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STATE-OF-THE-ART REVIEW

The Causal-Benefit Model to Prevent Cardiovascular Events

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ABSTRACT

Selecting individuals for preventive lipid-lowering therapy is presently governed by the 10-year risk model. Once a prespecified level of cardiovascular disease risk is equaled or exceeded, individuals become eligible for preventive lipid-lowering therapy. A key limitation of this model is that only a small minority of individuals below the age of 65 years are eligible for therapy. However, just under one-half of all cardiovascular disease events occur below this age. Additionally, in many, the disease that caused their events after 65 years of age developed and progressed before 65 years of age. The causal-benefit model of prevention identifies individuals based both on their risk and the estimated benefit from lowering atherogenic apoB lipoprotein levels. Adopting the causal-benefit model would increase the number of younger subjects eligible for preventive treatment, would increase the total number of cardiovascular disease events prevented at virtually the same number to treat, and would be cost-effective. (JACC Adv 2024;3:100825) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

The increased use of low-cost, potent statin medications, coupled with a risk-based paradigm for patient selection, has contributed to substantial reductions in atherosclerotic cardiovascular disease (ASCVD) events. Notwithstanding this major achievement, much remains to be done, particularly with regard to the prevention of premature ASCVD events. Accordingly, we propose that a new paradigm—the causal-benefit model—be incorporated into the standard approach to select individuals for primary prevention lipid-lowering treatments. The causal-benefit model of cardiovascular prevention integrates the benefits of therapy as well as the risks of a clinical event to select patients for lipid-lowering therapy. It is a more efficient and effective strategy for the prevention of premature ASCVD than the conventional 10-year risk-based paradigm, in which selection is based primarily on age and sex and not on the causal factors of disease.[1,2]

Public health policy should be governed by what we know and what we can afford. For ASCVD prevention, both have changed with time. Blood pressure, low-density lipoprotein cholesterol (LDL-C), and apolipoprotein B (apoB) have been established as causes of, not merely risk factors for, ASCVD. Moreover, the absolute success of preventive statin therapy depends not only on those selected for therapy and the intensity of therapy, but also on when

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ABBREVIATIONS AND ACRONYMS

ACC/AHA = American College of Cardiology/American Heart Association

ApoB = apolipoprotein B

ARR = absolute risk reduction

ASCVD = atherosclerotic cardiovascular disease

CVD = cardiovascular disease

ESC/EAS = European Society of Cardiology/European Atherosclerosis Society

HDL-C = high-density lipoprotein cholesterol

ICER = incremental cost effectiveness ratio

LDL-C = low-density lipoprotein cholesterol

NICE = National Institute for Health and Care Excellence

therapy is started in the course of the disease.[3] Critically, the cost of standard, effective pharmacologic lipid-lowering therapy has plummeted.

Despite an impressive reduction in the rates of ASCVD since the 1950s, the steep decline in the incidence of ASCVD is over. Indeed, ASCVD rates appear to be increasing in association with the dramatic increases in the incidence and prevalence of obesity and diabetes that are occurring virtually worldwide.[4] While these adverse trends have raised concern, another issue, arguably as important, has gained little or no attention: the limitations of the 10-year risk model in the prevention of atherosclerosis in general and premature ASCVD in particular. Accordingly, our objective is to lay out the strengths and limitations of the present 10-year risk model and then to demonstrate how the causal-benefit model could improve the prevention of ASCVD. We will do so primarily within the framework of the atherogenic lipoproteins, and we acknowledge this is both a strength and limitation of the present essay. However, the principles outlined here apply to the other causal factors, such as blood pressure, which will also be discussed, although more briefly.

