Replacing the Framingham-based equation for prediction of cardiovascular disease risk and adverse outcome by using artificial intelligence and retinal imaging

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Short Title: Accurate prediction of heart failure using retinal imaging and AI

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Conflict of interest
Ehsan Vaghefi and David Squirrell are co-founders of Toku Eyes®, which is a start-up out of The University of Auckland, looking into commercialization of this artificial intelligence system. No other conflict of interest for co-authors.

Authors contribution
E.V. proposed the original research, developed the original methodology and developed the first draft of the manuscript. S.Y. & S.A supervised the technical aspect of the trial. D.S. supervised the clinical aspects of the trial and reviewed the manuscript. JM supported clinical aspects of the study and reviewed the manuscript.

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Abstract

Purpose: To create and evaluate the accuracy of an artificial intelligence Deep learning platform (ORAiCLE) capable of using only retinal fundus images to predict both an individuals overall 5 year cardiovascular risk (CVD) and the relative contribution of the component risk factors that comprise this risk.

Methods: We used 165,907 retinal images from a database of 47,236 patient visits. Initially, each image was paired with biometric data age, ethnicity, sex, presence and duration of diabetes a HDL/LDL ratios as well as any CVD event within 5 years of the retinal image acquisition. A risk score based on Framingham equations was calculated. The real CVD event rate was also determined for the individuals and overall population. Finally, ORAiCLE was trained using only age, ethnicity, sex plus retinal images. Next, ORAiCLE was modified and solved images only, and age, ethnicity, sex parameters only. The results of each of these restrictive models was also compared to those generated by the comprehensive ORAiCLE model.

Results: Compared to Framingham-based score, ORAiCLE was up to 12% more accurate in predicting cardiovascular event in the next 5-years, especially for the highest risk group of people. The reliability and accuracy of each of the restrictive models was suboptimal to ORAiCLE’s performance indicating that it was using data from both sets of data to derive its final results.

Conclusion:. Retinal photography is inexpensive and only minimal training is required to acquire them as fully automated, inexpensive camera systems are now widely available. As such, AI-based CVD risk algorithms such as ORAiCLE promise to make CV health screening more accurate, more affordable and more accessible for all. Furthermore, ORAiCLE’s unique ability to assess the relative contribution of the components that comprise an individuals overall risk would inform treatment decisions based on the specific needs of an individual, thereby increasing the likelihood of positive health outcomes.
Background

Cardiovascular disease (CVD) is the commonest cause of hospitalization and premature death in the U.S. [1]. The risk of an individual experiencing a CVD event includes both non-modifiable; age, sex, and ethnicity, and modifiable variables such as diabetes [2], hypertension [3], hyperlipidemia [4], and smoking [5]. Across a population the risk of experiencing a CVD event varies greatly and risk based equations have therefore been developed to identify those individuals who are greatest risk of a CVD event so that the treatments can be instigated appropriate to the individuals risk [6]. The landmark Framingham Heart Study was the first to demonstrate that multivariable equations could identify an individual’s CVD risk with far greater accuracy than the existing metrics based solely on blood pressure and cholesterol [7].

Since the Framingham-based equations were first published other equations have been developed designed to serve different populations with refined accuracy [8-15]. Kavousi et al reviewed the differences in prevention risk scores between three different guidelines (American College of Cardiology/American Heart Association, the Adult Treatment Panel III, and the European Society of Cardiology guidelines) on a sample of 4854 participants from the Netherlands. They found that these three models provided poor calibration and only moderate to good discrimination between subjects and their findings highlight the importance of both continuing to improve risk predictions and setting appropriate population-wide thresholds [8].

The use of multivariable equations has not only improved the accuracy of calculating an individual’s CVD risk, they have also improved our understanding of the complex interplay of factors that underpin this risk. This statistical approach does however have limitations. A recent systematic review and meta-analysis found that the Framingham-based risk models and pooled cohort equations for predicting 10-year risk of CVD not only had a tendency to overestimate the risk level, especially in higher-risk populations [16], they prove unreliable for people living with diabetes [17]. Similarly, [10] compared the Framingham-based risk equations with two local models on a population sample in Spain and found that the REGICOR model, developed locally, provided a better prediction compared to the Framingham risk equations, highlighting the usefulness of having models based on specific populations.

