Prediction of Major Adverse Cardiovascular Events From Retinal, Clinical, and Genomic Data in Individuals With Type 2 Diabetes: A Population Cohort Study

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OBJECTIVE

Improved identification of individuals with type 2 diabetes at high cardiovascular (CV) risk could help in selection of newer CV risk-reducing therapies. The aim of this study was to determine whether retinal vascular parameters, derived from retinal screening photographs, alone and in combination with a genome-wide polygenic risk score for coronary heart disease (CHD PRS) would have independent prognostic value over traditional CV risk assessment in patients without prior CV disease.

RESEARCH DESIGN AND METHODS

Patients in the Genetics of Diabetes Audit and Research Tayside Scotland (GoDARTS) study were linked to retinal photographs, prescriptions, and outcomes. Retinal photographs were analyzed using VAMPIRE (Vascular Assessment and Measurement Platform for Images of the Retina) software, a semiautomated artificial intelligence platform, to compute arterial and venous fractal dimension, tortuosity, and diameter. CHD PRS was derived from previously published data. Multivariable Cox regression was used to evaluate the association between retinal vascular parameters and major adverse CV events (MACE) at 10 years compared with the pooled cohort equations (PCE) risk score.

RESULTS

Among 5,152 individuals included in the study, a MACE occurred in 1,017 individuals. Reduced arterial fractal dimension and diameter and increased venous tortuosity each independently predicted MACE. A risk score combining these parameters significantly predicted MACE after adjustment for age, sex, PCE, and the CHD PRS (hazard ratio 1.11 per SD increase, 95% CI 1.04–1.18, $P = 0.002$) with similar accuracy to PCE (area under the curve [AUC] 0.663 vs. 0.658, $P = 0.33$). A model incorporating retinal parameters and PRS improved MACE prediction compared with PCE (AUC 0.686 vs. 0.658, $P < 0.001$).

CONCLUSIONS

Retinal parameters alone and in combination with genome-wide CHD PRS have independent and incremental prognostic value compared with traditional CV risk assessment in type 2 diabetes.

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Patients with type 2 diabetes have a disproportionately higher risk of atherosclerotic cardiovascular disease (ASCVD) morbidity and mortality compared with individuals without type 2 diabetes (1,2). Most of this excess risk has been attributed to the higher prevalence of conventional cardiovascular (CV) risk factors in patients with type 2 diabetes. Currently, risk estimates using scores, such as the American College of Cardiology/American Heart Association ACVD Pooled Cohort Equation (PCE) risk score, are recommended in clinical guidelines to identify at-risk patients for primary prevention therapy (3,4). While these risk scores are useful in identifying high-risk patients, they can overestimate CVD risk across the population and have poor calibration in those with type 2 diabetes (5). It is also worth noting that the relationship between the presence of traditional CVD risk factors and atherosclerosis development is not necessarily direct and that CVD events can occur despite effective traditional CVD risk management. Thus, substantial improvement in identifying individuals remaining at high CVD risk in type 2 diabetes is urgently needed, particularly in light of novel therapies such as sodium–glucose cotransporter 2 inhibitors and glucagon-like peptide-1 receptor agonists, which reduce CVD risk (6,7).

Recent studies have shown that assessment of the genomic risk of coronary heart disease (CHD) using genome-wide polygenic risk scores (PRS) can be integrated into traditional clinical risk prediction models (8). These CHD PRS have shown equivalent predictive accuracy to clinical risk scores, although they have not specifically been examined in the higher-risk type 2 diabetes population (9,10).

