Implementing Cardiovascular Risk Prediction in Clinical Practice: The Future Is Now

Kunal N. Karmali, MD, MS; Donald M. Lloyd-Jones, MD, ScM

Risk prediction equations have been a cornerstone of cardiovascular disease prevention strategies for 2 decades. These equations serve as tools to convert data on multiple risk factors into a summary estimate of a person's likelihood of experiencing a cardiovascular event over a given period. The first widely used cardiovascular risk prediction equation was the Framingham Risk Score (FRS), developed from the country's first longitudinal cardiovascular cohort study. Eventual adoption of the FRS into the Third Report of the National Cholesterol Education Program's Adult Treatment Panel (ATP-III) cholesterol guidelines in 2001 firmly established absolute risk assessment as an integral part of primary prevention, operationalizing the widely accepted paradigm that more intensive prevention efforts, specifically drug therapy, should be directed to those at higher risk.[1]

In 2013, the American College of Cardiology and American Heart Association released updated clinical practice guidelines for the treatment of blood cholesterol to reduce atherosclerotic cardiovascular disease event risk.[2] These guidelines reaffirmed the risk-based prevention paradigm but moved one step further by eliminating cholesterol goals, instead identifying evidence-based risk thresholds to define groups with net benefit from statin therapy, in order to guide clinician–patient decision making in primary prevention. The prominent role of absolute risk assessment in these guidelines led to an intense focus on the new cardiovascular risk prediction equations recommended by these guidelines, the Pooled Cohort Equations (PCE).[3]

Since release of the 2013 American College of Cardiology/American Heart Association prevention guidelines, there have been numerous studies evaluating the performance of the PCE in different settings; reported results have been mixed, and findings have been heavily influenced by diverse and contentious methodological approaches in those reports.[4–6] Some analyses have identified overprediction of risk with the PCE,[7–11] while others have found acceptable calibration, particularly at clinically relevant risk levels near decision thesholds.[12–15] The prevailing uncertainties have led to calls for transformative changes in the way risk prediction algorithms are developed and validated.[6,16] One potential approach is to move away from population-based cohort studies toward contemporary and real-world populations from electronic health records (EHRs) that reflect current trends in racial diversity, risk factor prevalence, preventive medication use, and disease incidence.

Yet, the use of EHRs as a tool for clinical research is still in its infancy, and few health systems have follow-up long evaluations to advance the field.[17]

In this issue of *JAHA*, Wolfson et al report a new analysis that evaluates the performance of 2 cardiovascular risk prediction equations in an integrated healthcare system with a mature and comprehensive EHR.[18] The investigators analyzed data from 84 116 adults aged 40 to 79 years who were part of the HealthPartners system in Minnesota from 2001 to 2011 to determine the discrimination and calibration of the 2007 general FRS equations[19] and the PCE.[3] Using accepted methods for recalibration, the investigators also evaluated the performance of refitted FRS and PCE models within their system. In keeping with the pragmatic nature of EHR-based studies, the authors used risk factor measurements that were collected (or imputed values for those not collected) as part of routine clinical care and identified cardiovascular events by insurance claims data and state vital records that are included in the HealthPartners system.

Importantly, the authors found that, in this real-world EHR cohort, both the published and refitted FRS and PCE produced relatively accurate risk predictions. Specifically, the original FRS had a C-index of 0.740 (95% CI, 0.724–0.755) and a calibration statistic of 9.1 (P=0.028), while the PCE had a

C-index of 0.747 (95% CI, 0.727–0.768) and a calibration statistic of 43.7 (*P*<0.001). Furthermore, visual assessment of both calibration plots was acceptable. Not surprisingly, calibration was better with refitted models but results were qualitatively similar.

A key strength of this analysis is the inclusive selection criteria used by the investigators that produced a real-world and representative primary care population. Overly restrictive selection criteria in such validation studies can lead to bias, an underappreciated threat that has plagued previous attempts to study these equations in EHR cohorts.[6,10] Additionally, the authors employed robust, multiple imputation methods to account for missing lipid data, a reality of working with real-world EHR data.

There are, however, some limitations worth noting. First, the studied population was quite similar in racial and demographic characteristics to the cohorts from which the FRS and PCE were derived. This likely explains the minimal effect of recalibration on model performance, a finding that may differ in more heterogeneous samples and settings. It is worth remembering that recalibration analyses were critical in gaining broader acceptance of the original FRS,[20] and these techniques will continue to remain relevant when applying risk prediction equations to new settings or different populations. Second, because of the authors' reliance on administrative data for outcome assessment, the risk for misclassification exists, particularly for the outcomes of peripheral arterial disease and heart failure predicted by the general FRS equations.[21,22] While this decision resulted from pragmatic and defensible considerations, future research will be needed to fully appreciate how this compares with the standardized methods used for outcome adjudication in many population-based cohorts. Third, although the general FRS equations have been available for nearly a decade, they have not been incorporated into any clinical practice guideline, and they contain heterogeneous atherosclerotic and nonatherosclerotic clinical outcomes. Therefore, risk estimates from this FRS do not align with any specific guideline recommendation. In the 2013 American College of Cardiology/American Heart Association cholesterol guidelines, for example, the 10-year absolute risk threshold of 7.5% was specifically identified to mark a risk level where clinical trial data demonstrated that benefits of statin treatment for fatal and nonfatal atherosclerotic events clearly outweighed known risks of adverse events.[2]

