

## Sick Individuals and Sick Populations by Geoffrey Rose: Cardiovascular Prevention Updated

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In 1985, Geoffrey Rose distinguished between prevention of cardiovascular disease in individuals and in populations.<sup>1</sup> Individual prevention was based on the high-risk medical approach, which identified and treated a small group of individuals, versus the lifestyle approach, which required a broad public health intervention aimed at everyone. The lifestyle approach, he predicted, would produce greater overall benefit because small changes for good in a total population would produce much greater net benefit than large changes in a small segment of the population. The distinctions he drew became foundational principles of preventive medicine, and his engaging and elegant exposition richly rewards rereading and review.

However, the impacts of lifestyle changes have turned out to be far more complex than anticipated, and unintended consequences of dietary changes may have adversely affected cardiovascular health. Accordingly, any lifestyle population approach must be approached just as prudently as any medical approach. Conversely, contrary to Rose's expectations, medical therapy has become the favored form of primary prevention of cardiovascular disease. As the evidence for the effectiveness of statins has increased and as the cost of statins has decreased, the threshold at which risk is judged to be "high" has been dramatically lowered, and so large numbers of subjects are now included. At the present threshold of a 10-year risk of 7.5%, when all categories in

which therapy is permitted are considered,  $\approx 40\%$  of the adult US population are eligible for statin therapy,<sup>2</sup> and this number is almost certainly going to increase as new guidelines appear. The high-risk medical approach has become the medical population approach: where we are is different from where we were. But where should we go from here? What are the limitations in the models that Rose put forward and how could the medical population model of prevention evolve? These are issues we will address in this essay.

### Limitations of the Lifestyle Population Approach to Prevent Cardiovascular Disease

Rose posited that small changes in all the members of a society will produce large changes in disease outcome. The example he used of a mean decrease of 10 mm Hg in blood pressure is not appropriate because that would represent a large overall difference, even with pharmacological therapy. Rather, the question is if small changes (eg, a 2-mm Hg decrease) would be sufficient to meaningfully decrease the event rate in the population. But data to support this notion are lacking. However, a thought experiment suggests this will not necessarily be the case. Between 1988–1991 and 2005–2008, the National Health and Nutrition Examination Surveys demonstrated there was 5-mg/dL decrease in mean total cholesterol of Americans free of diabetes mellitus or pre-diabetes mellitus.<sup>3</sup> Applying the results of the Cholesterol Treatment Trialists suggests this change would reduce the relative rate of cardiovascular disease events by  $\approx 2.5\%$ .<sup>4</sup> This means, of course, that 97.5% of the risk persists. To be sure, given that the whole population is involved, an important absolute number of events will be avoided. Whether this gain is worthwhile would depend on the costs and risks of the societal intervention that produced it, but it is clearly not the final answer for prevention. To be sure, Ahern et al have produced estimates demonstrating considerable benefit were blood pressure to be reduced for the entire population.<sup>5</sup> However, the decrease they selected (a 4-mm Hg reduction in systolic blood pressure) seems unreasonably high given that pharmacological therapy in hypertensive individuals

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would be expected to produce, at least on average, only a slightly greater decrease (5.4 mm Hg) on the basis of a meta-analysis of multiple randomized clinical trials of antihypertensive therapy.<sup>6</sup> To be fair, as Rose documents in his article, large differences in blood pressure can occur between societies. However, these are societies with extreme differences in lifestyle, such as Kenyan nomads and London civil servants.<sup>1</sup>

Moreover, the societal pathway to prevention with diet is more complex and potentially more hazardous than Rose appreciated. On the basis of scientific evidence that, in retrospect, was inadequate, multiple scientific and governmental organizations in multiple countries advocated that their populations adopt a low-fat, low-cholesterol diet to reduce the risk of cardiovascular disease. Consumers may have focused on fat and cholesterol, but the critical change in their behavior was a marked increase in the intake of refined sugars. Concurrently, the prevalence of obesity and the incidence of type 2 diabetes mellitus increased. Indeed, if present trends continue, by the age of 35 years, it has been estimated  $\approx 60\%$  of Americans will be obese.<sup>7</sup> Whether the diet recommendations led directly or indirectly to the changes in obesity and type 2 diabetes mellitus remains unclear; however, a causal relation is plausible and possible.<sup>8</sup> We must face the possibility that the increases in obesity and type 2 diabetes mellitus, with their associated adverse changes in dyslipidemia and hypertension, account for the fact that the decrease in cardiovascular events seems to have halted.<sup>9</sup>

But even if this sequence of events is not causally linked, the example illustrates that the wider the exposure to change, the greater the potential for unintended adverse consequences. This highlights the need for more caution with our recommendations for lifestyle therapies. Diet, exercise, smoking, and other features of lifestyle do matter, but recommendations must be based on adequate evidence that has been rigorously assessed. The evidence-based approach, which relies on randomized controlled experiments required of medical therapies, is essential for the assessment of benefits and risks associated with lifestyle therapies. For smoking, the evidence for net benefit is convincing, whereas for nutrition and diet, the evidence remains incomplete. Moreover, these causal factors cannot be examined in isolation. The social determinants of cardiovascular disease also matter because they promote disease by promoting the factors that cause cardiovascular disease and they impede the application of medical therapy to prevent cardiovascular disease.<sup>10</sup>