Patients in the U.K. with type 2 diabetes undergo regular diabetes retinal screening (DRS) to manage risk of diabetic retinopathy. There is increasing interest in the potential use of DRS screening photographs as a source of screening for more global risk of diabetes complications beyond diabetic retinopathy, including CVD. Such a noninvasive direct assessment of global vascular risk would greatly enhance the efficiency of DRS and might provide incremental value beyond traditional CV risk markers. Previous work has demonstrated that the presence of retinopathy is associated with adverse CV events in individuals with and without type 2 diabetes (11–14). Studies have also reported the association of specific retinal vascular morphometric parameters, such as retinal vessel diameter (15,16), tortuosity (17), and fractal dimension (a measure of branching complexity) (18), with both CVD risk factors and CVD events. Recently, automated deep-learning approaches have been used to predict the presence of CVD risk factors on the basis of a retinal photograph alone (19), further indicating the retina can provide relevant information on CVD risk. Promisingly, this approach was also able to predict CV outcomes with a similar accuracy as traditional risk factors.

The aim of this study was to determine whether retinal vascular parameters measured from DRS photographs, alone and in combination with a genome-wide CHD-PRS would have independent and incremental prognostic value over traditional CVD risk assessment.

RESEARCH DESIGN AND METHODS

Study Cohort

Individuals with type 2 diabetes from the Genetics of Diabetes Audit and Research Tayside Scotland (GoDARTS) study were used for this study. GoDARTS has been previously described (20). In brief, GoDARTS is a cohort study in the Tayside region of Scotland (population ~400,000) that began recruiting in 1996 and up to 2015 and included 10,149 individuals with type 2 diabetes and 8,157 control subjects without type 2 diabetes at the time of recruitment. Data on clinical and lifestyle parameters were collected at the time of recruitment, and participants also provided consent to electronic health record linkage for past and future clinical events, including laboratory tests, eye screening, hospital admissions, and death. Patients also provided a sample of blood for genotyping, and genome-wide association was performed using a number of separate genotyping arrays, including the Affymetrix Genome-Wide Human SNP (single nucleotide polymorphism) Array 6.0, the Illumina HumanOmniExpress, Immunochip, Metabochip, or the Human Exome array. The GoDARTS study and electronic health record (EHR) linkage has been approved by the East of Scotland Research Ethics Committee (Dundee, U.K.). The EHR is fully anonymized and provided to researchers through robust information governance protocols administered by the Health Informatics Centre (HIC) Safe Haven, including research ethics approval for studies conducted within the Safe Haven environment.

Derivation of the cohort for this study is summarized in Supplementary Fig. 1. According to current recommendations for use of the PCE risk score, we selected patients aged between 40 and 79 years old with no prior history of hospitalization for myocardial infarction (MI) or stroke using ICD-10 codes I21–I23 and I60–I63. We used the date of the retinal photograph used for obtaining the vascular parameter as the study entry date. For clinical measurements (e.g., blood pressure, glycated hemoglobin, and cholesterol) where there was more than one measure prior to the date of retinal imaging, the median of values within the preceding 3 years was used to provide a measurement reflective of the true value. These values were used to calculate the PCE risk score for 10-year risk of CVD events at the time of retinal imaging (21). The genome-wide CHD PRS was assembled for each GoDARTS participant by integrating data across the various genotyping platforms based on the genome-wide analysis and data provided by Khera et al. (22). We used the "score" function in plink 1.9 to generate the PRS (the file was preprocessed to include one line per scored variant). To avoid issues of variable availability of SNP assays between genotyping arrays, giving rise to individual variability in score simply due to available SNP numbers, the CHD PRS was *z*-transformed.

Retinal Vascular Parameters

The Scottish National DRS uses standardized protocols that are used across all participating centers. Further details are available at https://www.ndrs.scot.nhs.uk/. In the Scottish DRS, the retina is photographed with a 45° view centered on the macula. The earliest available DRS digital retinal photographs were obtained for patients with type 2 diabetes in GoDARTS. These photographs had been previously reported for the presence of retinopathy by trained ophthalmologists for the purposes of clinical management at the time. No further analysis or selection was performed prior to assessment using the VAMPIRE (Vascular