THE RISK MODEL OF CARDIOVASCULAR PREVENTION

The risk model is based on evidence from multiple, long-term, prospective, observational studies, which showed that older age, male sex, elevated blood pressure, elevated total cholesterol, lower high-density lipoprotein cholesterol (HDL-C), smoking, and diabetes were independently associated with an increased risk of the clinical complications of coronary artery disease—angina pectoris, myocardial infarction, heart failure, arrhythmias, stroke, and sudden death. The effects of these 'risk factors' for coronary artery disease were integrated within a multiple regression equation that expressed the short-term risk of a clinical event. Among these risk models, the first and best known was the Framingham Risk Score, which allowed the risk of a coronary event for any individual aged more than 40 years to be calculated over the next 10 years.[5] Over time, multiple other algorithms were developed, which were validated for the specific populations or subpopulations from which they were derived.[6]

HIGHLIGHTS

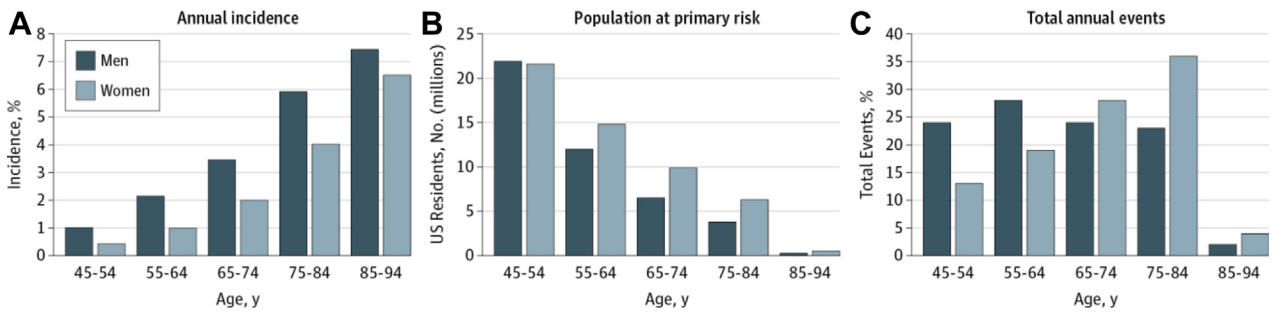
- The decline in cardiovascular events has stalled.
- The 10-year risk model operates suboptimally to prevent premature disease.
- The causal-benefit model selects subjects for preventive therapy based both on baseline risk and baseline level of the apoB lipoproteins.
- The causal-benefit model is more efficient and cost-effective than the 10-year risk factor model.
- The causal-benefit model should be adopted as a new paradigm for selecting patients for lipid-lowering therapies.

However, these risk scores were most often derived from relatively small cohorts and often represented decades old data from relatively homogenous populations. Hence, they may not be ideally calibrated to estimate ASCVD risk in more contemporary and heterogeneous populations. Predictive validity can be improved by recalibrating risk scores with risk factors and ASCVD incidence information of target populations.[7] Unfortunately, such adjustments, while worthwhile, are not sufficient to overcome the fundamental limitations in the operation of the risk model.

CONVENTIONAL DEFINITIONS OF PRIMARY AND SECONDARY PREVENTION

Currently, prevention of ASCVD is divided into general population measures that are directed at everyone, such as eliminating smoking and promoting a healthy lifestyle, vs more intensive strategies involving medical treatments directed at restricted groups of individuals. The latter are divided into primary and secondary prevention strategies. Primary prevention includes all those with a calculated 10-year risk of ASCVD that exceeds a specified value, plus those with diabetes mellitus or extremely high levels of LDL-C. Secondary prevention includes all those who have suffered the clinical consequences of atherosclerosis or who have anatomic evidence of atherosclerosis. All these individuals are automatically eligible for pharmacological therapy to reduce LDL-C. In both primary and secondary prevention, the explicit objective is to prevent clinical ASCVD events.

FIGURE 1 How the Risk of an ASCVD Event and the Number at Risk Interact to Produce the Total Number of Events



(A) Average primary annual incidence rates of coronary heart disease, heart failure, stroke, or intermittent claudication. (B) Numbers of U.S. residents without clinical atherosclerotic cardiovascular disease represented in the 2005 to 2010 National Health and Nutrition Examination Survey. (C) Percentage of the expected total of 930,621 annual primary events in men and 702,105 in women by age group. ASCVD = atherosclerotic cardiovascular disease.

