Drug Therapies for the Primary Prevention of Cardiovascular Events: Trials and Errors

2009 Ancel Keys Memorial Lecture

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Ante omnia, iuvari amplius quam nocere (Above all, do more good than harm).

—John R. Senior

I am grateful to the Epidemiology and Prevention Council for the honor and the opportunity to speak today. Henry Blackburn entitled his introduction to the first Ancel Keys lecture “Ancel Keys, pioneer” and summarized Keys’ astonishing array of work in nutrition and physiology, methods, and prevention, including the diet-heart hypothesis and efforts to bridge biology, preventive medicine, and public health. As a result of his work and the work of many others over the last 50 years, the mortality rate from coronary heart disease (CHD) declined by about 50% between 1980 and 2000, a decline attributable in part to changes in medical treatments after coronary events and in part to changes in levels of risk factors in the population. In this lecture, as an admiring follower and a northwest settler, I consider some potential next steps in CHD prevention.

This talk has 2 related parts. The first reviews how we approve preventive drug therapies in America. High-quality drug evaluations serve as an essential foundation for future CHD prevention efforts. The second part considers 2 potential approaches to the use of drug therapies in intermediate-risk individuals. A comparative effectiveness trial evaluating the risks and benefits of these 2 approaches would help guide future prevention efforts.

Distributions of Serum Cholesterol

Ancel Keys was among the first to put forward hypotheses about population-level and individual-level causes of cardiovascular disease (CVD). In Keys’ Seven Countries Study, the distribution curves scarcely overlap for total cholesterol levels in individuals from south Japan and east Finland (Figure I in the online-only Data Supplement). Within populations, however, even though cholesterol is strongly associated with cardiovascular events, the cholesterol level overlap between those who do and do not go on to have a CHD event is substantial (Figure II in the online-only Data Supplement).

Geoffrey Rose distinguished between 2 methods of CVD prevention. The aim of the population-based strategy is to reduce the level of a risk factor in many people and thus shift its distribution. Interventions such as smoking cessation and low-fat diets, which restore biological normality for the species, can be “presumed to be safe.” Rose used the term “prevention paradox” to describe the fact that for mass preventive measures, the number needed to treat to prevent 1 event would be high and provide “little [benefit] to each participating individual.” In contrast, the high-risk strategy focuses on the individuals who have high levels of a risk factor and frequently relies on drugs treatments. The use of preventive drug therapies in individuals with extreme levels of risk factors represents an efficient use of resources in individuals most likely to benefit, but this high-risk strategy entails another paradox, the “treatment paradox”: because many events occur among those with average or intermediate levels of risk, the high-risk approach may do little to reduce the overall burden of CHD in the population (the Figure).

In the early 1980s, the available lipid-lowering drug therapies were limited. The results of the World Health Organization clofibrate study profoundly influenced Rose’s thinking about drug therapies. In this randomized trial, clofibrate not only reduced the incidence of ischemic heart disease but also increased the risk of total mortality. Indeed, for every 15 CVD events that might be prevented by clofibrate, there were about 11 extra deaths. This risk-benefit profile argued against the widespread use of clofibrate as a “long-term mass preventive medication” in the primary prevention setting, which includes low-risk people who are well, who are without clinical disease, and who are even without symptoms. As another side effect, the mixed results of the clofibrate trial would later prompt the US Food and Drug Administration to request or require large long-term trials to evaluate new lipid-lowering drugs such as the statins.

Drug Approval and Rosiglitazone for the Treatment of Type 2 Diabetes Mellitus

Drug therapies for risk factors such as high levels of blood pressure, lipids, and glucose represent, in Rose’s terms, a
high-risk approach to a population-based problem. The purpose of these therapies is to prevent cardiovascular events, yet the US Food and Drug Administration generally approves new medications for these conditions on the basis of premarket studies that use biomarkers or surrogate end points. This approach typically reduces the costs of development and the time to approval but often provides incomplete information about the risks and benefits of new drug therapies.\textsuperscript{10}

In observational studies of patients with type 2 diabetes mellitus, the relative risk for cardiovascular events associated with a 1% increment in glycohemoglobin is 1.18.\textsuperscript{11} These data suggest that in clinical trials, a 1% reduction in glycohemoglobin would be expected to reduce the relative risk of cardiovascular events by about 15%. Do drug treatment effects on glycohemoglobin serve as a valid and accurate proxy for their effects on the incidence of cardiovascular events?