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Assessment and Measurement Platform for Images of the Retina; version 3.1, University of Edinburgh, Edinburgh, and University of Dundee, Dundee, U.K.) software platform. Further details on the VAMPIRE analysis pipelines, including interobserver variability, have been published previously. The right eye was prioritized for measurement of vascular parameters. Where the right eye photograph was not of sufficient quality, based on the related Scottish DRS data, the left eye photograph was selected. The measurement methodology, variability, and workflow for VAMPIRE has been previously described (23–27). While VAMPIRE measures a comprehensive range of retinal vascular parameters using a semiautomated artificial intelligence approach, for this analysis we considered three of the most widely investigated retinal vascular parameters for both retinal arterioles and venules—fractal dimension (FD) of the retinal vascular pattern (FDa and FDv), tortuosity (arterial and venous), and central retinal artery and vein equivalent (CRAE and CRVE), which summarize vessel caliber.

Clinical Outcomes

The primary outcome for this study was the time-to-first incidence of a composite three-point major adverse CV event (MACE) comprising CV death, nonfatal myocardial infarction (MI), and nonfatal stroke after the date of the retinal photograph. Patients were followed up to December 2017 for a maximum of 10 years up from the date of the analyzed retinal photograph until the first qualifying event (CV death, MI, or nonfatal stroke) or censored at non-CV death. Follow-up was limited to 10 years to correspond to the duration of CVD prediction from the PCE risk score. Cause and date of death was obtained from the General Register of Scotland, with any ICD-10 code from I00–I99 within the first 2 causes of death recorded as a CV death. Nonfatal MI and stroke events were determined from the Scottish Morbidity Record of hospitalizations using the same ICD codes.

Statistical Analysis

Continuous variables are reported as mean ± SD or median and interquartile range, as appropriate, and categorical variables as number and percentage. Retinal vascular parameters were standardized by *z*-transformation to facilitate comparisons. The correlations between continuous clinical variables, the PCE 10-year CV risk score, and the CHD PRS and retinal vascular parameters were assessed using the Pearson correlation coefficient; *t* tests were performed to assess differences between categorical clinical variables and retinal parameters.

Associations between the PCE risk score, CHD PRS, and retinal vascular parameters and time to first MACE were evaluated using Cox proportional hazards regression with adjustment for age and sex. Hazard ratios (HRs) for retinal vascular parameters and the CHD PRS are reported per SD increase in the *z*-transformed value. We created a combined retinal risk score based on the β-coefficients from the adjusted Cox regression model of retinal vascular parameters that were significantly associated with MACE. The independent association of the retinal risk score with MACE was assessed using Kaplan-Meier analysis and multivariable Cox regression with adjustment for age, sex, duration of diabetes, glycated hemoglobin, PCE risk score, and the CHD PRS. The incremental predictive value of the retinal risk score and the CHD PRS, in addition to PCE risk score, was assessed using receiver operating characteristic (ROC) curves, with the area under the curve (AUC) compared. Additionally, we calculated the continuous net reclassification index (NRI) and integrated discrimination index (IDI). All tests were two-sided, and a P value of <0.05 was considered significant. All analyses were performed using R 3.5.1 software.

RESULTS

Baseline Characteristics

The primary analysis included 5,152 individuals with type 2 diabetes without a prior MACE (Supplementary Fig. 1). Baseline cohort characteristics are summarized in Table 1. The selected cohort was similar to the overall type 2 diabetes population in GoDARTS (Supplementary Table 1). On the date of the photograph used for measurement and entry into the study, the cohort was a mean age of 65.2 ± 9.3 years, and 43.9% of the cohort was female. The median duration since diagnosis of diabetes was 6.7 years, and mean glycated hemoglobin was 59.1 ± 12.7 mmol/L (7.6 ± 1.2%). At the time of retinal screening, 1,130 individuals (21.9%) had any level of diabetic retinopathy, whereas only 11 individuals (1.9%) had proliferative retinopathy. Median total cholesterol was 4.4 mmol/L. As expected, the population was at a relatively high CV risk, with a median PCE 10-year risk of ASCVD estimated at 29%. The majority of the population (74%) was on statin therapy at the time of retinal imaging.