## Limitations of the High-Risk Strategy

At the time that Rose thought and wrote, the term “high-risk” applied only to those who were markedly deviant from the

norm. If so, by definition, any high-risk group treated medically would be small. However, cardiovascular events are common. The high-risk model is, therefore, mathematically manifestly inadequate as a strategy to substantially reduce the overall incidence of cardiovascular events. However, while keeping the terminology intact, all current primary prevention guidelines substantially lowered the threshold defining high risk, with the result that all now target substantial portions of the population for primary prevention. For example, the 2013 American College of Cardiology/American Heart Association guidelines effectively lowered the high-risk threshold from a 10-year projected risk of 20% to 7.5%, with the result that in the United States, for example, statin preventive therapy is recommended for virtually all men and more than half of the women aged  $>65$  years.<sup>2</sup> The new target group may be labelled high risk as before, but the numbers involved are many multiples more than before. A high-risk strategy has been converted into a not-so high-risk strategy.

Nevertheless, is a risk-only strategy, even with a lowered threshold for medical intervention, the most effective approach to primary prevention of cardiovascular disease? Using Down syndrome as an example, Rose illustrated the distinction between the risk of a group of individuals and the number at risk within a group as determinants of the total number of clinical events.<sup>1</sup> Thus, far more children with Down syndrome are born to younger women than to older women because far more pregnancies occur in younger women than older women. His example has a striking parallel in cardiovascular disease prevention. The risk of cardiovascular disease increases dramatically after the age of 60 years.<sup>11</sup> Therefore, the great majority of those eligible for primary prevention of cardiovascular disease on the basis of risk are aged  $>60$  years. However, almost half of cardiovascular events in men and almost one third in women occur before the age of 60 years.<sup>11</sup> This discrepancy between total number of cardiovascular events and risk has the same explanation as Down syndrome. The number of those aged  $<60$  years is much greater than the number of those aged  $>60$  years. The problem is that risk is a standardized estimate: the number of cases per a standard number of the population. Expressing risk as a ratio with a constant denominator is what allows the relative rates of cases at different ages to be compared. The relative rates are important but so are the absolute rates. Premature cardiovascular events cut short lives during the life periods of greatest personal contributions and responsibilities. Because risk is, with few exceptions, the criterion to select individuals for preventive therapy, the present higher-risk strategy disadvantages those who are younger. To be more effective, medical prevention of cardiovascular disease will need to start earlier than presently, and none of the present guidelines deals adequately with this challenge.

## Moving Forward

### The Lifestyle Population Model

The lifestyle population model for the prevention of cardiovascular disease must be strengthened, not abandoned. The evidence that smoking is causal is undeniable, and a population prevention approach that has combined education and financial disincentives has significantly reduced, although far from eliminated, societal rates of smoking. The evidence linking obesity to cardiovascular risk is strong. But to what extent is this relation the consequence of obesity per se or the consequences of the dysglycemia and dyslipidemia that are so often associated with obesity?

Indeed, for cardiovascular health in general, we still do not know whether a particular diet will be beneficial for a particular patient, even in the short term, never mind acceptable over a prolonged period. Randomized clinical trials of diet may be more difficult to perform than randomized clinical trials of pharmaceutical agents, but this is no reason to allow a lesser standard of proof, to accept imperfect protocols, or to allow deviations from protocols. Perhaps there is not one right diet for everyone who is obese just as there is not one right medication for everyone who is hypertensive. What we are sure of is that, in addition to well-designed clinical trials, we must prioritize understanding the biological and physiological characteristics of fatty acid retention and release by adipocytes and learn much more about the metabolic interactions between fatty acid and glucose metabolism as well as the drivers of fatty acid versus glucose use by myocytes. Perhaps most critically, we must make the effort to grasp more clearly the biological and physiological characteristics of hunger and satiety. There is no short cut. Basic science is the foundation for effective applied science.

In the interim, as Ahern et al rightfully emphasize,<sup>5</sup> we need to acknowledge the fundamental distinction Rose drew between the causes of disease in the individual and the causes of disease among populations.<sup>5</sup> The known causes of cardiovascular disease in the individual are the same in all the major population groups around the world.<sup>12,13</sup> Nevertheless, their prevalence and intensity within populations vary between populations. Identifying the social determinants of disease, such as poverty and racism, and working to alleviate them represent major opportunities to improve the prevention of cardiovascular disease.

