The Relative Merits of Population-Based and Targeted Prevention Strategies

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Context: Preventive medicine has historically favored reducing a risk factor by a small amount in the entire population rather than by a large amount in high-risk individuals. The use of multivariable risk prediction tools, however, may affect the relative merits of this strategy.

Methods: This study uses risk factor data from the National Health and Nutrition Examination Survey III to simulate a population of more than 100 million Americans aged thirty or older with no history of CV disease. Three strategies that could affect CV events, CV mortality, and quality-adjusted life years were examined: (1) a population-based strategy that treats all individuals with a low- or moderate-intensity intervention (in which the low-intensity intervention represents a public health campaign with no demonstrable adverse effects), (2) a targeted strategy that treats individuals in the top 25 percent based on a single risk factor (LDL), and (3) a risk-targeted strategy that treats individuals in the top 25 percent based on overall CV risk (as predicted by a multivariable prediction tool). The efficiency of each strategy was compared while varying the intervention's intensity and associated adverse effects, and the accuracy of the risk prediction tool.

Findings: The LDL-targeted strategy and the low-intensity population-based strategy were comparable for CV events prevented over five years (0.79 million and 0.75 million, respectively), as were the risk-targeted strategy and

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moderate-intensity population-based strategy (1.56 million and 1.87 million, respectively). The risk-targeted strategy, however, was more efficient than the moderate-intensity population-based strategy (number needed to treat [NNT] 19 vs. 62). Incorporating a small degree of treatment-related adverse effects greatly magnified the relative advantages of the risk-targeted approach over other strategies. Reducing the accuracy of the prediction tool only modestly decreased this greater efficiency.

Conclusions: A population-based prevention strategy can be an excellent option if an intervention has almost no adverse effects. But if the intervention has even a small degree of disutility, a targeted approach using multivariable risk prediction can prevent more morbidity and mortality while treating many fewer people.

Keywords: Risk stratification, prevention, multivariable prediction tools, cholesterol.

Population-based prevention approaches that attempt to lower the risk of the entire population can have overwhelming appeal, especially when applied to environmental exposures. For example, decreasing the amount of trans fats or salt in commonly eaten foods could efficiently and cheaply reduce disease in the overall population to a degree that would be difficult to do using a medical model of intervention (Stamler et al. 1989). However, a commonly quoted argument in favor of population-based prevention is that in most cases more disease is prevented by reducing a risk factor by a small amount in the general population than by selectively reducing it by a large amount in high-risk individuals (Stamler et al. 1989; Rose 1985, 1992). This principle of prevention was introduced by Geoffrey Rose in the 1980s (Rose 1985). Using risk factors such as cholesterol and blood pressure as examples, Rose demonstrated that a strategy that reduced the population average would lower the prevalence of clinical heart disease more than would a strategy that focused on those people with the highest cholesterol and blood pressure values (Rose 1992).

Early epidemiological and modeling studies in cardiovascular (CV) disease confirmed Rose's theory (Kottke et al. 1985). These results were based on the premise that CV risk was distributed so that the majority of events and deaths occurred among the large number of persons with

only a modest elevation in the targeted risk factor and that individuals with the highest cholesterol and blood pressure levels accounted for only a small proportion of events in the population. More recently, an analysis of the World Health Organization's Global Burden of Disease database supported this pattern for most major global diseases (Rodgers et al. 2004). These findings reinforce the concept of reducing the disease burden by using prevention strategies that shift the distribution of risk factors across the population.