Association of Individual Retinal Vascular Morphological Parameters With Clinical Variables

Correlations between retinal vascular parameters and continuous clinical and genomic risk were weak, with all r values between -0.1 and 0.1 (Supplementary Fig. 2). Each individual retinal parameter was only weakly correlated with PCE 10-year ASCVD risk (r values between -0.07 and 0.05) and the CHD PRS (r values between -0.03 and 0.05).

Association Between Individual Retinal Vascular Parameters and Cardiovascular Outcomes

At 10 years (median follow-up 9.8 years), 1,017 individuals had a MACE occurrence (19.7% of the whole cohort), including 794 CV deaths (15.4%), 274 nonfatal MIs (5.3%), and 151 nonfatal strokes (2.9%).

After adjustment for age and sex, increased FDa, decreased tortv, and increased CRAE were all significantly associated with MACE incidence (Table 2). After additional adjustment for PCE risk score and the CHD PRS, these variables remained independently associated with MACE, with little change in the HR estimates (FDa HR 0.93 per SD increase, 95% CI 0.86–1.00, $P = 0.040$; tortv HR 1.08, 95% CI 1.01–1.15, $P = 0.019$; CRAE HR 0.90, 95% CI 0.83–0.98, $P = 0.015$).

Combined Retinal Score and Association With Clinical Risk Factors and Outcomes

Using the β-coefficients from the Cox model adjusted for age, sex, PCE risk score, and CHD PRS (shown in Table 2) for the association of FDa ($\beta = -0.08$), tortv ($\beta = 0.07$), and CRAE ($\beta = -0.10$) with MACE, we constructed an overall retinal risk score as follows:

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Table 1—Baseline characteristics

	Patients (N = 5,152)
Age (years)	65.2 ± 9.3
Female sex	2,263 (43.9)
Diabetes duration (years)	6.7 (3.8–10.6)
Smoking history	2,602 (50.5)
Glycated hemoglobin (mmol/mol)	59.1 ± 12.7
Glycated hemoglobin (%)	7.6 ± 1.2
Systolic blood pressure (mmHg)	139 ± 11
Diastolic blood pressure (mmHg)	77 ± 8
BMI (kg/m^2)	32 ± 6
Total cholesterol (mmol/L)	4.4 ± 0.9
HDL cholesterol (mmol/L)	1.3 ± 0.3
PCE 10-year ASCVD risk (%)	29 (16–42)
Oral antihyperglycemic therapy only	1,935 (37.6)
Insulin use	1,408 (27.3)
Aspirin use	2,243 (43.5)
Statin use	3,817 (74.1)
Any retinopathy	1,229 (23.9)

Continuous variables are reported as mean ± SD or median (interquartile range) and categorical variables as *n* (%).

$$\text{Retinal risk score} = (-0.08 * \text{FDa}) + (0.07 * \text{tortv}) + (-0.10 * \text{CRAE})$$

Men had higher retinal risk scores than women (1.99 vs. 1.79, $P < 0.001$). There was no difference in the retinal risk score between smokers and nonsmokers (1.90 vs. 1.91, $P = 0.89$). Similar to individual retinal vascular parameters, correlations between the retinal risk score and continuous clinical risk factors were weak (Supplementary Fig. 2), with the greatest correlation being with systolic blood pressure ($r = 0.084$), followed by duration of diabetes ($r = 0.074$) and age ($r = 0.062$). While the retinal risk score was weakly correlated with the PCE risk score ($r = 0.094$) there was no correlation with CHD PRS ($r = -0.021$).

