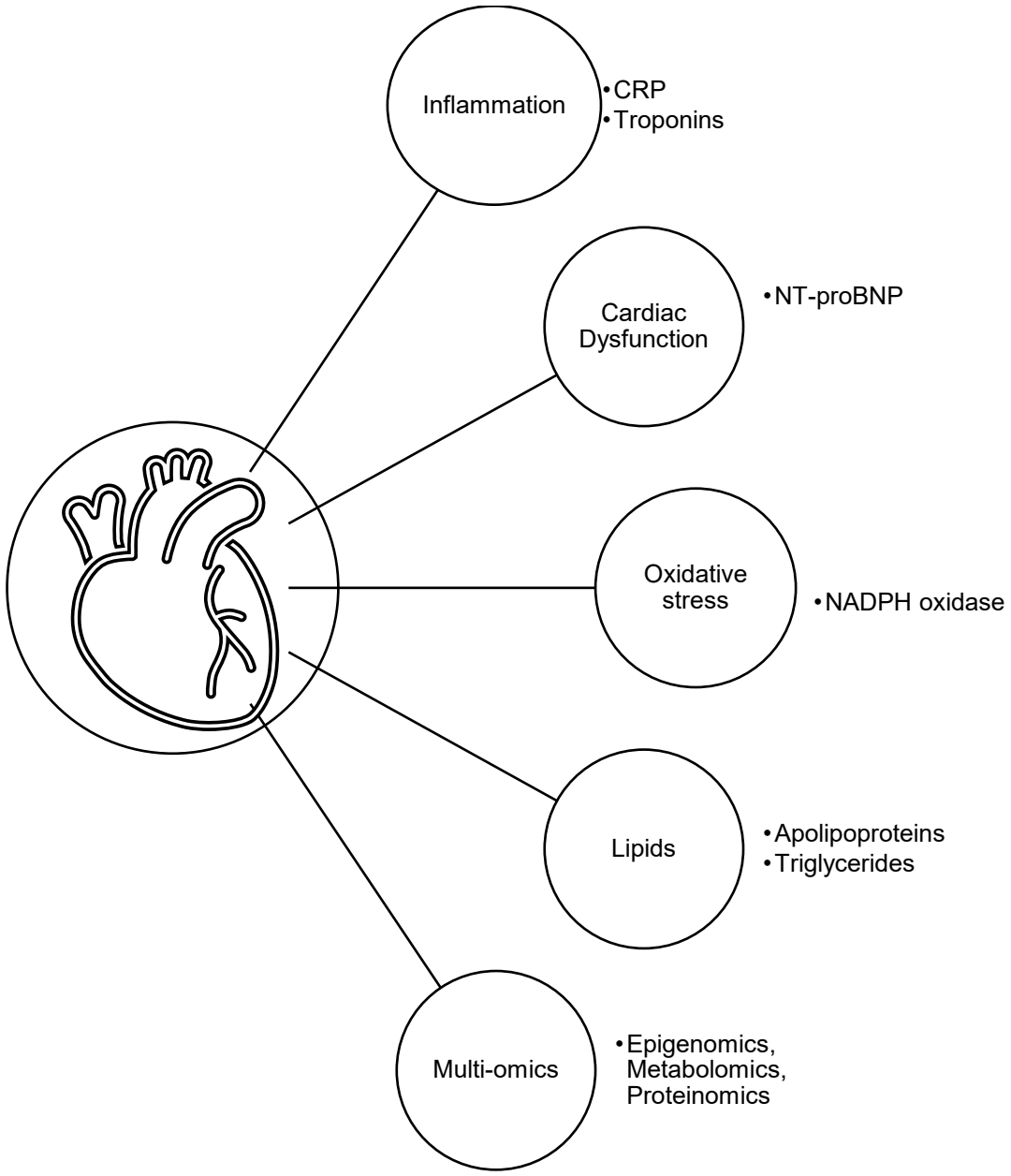

Figure 2. Biomarkers associated with cardiovascular disease

CRP= C-Reactive Protein; NT-proBNP= N-Terminal pro B-type Natriuretic Peptide; NADPH= Nicotinamide Adenine Dinucleotide Phosphate

6. Medical Imaging and Clinical Risk Factors

For participants with an ASCVD risk ≥10% in the prospective analysis conducted by Niu *et al.* (2020), the addition of electrocardiography (ECG) screening improved reclassification for those who did not experience events [62]. For low ASCVD risk individuals there was no significant association or improvement with the addition of ECG screening. Juxtaposing these findings, the earlier study by Goldman *et al.* (2019) suggests that

ECG screening in low-risk individuals may improve cardiovascular disease risk stratification [63]. Badheka *et al.* (2013) suggest that the addition of ECG abnormalities to the Framingham Risk Score improves model discrimination and calibration [64].