One weakness of existing multivariate equations is that the predictors used are not a direct measure of CVD. Instead the equations are based on regression models which utilise parameters known to correlate with CVD, including age, sex, ethnicity, socioeconomic deprivation, smoking, diabetes duration, systolic blood pressure (SBD), total cholesterol-to-HDL ratio (TCHDL), glycated hemoglobin A1c (HbA1c), and urine albumin-to-creatinine ratio (ACR) [18]. This approach is limited by the fact that the strength of these correlations will differ between groups, and, as such, the predictive power of the equation will vary depending on an individual’s clinical profile [19]. Additionally, the majority of CVD risk equations attempt to identify patients who are at risk of
experiencing cardiovascular events based on data obtained within a specific period of time. Invariably not all data is available at all time points [20] and the issue of missing data means that the equations may not accurately reflect risk in those who do not engage with or have access to healthcare services [21].

The retina is the only part of the human vasculature that is visible by non invasive means and in recent years there has been an exponential increase in the number of studies that have used Artificial intelligence (AI), and deep learning (DL) in particular, to extract data from retinal images [22]. Having recognised the power of DL to extract data from retinal images there is now intense interest in using the retinal image data generated by DL algorithms to augment the traditional means of estimating CVD risk [23]. To date algorithms have already been developed that generate a modifier to an individual chronolgical age to predict their biological Cardiovascular age [24]. Others have been developed that can predict coronary artery calcium (CAC) scores [25], [26] CT-based coronary artery disease [28], atherosclerosis [27] and those modifiable and non-modifiable CVD risk factors that contribute to CVD risk [28]. More recently, DL algorithms have been developed that directly predict CVD risk in given Chinese and UK populations [29]. Furthermore, a study conducted a genome-wide association study investigating the genetic component of retinal vasculature measured as fractal dimension and analyzed its relationship with CVD [30]. More recently, Cheung et al described a DL model for the assessment of cardiovascular disease risk via the measurement of retinal-vessel calibre [25]. The model was trained on multiethnic multicountry datasets that comprised more than 70,000 retinal images and provided performance that was comparable to, or better than, expert graders in associations between measurements of retinal-vessel calibre and CVD risk factors (e.g., blood pressure, body-mass index, cholesterol and glycated-haemoglobin levels).

We have developed a DL model (ORAiCLE), that predicts an individuals 5 year CVD risk based on data obtained solely from a retinal photograph. Unlike traditional CVD risk equations and existing DL prediction models, ORAiCLE calculates the interactions between modifiable factors when assessing the risk contribution of each to the total risk score. By doing so ORAiCLE learns if changes to one modifiable factor correlate with changes in other modifiable factors. In this study, we used 165,907 fundus images from a database of 47,236 patient visits to calculate a CVD risk score based on our DL platform ORAiCLE. We then calculated the predicted risk produced by the Framingham-based equations and compared the results of each with the actual CV event rate to determine the relative accuracy of the 2 prediction methods.
Methods

We used 165,907 fundus images from a database of 47,236 patient visits [Figure 1]. The make up of the data can be accessed through this dashboard https://public.tableau.com/app/profile/toku.eyes/viz/Predict2_16571562089950/Story. The dataset was acquired from multiple eye clinics in several countries, minimum of 5 years using several different commercial fundus cameras. These images were linked to information that were required for the Framingham-based equation [31], including age, ethnicity, sex, presence and duration of diabetes and cholesterol levels as well as any CVD event within 5 years of the retinal image acquisition. The data was split 60 / 20 /20 for training, validation and testing respectively. For the test set, the actual CVD events identified and the Framingham-based risk score was calculated [32].

To extract features from the fundus images for the CNNs base, we created an ensamble of 30 CNNs to look at a variety of changes in the fundus image. For each CNN, the dataset was then split for training, validation, and testing. The fundus images were first cropped and resized to 800x800 pixel size. The batch size was set to 6 to optimize the use of the GPU memory during training.