A critical question is whether inadequate funding is responsible for the limited successes to date of the lifestyle population approach. The financial support for medical measures to improve health seems to overwhelm the financial support for public health measures to improve health. Notwithstanding, the overall impact of public health interventions, such as ensuring the purity of the water and vaccinations, on the health of the public overwhelms the impact of

specific medical interventions, including statin therapy to prevent cardiovascular disease. To be sure, the mandatory character of some of these advances has been essential for their success. Nevertheless, although smoking has not been eliminated, substantial success has been achieved. The consumption of trans-fatty acids has been dramatically reduced on the basis of a public education campaign generated by observational epidemiological studies, which produced regulatory action by governmental agencies.<sup>14</sup> The conclusion we draw is that the weapons available to the population lifestyle approach may be limited, but they are potent. Therefore, the quality of the evidence for any proposed lifestyle change matters.

### Population Prevention Medicine

Given the numbers now involved, we suggest the high-risk model for prevention of cardiovascular disease be renamed the population medical model for prevention of cardiovascular disease. High risk has become moderate risk, and moderate risk means many, not a few, are eligible for prevention. This great expansion has been criticized as a “pseudo-high-risk prevention strategy” by Chioloro et al,<sup>15</sup> who argue that broadening the medical approach will not succeed because “most of the cases occur in individuals with levels of risk factors around the population average, where most people are found if risk factors are normally distributed.”

We believe this argument fails at 2 levels: first, the utilitarian level; and second, the epidemiological level. At the utilitarian level, the evidence from randomized clinical trials demonstrates unequivocally that the rates of cardiovascular disease can be meaningfully decreased in a broad portion of the population.<sup>16</sup> Given the plummeting costs of statins, therapy of individuals at moderate 10-year risk is demonstrably cost-effective.<sup>17</sup> At the epidemiological level, we do not accept it as a given that no significant number of individuals can be identified on the basis of the expression of the factors known to be causal for atherosclerosis. On the contrary, we have shown this can be done using non-high-density lipoprotein cholesterol alone.<sup>18</sup> The issue is not whether all individuals who will become cases can be identified in advance but rather whether a meaningful number at risk who merit medical prevention can be identified on the basis of reliable and available technologies, such as blood pressure or atherogenic lipids.

Nevertheless, whatever its successes, the medical model of prevention of cardiovascular disease also has its challenges: in particular, as we have noted, too few younger subjects and women are selected for medical prevention notwithstanding that the absolute numbers of cardiovascular events in younger subjects and in women are substantial.<sup>11</sup>

Moreover, even for those who do not experience a cardiovascular event before the age of 60 years, because risk is so strongly tied to age, medical prevention often does not begin until cardiovascular disease is already advanced in a substantial number of individuals (ie, much of the anatomic disease that produces the clinical events after the age of 60 years developed in the decades before the age of 60 years).<sup>11</sup>

Two strategies to overcome these critical shortcomings are possible. The first is to lower the risk threshold even further: in the case of the American College of Cardiology/American Heart Association guidelines, this might be to substitute a threshold of 5% for the previous 7.5%. This would expand the number treated, decrease the age at which treatment might begin, and increase the number of events prevented. Given the low cost of statins, this approach will almost certainly be cost-effective.

The benefit strategy offers an alternate approach. In the benefit model of cardiovascular prevention, the risk threshold is first established and then the benefit from therapy is evaluated. The benefit from low-density lipoprotein (LDL)-lowering therapy for a particular individual is a function of both his/her baseline risk and baseline level of LDL-cholesterol because for every mmol/L lowering of LDL-cholesterol, risk is lowered by  $\approx 20\%$ . Accordingly, the higher the baseline LDL-cholesterol, the greater the potential benefit in any individual. On the basis of this relation, we and others<sup>19–21</sup> have shown that at any given threshold level of risk, the absolute risk reduction can be the same in those with higher levels of LDL-cholesterol but lower levels of risk. Critically, those who are added by the benefit approach are younger than the average of those selected by the risk approach. The level of LDL is, obviously, a property of the individual and the selection, therefore, is tied to the individual. This should make it easier for the individual to understand the potential benefits for therapy in his/her specific case. In fact, it can be shown mathematically that the benefit model is the most efficient model possible to select subjects for prevention of cardiovascular disease.<sup>20</sup>

## Summary

Prevention of cardiovascular disease today is as different from Geoffrey Rose's day as day is to night. In his time, net benefit from medical therapy was uncertain because there were no therapies that had been proved to be safe, effective, and affordable. However, the evidence that therapies that lower blood pressure and cholesterol prevent cardiovascular events is now incontrovertible with the result that guidelines recommend medical treatment of a large segment of the population to prevent cardiovascular disease. Population prevention medicine is not something that may occur

tomorrow. Population prevention medicine is being practiced today.

Yet, much remains to be done. The medical treatments of hypertension and hyperlipidemia both take place within a medical model that was not designed to deal with the numbers that could benefit from preventive medical therapy, and we need to refine our present system of care to take the realities of population medicine into account.

## Disclosures

Thanassoulis is a consultant for Ionis Pharma; is on the advisory boards of Ionis Pharma, Amgen, and Servier Canada; is a member of the speaker's bureau of Amgen, Sanofi, Servier Canada, and Boehringer Ingelheim; and has received a research grant from Ionis Pharma. Pencina holds a grant from Sanofi/Regeneron. The remaining authors have no disclosures to report.

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