In a meta-analysis of the 3 recent trials of intensive treatment of patients with type 2 diabetes mellitus,\textsuperscript{12–15} the relative risk reduction was only 6% (95% confidence interval [CI], 14 to −2). This 95% CI excludes the expected value of 15%, and the observed benefit for the prevention of cardiovascular events is less than half the predicted risk reduction. The reasons are not clear. Perhaps aggressive lowering of glucose does little to influence the adverse effects of insulin resistance, obesity, and inflammation typically associated with type 2 diabetes mellitus.\textsuperscript{16} Additionally, the increased risk of hypoglycemia associated with intensive treatment may precipitate cardiovascular events or cause deaths that are mistakenly attributed to CVD. Finally, drug therapies often have a number of actions, some of which may lead to serious adverse events.

Rosiglitazone, used in both US trials,\textsuperscript{13,15} activates genes that influence the control of glucose and lipids. Approved in 1999, the drug was heavily promoted and rapidly became a blockbuster. The 58 million rosiglitazone prescriptions sold in the US between 2000 and 2006 represent ≈4.8 million person-years of use.\textsuperscript{17} The manufacturer’s internal meta-analysis in August 2005,\textsuperscript{18} like Nissen and Wolski’s\textsuperscript{19} meta-analysis published almost 2 years later, suggested that rosiglitazone might be associated with an increased rather than a decreased risk of myocardial infarction (MI; hazard ratio, 1.31; 95% CI, 1.01 to 1.70). The history of its evaluation illustrates some of the pitfalls of the current system.

In the phase III trials, the use of rosiglitazone at 4- and 8-mg doses reduced both fasting glucose and glycohemoglobin. The same doses, however, increased both low-density lipoprotein cholesterol and body weight. For instance, in 1 trial,\textsuperscript{20} the total cholesterol difference between rosiglitazone 4 mg and placebo was 0.6 mmol/L (23 mg/dL), a difference larger than the total cholesterol difference of 0.4 mmol/L (15 mg/dL) between controls and cases with MI.\textsuperscript{21} Based on the evidence from these several biomarkers, it is difficult to predict the overall expected effect on the risk of cardiovascular events. The US Food and Drug Administration medical reviewer expressed concern about the potential “detrimental long term effects [of rosiglitazone] on the heart” and recommended a postmarketing study to evaluate “the CVD risk” as “a condition of approval.”\textsuperscript{22} The sponsor conducted 3 phase IV trials.

In the A Diabetes Outcome Progression Trial (ADOPT),\textsuperscript{23} patients with new-onset diabetes mellitus were randomized to receive rosiglitazone, metformin, or glyburide as monotherapy, and the primary outcome was length of time before the first-line treatment failed to provide adequate glycemic control. MI and stroke events were not included or prospectively evaluated as a primary or secondary outcome except incidentally as reported in adverse-event forms.

In the Diabetes Reduction Assessment With Ramipril and Rosiglitazone Medication (DREAM) study,\textsuperscript{24} patients with impaired glucose tolerance or impaired fasting glucose were randomized to receive rosiglitazone or placebo, and the primary outcome was the development of chemical diabetes mellitus or death. In this study of low-risk patients, the evaluation of cardiovascular events was a secondary outcome, and although the study was underpowered, the results were not reassuring (hazard ratio for MI, 1.66; 95% CI, 0.73 to 3.80; hazard ratio for heart failure, 7.03; 95% CI, 1.60 to 30.9). The DREAM trial represents an effort, based solely on biomarkers, to transform a predisease state into a treatable