Figure 1: the flowchart of study design and execution
Adam optimizer was adopted with a learning rate $1 \times 10^{-3}$ to update parameters towards the minimization of the loss. Dropout was enabled with a rate $p = 0.2$, and the model was trained for at least 100 EPOCHs. All codes related to this work were implemented by Python 3.7. programming language.

The cross-entropy loss function was employed to guide the model parameters optimization. The training objective was to minimize the loss function to get the most accurate probability prediction of CVD events. Typically, cross-entropy loss is utilized in classification problems. Although the CVD event risk prediction is not a classification task, our label was 1 or 0, which represents whether a CVD event happened or not, respectively. Therefore, we adopted the cross-entropy loss. The overall loss can be formalized as

$$L = -\frac{1}{N} \left[ \sum_{j=1}^{N} [y_j \log (p_j) + (1 - y_j) \log (1 - p_j)] \right]$$

where $N$ is the number of training samples, $y_j$ is the ground truth of sample $j$, and $p_j$ is the predicted probability of CVD risk for sample $j$. The model performance was also measured by calculating the the cross-entropy.

Due to the amount of vasculature-related information that can be extracted from the retina, it should be possible to improve or match the performance of existing CVD risk calculators which require the results of invasive laboratory tests such as cholesterol and HbA1c [28]. During the development of ORAiCLE, model explanation mechanisms (SHapley Additive exPlanations – aka SHAP) were implemented to better understand the contribution of each aspect of the retinal image, and the retinovasculature in particular, on the final score [33, 34]. In brief, this process meant that it was possible to link the retinal changes to the physiological basis of these changes [28]. Utilising tools that can help explain the algorithm’s results offers unique insights into the contribution of each retinal change and its physiological basis to the overall CVD risk ORAiCLE generates. This is in contrast to the Framingham-based equations (gold standard) that are unable to identify errors within its underlying math due to the forced linearity between the parameters.

Once the model had been trained, it was tested on a separate random sample of 7,320 patient data presented as an input to the model for the first time. This dataset was then sorted by their ORAiCLE score and split into 4 equal groups of 1,830 people, where the actual CVD event rate, the average ORAiCLE score, and the average Framingham-based equation score was calculated for each group [Figure 2]. The standard deviations were also calculated for the ORAiCLE and Framingham-based equation scores.

Finally, in order to examine the extent to which ORAiCLE learnt from the retinal images and the biomarker data, ORAiCLE was modified at the input layer to use a) only fundus images or b) only biomarkers (i.e. age, ethnicity, gender). The results generated by these restricted learning models was then compared to the results generated by the original version of ORAiCLE that was trained on both datasets.
Results

Overall, ORAiCLE, using only retinal photographs plus age, ethnicity and gender provided a 5-year CV risk prediction that was significantly closer to the actual CVD events than those generated by the Framingham-based equations across all risk groups. (Figure 2, Table 1). Overall, in 88% of patients ORAiCLE provided a CV risk prediction that was closer to the actual event rate than those generated by the Framingham equations.

![Comparison of PREDICT vs Framingham vs actual CVD events](image)

*Figure 2: ORAiCLE score vs. Framingham-based score vs. actual CVD event rates. The error bars represent standard deviation.*

Furthermore, the full ORAiCLE model risk predictions were significantly more accurate when compared to those produced by the 2 restricted models that were trained on images only or biomarkers only, (Figure 3, Table 2) As shown in the histogram the results produced by both the images only and biomarkers only derived models display error bars that were three times larger than those associated with the comprehensive ORAiCLE model. This indicated that the comprehensive model had a significantly greater level “of certainty” than the restrictive models. It also indicates that the final comprehensive model of ORAiCLE learnt from the data contained within both the retinal images and the biomarkers when producing its final output. [28]. Thus despite ORAiCLE requiring nothing more than a retinal image as an input, it extracts data derived from both the original biomarker and image datasets to produce its final CVD risk prediction.
**Figure 3** Error rate: Image only ORAiCLE vs. biomarkers only ORAiCLE vs actual CVD rate. The error bars represent standard deviation.