HOW DOES A 10-YEAR PERIOD OF RISK LIMIT THE UTILITY OF THE RISK MODEL TO PREVENT ASCVD EVENTS?

No matter what conventional risk algorithm is applied, any 10-year risk model prioritizes prevention in older vs younger subjects. For example, under the present U.S. threshold of 7.5% 10-year risk, 29.7% of individuals aged 40 to 60 years are eligible for prevention, compared to 77.3% of individuals aged 60 to 75 years.[8] What explains this extreme difference in eligibility based on a single cut-off in age?

Age is, by far, the strongest predictor of ASCVD risk because ASCVD risk is so strongly related to age. This relation is exponential, not linear. For the first 40 years of life, the incidence of clinical ASCVD in a population is extremely low. For the next 20 years, ASCVD risk begins to increase, slowly at first, then steadily more steeply, and finally, with each decade after 60 years of age, the rate of ASCVD appears to multiply. It is this powerful exponential relationship that accounts for the profound predictive power of age for ASCVD and the extreme difference in risk after age 60 years vs before (**Figure 1A**).

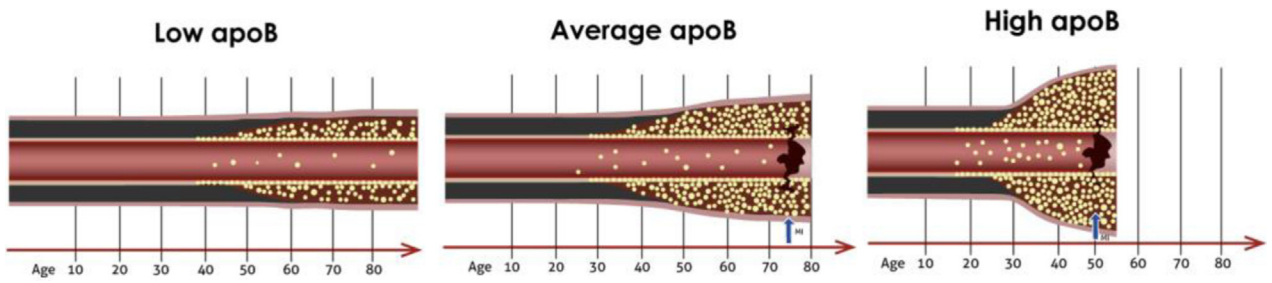
Yet this does not answer why age is such a singularly powerful 'risk factor'? Age is not like the other risk factors. Age has 2 different impacts on risk.[9] First, as we age, the composition of our tissues changes. Our aortas become stiffer, and as a result, our systolic blood pressure increases and our diastolic blood pressure decreases. Whether such a change within our coronary arteries affects the rate at which atherosclerosis develops within them or whether coronary events occur is unknown. Nevertheless, the increase in systolic blood pressure certainly contributes substantially to the increase in cardiovascular risk with age. Unfortunately, our ignorance of the biology governing aging means these changes and their impacts are not preventable.

The second effect of aging is both potent and preventable: the injury to the arteries that is directly related to their duration of exposure to the casual factors of atherosclerosis.[9] Trapping of apoB particles within the arterial wall occurs over time. The injury this produces occurs over time. Injury to the arterial wall from the other causal factors of atherosclerosis also occurs over time. However, in all risk algorithms, age is treated as an independent variable. But its dominant known effects on atherosclerosis relate to the duration of exposure to the causal factors of disease. Treating age as an independent statistical variable ignores the reality that age and time are, to a large extent, biological synonyms.