Figure. Distributions of cholesterol levels and age-adjusted CHD deaths. Bars represent the number of Multiple Risk Factor Intervention Trial (MRFIT) screenees with cholesterol levels between 3.1 and 8.3 mmol/L (120 and 320 mg/dL).\textsuperscript{6} Six-year age-adjusted CHD mortality rates range from 3.16 (cholesterol ≥4.3 mmol/L [167 mg/dL]) to 13.05 (cholesterol ≥6.8 mmol/L [264 mg/dL]).\textsuperscript{7} Open boxes indicate the number of age-adjusted CHD deaths that occurred over a 6-year period among screenees within each group. Compared with the distribution of the population (bars), the distribution of the deaths (line) is shifted to the right. About 25% of the screenees have cholesterol levels ≥6.2 mmol/dL (240 mg/dL), and ≈38% of the CHD deaths occur among those with cholesterol levels ≥6.2 mmol/L (240 mg/dL). The other 62% of CHD deaths occurred among those with cholesterol levels <6.2 mmol/L (240 mg/dL).
condition. Both ADOPt and DREAM targeted marketing or marketable issues, the durability of monotherapy, and drug treatment for predisease. At the same time, they conspicuously avoided a direct well-powered answer to the cardiovascular risk-benefit question posed by the US Food and Drug Administration medical officer.

In the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD) trial, patients with type 2 diabetes mellitus on metformin or sulfonylurea were randomized to the addition of rosiglitazone or to active therapy with metformin plus a sulfonylurea.25 The primary outcome was cardiovascular hospitalization or death. During the trial, the investigators had expected >1000 events in the control group, but they ascertained only 322; about two thirds of the expected events were missing. The low event rate in an open trial with a noninferiority design raises questions about the conduct of the RECORD trial, which also documented increased risks of heart failure and fracture.26

The analysis of the outcome of MI in the RECORD trial could not exclude a 63% increase in risk (hazard ratio, 1.14; 95% CI, 0.80 to 1.63).

In summary, these 3 postmarket trials provide no clear answer to questions about the MI risk-benefit profile. If rosiglitazone increases the MI risk by the sponsor’s estimate of 30%, the prescriptions dispensed between 2000 to 2006 might have been the occasion of an additional 20 000 heart attacks in the United States. With several notable exceptions such as Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)27 and the Women’s Health Initiative (WHI),28 the National Institutes of Health has largely turned the evaluation of drug treatments over to industry. The duty to provide a return on investment to shareholders tends to create for industry an asymmetrical interest in safety and efficacy. As a result, the design, conduct, and reporting of some industry-funded studies—the rosiglitazone and ezetimibe trials are examples—remain an enduring public-health problem.29–31 In short, the current approach to the evaluation of the efficacy and safety of medicines occasionally provides an unreliable patchwork of evidence about health outcomes and incomplete information about the risk-benefit profiles of some new drug therapies.

Although flawed, the current drug evaluation system is quirky and can work fairly well for drugs such as the statins that turn out to be safe and effective. The favorable risk-benefit profile in secondary prevention studies encouraged trials in primary prevention. Over the years, the indications for statins expanded. In 2008, sales of atorvastatin reached $5.8 billion in the United States. In a recent meta-analysis that included 10 primary prevention trials and >70 000 patients,32 statins were associated with major reductions in the risk of coronary events, stroke, and total mortality. The CHD relative risk reduction is typically 25% to 30% and similar among various risk groups. For this reason, the number needed to treat to prevent 1 CHD event depends largely on the baseline absolute risk.

Next Steps in CHD Prevention

Let me turn now to 2 potential approaches to prevent CHD among intermediate-risk patients. The National Cholesterol Education Program (NCEP) guidelines,33 simplified here, serve as a framework. A treatable level of low-density lipoprotein cholesterol depends not only on the cholesterol level itself but also on the patient’s 10-year risk of CVD as assessed by the Framingham Risk Score (FRS). High-risk patients with a 10-year risk >20% merit aggressive treatment, but the approach for those at intermediate risk, with a 10-year risk of 10% to 20%, is less clear and depends in part on the low-density lipoprotein level. Efforts to improve risk prediction use novel biomarkers or measures of subclinical disease to reclassify “intermediate-risk” persons into a high-risk category that merits drug treatment. In contrast, expanding the eligibility for drug treatment involves shifting the treat-or-not boundary well into the intermediate-risk category.

Risk Prediction Models

The FRS, which is well validated, uses traditional risk factors, including age, sex, blood pressure, lipids, and smoking.34,35 Efforts to improve risk prediction add novel biomarkers or measures of subclinical disease to the FRS. The quality of a risk score model depends on several measures. Calibration evaluates the degree to which the observed and predicted events rates are similar. Discrimination assesses how well the model distinguishes between those who do and do not have an event. The C statistic is analogous to the area under the receiver-operating characteristics curve (AUC), which plots the sensitivity of the test against the false-positive rate. The AUC provides an estimate of the probability that the model assigns a higher risk to those who develop CHD than to those who do not. Finally, reclassification methods evaluate the performance of the model at clinically relevant boundaries such as treatment thresholds.