**Table 1**: comparison of Framingham-based score / ORAiCLE score, / scores when ORAiCLE solved using image only or biomarkers only with the actual event rate in each Quartile of risk

| Error rate          | Framingham-based score | ORAiCLE score | Biomarker only score | Image only score |
|---------------------|------------------------|---------------|----------------------|------------------|
| 1<sup>st</sup> Quartile of risk | 1.59%                  | 0.38%         | -1.20%               | -3.59%           |
| 2<sup>nd</sup> Quartile of risk | 2.35%                  | -0.93%        | -1.15%               | -4.00%           |
| 3<sup>rd</sup> Quartile of risk | 5.15%                  | -1.28%        | 0.31%                | -1.82%           |
| 4<sup>th</sup> Quartile of risk | 11.19%                 | -2.00%        | 4.31%                | 1.65%            |

In order to better understand ORAiCLEs performance and investigate how the results produced relate to an individuals overall risk, four individual case studies were created. The results of the four cases and the impact of modifying the component risk factors that comprise this overall risk.
are summarised in table 2. These demonstrate that ORAiCLE was capable of identifying the “most important modifiable risk factor” for each patient.

Case Studies

Scenario 1
A European male, aged 52 years, with no diabetes. He is not a smoker, has a family history of cardiovascular disease but no atrial fibrillation. His systolic blood pressure (SBP) was 205 mmHg, and the ratio of total cholesterol to HDL cholesterol (TC/HDL) was 3.3 units. The HbA1C was 46mmol/mol. He was not taking blood pressure-lowering medications (OBPLM) or lipid-lowering medications, but was taking antithrombotic medications.

ORAiCLE estimated a CVD risk for this patient of 19.35%. The analysis revealed the following:

- Systolic blood pressure is a major contributor to the risk. By improving the BP to a healthy value of 100 mmHg, the newly calculated ORAiCLE risk score is only 7.74%.
- Cholesterol is not a contributing factor. By reducing cholesterol to healthy levels, the ORAiCLE risk score recuces to just 19.18%
- Diabetes is a not a contributing factor. By reducing HbA1c to healthy levels, the ORAiCLE risk score would be 17.43%

Scenario 2
A Polynesian male aged 45 years with type 2 diabetes. At the time of presentation, he was a smoker, had a family history of cardiovascular disease but no atrial fibrillation, and had a NZDep score in quintile 4. His SBP was 120 mmHg, his TC/HDL was 7.3 units, and his HbA1c was 112mmol/mol. The patient was not taking any blood pressure-lowering medications, antithrombotic medications, or lipid-lowering medications.

ORAiCLE calculated a CVD risk score of 33.3%. Findings include:

- SBP was not a major contributor to the risk. By improving SBP to a healthy value of 100 mmHg, the newly calculated ORAiCLE risk score was 28.68%
- Cholesterol was a significant contributing factor. By reducing cholesterol to healthy levels, the ORAiCLE risk score would be 16.93%
- Diabetes was a major contributing factor. By reducing HbA1c to healthy levels, the ORAiCLE risk score would be 10.96%.

Scenario 3
A European woman, aged 52 years, with no diabetes. She was a smoker, and had no family history of cardiovascular disease or atrial fibrillation. Her systolic blood pressure (SBP) was 100 mmHg, her ratio of total cholesterol to HDL cholesterol (TC/HDL) 5 units, and her HbA1C was
38mmol/mol. She was not taking blood pressure-lowering medications (OBPLM), lipid-lowering medications, or antithrombotic medications.

ORAiCLE estimated a CVD risk for this patient of 8.99%. The analysis revealed the following:

- Systolic blood pressure is not a contributor to the risk. By improving the BP to a healthy value of 100 mmHg, the newly calculated ORAiCLE risk score remained 8.99%.
- Cholesterol is a major contributing factor. By reducing cholesterol to healthy levels, the ORAiCLE risk score would be 6.74%
- Diabetes was not contributing factor. By reducing HbA1c to healthy levels, the ORAiCLE risk score will be 8.35%

