

## New risk prediction models in England may lead to targeted PCSK9i treatment, for patients with established CVD

Taavi Tillmann, Centre for Global Non-Communicable Disease, Institute for Global Health, University College London [t.tillmann@ucl.ac.uk](mailto:t.tillmann@ucl.ac.uk)

More than 40 years ago, Kannel *et al.* published perhaps the world's first cardiovascular disease (CVD) risk prediction model, using data from the Framingham cohort study.<sup>1</sup> Since then the quantity, complexity and utility of risk prediction models has grown exponentially, particularly during the last decade when clinical guidelines have begun to recommend their use for certain clinical situations. Just like the initial model by Kannel *et al.*, the most common application has been for healthy people to estimate their risk of developing a first-ever ischaemic or coronary event in the next 10 years. For such situations, the *European Society of Cardiology* recommended in 2003 to use the SCORE<sup>2</sup> risk model (unless country-specific models are available, such as QRISK<sup>3</sup> which was published for the English population in 2007). By today, such risk prediction models are becoming routine practice in primary care opportunistic work, as well as among public health specialists implementing population-based CVD screening programmes. One of its functions is to help target preventative interventions such as statins to those with the most favourable ratio of risks-to-benefits. A key component in the success of this translational work in countries with high implementation (like England) has been the widespread adoption of the risk prediction model into the routine IT systems that clinicians use, thereby not taking too much clinical time. This story, of moving from basic science, to prediction science, to updated clinical guidelines, altered IT systems and better clinical practice (in some countries), serves as an illuminating example for other clinical questions where prediction science is evolving, but has yet to become an integral part of routine care. Another example might be the development of risk prediction models for people with Atrial Fibrillation, to estimate their risk of stroke and likely utility from targeted anti-coagulation. Here too, various prediction models like CHA2DS2-VASC have been proposed, externally validated, and are making their way into routine practice of primary and acute medical care.<sup>4</sup> This optimism should also be counterbalanced by some realism. A recent report by the "*ESC Prevention of CVD Programme*" has rightly pointed out how implementation remains far from optimal across many if not most European countries.<sup>5</sup> More needs to be done to disseminate, standardise and normalise good multidisciplinary practice like this.

In contrast to general practitioners who often see patients without overt cardiovascular CVD, cardiologists tend to see patients later in their lifecourse, who have often had at least one cardiovascular event. Risk prediction science for such patients remains a step or two behind, but is catching up fast. In 2012 the REACH prediction model was derived (on 33'419 persons from 44 countries with existing cardiovascular disease) to predict the risk of recurrent CVD events (with 2394 events detected over 2 years of follow-up).<sup>6</sup> In 2013 a similar model was published by Rapsomaniki *et al.*<sup>7</sup>, using data from a larger cohort of 102'023 patients in England (with 22'999 events or deaths in the next 5 years). The larger size of Rapsomaniki *et al.*'s derivation dataset allowed them to model the hazard ratios associated with detailed cardiovascular event histories, arising from concurrent comorbidities such as stable angina, unstable angina, MI, STEMI, NSTEMI, stroke, peripheral arterial disease and non-cardiovascular disease. However, as this model was derived exclusively on patients from England, it is less clear to what degree their model might be generalisable to other countries. The REACH model might be better suited to settings that are dissimilar to England. Both models have been well cited by other academic studies, however neither has been endorsed by leading clinical guidelines (such as those of the *European Society of Cardiology*). Three recent Health Technology

Assessments conducted in Scotland, Sweden and the Netherlands have cited the REACH model, when evaluating the potential applications Evolocumab, a new PCSK9-inhibitor developed by Amgen.<sup>8</sup>

In this issue of the *European Journal of Preventative Cardiology*, Danese et al.<sup>9</sup> looked at 60'838 patients in England with existing cardiovascular disease, to predict recurrent cardiovascular events over 5 years of follow-up. They demonstrate convincingly that the 11% of patients with severe atherosclerotic disease (as denoted by recurrent myocardial infarcts or strokes, and/or multimorbidity with more than one concurrent CVD) had an elevated risk of recurrent events, when compared to the 89% patients who lacked such features. It is reassuring that these results align with those reported by Rapsomaniki *et al*, who also reported cardiovascular past medical history predictors were more useful than others, when guiding treatment decisions.

Altogether, this body of risk prediction science appears ripe for transitioning to the next stage, in exploring more targeted application of a therapies such as PCSK9 inhibitors. These new drugs are effective in lowering cholesterol and preventing cardiovascular events, however at current on-patent prices they are not cost-effective when used in an untargeted manner.<sup>10</sup> It is plausible that if their use could be rationed or targeted for higher risk patients, it may become cost-effective for some health insurance systems. The authors rightly point out the need now for more sophisticated simulations and cost-effectiveness analyses to help inform these decisions. One way of making this applied work even more robust against type I error would be to conduct sensitivity analyses, where the hazard ratios derived by Danese *et al*. are replaced by those derived by Rapsomaniki *et al*, to check if the subsequent simulations arrive at similar recommendations and treatment thresholds. Another strength of both current models is that they were derived from administrative data, and hence in real-life application need not create any additional data entry burdens for clinicians. If a subgroup of patients could be identified where PCSK9i therapy is cost-effective, then IT companies could create software solutions that help identify such patients relatively automatically, with as little clinical time as possible.