After adjustment for age, sex, glycated hemoglobin, diabetes duration, PCE risk score, and the CHD PRS, the retinal risk score was significantly associated with incidence of MACE (HR 1.11, 95% CI 1.04–1.18, $P = 0.002$) (Table 3). Patients in the highest tertile of retinal risk score had a significantly increased likelihood of MACE incidence than those in the lowest tertile (HR 1.32, 95% CI 1.13–1.55, $P < 0.001$) (Supplementary Fig. 3). There was a significant interaction between the retinal risk score and age, with the retinal risk score being more strongly associated with outcome in younger patients (median age 66.3 years to <66.3 years old HR 1.23, 95% CI 1.09–1.38, $P < 0.001$; ≥66.3 years HR 1.05, 95% CI 0.97–1.14, $P = 0.20$; interaction $P = 0.012$). The retinal risk score was more strongly associated with MACE in individuals at the lowest genetic or clinical risk; however, the interaction between the retinal risk score and the PRS or PCE scores did not reach statistical significance ($P = 0.14$ and $P = 0.09$, respectively) (Supplementary Table 2).

A model combining age, sex, and the retinal risk score had similar predictive performance to the PCE risk score (AUC 0.663 vs. 0.658) (Fig. 1 and Supplementary Table 3). There was a small improvement in NRI (0.080, 95% CI 0.010–0.150, $P = 0.024$), although there was no improvement in the IDI. A model including age, sex, retinal risk score, and the CHD PRS performed significantly better than the PCE risk score (AUC 0.686 vs. 0.658, $P < 0.001$; IDI 0.019, 95% CI 0.013–0.025; NRI 0.240, 95% CI 0.147–0.285, both $P < 0.001$). The addition of the PCE score to a model with age, sex, retinal risk score, and the CHD PRS did provide modest improvement (AUC 0.690 vs. 0.686, $P = 0.033$; IDI 0.004, 95% CI 0.002–0.006, $P < 0.001$; NRI 0.07, 95% CI 0.00–0.14, $P = 0.05$).

CONCLUSIONS

We have identified several key findings in this analysis of patients with type 2 diabetes without a prior history of MI or stroke. First, we have shown that a

Table 2—Association of individual retinal vascular parameters with incidence of MACE at 10 years

	HR adjusted for age and sex (95% CI)	P value	HR adjusted for age, sex, PCE, and CHD PRS (95% CI)	β (SE)	P value
FDa	0.92 (0.85–0.99)	**0.020**	0.93 (0.86–1.00)	−0.077 (0.038)	**0.040**
FDv	1.01 (0.94–1.09)	0.77	1.02 (0.94–1.10)	0.016 (0.039)	0.69
Tortuosity (arterial)	0.99 (0.93–1.05)	0.64	0.97 (0.91–1.04)	−0.030 (0.033)	0.37
Tortuosity (venous)	1.08 (1.01–1.15)	**0.022**	1.08 (1.01–1.15)	0.077 (0.033)	**0.019**
CRAE	0.88 (0.81–0.96)	**0.003**	0.90 (0.83–0.98)	−0.104 (0.043)	**0.015**
CRVE	1.06 (0.98–1.14)	0.16	1.05 (0.97–1.14)	0.047 (0.040)	0.25

All HRs per SD increase. The bold P values are statistically significant ($P < 0.05$).

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Table 3—Association of retinal, clinical, and polygenic risk scores with incidence of major adverse cardiovascular events at 10 years

	Unadjusted HR (95% CI)	*P* value	Adjusted HR (95% CI)	*P* value
Retinal risk score (per SD increase)	1.21 (1.13–1.28)	**<0.001**	1.11 (1.04–1.18)	**0.002**
PCE (per 5% increase)	2.01 (1.86–2.17)	**<0.001**	1.40 (1.20–1.63)	**<0.001**
CHD PRS (per SD increase)	1.60 (1.44–1.79)	**<0.001**	1.68 (1.49–1.90)	**<0.001**

Combined retinal risk score = (−0.08*FDa) + (0.07*tortv) + (−0.10*CRAE). Multivariable model included age, sex, glycated hemoglobin, duration of diabetes, retinal risk score, PCE, and CHD PRS. All HRs per SD increase. The bold *P* values are statistically significant ($P < 0.05$).