One of the reasons that population-based strategies were favored in the past is that a strategy targeting high-risk individuals requires an accurate method of predicting future disease (Rodgers et al. 2004). When Rose developed his concepts of population-based prevention in the 1970s and 1980s, risk prediction was in its infancy, and a person's risk was generally estimated by one or two risk factors or by a simple point-based system. Rose acknowledged the limitations of risk prediction at that time, stating, "Unfortunately the ability to estimate the average risk for a group, which may be good, is not matched by any corresponding ability to predict which individuals are going to fall ill soon" (Rose 1992, 48). Today, however, we have robust multivariable risk prediction tools for many common health outcomes (Avins and Browner 1998; Cheung et al. 2001; Fiaccadori et al. 2000; Hayward et al. 2005; Le Goff et al. 2000; Moscucci et al. 2001; Pocock et al. 2001; Selker et al. 1997; Slotman 2000; Stier et al. 1999; Tekkis et al. 2003; Teno et al. 2000; Wilson et al. 2007; Zimmerman et al. 1998). These tools use clinical data in a regression model to estimate an individual's risk of developing disease. Recent work has shown that multivariable risk prediction can detect heterogeneity in a clinical trial population's treatment benefit much more precisely than prediction using single risk factors (Hayward et al. 2005, 2006; Kent et al. 2002; Kravitz, Duan, and Braslow 2004; Rothwell and Warlow 1999). These improved risk prediction tools have demonstrated that most people have a very low risk for CV events in the next five to ten years (Avins and Browner 1998; Selker et al. 1997). Thus, a majority of the people who are exposed to a population-based strategy may be very unlikely to develop clinically significant disease.

Previous studies that compared population-based and targeted prevention strategies raised concerns that the accuracy of risk prediction tools could be substantially diminished when used in routine clinical practice (Emberson et al. 2004; Strachan and Rose 1991). This can happen when high-risk individuals face barriers to health care access or if

their health care providers cannot easily identify them as being at high risk. A model that cannot be generalized from one population to another may also cause problems. In addition, if the model considers too many variables, it may be "overfit" to the study population, and if risk factors are measured less accurately in practice than in clinical studies, regression dilution due to measurement error can weaken the risk factor's ability to accurately predict individual risk (Knuiman et al. 1998; MacMahon et al. 1990). Such concerns about inaccuracies in risk prediction tools have led to more misgivings about risk-stratified approaches (Emberson et al. 2004).

Given the dramatic advances in multivariable risk prediction tools, we were interested in exploring how these tools influence the relative efficacy of targeted and population-based interventions in preventive medicine. We examined this phenomenon in the general U.S. population using one of the two scenarios that Rose used more than twenty-five years ago, namely, LDL cholesterol and CV disease. Specifically, we looked at both the population benefit, defined as the amount of harm reduced in the total population, and the efficiency, defined as the amount of harm reduced for each person treated. We examined how these elements vary according to (1) the degree to which the population can be stratified by risk (no risk stratification vs. single-variable risk stratification vs. multivariable risk stratification), (2) the degree of treatment-related adverse effects (disutility related to complications, side effects, and inconvenience of the intervention), and (3) the accuracy of the risk prediction tool. The aim of our analysis was not to determine whether a targeted approach is always better or worse than a population-based strategy (because the answer to that question depends on the intervention and condition-specific circumstances and assumptions) but to better quantify how specific factors can influence the relative merits of the two approaches.

Methods

Population Estimates

The distribution of risk factors in the U.S. population was estimated using data from the National Health and Nutrition Examination Survey (NHANES), which uses interviews, physical examinations, and

diagnostic tests to obtain nationally representative information about the health of the U.S. population. We chose NHANES III (conducted between 1988 and 1994) for our analyses because we wanted data representing the natural distribution of LDL cholesterol in the population before the widespread use of statin therapy. Although other cholesterol-lowering medications were used during this period, they were used infrequently for primary prevention, and owing to their lower potency and low adherence, they were only marginally effective in reducing LDL (Goldman et al. 1991; Leitha et al. 1994; Watts et al. 1992).

Model Population

To estimate the distribution of CV risk factors, we used data from NHANES III for persons aged thirty or older with no history of a heart attack. Although few clinical trials have included large numbers of individuals older than seventy-five years, subgroup analyses have demonstrated clear benefits of lowering cholesterol in all age groups studied, and national guidelines do not include an age cutoff. We therefore opted to include all age groups in our population-based analysis and to exclude persons with no record of LDL cholesterol measurement. Results for the 4,922 subjects meeting our inclusion criteria were extrapolated to construct a simulated population of more than 100 million individuals, which approximates the U.S. population aged thirty or older with no history of CV disease (U.S. Census Bureau 2004).

