

New risk prediction models in England may lead to targeted PCSK9 inhibitor treatment, for patients with established cardiovascular disease

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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.¹ Since then the quantity, complexity and utility of risk prediction models has grown exponentially, particularly during the past 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 (ESC) recommended in 2003 to use the SCORE² risk model (unless country-specific models are available, such as QRISK,³ which was published for the English population in 2007). By now, 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 preventive 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 (such as 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 in which 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 anticoagulation. Here too, various prediction models such as CHA2DS2-VASC have been proposed, externally validated, and are making their way into routine practice of primary and acute medical care.⁴

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.⁵ 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 CVD, cardiologists tend to see patients later in their life course, 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 CVD) to predict the risk of recurrent CVD events (with 2394 events detected over 2 years of follow-up).⁶ In 2013 a similar model was published by Rapsomaniki et al.,⁷ 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 the derivation dataset of Rapsomaniki et al. allowed the authors to model the hazard ratios associated with detailed cardiovascular event histories, arising from concurrent comorbidities such as stable angina, unstable angina, myocardial infarction, ST-segment elevation myocardial infarction, non-ST-segment elevation myocardial infarction, stroke, peripheral arterial disease and non-CVD. 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.

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Both models have been well cited by other academic studies; however, neither has been endorsed by leading clinical guidelines (such as those of the ESC). Three recent health technology assessments conducted in Scotland, Sweden and The Netherlands have cited the REACH model, when evaluating the potential applications of evolocumab, a new PCSK9 inhibitor developed by Amgen.⁸

In this issue of the *European Journal of Preventive Cardiology*, Danese et al.⁹ looked at 60,838 patients in England with existing CVD, 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 with the 89% patients who lacked such features. It is reassuring that these results align with those reported by Rapsomaniki et al., who also reported that 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 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.¹⁰ 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, in which 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 in which PCSK9 inhibitor 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 standardise these into sizeable cohorts, ideally with over 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.

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