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The development of effective pharmacological strategies for lowering blood pressure was one of medical science's major success stories of the 20th century. Blood pressure was proven beyond doubt to be causally and continuously related to future risk of cardiovascular events,[1] and lowering blood pressure was proven to reduce that risk.[2–4] Pooled data from randomized trials collectively showed that lowering systolic blood pressure by 10 mmHg reduced coronary heart disease risk by about a quarter and risk of stroke by about a third, irrespective of prior disease history, initial blood pressure level, or the type of agent used. These studies also demonstrated that more intensive blood pressure lowering resulted in additional risk reduction, with the benefits proportional to the size of the fall in pressure.[4,5]

In face of such impressive evidence, it is perhaps both surprising and disappointing that elevated blood pressure today remains the leading cause of the global disease burden:[6] more than nine million people die each year from this cause. While population-level blood pressure values have been declining in some high-income countries, the size of that decline is modest and highly variable by region.[7] More worryingly, however, is the observation that blood pressure levels seem to be increasing in most low- and middle-income countries.[7] Additionally, the clinical management of high blood pressure remains less than adequate in most countries, rich and poor. Recent global estimates suggest that less than half of those who have elevated blood pressure (defined as blood pressure greater than 140/90mmHg) are aware of it and of those who are receiving pharmacological treatment only a third have blood pressure levels lower than 140/90 mmHg.[8] In view of such profound shortcomings in the control of high blood pressure and its associated cardiovascular risks, it is important to reconsider the prevailing strategies for clinical management.

The question of how to manage continuous risk factors, such as blood pressure, in order

to gain maximal benefits for individuals as well as societies has been a matter of debate ever since the British epidemiologist Geoffrey Rose published an article entitled ‘sick individuals and sick populations’ in 1985.[9] He argued that targeting interventions to whole populations would prevent more adverse events than treating smaller groups of ‘high-risk’ individuals. This is because single risk factors are rarely accurate enough in predicting future risk for individuals. For example, for a binary risk marker to provide good discrimination between those who will suffer an event from those who will not, the odds ratio of that marker with the outcome would need to be greater than about nine, which is of course not the case for any usual definition of elevated blood pressure.[10] A related issue is that blood pressure is not a binary risk factor. The risk of cardiovascular disease increases progressively as blood pressure levels increase, with no apparent threshold beyond which one could safely classify individuals as ‘normotensive’ or ‘hypertensive’. While, on average, people who have higher blood pressure levels are more likely to suffer an event, a very large proportion of events will still occur in those with so-called ‘normal’ blood pressure simply because there are so many more of them. Consequently, if we were able to reduce blood pressure levels modestly across the whole population, we would potentially prevent more events than if we were to focus our efforts on intensive management of a small group of ‘hypertensive’ patients.

The principal of Rose’s argument for treating populations as opposed to individuals is still as relevant today as it was 30 years ago. In fact, this population-based strategy remains the most viable option for many important public health interventions, such as policies designed to reduce tobacco use, trans fatty acid intake and salt consumption, which target individuals only indirectly. However, for drug-based interventions, the merits of population-based interventions are less certain since side-effects are not infrequent and many, if not most, would be

unconvinced by the expected absolute benefits for any one individual. So, if pharmacological treatment of whole populations is not an option, then we need alternative strategies by which to decide whom to screen and whom to treat. Approaches to the selection of at-risk-individuals are wide ranging from crude and simple rules that would result in recommendations to treat all above a certain age to highly precise algorithms that would provide treatment to a very small group of high-risk individuals.

In this issue of *Circulation*, Sussman and colleagues report a simulation study in which they compare the effect of two strategies for selection and treatment of at-risk-patients along the spectrum of risk.[11] The first strategy is the widely recommended 'treat-to-target' or 'TTT' approach in which anti-hypertensive treatment for 'hypertensive patients' is initiated and titrated towards a fixed blood pressure target of 140/90 mmHg (unless the patient has diabetes in which case the target blood pressure is 130/85 mmHg). The second strategy uses a more sophisticated decision rule to identify those who are more likely to benefit from antihypertensive therapy (which the authors call 'benefit-based tailored treatment' or 'BTT'). This strategy is based on a probabilistic model that calculates the expected net treatment benefit for each individual. This is done by first estimating each individual's absolute risk of suffering a cardiovascular event (using the Framingham Heart Score) and then multiplying this by the expected relative risk reduction from anti-hypertensive therapy (based on randomized evidence[4]). Finally, deduction of expected treatment harms (again, based on randomized evidence[4]) from the calculated expected absolute risk reduction provides an estimate of absolute benefit for each individual. The authors apply both strategies to a nationally representative sample of the US population and conduct a Markov model over 5 years to estimate the effect of both intervention strategies on quality adjusted life years (QALYs) across the whole population. To enable a more direct comparison of clinical

outcomes between the two strategies, they set the threshold for treatment in the BTT strategy at a level that would lead to the treatment of the same numbers of individuals as in the TTT strategy.