Modification of blood pressure cut-offs failed to improve the discrimination of 10-year cardiovascular disease mortality in the study by Peng and Wang (2020) [65]. Likewise, blood pressure load was reported to not improve risk prediction based on 24-hour blood pressure levels [66]. However, the study also suggests that modification of blood pressure cut-offs may still be beneficial in the calibration and classification of high cardiovascular disease risk. Additionally, Bell *et al.* (2012) suggests that averaging 2 measurements of blood pressure and lipid biomarkers (total cholesterol and HDL) markedly improves overall cardiovascular risk prediction [67].

Systolic blood pressure variability was added to the QRISK3 score; however, Stevens *et al.* (2019) infer that despite blood pressure variability being significant in a large dataset, it did not conclusively improve performance of cardiovascular risk scores in the validation dataset [68]. Similarly, Ayala Solares *et al.* (2019) and Pool *et al.* (2018) found that using multiple blood pressure recordings from patients' electronic healthcare record had negligible effects on models used to predict cardiovascular disease; but also, that using multiple blood pressure recordings resulted in a stronger association with incident cardiovascular disease than single measurements [69, 70]. Interestingly, Darabont *et al.* (2013) SEPHARII Study results found that visit-to-visit systolic blood pressure variability strongly correlated with arterial stiffness, and this combination may strengthen cardiovascular risk prediction [71]. Said *et al.* (2018) also suggests arterial index as a predictor variable, but alongside pulse pressure to improve cardiovascular disease risk prediction [72]. Inflammation and hemostasis blood biomarkers alongside arterial stiffness were again shown to support cardiovascular disease risk stratification in another study by Arnold *et al.* [73].

The ankle-brachial index (ABI) has also been proposed by previous studies to be a potential addition to cardiovascular disease risk prediction tools. Fores *et al.* (2018) is one such study that supports ABI as a tool for cardiovascular disease risk stratification, with results of the ARTPER cohort suggesting an ABI <0.9 was associated with an increased cardiovascular disease risk [74]. The study demonstrated improvements of the REGICOR scale and the Framingham Risk Score following the addition of ABI.

Flow-mediated dilation (FMD) is a measurement also considered in relation to cardiovascular disease risk. Irace *et al.* (2014) investigated FMD and found delayed vasodilation to be associated with increased cardiovascular disease risk [75]. Similarly, vascular functional robustness was propositioned by Kraushaar *et al.* (2018) as a potential biomarker for cardiovascular disease risk prediction [76].

Pulse wave analysis is a method suggested to assess potential biomarkers of cardiovascular disease risk. Results of the investigations by Cheng *et al.* (2016) found the systolic and diastolic rate constant for the central arterial pressure waveforms from pulse wave analysis to be valuable parameters for cardiovascular risk stratification [77]. A multi-marker approach was suggested by Greve *et al.* (2015) that utilises the presence of atherosclerotic plaque alongside albuminuria [78]. In this study carotid-femoral pulse wave velocity was not found to support cardiovascular risk stratification. Berard *et al.* (2020) also reported classification improvements from including the number of carotid or femoral atherosclerotic plaques within cardiovascular disease risk prediction [79].

van der Aalst *et al*. (2020) showed through the ROBINSCA trial, that when compared with SCORE, the coronary artery calcium (CAC) scoring classed significantly fewer subjects as high risk [80]. The study highlights weaknesses of SCORE (such as lack of adaption to different ethnic or age groups) and suggests CAC may be better for identifying patients who would benefit most from preventative treatment. A similar conclusion was reached in the study by Rana *et al.* (2012) that reports improvements of cardiovascular disease risk classification with CAC alone [81]. Craiem *et al.* (2020) also found that an increased CAC was associated with a higher cardiovascular disease risk, and that further details to include calcification size and density also improves the risk classification [82]. Yano *et al.* (2017) further conveys that CAC may be an alternative to age in cardiovascular disease risk prediction [83]. However, Stigall-Weikle *et al.* (2022) argue that the use of ionising radiation may not be justified for risk prediction particularly for individuals who are asymptomatic, and alternatively recommend non-invasive methods [84]. Like the proposed ocular vessel imaging, it could be argued that there may be more inexpensive and easily administered methods of assessing vasculature in cardiovascular disease risk prediction. The novel medical imaging methods of visualising the ocular microcirculation as previously discussed in the study by Brennan *et al*. [3] were updated to permit automated 4K resolution video processing in the study by Jing *et al.* [85]. Future research should encompass such techniques for application in telemedicine.