Risk of CV Events and Mortality

We estimated the risk of CV events (angina, myocardial infarction, peripheral vascular disease, stroke, and heart failure) and CV death over a five-year period using sex-specific Weibull regression models based on the Framingham Cohort Study (Anderson et al. 1991). The risk prediction tool includes age, sex, systolic blood pressure, current smoking status, serum total and high-density lipoprotein cholesterol concentrations, diabetes, and evidence of left ventricular hypertrophy as detected using ECG. The end points were the incidence of CV events and CV mortality. We chose a five-year interval based upon the assumption that most patients would be reevaluated for preventive care and medical intervention at least every three to five years.

Intervention Efficacy

We assigned a 10 percent, 25 percent, and 35 percent relative risk reduction (RRR) for low-, moderate-, and high-intensity interventions, respectively. These numbers roughly correspond to the effects of low-, moderate-, and high-dose statin therapy (Heart Protection Study Collaborative Group 2002; Jacobson et al. 1998; LaRosa, He, and Vupputuri 1999; Pignone, Phillips, and Mulrow 2000), which produce a constant RRR, or log-linear response, in CV events and mortality (Grundy et al. 2001).

Population and Targeted Intervention Strategies

Table 1 summarizes the treatment approaches we evaluated, including each treatment's efficacy and adverse effect rate. First we examined two population-based prevention strategies that simulated low-intensity and moderate-intensity population-wide interventions. We then stratified the population first by a single risk factor (LDL) and second by the overall CV risk as determined by the multivariable Framingham risk prediction tool described earlier (Anderson et al. 1991). For the LDL-targeted strategy, we evaluated the benefits of treating individuals with moderate-intensity therapy if their LDL was in the seventy-fifth to ninetieth percentile and with high-intensity therapy if their LDL was higher than the ninetieth percentile. For the risk-targeted strategy, we evaluated the benefits of treating individuals with moderate-intensity therapy if their CV risk was in the seventy-fifth to ninetieth percentile and with high-intensity therapy if their CV risk was higher than the ninetieth percentile.

Benefits of Prevention Strategies

For each treatment model, we calculated the number of CV events and deaths prevented and the number needed to treat (NNT) to prevent one event or death. We then estimated the quality-adjusted life years (QALYs) gained in each model and compared the population benefit (QALYs gained over five years in the U.S. population) and the efficiency (QALYs gained per 1,000 adults treated, and NNT to gain one QALY). We computed the gain in QALYs for each person using the following calculation (where 0.25 represents the disutility associated with a

TABLE 1
Characteristics of Treatment Scenarios

Treatment Scenario	Focus of Intervention	Basis for Stratification		Intensity of Intervention	% Adult Population Treated	RRR[a] of Intervention (%)	Treatment-Related Adverse Effects (%)[b]
Population-based strategy	All adults aged 30 or older	—		Low	100	10	None
				Moderate	100	25	0.1–0.2
LDL-targeted strategy	Individuals with elevated LDL	Single risk factor (LDL)	75th–90th percentile	Moderate	15	25	0.1–0.2
			> 90th percentile	High	10	35	0.2–0.4
Risk-targeted strategy	Individuals with elevated CV risk	Overall CV risk	75th–90th percentile	Moderate	15	25	0.1–0.2
			> 90th percentile	High	10	35	0.2–0.4

Notes: [a]RRR = Relative risk reduction.
[b]Disutility.