simple retinal risk score based on these retinal parameters is independently associated with MACE and has similar performance to an established clinical risk score for prediction of 10-year MACE incidence. Second, we found that the combination of the retinal risk score plus a CHD polygenic risk score had incremental prognostic value for prediction of MACE over the PCE risk score alone. These findings raise the possibility that clinical CV risk prediction could potentially be achieved using routinely obtained retinal photographs, obviating the need for logistically more complex, costly, and inconvenient clinic attendances for blood sampling and blood pressure assessments, and clinical history taking, etc. Such an approach may have particular benefits in remote rural communities where access to health care is limited, because retinal photography can be relatively easily acquired using mobile phone technology and portable cameras (28). Genome-wide data also provide improved prediction, only need to be obtained once, are increasingly cheap and convenient to obtain, and also can be obtained remotely by relatively simple procedures. Use of routinely obtained retinal photographs may be a particularly efficient method of determining CV risk in patients with type 2 diabetes.

Previous studies have shown that some retinal vascular parameters are associated with increased CV risk, although many of these studies are limited by their cross-sectional study design. Most have reported only associations of retinal vascular diameter (CRAE and CRVE) with CV risk factors. A recent cross-sectional study of >50,000 individuals from UK Biobank found an association between narrower retinal arterioles and higher systolic blood pressure and arterial stiffness (29). This study also reported opposing results for retinal venous diameter, which replicated results from previous studies (30,31). Consistent with other studies, we found that narrower retinal arterioles are associated with worse outcome (15,16,32,33).

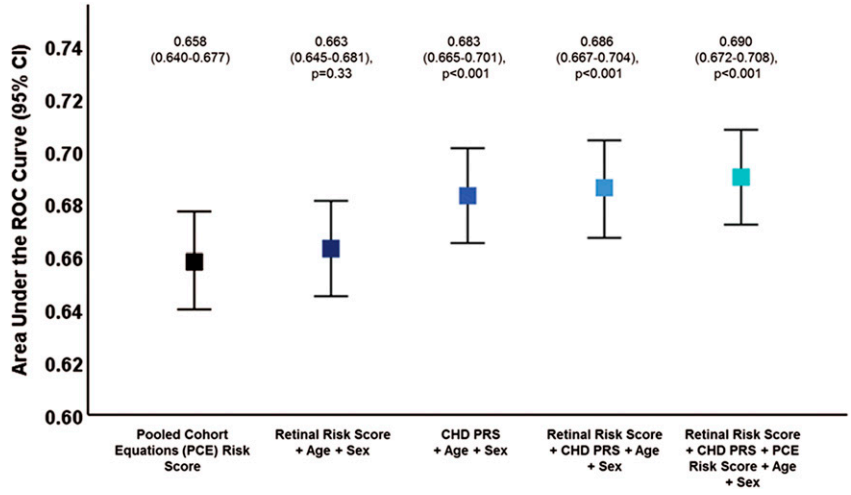

Figure 1—Area under the ROC curve analysis. Comparison of PCE, retinal, and genetic risk models for prediction of MACE at 10 years showing the AUC and 95% CIs. *P* values all vs. PCE risk score alone.

Fewer studies have evaluated the association of FD with CV risk. Importantly very few studies have considered the FDa and FDv separately, with most combining the two for an overall assessment. We found that FDa but not FDv was independently associated with MACE. Our finding that increased FDa was associated with reduced MACE incidence is supported by other studies showing that lower overall FD was associated with older age and higher mean arterial blood pressure (34–36). Liew et al. (18) evaluated 3,303 individuals and reported a U-shaped association between overall FD and CV outcomes, with those with FD in the lowest and highest quartiles having the highest risk of CHD mortality. This has not been replicated elsewhere; we found that FDa and FDv dimension had opposing associations with MACE, which may explain their findings. A small cross-sectional study of 55 individuals did document opposing associations between retinal FDa and FDv and cerebrovascular MRI findings (37).