Coronary artery calcium, a measure of subclinical disease, is strongly associated with the incidence of cardiovascular events.36,37 The relative risks comparing a coronary artery calcium score of ≥300 with a score of 0 are in the range of 3.9 to 6.8, much larger than the relative risks for many traditional risk factors such as smoking, which doubles the risk of CHD; but the improvement in AUC occasioned by the addition of imaging study results to a model that includes traditional risk factors alone is still modest, increasing the AUC from 0.79 to 0.83 in 1 study.37

In a recent meta-analysis,38 C-reactive protein (CRP) was associated with a modest increase in the risk of CHD (relative risk, 1.6; 95% CI, 1.4 to 1.8 for CRP >3 versus <1). In 8 studies that evaluated the improvement in discrimination achieved by the FRS when CRP is added to the model,39 the increment in the AUC is small or absent at 2 significant digits (range of AUC change, 0.00 to 0.02). For an independent risk factor, the weak evidence of model improvement may seem to be counterintuitive. But because the values of those who do and do not go on to have a CHD event overlap so extensively, CRP in particular and risk factors in general do not function well as diagnostic tests.

Reclassification methods are another approach to evaluate the addition of a new marker to a model that includes traditional risk factors. In 1 study,39 the 10-year risk was estimated for the FRS alone and the FRS plus CRP. Among
those without CHD, 331 moved to a higher-risk category and 325 to a lower-risk category; among those with CHD, 37 were moved to a higher-risk group and 23 were moved to a lower-risk group. Overall, slightly more patients were reclassified in the correct direction, and the net reclassification was 8.5% (95% CI, −1.3 to 18.3). The US Preventive Services Task Force recently reported similar findings for CRP.38

Because the CRP-CHD association is strong, graded, and continuous, a large number of events occur among the majority of people with average or intermediate CRP values. As a consequence, the model improvement attributable to CRP is small, and its predictive utility is limited.40 As a general internist, I use intermediate-risk status in a patient not as an occasion for new diagnostic tests but as an opportunity for shared decision making. What are patients’ preferences about various forms of treatment, concerns about outcomes, fears about side effects, and their ability or willingness to pay?

The prediction problem arises from the fact that continuous risk factors such as CRP do not function well as diagnostic tests.41 The distributions of risk factor levels in those with and without disease overlap considerably, especially for the odds ratios typically seen for most CVD risk factors.42 The odds ratios for CRP and smoking are in the range of 1.5 to 3. Even risk factors such as coronary calcium with odds ratios as high as 7 have widely overlapping distributions, produce AUC levels closer to 0.5 than to 1.0, and improve discrimination only marginally. In contrast, odds ratios in the range of 50 to 400 have distributions that differ markedly, and their risk factors perform better as diagnostic tests with AUC levels much closer to 1.0. Known CVD risk factors, however, are not associated with odds ratios of this magnitude. What about the use of multiple independent risk factors?

With 2 independent risk factors, each associated with a detection rate or sensitivity of 15%, it is tempting to think that the detection rate would be twice as high—30% rather than 15%.42 Doubling the detection rate in this manner, however, also doubles the false-positive rate. If we wish to hold the false-positive rate constant at 5%, the increment in detection achieved by a model that includes 2 independent risk factors is in fact much more modest, increasing from 15% for 1 risk factor to 22% for the model with 2 independent risk factors. For risk factors, each with an odds ratio of 3 comparing the first and fifth quintiles, 15 independent risk factors would be required to achieve an overall model sensitivity of 40%. For risk factors with an odds ratio of 5 each, 15 independent risk factors would be required to achieve an overall model sensitivity of almost 80%.43 Given the available risk factors, including measures of subclinical disease, the epidemiological limits of risk prediction are formidable.