Returning to academic risk prediction science, future work could seek to make these models even more accurate, by testing the added value of clinical markers of disease severity that are captured in routine cardiological care, but rarely make it to billing details and discharge summaries that comprised the datasets used to date. For example, specific ECG parameters (e.g. QRS width), Echocardiogram findings (e.g. ejection fraction) or blood markers (e.g. peak troponin) are just some examples of the trove of clinical data available to cardiologists. The challenge is to aggregate and standardize these into sizable cohorts, ideally with >50 000 patients. Once done, this may also be ripe territory to experiment with machine learning and artificial intelligence approaches, in picking up increased signal from noise about who is at highest risk of recurrent events, potentially benefitting from enhanced care.

Declaration of conflicting interests: The author declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding: The author received no financial support for the research, authorship, and/or publication of this article. The author is funded by an NIHR Academic Clinical Lectureship.

---

<sup>1</sup> Kannel WB, McGee D, Gordon T. A general cardiovascular risk profile: the Framingham Study. *Am J Cardiol* 1976;38(1):46-51.

---

<sup>2</sup> Conroy R, Pyörälä K, Fitzgerald Ae, Sans S, Menotti A, De Backer G, et al. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. *Eur Heart J* 2003;24(11):987-1003.

<sup>3</sup> Hippisley-Cox J, Coupland C, Vinogradova Y, Robson J, May M, Brindle P. Derivation and validation of QRISK, a new cardiovascular disease risk score for the United Kingdom: prospective open cohort study. *Br Med J* 2007;335(7611):136.

<sup>4</sup> van den Ham HA, Klungel OH, Singer DE, Leufkens HG, van Staa TP. Comparative performance of ATRIA, CHADS2, and CHA2DS2-VASc risk scores predicting stroke in patients with atrial fibrillation: results from a national primary care database. *J Am Coll Card* 2015 66(17):1851-1859.

<sup>5</sup> Rossello X, Dorresteijn JA, Janssen A, Lambrinou E, Scherrenberg M, Bonnefoy-Cudraz E, Cobain M, Piepoli MF, Visseren FL, Dendale P, This paper is a co-publication between European Journal of Preventive Cardiology, European Heart Journal: Acute Cardiovascular Care and European Journal of Cardiovascular Nursing. Risk prediction tools in cardiovascular disease prevention: A report from the ESC Prevention of CVD Programme led by the European Association of Preventive Cardiology (EAPC) in collaboration with the Acute Cardiovascular Care Association (ACCA) and the Association of Cardiovascular Nursing and Allied Professions (ACNAP). *Eur J Preventive Cardiol* 2019:2047487319846715.

<sup>6</sup> Wilson PW, D'Agostino Sr R, Bhatt DL, Eagle K, Pencina MJ, Smith SC, Alberts MJ, Dallongeville J, Goto S, Hirsch AT, Liao CS. An international model to predict recurrent cardiovascular disease. *Am J Med* 2012 Jul 1;125(7):695-703.

<sup>7</sup> Rapsomaniki E, Shah A, Perel P, Denaxas S, George J, Nicholas O, Udumyan R, Feder GS, Hingorani AD, Timmis A, Smeeth L. Prognostic models for stable coronary artery disease based on electronic health record cohort of 102 023 patients. *Eur J H* 2013 Dec 17;35(13):844-52

<sup>8</sup> Betts MB, Milev S, Hoog M, Jung H, Milenković D, Qian Y, Tai MH, Kutikova L, Villa G, Edwards C. Comparison of Recommendations and Use of Cardiovascular Risk Equations by Health Technology Assessment Agencies and Clinical Guidelines. *Value in Health* 2019 Feb 1;22(2):210-9.

<sup>9</sup> Danese M, Pemberton-Ross P, Catterick D. Estimation of the Increased Risk Associated with Recurrent Events or Poly-Vascular Atherosclerotic Cardiovascular Disease in the United Kingdom. *Eur J Prev Cardiol* 2020. PAGE REF HERE.

<sup>10</sup> Kazi DS, Moran AE, Coxson PG, Penko J, Ollendorf DA, Pearson SD, Tice JA, Guzman D, Bibbins-Domingo K. Cost-effectiveness of PCSK9 inhibitor therapy in patients with heterozygous familial hypercholesterolemia or atherosclerotic cardiovascular disease. *J Am Med Assoc* 2016 Aug 16;316(7):743-53.