**Scenario 4**

A Polynesian male aged 58 years with type 2 diabetes. At the time of presentation, he was not a smoker, had no family history of cardiovascular disease or atrial fibrillation, and had a NZDep score in quintile 5. His SBP was 118 mm Hg, TC/HDL was 5.5 units, and HbA1c was 77 mmol/mol. The patient was taking blood pressure-lowering medications, antithrombotic medications, and lipid-lowering medications. His risk of cardiovascular disease, as predicted by the ORAiCLE model was 26.51%. We also found the following:

- Systolic blood pressure is a significant contributor to the overall risk. Improving SBP to a healthy value of 100 mmHg, the newly calculated ORAiCLE risk score would be 14.68%
- Cholesterol was not contributing factor. By reducing cholesterol to healthy levels, the ORAiCLE risk score would be 26%
- Diabetes was a major contributing factor. By reducing HbA1c to healthy levels, the ORAiCLE risk score would be 19.07%.

**Summary of cases**

*Table 2: summary of the error rate in case scenarios*

| Scenario # | ORAiCLE score | Improvement via optimizing cholesterol | Improvement via optimizing HbA1c | Improvement via optimizing blood pressure |
|------------|---------------|----------------------------------------|----------------------------------|------------------------------------------|
| 1          | 19.35%        | 19.18%                                 | 17.43%                           | 7.74%                                    |
| 2          | 33.30%        | 16.93%                                 | 10.96%                           | 28.68%                                   |
| 3          | 8.99%         | 6.74%                                  | 8.35%                            | 8.99%                                    |
| 4          | 26.51%        | 26.00%                                 | 19.07%                           | 14.68%                                   |
Discussion

Previously we have demonstrated that it is possible to train an artificial intelligence (AI) deep learning (DL) algorithm on retinal images to grade diabetic retinopathy and maculopathy for diagnostic, screening and risk assessment purposes [35-45]. In this study we used 165,907 fundus images from a database of 47,236 patient visits to train a novel DL platform (ORAiCLE) to calculate a 5 year CVD risk score for these individuals. The corresponding risk predicted by the Framingham equation for these same individuals were also calculated. The 5 year predicted risk produced by both the Framingham Equations and ORAiCLE were compared to the actual CV event rate to determine the relative accuracy of the 2 prediction methods. We found that ORAiCLE provided values that were significantly closer to the actual CVD events compared to the Framingham-based equations across all risk groups. More specifically, ORAiCLE showed that it was capable of identifying the most important modifiable risk factor for each individual.

Our results are in line with other reports which have demonstrated that DL algorithms can make use of retinal fundus images to predict modifiable CVD risk factors, including diabetes, hypertension, and cholesterol [25, 28, 30, 46-48] and non modifiable risk factors such as chronological age [24]. However, like the Framingham equations, the existing algorithms are unable examine the relative contribution of each of the individual factors that comprise risk as they utilise a statistical method which imposes linearity between these individual parameters during analysis. Consequently these models are trained against a single label such as cardiovascular event or chronological age. They are therefore incapable of identifying the most significant contributors to CVD risk in any given individual as the math underpinning them do not consider the interactions between the variables that comprise the individuals overall risk. Furthermore, most existing algorithms simply measure success in terms of detection accuracy, where the CVD risk is calculated by conventional equations. For instance, [26, 28, 29, 49] report the outcomes of their algorithms in terms of AUC, regarding successful models as those that have an AUC < .70. Although this approach has its merits - a model whose predictions are 100% wrong will have an AUC of 0.0, and one whose predictions are 100% correct will have an AUC of 1.0, merely knowing that a model can predict CVD risk with an AUC > 0.70 will not tell the user anything about the contribution of each risk factor to the overall risk score for a given patient.

In contrast, we have demonstrated that it possible to train a DL algorithm that is not only able to assess CVD risk factors at the individual level but is also to establish the relative contribution of each risk factor to the overall CVD risk score based on an individuals personal circumstances. We describe four case studies that illustrate the ability of ORAiCLE to identify the largest contributing factor to CVD. In both cases who had diabetes, ORAiCLE identified that diabetes was a significant factor that contributed to their 5 year risk. Moreover, it identified that the magnitude of the risk reduction was proportional to the magnitude of the HbA1C (Case 2: 112mmol/mol 33.3% down to 10.9% , Case 4: HbA1C 77mmol/mol 26.5% to 19%). In contrast, ORAiCLE identified correctly
that improving glycaemic control would make no material difference to the 2 individuals who did not have diabetes. A similar trend was observed for both hypertension and Cholesterol. ORAiCLE correctly identified that SBP was the principle facotr driving the 5 year risk in Case 1 (SPB 205mmHg) and a contributotary factor in case 4 (SBP 118). In contrast SBP did not contribute to the 5 year risk in case 3 whose blood pressure was already normal.