What does this decision analytical model tell us? As the authors acknowledge, the qualitative aspect of their findings is neither surprising nor novel:[12] Selecting and treating individuals who are ranked to have the highest expected net treatment benefit will certainly lead to larger absolute clinical benefits than treating the same number of individuals selected on the basis of a very crude marker of risk, namely their elevated blood pressure. In fact the outcomes are so intuitive that many would be puzzled by the fact that most doctors and patients are still focused on controlling blood pressure as opposed to minimizing cardiovascular risk. However, what is perhaps less expected is the quantitative aspect of the findings. Not only was a BBT strategy more effective but it was *twice* as effective as the TTT in saving QALYs among the 45% of the population whose treatment differed between the two strategies (TTT and BTT did not make any difference to management of 55% of the population).

Of course, models are almost always simplification of reality and the validity of their outputs greatly depends on the assumptions made in designing the models and the data used to populate them. For instance, one could argue that the absolute risk estimation taken from Framingham Risk Score and its application to the US population is neither very accurate nor particularly relevant to other settings. Adherence rates, treatment efficacy and potential harms may also differ substantially between subgroups of individuals and hence may render the simulation findings unreliable. The counterarguments are that this study uses the best evidence that is available today to compare one model against another one and that many of the assumptions were conservative and in favor of TTT. The authors report several sensitivity analyses to assess the impact of some of the uncertainties around the assumptions made. For

example, assuming a greater treatment-related disutility (a measure of harms, costs and preferences) would lead to an even greater benefit from the BTT strategy because as disutility increases, in a risk-based approach less people will be exposed to treatment and hence the superiority of BTT becomes more pronounced. Other changes to the model inputs, such as increasing the accuracy of blood pressure measurement or lowering the drug adherence rates (in both strategies) similarly did not change the relative superiority of BTT substantially either.

So what are the implications of this simulation study for clinical practice and research? This study, together with evidence from previous research[12–14], supports the concept of treating cardiovascular risk as opposed to individual risk factors, such as blood pressure and cholesterol. The findings are very timely given that some of the international blood pressure guidelines have recently departed from such risk-based strategies.[15] With ever increasing accuracy and precision in the estimation of disease risks and treatment benefits, we can expect risk-based management strategies to become even more powerful. For example, randomized comparisons (e.g. from large individual patient data meta-analyses) will provide more granular information about the safety and efficacy of specific anti-hypertensive drugs in specific subgroups of patients for different types of outcomes. On the other hand, large-scale observational studies investigating the utility of new biomarkers, both phenotypic and genotypic, will help improve the accuracy of existing risk calculators. However, the challenge of maximizing benefits of preventive therapies for individuals as well as societies will not be solved by developing better risk engines alone, even if these are recommended by clinical practice guidelines.

Previous research suggests that cardiovascular risk calculators are not widely used, partly because many clinicians find risk calculation too time consuming and remain unconvinced of the value of information derived.[16] The use of innovative technologies and processes, such as

automated data capture systems and better techniques for risk visualization could minimize user burden and facilitate communication of risks and uncertainties to patients and their families.[17] Similar tools could also make information directly accessible to consumers, which might well increase their engagement, as well as that of their healthcare providers. Ultimately, a scenario could be envisaged in which there was seamless linkage between data capture, risk and benefit estimation, and clinical practice guidelines, resulting in the routine provision of personalized guidance for care that is both evidence-based and cost-effective. However, given that the introduction of such innovative models in complex healthcare environments can have multiple intended and unintended effects,[18] appropriately-designed studies are needed next to evaluate the actual effects of such system changes before more general recommendations are made.

The findings of Sussman and colleagues will challenge current blood pressure guidelines and their recent departure from risk-based approaches. The case to move on from blood pressure targets to risk-based targets is (and has always been) compelling. But bringing about actual change in the clinic requires much more work. An important part of this involves the development of innovative strategies by which to more effectively incorporate risk-based management approaches into usual clinical practice.

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