A key novel aspect of our study is the fact that we have simultaneously considered multiple retinal parameters, and this allowed us to combine the independent features into a simple retinal risk score and compare this with the PCE risk score. While we only found very weak correlations between the retinal risk score and conventional clinical risk factors, the retinal risk score was independently associated with MACE even after adjustment for clinical and genetic risk. This may indicate that the information provided by the retina is, to an extent, independent of and additional to conventional clinical and genomic risk factors and may indicate endogenous phenotypic susceptibility to lifestyle and genetic background. Our finding that the retinal risk score performed at least as

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well as the PCE score further underscores the potential for routinely obtained retinal photographs to provide an assessment of global CV health, providing added value to diabetes retinal screening programs. The ability to directly image the vasculature via the retina is particularly attractive, and assessment of the retina appears to provide novel information related to CV risk.

A further unique aspect to our study is the incorporation of a large genome-wide polygenic risk score for CHD. These PRS are becoming increasingly available (https://www.pgscatalog.org), and recent studies have tested their ability to provide incremental risk prediction in addition to traditional CV risk markers. Inouye et al. (8) showed that a large CHD PRS was able to predict adverse outcome and had a higher C-statistic than any individual risk factors. As in our study, a CHD PRS has also been shown to have incremental value over the PCE risk score (10). Taking this approach one step further, we have shown that the combination of retinal and polygenic risk scores (in addition to age, sex, glycated hemoglobin, and duration of diabetes) performs significantly better for prediction of MACE than the PCE risk score.

Our study may have useful clinical implications. While we do not suggest that retinal and PRS could completely replace clinical risk factor measurements, their use could have additional clinical value in identifying higher-risk patients who could benefit from cardioprotective therapies such as sodium–glucose cotransporter 2 inhibitors and glucagon-like peptide 1 receptor agonists. Recent work has demonstrated the use of a CHD PRS in the Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab (ODYSSEY OUTCOMES) trial independent of LDL-cholesterol, and those with higher PRS derived greater benefit from alirocumab (38). With low-cost genome-wide genotyping becoming increasingly available, and routine type 2 diabetes retinal screening conducted in many countries, it is likely that these could be readily incorporated into routine clinical practice.

Our study does have some limitations. Despite our large sample size and longitudinal data incorporating genetics, it remains an observational study with its inherent limitations. Our cohort only includes individuals with type 2 diabetes and so cannot necessarily be extrapolated to individuals without type 2 diabetes. It would be interesting in future work to apply this approach to individuals without diabetes. Similarly, our cohort is predominantly Caucasian, so the influence of the CHD PRS may be different in other ethnicities. We only used three retinal parameters, and it is possible that other retinal parameters may also provide independent prognostic value. The retinal risk score was created and validated within one cohort and thus lacks external validation. Finally, we used specific software to analyze retinal images, and parameter values may not be the same as those obtained from other retinal image analysis (26). Further work needs to be undertaken to standardize and refine analytical pathways to allow adoption into clinical practice (26,39).

In individuals with type 2 diabetes with no prior history of MACE, a simple retinal risk score obtained from routine retinal photographs using a semiautomated artificial intelligence approach to artery and vein classification was able to predict incident MACE at 10 years with similar performance to the pooled cohort equations ASCVD risk score, particularly in younger individuals. The combination of retinal and genomic risk scores had independent and incremental prognostic value over the clinical risk score. Incorporation of these measures into routine clinical practice might help identify individuals at high CV risk over and above traditional clinical risk factors who might benefit from intensified CV-protective therapy and may even represent a feasible alternative to traditional clinical risk assessment.

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Author Contributions. I.R.M., E.T., C.C.L., and A.S.F.D. conceived and designed the study and analyzed and interpreted the data. I.R.M. and A.S.F.D. drafted the manuscript. M.G.S., T.M., A.N., Y.H., G.G., S.H., V.R., V.P., R.M.A., V.M., C.N.A.P., and E.R.P. critically revised the manuscript. I.R.M. and A.S.F.D. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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