Finally, the analyses by Wolfson et al focus only on statistical metrics that evaluate model performance (discrimination and calibration) but do not indicate the downstream implications of these estimates on treatment decision-making. From a clinical perspective, calibration in particular is a visual exercise more than a statistical exercise. *P*-values for calibration are notoriously sensitive to sample size, and

they do not indicate in which part of the risk spectrum any miscalibration may be occurring. Obviously, good calibration is most important near potential decision thresholds, and it is less important (or even irrelevant) at the extremes of the risk distribution. In the Wolfson et al analysis, for example, the PCEs were very well calibrated at low and moderate risk ranges, and overpredicted only in ranges above the clinical decision threshold of 7.5%, where "overprediction" is far less important, and may actually be a function of the application of risk-reducing therapies during follow-up that altered the predicted natural history of atherosclerotic cardiovascular disease risk. At lower levels of risk, such as 10-year risk levels of 5% to 7.5% and 7.5% to 10%, predicted event rates for the FRS were lower than the observed rates (6.1% predicted versus 6.5% observed and 8.6% predicted versus 10.4% observed, respectively). In contrast, the PCE slightly overpredicted risk at these same thresholds (6.1% predicted versus 5.6% observed and 8.6% versus 7.4% observed, respectively). While the former might have better calibration, one might accept a more sensitive risk estimator from a public health perspective, particularly when considering the use of safe, effective, and low-cost medications such as statins. These limitations notwithstanding, the analysis by Wolfson et al is an important and valuable demonstration of the successful application of the FRS and PCE to a modern EHR system and should hopefully address uncertainties about the relevance of these equations in the contemporary era.

As clinical practice guidelines continue to move toward personalized treatment recommendations that are tailored to the unique benefit–harm assessments of a given patient, integration of clinical risk prediction equations will remain essential for guiding absolute risk assessment. Continued progress in health information exchanges and the establishment of standards for data harmonization, data quality, and electronic outcome assessment may one day lead to a nationwide electronic cohort capable of supporting ongoing refinement of risk prediction equations using real-world clinical data.[23] However, until that time, we will likely save far more lives and prevent many more events by focusing on implementation of existing guideline-linked equations such as the PCE, with decision-support algorithms, in EHR platforms.

Predicting the future is an inherently imperfect science, but we must not forget that quantitative risk assessment is just the start, not the end, of a treatment decision. Risk estimates must be contextualized by clinicians for patients during a shared treatment discussion.[2] Although recent years have seen great interest in the accuracy of cardiovascular risk prediction equations, there remains uncertainty over whether use of any cardiovascular risk estimate in clinical practice actually improves cardiovascular outcomes,[24] and there are very limited data on how to best present this information for clinical decision making.[25] Ultimately, analyses such as those

by Wolfson et al should serve to remind us that currently available risk prediction equations, even those derived from "historical" cohorts, remain applicable today. Now, we must continue the difficult work of identifying the best strategies for implementing these tools in practice to end the epidemic of cardiovascular disease in the population.

Disclosures

None.

References

1. Third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III) final report. *Circulation*. 2002;106:3143–3421.

2. Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, Goldberg AC, Gordon D, Levy D, Lloyd-Jones DM, McBride P, Schwartz JS, Shero ST, Smith SC Jr, Watson K, Wilson PW, Eddleman KM, Jarrett NM, LaBresh K, Nevo L, Wnek J, Anderson JL, Halperin JL, Albert NM, Bozkurt B, Brindis RG, Curtis LH, DeMets D, Hochman JS, Kovacs RJ, Ohman EM, Pressler SJ, Sellke FW, Shen WK, Smith SC Jr, Tomaselli GF. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;129:S1–S45.

3. Goff DC Jr, Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB, Gibbons R, Greenland P, Lackland DT, Levy D, O'Donnell CJ, Robinson JG, Schwartz JS, Shero ST, Smith SC Jr, Sorlie P, Stone NJ, Wilson PW, Jordan HS, Nevo L, Wnek J, Anderson JL, Halperin JL, Albert NM, Bozkurt B, Brindis RG, Curtis LH, DeMets D, Hochman JS, Kovacs RJ, Ohman EM, Pressler SJ, Sellke FW, Shen WK, Smith SC Jr, Tomaselli GF. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;129:S49–S73.

4. Ridker PM, Cook NR. Statins: new American guidelines for prevention of cardiovascular disease. *Lancet*. 2013;382:1762–1765.

5. Lloyd-Jones DM, Goff D, Stone NJ. Statins, risk assessment, and the new American prevention guidelines. *Lancet*. 2014;383:600–602.

6. Lloyd-Jones DM, Goff DC Jr. Need for better methodology in assessing Pooled Cohort Equations. *J Am Coll Cardiol*. 2017;69:365–366.