A diagram summarising a selection of medical imaging techniques discussed in this review is shown in Figure 3.

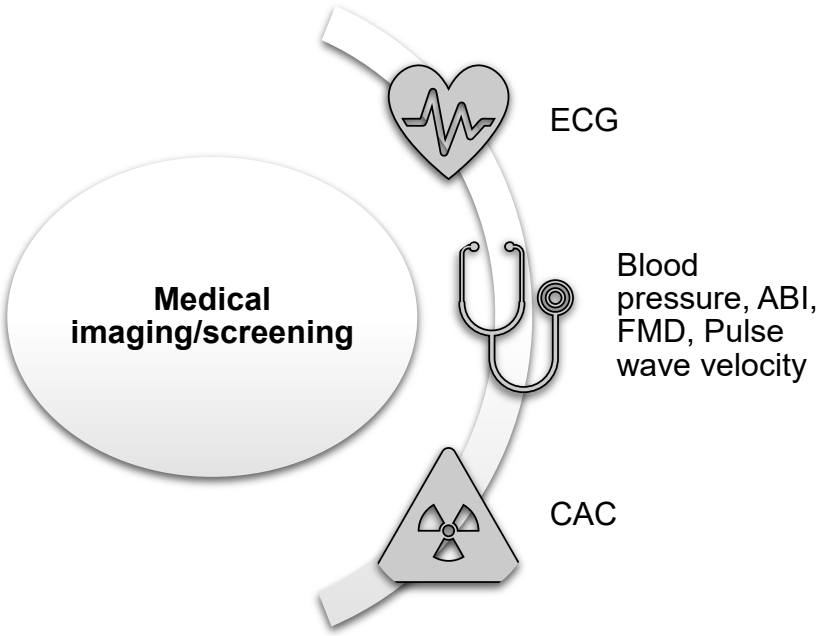

Figure 3. Medical imaging and clinical risk factors literature summary

ECG= Electrocardiogram, ABI= Ankle Brachial Index, FMD= Flow Mediated Dilation and CAC= Coronary Artery Calcium.

7. Conclusion

Standardised yet individualised risk assessments may support screening and augment patient care pathways. The addition of easily measured and interpreted vascular measurements to cardiovascular disease risk assessments, such as has been proposed with screening of the conjunctival vasculature, may be beneficial. Refinement of practical multi-marker algorithms or machine learning approaches incorporating lifestyle, family history, clinical history, biomarkers and medical imaging results may be beneficial to support clinical decision-making. Future risk prediction scores should also be more accessible and encourage patients to actively make positive lifestyle changes where possible.

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Table S1. Machine learning methods

Study	**Design**	**Aims**	**Risk Factors Assessed**	**Key Findings**
Alaa *et al.* 2019 [13]	A prospective study of 423,604 UK Biobank participants.	The study aims to assess the potential value of using ML approaches to derive risk prediction models for CVD.	473 variables were assessed. Physical activity (usual walking pace) and information on blood measurements were the top predictor variables.	AutoPrognosis model improved risk prediction (AUC-ROC: 0.774, 95% CI: 0.768-0.780) compared to Framingham score (AUC-ROC: 0.724, 95% CI: 0.720-0.728, $p < 0.001$), Cox PH model with conventional risk factors (AUC-ROC: 0.734, 95% CI: 0.729-0.739, $p < 0.001$), and Cox PH model with all UK Biobank variables (AUC-ROC: 0.758, 95% CI: 0.753-0.763, $p < 0.001$). Out of 4,801 CVD cases recorded within 5 years of baseline, AutoPrognosis was able to correctly predict