cardiovascular event) (Nowels et al. 2005; Tsevat et al. 1991): Gain in QALYs over five years due to intervention equals QALYs lost over five years without intervention minus QALYs lost over five years with intervention. If the five-year CV mortality risk without intervention is M_0, the five-year CV event risk without intervention is E_0; M_{Rx} and E_{Rx} are the comparable rates in the presence of the intervention, δ_{Rx} is the disutility associated with treatment, and a constant rate of outcomes over a five-year period is assumed (with 2.5 representing the average time over which events and deaths would take place during that period), then:

$$\text{QALYs gained} = [(2.5 * M_0) + (0.25 * 2.5 * (E_0 - M_0))]$$

$$-[(2.5 * M_{Rx}) + (0.25 * 2.5 * (E_{Rx} - M_{RX})) + (\delta_{Rx} * (5 - (2.5 * M_{Rx})))]$$

Treatment-Related Adverse Effects

We incorporated various degrees of treatment-related adverse effects (disutility) into our calculation of QALYs. We used values that ranged from 0.001 to 0.004 based on previous estimates of disutilities associated with lifestyle modifications and medications (e.g., taking an aspirin a day has been estimated to have a disutility of 0.002) (Gage et al. 1995; Krahn et al. 1991; Revicki and Wood 1998). We examined the impact on QALYs if the intervention had a "very small adverse effect rate" (0 for low-intensity treatment, 0.001 for moderate-intensity treatment, and 0.002 for high-intensity treatment) and a "small adverse effect rate" (0 for low-intensity treatment, 0.002 for moderate-intensity treatment, and 0.004 for high-intensity treatment). The low-intensity population strategy was intended to mimic a public health intervention with no direct or indirect adverse effects (as might be the case in an educational campaign with no demonstrable downside).

Accuracy of the Risk Prediction Tool

We examined how the accuracy of the risk-prediction tool influences the total population benefit and the efficiency of treatment effects. Using the Framingham risk tool to predict both risk and benefit may augment the advantages of a risk-stratified approach because prediction tools are

often less accurate when used in the real world than in the populations in which they are developed. On the other hand, using the Framingham risk tool may result in underestimating the benefits of optimal risk-stratification because other tools offer more precise estimates of risk (Empana et al. 2003; Ferrario et al. 2005; Grundy et al. 2001; Hense et al. 2003; Liu et al. 2004). To account for these possibilities, we varied the accuracy of the risk prediction tool in our sensitivity analysis to determine how deterioration of the predictive model in actual practice would affect the results. We first randomly assigned outcomes to our simulated U.S. population assuming no attenuation in the model (meaning that the model works as well in practice as it did in the study population). Next we progressively increased the measurement error in the prediction tool's estimated probability of CV events and deaths by adding a uniform error component until the C-statistic (the area under the receiver operator curve) decreased by approximately 20 percent and 40 percent. We then examined how this variation in the accuracy of the model affected our results (Hayward et al. 2006).

Results

Table 1 shows the different strategies we tested for preventing CV events and mortality in U.S. adults aged thirty or older with no history of CV disease. The low-intensity population-based strategy would prevent an estimated 0.75 million CV events and 0.14 million CV deaths over five years in the U.S. population (compared with no intervention), whereas the moderate-intensity population-based strategy would prevent 1.87 million events and 0.34 million deaths (table 2). The LDL-targeted strategy would prevent an estimated 0.79 million events and 0.15 million deaths, and the risk-targeted strategy would prevent about 1.56 million events and 0.40 million deaths in the population.

Although the LDL-targeted strategy and the low-intensity population-based approach would prevent a comparable number of CV events (0.79 million and 0.75 million, respectively), the LDL-targeted approach is much more efficient. For example, the NNT for five years to prevent one event is 156 using a low-intensity population-based approach, but only 37 using the LDL-targeted approach. The risk-targeted strategy, however, would prevent twice as many events as the low-intensity population strategy would (1.56 million and 0.75

TABLE 2
Number of Outcomes Prevented with Population-Based and Targeted Prevention Strategies

