Machine learning to predict cardiac events in asymptomatic individuals

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Editorial

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Identifying which patients are at risk of cardiac events is an important goal and enables the application of interventions to prevent future cardiovascular events. Current cardiovascular risk scores incorporate clinical features and biochemical measures to stratify patients into risk groups [1,2]. However, they have a number of limitations, including differences when applied to populations in different countries [3], overestimation of risk in contemporary multi-ethnic cohorts [4] and underestimation of risk in women [5]. A variety of novel blood biomarkers have been assessed for their ability to predict cardiovascular events, including those related to inflammation, extracellular matrix remodelling, myocardial injury and repair, oxidative stress, neurohumoral response and lipid regulation. Coronary artery calcification identified on computed tomography can further improve risk stratification [6,7] by identifying the presence of underlying coronary artery disease itself. However, to date, the optimum method to combine all of these overlapping measures to predict individual cardiovascular risk has not been established.

Machine learning techniques offer great promise in cardiovascular risk prediction due to their ability to combine information from multiple overlapping sources. In this issue of the journal, Tamarappoo et al. demonstrate that a machine learning model incorporating clinical characteristics, non-contrast computed tomography, and serum biomarkers improved the prediction of myocardial infarction or cardiac death in an asymptomatic population [8]. This was a sub-study of the EISNER (Early Identification of Subclinical Atherosclerosis by Noninvasive Imaging Research) trial, which included 1069 patients who have been followed up for 14 years with an overall event rate of myocardial infarction or cardiac death of 4.7%. Their machine learning model outperformed both the ASCVD (AtheroSclerotic CardioVascular Disease) risk score and coronary artery calcium score, with an area under the curve (AUC) of 0.81 (95% confidence interval 0.75 to 0.87). These results have the potential to improve our understanding of cardiac risk in asymptomatic individuals.

Apart from age and systolic blood pressure, the "top 10 variables" in the machine learning model were dominated by imaging and serum biomarkers. Interestingly, gender is not amongst the most important variables in terms of information gain, whereas it features prominently in traditional cardiovascular risk scores. Coronary artery calcium score, number of coronary lesions and aortic valve calcium score were of particular importance in the machine learning model. It is not surprising that coronary artery calcium score was a key variable, as this has been established in other studies incorporating machine learning [9–11]. Recently, the importance of additional calcium parameters has been recognised, over and above the Agatston calcium score, including measures such as number, position, density and radiomic characteristics [12–14]. It would be interesting to know how these other variables perform in this dataset. Nevertheless, Tamarappoo et al. provide further evidence to support research into a new and improved version of the "calcium score".

The inclusion of aortic valve calcium score in the "top 5 variables" is intriguing as it highlights the overlap between coronary artery disease and valvular heart disease, and the prognostic importance of asymptomatic aortic sclerosis and stenosis. Aortic valve calcification on computed tomography shares risk factors with coronary artery disease and is now part of guidelines for assessing patients with aortic stenosis as it is an effective way to assess aortic stenosis severity. However, in both symptomatic [15] and asymptomatic populations [16], aortic valve calcification is not a predictor of subsequent events when coronary artery calcification is included in multivariable models. Thus, although previous studies have shown that coronary artery calcification is more important than aortic valve calcification for assessing prognosis, Tamarappoo et al. have shown that using machine learning both of these factors can be used advantageously to assess cardiovascular risk.

Although 46 serum biomarkers were assessed in the EISNER study, only the top 15 were included in the machine learning model presented in this paper, due to the limited information gain provided by the other markers. The serum biomarkers which were particularly critical in the machine learning model were those that involved in lipid metabolism,

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inflammation, extracellular matrix remodelling and fibrosis. These included routinely performed biomarkers such as low-density lipoprotein cholesterol and D-dimer, and some more novel biomarkers including matrix metalloproteinase-9, pentraxin and polymeric immunoglobulin receptor. The identification of individual or combined serum biomarkers which could replace imaging tests is attractive, due to the time and expense of imaging tests as well as the exposure to ionising radiation required for computed tomography. However, the additive value of serum biomarkers to clinical variables and CT measures in the machine learning model was primarily due to the reclassification of non-events rather than the identification of new patients with events. Thus, at present, serum biomarkers are best used in combination with other variables for the assessment of cardiovascular risk.

The accuracy of the machine learning model developed by Tamarappoo et al. incorporating clinical risk factors, serum biomarkers and quantitative CT parameters for the prediction of myocardial infarction or cardiac death remained modest at 76% (sensitivity 79%, specificity 76%). This shows that there is still work to be done in this area of research and the fundamental question of who will suffer myocardial infarction in the future remains unanswered. Whether the missing piece of information will be an entirely new biomarker, or a combination of biomarkers in machine learning model is currently uncertain.

A constant problem with developing and validating machine learning models is the availability of suitable datasets. The machine learning model produced by Tamarappoo et al. has not been validated in an external cohort, partly because it is challenging to find a cohort that has undergone similar clinical, imaging and biochemical assessments. Nevertheless, validation in other cohorts will be an important stage in translating this research into clinical practice. We know that traditional cardiovascular risk scores are influenced by the underlying prevalence of cardiovascular disease and risk factors in the population used to generate the risk score, and therefore we need to be careful when attempting to transfer machine learning based risk scores to other populations. We do not currently know how these machine learning models will perform in populations which are different to those which were used to develop them.

The question of what is the optimum method to assess and to manage cardiovascular risk in asymptomatic individuals is the subject of a number of ongoing randomised controlled trials. The ROBINSCA (Risk or Benefit IN Screening for Cardiovascular disease) trial is randomising patients 1:1:1 to usual care, screening for traditional risk factors or coronary artery calcium scoring [17] and the SCOT-HEART2 (Scottish Computed Tomography of the HEART) trial (NCT03920176) is currently randomising patients 1:1 to computed tomography coronary angiography or standard care. The use of machine learning to improve risk prediction in these ongoing clinical trials will be of particular interest.

When it comes to deciding which variables to use in cardiovascular risk assessment it can be said that "No man is an Island, entire of it self" (John Donne, 1624). Machine learning gives us a powerful tool by which to combine risk factors and disease markers to improve both our ability to predict cardiac events and target primary prevention advice and therapy. There are however many different machine learning models which are being developed by different groups using different datasets. The next evolution of this technology will move on from using these techniques to understand the research data, to assess the essential question of how we use these techniques in clinical practice.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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