				368 more cases compared to the Framingham score.
Dimopoulos *et al.* 2018 [14]	10-year ATTICA prospective study (n=2020 adults)	To explore the potential of using machine learning methodologies on cardiovascular disease prediction, especially compared to established risk tool, the HellenicSCORE.	A total of 16 variables were assessed to include age, sex, smoking status, systolic blood pressure and total cholesterol levels.	HellenicSCORE showed accuracy 85%, specificity 20%, sensitivity 97%, PPV 87%, and NPV value 58%, whereas for the ML methodologies, accuracy ranged from 65 to 84%, specificity from 46 to 56%, sensitivity from 67 to 89%, PPV from 89 to 91%, and NPV from 24 to 45%; random forest gave the best results, while the k-NN gave the poorest results.
Hathaway *et al.* 2021 [15]	6814 participants from the Multi-Ethnic Study of Atherosclerosis (MESA) were followed over 16 years	To investigate whether novel deep learning survival models can augment atherosclerotic cardiovascular disease (ASCVD) risk prediction over existing statistical and machine learning approaches.	A total of 33 variables were assessed, and age and coronary artery calcium score were found to be top predictor variables.	Compared to the COXPH model, DeepSurv significantly improved ASCVD risk prediction for MAE (AUC: 0.82 vs. 0.80, $P \leq 0.001$) and mortality (AUC: 0.87 vs. 0.84, $P \leq 0.001$) with traditional risk

				factors alone. Implementing non-categorical NRI, resulted in a >40% increase in correct reclassification compared to the COXPH model for both MAE and mortality ($P \leq 0.05$). Assessing the relative risk of participants, DeepSurv was the only learning algorithm to develop a significantly improved risk score criteria, which outcompeted COXPH for both MAE (4.22 vs. 3.61, $P = 0.043$) and mortality (6.81 vs. 5.52, $P = 0.044$). The addition of inflammatory or imaging biomarkers to traditional risk factors showed minimal/no significant improvement in model prediction.

Kakadiaris *et al.* 2018 [12]	Machine learning risk calculator was developed based on SVMs using a 13-year follow up data set from MESA (the Multi-Ethnic Study of Atherosclerosis) of 6459 participants who were atherosclerotic CVD-free at baseline.	Using machine learning and the same risk factors used by ACC/AHA Risk Calculator, the study aimed to improve CVD risk stratification. The approach was tested in MESA (the Multi-Ethnic Study of Atherosclerosis) and also used FLEMENGHO (the Flemish Study on Environment, Genes and Health Outcomes) for external validation.	Age, gender, ethnicity, total cholesterol, high density lipoprotein, systolic blood pressure, history of hypertension, history of diabetes and smoking history.	Sensitivity= 0.86, specificity= 0.95, and AUC= 0.92.
Mannan *et al.* 2013 [16]	The Framingham Heart Study Dataset was used	The study aims at illustrating SAS computer programs for estimating overoptimism in measures of discrimination using two bootstrap validation algorithms through a concrete example from an active research field of chronic disease risk prediction– validation of a CVD risk prediction model.	Systolic and diastolic blood pressure, total and high density lipoprotein cholesterol, smoking status, age, sex, diabetes status, triglycerides and body mass index.	The degree of overoptimism in both Harrell's C and Somers' D statistics were low. Both these statistics were corrected for overoptimism by subtracting overoptimism from their observed values. Between the two bootstrap validation algorithms, the degree of overoptimism was estimated to be higher for

				stepwise bootstrap validation.
Sajid *et al.* 2021 [17]	A case–control study	A total sample of 460, 230 cases and 230 matched controls, were selected from September 2018 to February 2019.	Age groups, hypertension, low fruit consumption, smoking history, low vegetables consumption, physical inactivity, red meat/poultry consumption, diabetes mellitus, consumption of high salty foods, abdominal obesity, high fried foods/ trans fats, parental history of cardiovascular disease and self-reported general stress.	The first finalised model (ANN with 1 hidden layer) provided a risk prediction model with 81.09% accuracy and 0.871 AUC. The sensitivity (0.780) and specificity (0.848) values of the ANN-based model showed consistency in predicting the TP and TN values of the dataset. The linear SVM reported the best hyperplanes with an accuracy of the model of 80.86%.
Unnikrishnan *et al.* 2016 [18]	3654 participants over 15-years (5-year follow-up intervals) via Blue Mountain Eye Study database	To determine if the parameters used by Framingham model are relevant to a different database, this study measured the sensitivity and specificity obtained using SVM.	Age, body mass index, smoking status, gender, total cholesterol, systolic blood pressure, high density lipoprotein cholesterol,	Sensitivity obtained from the FEq was 0.52 (95% CI: 0.4096 to 0.6275), from the LRA was 0.48 (95% CI: 0.3817 to 0.5809), and from the SVM was 0.682 (95% CI: 0.589 to