Treatment Scenario		% Adult Population Treated	Outcomes Prevented over 5 Years among Adults 30+Years of Age with No History of CV Disease					
			Total in U.S. Population (in Millions)		Rate per 1,000 Persons Treated		NNT[a]	
			Events	Mortality	Events	Mortality	Events	Mortality
Population-based strategy	Low intensity	100	0.75	0.14	6.4	1.2	156	850
	Moderate intensity	100	1.87	0.34	16.0	2.9	62	340
LDL-targeted strategy		25	0.79	0.15	27.1	5.2	37	193
Risk-targeted strategy		25	1.56	0.40	53.8	13.7	19	73

Note: [a]NNT = Number needed to treat to prevent one CV event or CV death.

million, respectively) and is substantially more efficient than the LDL-targeted strategy (NNT = 19 and 37, respectively). The efficiency of the risk-targeted approach is even greater for mortality, where the NNT to prevent one death is 73, compared with 850 in the low-intensity population-based strategy and 193 in the LDL-targeted strategy.

To evaluate how disutility influences the efficiency of each prevention strategy, we calculated the net gain in QALYs that would be expected with each approach if the intervention had a small degree of treatment-related adverse effects (table 3). For the low-intensity population-based strategy we estimated that the net QALYs gained in the U.S. population would be 0.72 million (NNT to gain one QALY was 161). This was the only strategy for which we assumed no treatment-related adverse effects, as might be the case in a large-scale educational campaign. When we incorporated treatment-related adverse effects into the model, the LDL-targeted strategy performed less well than the population-based strategies did in terms of QALYs gained for all adults, although it still was more efficient (NNT to gain one QALY was 51 to 77). Incorporating treatment-related adverse effects, however, made the risk-targeted approach even more effective relative to all other strategies for both overall benefit across the U.S. population (1.33 to 1.53 million QALYs gained) and efficiency (NNT to gain one QALY was 19 to 22).

When we adjusted the results of the risk-targeted strategy to account for a possible decrease in the predictive accuracy of the multivariable risk prediction tool, we found that the NNT to prevent one CV event rose by approximately 15 percent to 53 percent (table 4). Nevertheless, the risk-targeted strategy still had a greater overall population benefit than did the low-intensity population-based strategy. The risk-targeted strategy also remained substantially more efficient than the moderate-intensity population-based strategy, resulting in a gain of 34.4 QALYs per 1,000 adults treated (compared with a gain of 10.6 QALYs per 1,000 adults treated with the moderate-intensity population-based strategy).

Figure 1 provides a graphic explanation of why LDL-based targeting performs so much less well than CV risk-based targeting. As the figure illustrates, the correlation between LDL values and overall CV risk is relatively low (the correlation coefficient is 0.26 for LDL and risk of CV event, and 0.16 for LDL and risk of CV mortality). The risk of a CV event for an individual in the top 10 percent of LDL levels is only two times higher than that of an individual in the bottom 75 percent. But when the population is stratified using multivariable risk prediction,

TABLE 3
Consequence of Treatment's Adverse Effects on QALYs in Population-Based and Targeted Prevention Strategies

Treatment Scenario		% Adult Population Treated	Net QALYs[a] Gained over 5 Years among Adults 30+ Years of Age with No History of CV Disease					
			Total in U.S. Population (in Millions)		Rate per 1,000 Persons Treated		NNT[b]	
			Very Small Adverse Effect	Small Adverse Effect	Very Small Adverse Effect	Small Adverse Effect	Very Small Adverse Effect	Small Adverse Effect
Population-based strategy	Low intensity[c]	100	0.72	0.72	6.2	6.2	161	161
	Moderate intensity	100	1.23	0.65	10.6	5.6	95	179
LDL-targeted strategy		25	0.58	0.38	19.8	13.0	51	77
Risk-targeted strategy		25	1.53	1.33	52.4	45.5	19	22

Notes: [a]QALYs = Quality-adjusted life years.
[b]NNT = Number needed to treat to gain one QALY.
[c]The low-intensity population-based strategy was assumed to have no associated adverse effects.