### Expanded Use of Drug Therapies

Expanding the eligibility for drug therapies to intermediate-risk individuals is an alternative approach. The definition of a treatable level of CHD risk depends on the drug efficacy, safety, and cost. Shifting the treatable level to include intermediate-risk individuals means that the number needed to treat to prevent 1 event increases, so safety and cost, as well as efficacy, become important. With more than 20 trials in the 30 years since Geoffrey Rose expressed concern about “mass preventive medication,” the efficacy and safety of the statins, in contrast to clofibrate, are now well established.32-43

Trade statins cost $3 to $4 per day. At a local northwest pharmacy, generic statins cost 11 cents per day, a 40-fold difference in cost. The availability of generic statins has markedly reduced the costs to prevent 1 event. For a patient with a 20% 10-year risk and under the assumption of a 25% relative risk reduction, the use of rosvuvastatin costs about $288 000 to prevent 1 event, but for a patient with a 10% 10-year risk, the use of a generic statin now requires an investment of about $16 000 to prevent 1 event.

George Diamond and Sanjay Kaul45 estimated the likely cost-effectiveness of 3 prevention strategies for 50 million patients at intermediate risk: treat everyone at intermediate risk, use the NCEP methods, or use electron-beam computed tomography to evaluate coronary artery calcium and to identify high-risk “treatable” individuals. In this model, they assumed that statins cost $2 per day. The treatment savings come from the prevention of events that are assumed to cost the medical care system $100 000 each. Under these assumptions, the treat-everyone approach is the most expensive option with a net cost of $21 billion compared with net costs of $8 billion for the NCEP screening method and $17 billion for the electron-beam computed tomography method. At a cost of 11 cents per day for generic statins, the treat-everyone approach turns out to be the least expensive method. Indeed, the expanded-treatment approach is estimated to save $13 billion dollars compared with a cost savings of $2 billion for the NCEP approach and an increase in costs of $9 billion with the electron-beam computed tomography method.

Targeting high-risk individuals with ever more aggressive therapies may provide marginal additional benefit for the individuals concerned, but these high-risk approaches do little to reduce the overall burden of CVD in the intermediate-risk population (the Figure)—the treatment paradox. With the efficacy and safety of the statins well established and with the low costs of the generic statins, it may be time to evaluate a broader use of statins in intermediate-risk individuals.

### Proposed Comparative Effectiveness Trial

Last year, Michael Lauer45 called for new evidence from randomized trials about the risks and benefits associated with coronary calcium screening. The Institute of Medicine identified a comparative effectiveness study of CVD risk stratification methods as one of its 100 high-priority studies.46 No comparison group was identified. In the trial proposed here, eligible subjects would include those at intermediate risk or perhaps defined simply by age. Patients would be randomized either 1) to a risk stratification approach that used CRP, imaging studies, or any other risk factor and treated the high-risk patients identified by these methods or 2) to a low-dose statin therapy.43 This arm might include low-dose diuretics47 or other elements of a “polypill,”48 and it might include a factorial design to evaluate various methods of the delivery of population-based CVD risk screening, counseling, and treatment.
Concluding Observations

The current system of drug evaluation relies on industry, which has an asymmetrical interest in efficacy and safety. On occasion, industry’s approach to safety issues has represented a menace to the health of the public. In other instances, it has been difficult to obtain reliable and valid estimates of the risk-benefit profile of drugs such as rosiglitazone or ezetimibe. High-quality drug evaluations are essential to next-generation prevention efforts, especially those that consider expanding eligibility for “mass preventive medication” to the large number of individuals with normal, average, or intermediate levels of risk factors.

The current model of medical care in America seems to be inclined toward resource-intensive individualized risk management, the use of expensive vascular evaluations that incorporate new biomarkers and imaging tools, and an aggressive lowering of treatment targets for individuals deemed to be high risk. An alternative that may be effective for primary prevention is a primary care model that starts with individual patients, obtains simple estimates of their cardiovascular risk, and offers appropriate treatments that are known to be safe and effective to a wide spectrum of individuals. My hope is that this talk may promote discussion about 1 or more potential comparative effectiveness trials of public health importance.

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None.

References


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Supplemental figure legends

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Supplemental figure 1.

![Distribution curves of serum cholesterol levels in South Japan and East Finland from Keys’ Seven Countries Study.](image1)

Supplemental figure 2.

![Percentage distribution of serum cholesterol levels (mg/dl) in men aged 50-62 who did or did not subsequently develop coronary heart disease (Framingham Study).](image2)