			diabetes status, hypertension medications, retinopathy and diastolic blood pressure.	0.764). This shows that the sensitivity of the FEq and logistic analysis is comparable, while that of SVM is better and thus provides better risk assessment. The AUC test shows that the SVM results were greatly improved (0.71) compared with Framingham (0.57) or LRA (0.63).
Unterhuber *et al.* 2021 [11]	Using the OLINK-Cardiovascular-II panel, 92 proteins were measured in a cohort of 1,998 individuals from the LIFE-Heart Study (derivation) and 772 subjects from the PLIC (Progressione della Lesione Intimale Carotidea) cohort (external validation).	This study compared proteomics-enabled ML algorithms with classical and clinical risk prediction methods for all-cause mortality in cohorts of patients with cardiovascular risk factors in the LIFE-Heart Study, followed by validation in the PLIC study.	Age, sex, body mass index, smoking status, diabetes, use of antihyper-tensive medication, high-density lipoprotein cholesterol, total cholesterol, and triglyceride levels and influencing proteins to include brain natriuretic	On internal and external validation, the Framingham Risk Score achieved AUCs of 0.64 (95% CI: 0.59-0.68) and 0.65 (95% CI: 0.58-0.74), logistic regression AUCs of 0.65 (95% CI: 0.57-0.73) and 0.67 (95% CI: 0.59-0.74), Cox regression AUCs of 0.55 (95% CI: 0.51–0.59) and 0.65 (95% CI: 0.57-0.73), the XGBoost

			peptide, tumour necrosis factor-related apoptosis-inducing ligand receptor 2 and chymotrypsin.	classifier AUCs of 0.83 (95% CI: 0.79-0.87) and 0.91 (95% CI: 0.86-0.95), the XGBoost survival estimator AUCs of 0.83 (95% CI: 0.79-0.87) and 0.93 (95% CI: 0.88-0.97), and the neural network AUCs of 0.87 (95% CI: 0.83-0.91) and 0.94 (95% CI: 0.90-0.98), respectively (modern vs classical ML: $P < 0.001$).
Weng *et al.* 2017 [19]	Prospective cohort study (10 years) using routine clinical data of 378,256 patients from UK family practices, free from cardiovascular disease at outset.	The aim of this study was to evaluate whether ML can improve accuracy of cardiovascular risk prediction within a large general primary care population. The study also sought to determine which class of ML algorithm has highest predictive accuracy.	Gender, age, smoking status, systolic blood pressure, blood pressure treatment, total cholesterol, high density lipoprotein cholesterol and diabetes.	Compared to the established risk prediction algorithm (AUC 0.728, 95% CI 0.723–0.735), ML algorithms improved prediction: random forest +1.7% (AUC 0.745, 95% CI 0.739–0.750), logistic regression +3.2% (AUC 0.760, 95% CI 0.755–0.766), gradient boosting +3.3% (AUC

				0.761, 95% CI 0.755–0.766), neural networks +3.6% (AUC 0.764, 95% CI 0.759–0.769). The highest achieving (neural networks) algorithm predicted 4,998/7,404 cases (sensitivity 67.5%, PPV 18.4%) and 53,458/75,585 non-cases (specificity 70.7%, NPV 95.7%), correctly predicting 355 (+7.6%) more patients who developed CVD compared to the established algorithm.

Abbreviations:

ACC/AHA= American College of Cardiology/American Heart Association, ANN= Artificial Neural Network, AUC-ROC= Area Under the Curve- Receiver Operating Characteristic curve, CI= Confidence Intervals, CVD= Cardiovascular Disease, FEq= Framingham Equation, K-NN= K-Nearest Neighbour algorithm, LRA= Logistic Regression Analysis, MAE= Major Adverse Event, ML= Machine Leaning, NPV= Negative Predictive Value, NRI= Neural Relational Inference, PH= Proportional Hazards, PPV= Positive Predictive Value, SVM= Support Vector Machines, TN= True Negative, TP= True Positive