TABLE 4
Effects of Predictive Accuracy of Multivariable Risk Prediction Tool on Efficiency of Risk-Targeted Strategy

Treatment Scenario[a]		% Adult Population Treated	Net QALYs[b] Gained over 5 Years among Adults 30+ Years of Age with No History of CV Disease		
			Total in U.S. Population (in Millions)	Rate per 1,000 Persons Treated	NNT[c]
Population-based strategy	Low intensity	100	0.72	6.2	161
	Moderate intensity	100	1.23	10.6	95
Risk-targeted strategy	No decrease in predictive accuracy	25	1.53	52.4	19
	20% decrease in predictive accuracy	25	1.34	45.9	22
	40% decrease in predictive accuracy	25	1.00	34.4	29

Notes: Predictive accuracy refers to the accuracy of the multivariable prediction tool when applied in actual practice.
[a]All estimates assume that a low-intensity intervention reduces risk by 10 percent and has no disutility, that a moderate-intensity intervention reduces risk by 25 percent and has a disutility of 0.001, and that a high-intensity intervention reduces risk by 35 percent and has a disutility of 0.002.
[b]QALYs = Quality-adjusted life years.
[c]NNT = Number needed to treat to gain one QALY.

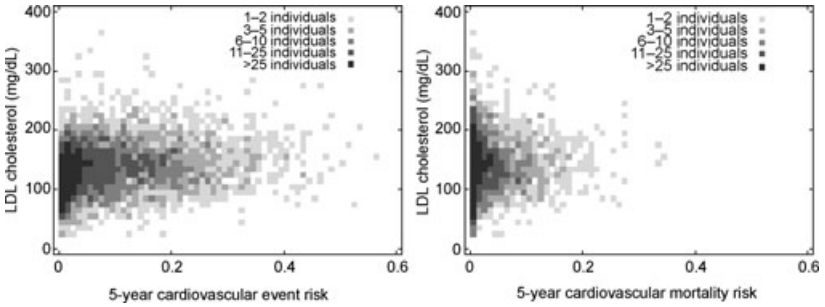

FIGURE 1. Relationship between Serum LDL and Five-Year Risk of CV Events and Mortality for 4,922 Individuals in NHANES III

Note: These graphs illustrate the correlation between LDL cholesterol and the risk of CV events and mortality over five years. The low correlation coefficients for LDL and risk of CV event (0.26) and LDL and risk of CV mortality (0.16) suggest that LDL levels alone are poor predictors of CV risk. In this scenario, a targeting strategy that focuses solely on persons with high LDL is likely to miss a substantial number who have low LDL levels but otherwise high CV risk.

this difference increases to nine times higher. These results are even more striking when analyzing a person's risk of dying from a CV event, as the difference between the top 10 percent and the bottom 75 percent is again two times when stratifying by LDL, but fifty-two times when stratifying by overall CV risk. Table 5 uses two hypothetical individuals to demonstrate this concept further. Individual B, who has low LDL but several other risk factors for CV disease (i.e., low HDL, high blood pressure, and history of tobacco use), has a risk of a CV event that is approximately thirty times higher than that of individual A, who has high LDL but no other major CV risk factors.

Discussion

This article explores how specific factors influence the relative merits of population-based and targeted prevention strategies. By modeling one of Rose's examples in his seminal work (1992), we demonstrate that reducing a risk factor by a small amount in the overall population is not as effective as reducing it by a moderate amount in high-risk individuals who are identified with a moderately accurate multivariable risk prediction tool. Furthermore, our results show that a targeted strategy can quickly become the dominant approach (fewer people are treated, and

TABLE 5
Examples of Extreme Discordance between LDL Levels and CV Risk

	A: High LDL, Low CV Risk	B: Low LDL, High CV Risk
Age	45	**68**
Sex	Female	**Male**
LDL	**175**	95
HDL	55	**25**
Triglycerides	100	**200**
Systolic blood pressure	120	**145**
Left ventricular hypertrophy by ECG	No	**Yes**
Tobacco use	No	**Yes**
5-year risk of CV event	1.3%	40.6%
5-year risk of CV mortality	< 0.1%	13.2%