To demonstrate that both retinal image data and biomarker data contributed to the final prediction generated by our DL algorithm, 2 restrcited models of ORAiCLE were subsequently used on either the retinal images only or the biomarkers only. We found that these restricted models were not only less accurate, but they also had higher degrees of uncertainty than the comprehensive model of ORAiCLE. We are therefore confident that ORAiCLE gleaned novel learnings both from, and between, the two datasets. Thus, although ORAiCLE, is not the first algorithm used to predict CVD risk from retinal fundus images, it is the first that is capable of identifying what is the largest contributing factor to an individuals CVD risk. This is made possible by its ability to account for the interactions between modifiable factors such as hypertension and diabetes when assessing the relative contribution of each to the total risk. As a result it becomes possible to predict whether a change in one modifiable factor will produce changes in other modifiable factors.

At the present, health guidelines in the U.S. recommend Clinicians make CVD treatment decisions that are informed in part by Framingham-based risk prediction equations. It is incontrovertable that the development of these equations has had a positive impact on individuals wellbeing; age-adjusted CVD deaths have been cut in half in developed countries, and a large part of this decline is attributed to targeting the risk factors identified by the Framingham Study [50]. However, these equations come with at least two limitations: 1) The equations are often based on old data gathered from a specific population group; 2) Patient data that needs to be used in the equations is not always available.

In recent years new CVD prediction equations have been developed, based on data gathered from samples that represent the demographics of broader populations in terms of ethnicity, socioeconomic status, and other variables. These developments should lead to an improved predictive power of these equations. [51]. Developing new CVD risk equations, however, requires significant resources, and require laboratory tests which can be difficult to implement in many developing countries where there are limited resources available for screening [50].

AI-based CVD prediction algorithms learn to predict the risk of CVD events from retinal information extracted from hundreds of thousands of patients. Based on patterns observed in large datasets, AI. algorithms can generate knowledge that will help progress the field of personalized diagnosis and treatment. We have demonstrated that using just a retinal image ORAiCLE, could improve CVD risk prevention strategies without requiring significant investment, which makes this technologies particularly relevant to low-income settings. Retinal photographs are routinely
taken from individuals living with diabetes, which means it is possible to feed ORAiCLE with data rapidly at a low cost [52]. Furthermore, AI-based prediction tools that assess risk levels at the individual level can inform treatment decisions that are based on the specific needs of an individual, thereby increasing the likelihood of positive health outcomes.

Conclusion

It is well recognised that many cardiovascular events can be prevented by making treatment recommendations based on an individual’s CVD risk profile. However, presently the methods used to quantify an individual’s risk have only a moderate predictive power. In this paper, we demonstrate that our DL algorithm ORAiCLE, using a retinal image as the sole input, is capable of assessing the risk of a cardiovascular event with a higher accuracy level than the Framingham-based equations and other AI prediction algorithms. Like other similar algorithms, ORAiCLE makes use of phenotypic information from retinal images to predict CVD risk at the individual level from parameters that include pigmentation and blood vessels. Unlike other similar algorithms, ORAiCLE is capable of identifying the largest contributing factor to CVD by making use of the interactions between modifiable factors.

Retinal photography is inexpensive and only minimal training is required to acquire them as fully automated, inexpensive camera systems are now widely available. As such, and if the potential of DL algorithms based on retinal images is realised, AI-based CVD risk algorithms such as ORAiCLE promise to make CV health screening more accurate, more affordable and more accessible for all. Furthermore, ORAiCLE’s unique ability to assess the relative contribution of the components that comprise an individual’s overall risk would inform treatment decisions based on the specific needs of an individual, thereby increasing the likelihood of positive health outcomes.
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