The main goal of personalized medicine is to tailor medical decisions to the individual patient based on his or her predicted response or risk of disease. Although traditionally, the concept of personalized medicine has referred to genetic personalization, this also applies to traditional clinical and demographic factors, which may affect the balance of risks and benefits a patient is expected to derive from a treatment. Clinical trial results report mean effects across the study population, and subgroup analyses are inherently limited. As such, we often conclude that the benefits of treatment apply consistently to the entirety of the study population, and the practice guidelines and performance measures generally reflect these conclusions. However, multivariable models can sometimes effectively quantify the heterogeneity of treatment benefit. In this way, patients can be identified who are at most (and least) likely to benefit from a treatment; such information could provide critically important guidance to clinicians and patients for many day-to-day management decisions. While this is a noble goal, the number of risk models that are created far exceed those used in clinical practice. There are multiple reasons for this, including the use of variables that are difficult to collect in routine clinic practice, modeling outcomes that are not clinically relevant or actionable, lack of external validation or concerns about model performance, and simple technology limitations and the ability to integrate these models into clinical care. Importantly, for a model to be useful, it should (1) be accurate at estimating risk, (2) be able to separate patients into distinct risk categories, (3) be able to be used with available data at the time of decision making, and (4) exert a substantial impact on a treatment decision.

In this issue of *Circulation: Cardiovascular Quality and Outcomes*, Kaasenbrood et al.*1* present the results of their study in which they developed and validated a risk model to estimate the benefit of statin treatment among patients with diabetes mellitus. Currently, the American College of Cardiology/American Heart Association,2 American Diabetes Association, and European Society of Cardiology3 guidelines recommend statin therapy for primary prevention of cardiovascular disease in the majority of patients with diabetes mellitus. Since the publication of the landmark study by Haffner et al.,4 diabetes mellitus has been considered a coronary heart disease risk equivalent. Although this notion has been disputed in subsequent analyses, the absolute event rate among patients with diabetes mellitus remains high, with a 10-year rate of major adverse cardiovascular events of ≥10%.5 Despite this strong association of diabetes mellitus with cardiovascular events, patients with diabetes mellitus are a heterogeneous group, with important differences in clinical and metabolic factors that can markedly alter the risks for individual patients and their potential benefit from various treatments. As such, Kaasenbrood et al.*1* sought to challenge the one size fits all approach to statins and diabetes mellitus and attempt to identify patients at sufficiently low cardiovascular risk to recommend against statin therapy for primary prevention.

The authors were limited by the variables they were able to include as potential predictors and therefore were not able to construct the most accurate model. However, this strategy was necessary to allow for external validation, a critical step in model development for which the authors should be commended. In addition, although discrimination of the model was limited, too often we inappropriately judge a model’s worth solely by its c-statistic. Although discrimination is important, the calibration of the model and its ability to separate patients into risk categories are key factors of the model’s clinical usefulness, particularly when perfect discrimination is not achievable.7 In this regard, we contend that the authors’ model is able to reasonably estimate a patient’s individual risk of the outcome and do so in clinically relevant ranges of probabilities that can influence decision making. The question that remains for us is whether this personalized approach is superior to the current one that recommends statins to most patients with diabetes mellitus. Using a personalized approach would not reduce cardiovascular events (in fact, it would be expected to increase them slightly) but would save a small percentage of patients from having to take a medication (thereby avoiding costs and potential side effects). The authors argue that the percentage of patients who would be saved from statins (estimated to be 13% in this study, using their cut point for number needed to treat, which is also debatable) would be higher in general practice as their model included only patients who had diabetes mellitus plus an additional risk factor. But the question remains as to whether using a model to save <20% of patients with diabetes mellitus from
having to take a statin is a superior approach to simply treating the patient. It is unclear whether personalization would help physicians think that the guideline applies or if it would add confusion by creating a subset of patients for which the guideline does not apply. In addition, for this approach to be effective, the model must save a patient from a treatment that carries a substantial risk. For example, using risk modeling to estimate benefit from carotid endarterectomy in asymptomatic carotid stenosis could save a patient from undergoing a costly surgery with real potential hazards, or predicting risk and benefit with prolonged dual antiplatelet therapy after myocardial infarction could save a patient from taking a medication with a substantial risk of bleeding. However, in the case of statins for primary prevention, the treatment is a medication that is generic and with low risk of serious adverse side effects. Furthermore, risks change over time. In particular, a patient may not need a statin but then will meet threshold for treatment in 5 years (because of the effect of age on absolute risk of cardiovascular events).

Although we are strongly supportive of personalized care based on a patient’s individual risk, models to guide this must move the needle and impact care substantially enough to be clinically useful. When the harm in treating a small proportion of additional patients is minimal, it is hard to justify adding further complexity to the current treatment paradigm. As we move into a medical landscape in which such models can be run with minimal to no effort by the treating clinician, perhaps this can provide additional value, or if an individual patient questions the benefit of a statin, the information from such a model could be useful. Sometimes, however, standardization has a role, allowing for simple, uniform rules that provide benefit to the vast majority of patients and allow for easy tracking and feedback of performance so as to improve the quality of care, and ultimately patient outcomes. Such standardization and tracking of care has proven useful in improving outcomes in cardiovascular disease during the past several decades, despite evidence of heterogeneity of benefit even for those treatments that are included in performance metrics. Estimating the heterogeneity of treatment benefit and using this information to guide treatment decisions can have great effect in improving care. However, until technology improves to make prediction models integrated into routine medical care with minimal to no additional input from the treating clinicians, the models we use must provide substantial value beyond the established benefit of standardization and trackable metrics.

Disclosures

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References


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Suzanne V. Arnold and Mikhail Kosiborod

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