Note: Values in **boldface** indicate risk factors for CV events and mortality.
To illustrate the concept of risk stratification, this table compares the risks of two individuals. Despite having a high LDL, individual A has a 1.3 percent risk of a cardiovascular event in the next five years, and less than 0.1 percent risk of mortality due to such an event. But individual B has a 40.6 percent risk of a cardiovascular event in the next five years and a 13.2 percent risk of mortality from such an event.

more morbidity and mortality are prevented) when the intervention has even infrequent adverse effects.

Our study suggests that the principle that "reducing a risk factor by a small amount in the overall population is more effective than reducing it by a large amount in high-risk individuals" may seldom be true when using multivariable risk prediction. The reason that a multivariable approach makes such a large difference is that the contribution of a single factor to overall risk is usually quite small (Hayward et al. 2005). Even a major risk factor rarely increases risk by more than a factor of 1.5 to 2, whereas multivariable tools can often stratify risk to the point that the risk of the highest quartile is five to forty times higher than that of the lowest quartile (Ioannidis and Lau 1998; Kent and Hayward 2007). This simple fact is what underlies much of the findings in our analyses.

In addition to renewing interest in evaluating "high-risk" or targeted approaches to prevention, the availability of risk stratification tools has enabled the incorporation of overall individual risk into certain clinical guidelines (Emberson et al. 2004; Manuel et al. 2006). The National Cholesterol Education Program (NCEP) guidelines are an example of this. The initial guidelines focused primarily on LDL levels. Over time, they were extended to major risk factors, such as diabetes and known

macrovascular or kidney disease, until finally the overall Framingham risk was added as a criterion in NCEP III (NCEP III 2002). Similarly, tighter blood pressure goals are currently recommended for patients with a higher CV risk than for those with a lower CV risk. Still, few guidelines recommend using robust multivariable prediction tools to assess the appropriateness of aggressive risk factor modification. Our results suggest that such strategies should at least be considered in future guideline deliberations in those instances for which multivariable tools exist.

A possible limitation of targeted strategies is that they may not identify certain high-risk individuals, such as in cases of inadequate health care access or an incomplete assessment of risk by a health care provider. In addition, the efficiency of a targeted strategy may be overestimated if the multivariable risk prediction tool is less accurate in practice than in studies (i.e., due to overfitting or poor generalizability) (Emberson et al. 2004; Strachan and Rose 1991). In order to evaluate the magnitude of these effects, we varied the accuracy of the risk prediction tool. We found that a less accurate tool, which would translate into fewer high-risk individuals being treated, did have a substantial effect on the overall population benefit. Even so, the targeted strategy remained much more efficient, as measured by NNT.

Another potential drawback of a targeted approach is that the benefits of preventive interventions often extend to several diseases and a targeted strategy may offer these benefits to fewer people. For example, a public health campaign encouraging physical activity could improve a community's risk profile not only for CV disease but also for diabetes, cancer, osteoporosis, and depression, to name just a few. When the risks of different disease outcomes are concentrated in subpopulations, targeted approaches could be directed at such groups. If this is not the case, however, a targeted approach may not be able to replicate the breadth of benefits of a population-wide strategy. The impact of an intervention on multiple disease processes is therefore an important consideration for policy decisions.

Although our model focused on CV outcomes, we believe that the results of our study could be extended to other conditions. While risk estimation models for CV disease are more refined than those for most other diseases, we found that only a modestly predictive tool (AUROC $>$ 0.6) was needed to make a moderate-intensity targeted intervention more effective than a low-intensity population-based strategy. Many

major outcomes, including end-stage renal disease, stroke, CV disease, hospitalization, ICU stays, and most cancers, have prediction tools with AUROC curves substantially greater than 0.6 even after considering likely regression dilution (Hayward et al. 2005). Furthermore, CV disease has a high absolute risk at the population level. This is important because how much even a small degree of treatment harm influences a preventive strategy depends on the absolute risk of disease-related morbidity and mortality in the population. By using the example of CV disease, we selected a "best-case scenario" for a population-based approach because CV disease is by far the leading cause of overall mortality.