7. Cook NR, Ridker PM. Further insight into the cardiovascular risk calculator: the roles of statins, revascularizations, and underascertainment in the Women's Health Study. *JAMA Intern Med*. 2014;174:1964–1971.

8. Kavousi M, Leening MJ, Nanchen D, Greenland P, Graham IM, Steyerberg EW, Ikram MA, Stricker BH, Hofman A, Franco OH. Comparison of application of the ACC/AHA guidelines, Adult Treatment Panel III guidelines, and European Society of Cardiology guidelines for cardiovascular disease prevention in a European cohort. *JAMA*. 2014;311:1416–1423.

9. DeFilippis AP, Young R, Carrubba CJ, McEvoy JW, Budoff MJ, Blumenthal RS, Kronmal RA, McClelland RL, Nasir K, Blaha MJ. An analysis of calibration and discrimination among multiple cardiovascular risk scores in a modern multiethnic cohort. *Ann Intern Med*. 2015;162:266–275.

10. Rana JS, Tabada GH, Solomon MD, Lo JC, Jaffe MG, Sung SH, Ballantyne CM, Go AS. Accuracy of the atherosclerotic cardiovascular risk equation in a large contemporary, multiethnic population. *J Coll Cardiol*. 2016;67:2118–2130.

11. Emdin CA, Khera AV, Natarajan P, Klarin D, Baber U, Mehran R, Rader DJ, Fuster V, Kathiresan S. Evaluation of the Pooled Cohort Equations for prediction of cardiovascular risk in a contemporary prospective cohort. *Am J Cardiol*. 2017;119:881–885.

12. Muntner P, Colantonio LD, Cushman M, Goff DC Jr, Howard G, Howard VJ, Kissela B, Levitan EB, Lloyd-Jones DM, Safford MM. Validation of the atherosclerotic cardiovascular disease Pooled Cohort risk equations. *JAMA*. 2014;311:1406–1415.

13. Ray KK, Kastelein JJ, Boekholdt SM, Nicholls SJ, Khaw KT, Ballantyne CM, Catapano AL, Reiner Z, Luscher TF. The ACC/AHA 2013 guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular disease risk in adults: the good the bad and the uncertain: a comparison with ESC/EAS guidelines for the management of dyslipidaemias 2011. *Eur Heart J*. 2014;35:960–968.

14. Andersson C, Enserro D, Larson MG, Xanthakis V, Vasan RS. Implications of the US cholesterol guidelines on eligibility for statin therapy in the community: comparison of observed and predicted risks in the Framingham Heart Study Offspring Cohort. *J Am Heart Assoc*. 2015;4:e001888. DOI: 10.1161/JAHA. 115.001888.

15. Mortensen MB, Afzal S, Nordestgaard BG, Falk E. Primary prevention with statins: ACC/AHA risk-based approach versus trial-based approaches to guide statin therapy. *J Am Coll Cardiol*. 2015;66:2699–2709.

16. Blaha MJ. The critical importance of risk score calibration: time for transformative approach to risk score validation? *J Am Coll Cardiol*. 2016;67:2131–2134.

17. Goldstein BA, Navar AM, Pencina MJ, Ioannidis JP. Opportunities and challenges in developing risk prediction models with electronic health records data: a systematic review. *J Am Med Inform Assoc*. 2017;24:198–208.

18. Wolfson J, Vock DM, Bandyopadhyay S, Kottke T, Vazquez-Benitez G, Johnson P, Adomavicius G, O'Connor PJ. Use and customization of risk scores for predicting cardiovascular events using electronic health record data. *J Am Heart Assoc*. 2017;6:e003670. DOI: 10.1161/JAHA.116.003670.

19. D'Agostino RB Sr, Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, Kannel WB. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. *Circulation*. 2008;117:743–753.

20. D'Agostino RB Sr, Grundy S, Sullivan LM, Wilson P. Validation of the Framingham coronary heart disease prediction scores: results of a multiple ethnic groups investigation. *JAMA*. 2001;286:180–187.

21. Hong Y, Sebastianski M, Makowsky M, Tsuyuki R, McMurtry MS. Administrative data are not sensitive for the detection of peripheral artery disease in the community. *Vasc Med*. 2016;21:331–336.

22. Rosamond WD, Chang PP, Baggett C, Johnson A, Bertoni AG, Shahar E, Deswal A, Heiss G, Chambless LE. Classification of heart failure in the Atherosclerosis Risk in Communities (ARIC) study: a comparison of diagnostic criteria. *Circ Heart Fail*. 2012;5:152–159.

23. Fleurence RL, Curtis LH, Califf RM, Platt R, Selby JV, Brown JS. Launching PCORnet, a national patient-centered clinical research network. *J Am Med Inform Assoc*. 2014;21:578–582.

24. Karmali KN, Persell SD, Perel P, Lloyd-Jones DM, Berendsen MA, Huffman MD. Risk scoring for the primary prevention of cardiovascular disease. *Cochrane Database Syst Rev*. 2017;3:CD006887.

25. Waldron CA, van der Weijden T, Ludt S, Gallacher J, Elwyn G. What are effective strategies to communicate cardiovascular risk information to patients? A systematic review. *Patient Educ Couns*. 2011;82:169–181.