Our study addresses only some of the factors influencing the merits of different preventive approaches. Essential to a successful targeted approach is that high-risk individuals be easily identified and treated. In contrast, a population-based approach relies on effective communication about and access to the intervention. The costs and risks of population-based interventions and targeted strategies may differ considerably, and limited resources may make one strategy preferable. For example, an affordable population-based intervention that offers short-term improvements in quality of life (such as a diet or exercise program that makes people feel better within a short time) will theoretically almost always be preferable to a targeted approach. But if resources are limited and the choice is between a cheap, low-intensity intervention that increases all persons' physical activity by a little and a more expensive but much more effective intervention that increases sedentary high-risk individuals' physical activity by a lot, the latter is likely to do much more good (Richardson et al. 2004). In most circumstances, however, the two approaches are not mutually exclusive and often are complementary. While comparing them can yield valuable information for policy development and implementation, the optimal prevention policy will often use both strategies.

Our study demonstrates that the benefits of prevention strategies can be substantially influenced by even a small magnitude of treatment-related adverse effects. If a treatment truly has no direct or indirect adverse effects, a population-based strategy will always prevent more bad outcomes than will a targeted intervention of equal intensity, because more people will benefit from the intervention and no one will suffer negative consequences. This is what makes public health campaigns, such as those promoting appropriate exercise or banishing trans fats from restaurants, so compelling. We chose to model this type of population-wide

intervention to show that even a risk-free, population-based strategy is less efficient (in terms of NNT to prevent a particular outcome or to gain one QALY) than an effective targeted strategy.

Even an educational campaign, however, is rarely without some disutility, be it in the form of lost time or the intrusiveness or cost of a lifestyle change. Even resentment of public health officials may sometimes need to be considered. For population-wide medical interventions like a proposed polypill (Wald and Law 2003), the disutility may be the traditional adverse effects of drugs, including mild side effects, rare serious complications, and drug interactions. Our analysis strongly suggests that even a minimal degree of treatment-related adverse effects, approximately half the disutility estimated for a daily aspirin (Gage et al. 1995), can quickly make a population-based strategy much less desirable. The relative inefficiency of the population-based approach may result in many people experiencing disutility but only a few gaining a clinically significant benefit.

In conclusion, population-based prevention strategies may be appropriate when the risk for a disease is widely dispersed in the population and the proposed intervention is very safe and cheap. Furthermore, the appeal of a population-based approach increases when it is more costly and difficult to identify and intervene on high-risk individuals. But with the advent of more refined multivariable prediction tools, we now are often able to identify those persons who account for the majority of clinically significant disease morbidity and mortality. Our study demonstrates that as risk stratification tools become more precise, a targeted prevention strategy that focuses on high-risk individuals is usually dramatically more efficient than a population-based strategy. In such situations, even a very small amount of treatment-related adverse effects or disutility can make a targeted strategy the preferred choice. Consequently, researchers and policymakers should consider the influence of these factors when discussing the optimal strategy for preventing many common diseases.

Summary Points

Population-based prevention strategies using cheap and safe interventions can be considerably more effective than strategies that target

individuals based on a single elevated risk factor (such as LDL or blood pressure).

Multivariable prediction tools have greatly enhanced our ability to identify individuals who are at higher or lower risk for developing complex diseases such as coronary heart disease.

As the precision of risk prediction tools increases, targeted prevention strategies that focus on high-risk individuals become dramatically more efficient than population-based strategies.

When there is even a small degree of disutility associated with an intervention, a targeted approach will result in greater prevention for less cost.

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