Higher levels of the apoB lipoprotein cause a level of injury to the arterial wall sufficient to cause a clinical event in shorter periods of time than lower levels of the apoB lipoproteins. **Figure 2** demonstrates that the net injury to the arterial wall is a product of the concentration of the apoB lipoproteins in plasma times the length of time the arterial wall is exposed to this concentration. The higher the level, the earlier the arterial wall becomes diseased, and therefore, the earlier clinical events occur. Conversely, the lower the concentration of the apoB lipoproteins in plasma, the later the arterial wall becomes diseased, and, therefore, the later clinical events occur.

As simple and obvious as this formulation is, its clinical consequences are not acknowledged by the 10-year risk model. Notwithstanding the dominance of age as a risk factor, almost one-half of all new

FIGURE 2 How the Rate at Which Atheroma Develops Within the Wall of a Coronary Artery Is Driven by the Number of apoB Particles Within the Lumen of the Artery



The rate at which complex atherosclerotic lesions develop within a coronary artery is determined, to a large degree, by the number of apoB particles within the lumen of the artery. The higher the number of particles, the earlier advanced disease develops and the earlier clinical complications ensue. apoB = apolipoprotein B.

events in men and one-third of all new events in women occur before age 65 years.[10] As a result, only a minority of those who suffer premature ASCVD events would be eligible for preventive treatment based on the current 10-year American College of Cardiology/American Heart Association (ACC/AHA) risk threshold. Moreover, analysis of the 2019 European Society of Cardiology and European Atherosclerosis Society guidelines revealed an even greater incidence of premature ASCVD. The failure to identify these younger subjects as high-risk is a critical and unacceptable limitation in the risk model of cardiovascular prevention.[11]

The Risk model fails to identify younger individuals who would benefit from lipid-lowering treatments for 2 reasons. First, risk is calculated as the number of events per standard number of people per standard unit of time. Ten-year risk is low in those aged <65 years, but the absolute number of people in this age group is much greater than in those over 65 years (**Figure 1B**). Therefore, while the relative rate of events is much lower in young and middle-aged adults, the absolute number of events is substantial because there are so many more of them[10] (**Figure 1C**).

Higher levels of apoB particles in plasma result in earlier events because complex atherosclerotic lesions develop earlier (**Figure 2**). Nevertheless, because high levels are present in the minority of the population, the risk of premature disease is low in the majority of the population. Because the causal factors contribute so little to the 10-year calculation of risk, the individuals with high levels of apoB lipoproteins do not stand out as being at high risk. Therefore, the actual short-term, intermediate-term, and long-term risks they, as individuals, face are not recognized, and consequently, they are not eligible for preventive therapy.

But there is a second clinical loss. Lower levels over longer periods of time eventually produce the mass of advanced disease at which the probability of a clinical event becomes substantial[9] (**Figure 2**). However, during the time the disease in the wall was developing and advancing, the patient was at a lower 10-year risk and therefore not eligible for preventive therapy, which would have inhibited the development of the disease that subsequently caused his or her clinical event.

It is the causal factors of atherosclerosis, such as apoB, that produce the disease, which causes the clinical events. It is the causal factors that, in their more extreme form, cause earlier disease, and it is the causal factors in their less extreme form that drive the risk of disease when we are older. However, at any moment in our life history, it is primarily the presence and the extent of disease, not the causal factors that drives the risk of events. This explains why the HRs of LDL-C, non-HDL-C, and apoB decrease as we age, although the risk of clinical events multiplies as we age. This also explains why all the causes of atherosclerosis only marginally add predictive power to the calculated risk, while age and sex dominate the risk calculated for any 10-year period.[12]

The net result is that few of those under 65 years of age, including those with significant elevations in LDL-C or apoB or blood pressure are eligible for primary prevention based on the 10-year risk model. So long as this is the case, it will remain impossible to substantially reduce the number of premature ASCVD event rates further. Events that occur in those under 65 years of age deprive or diminish individuals of their full creative and contributory capacities and

their families and society of these accomplishments and contributions. In these senses, it may be argued that premature ASCVD events are even more adversely impactful than events in older individuals.

As we have noted, the 10-year risk model also unfavorably impacts prevention in those aged over 65 years who have not yet suffered a clinical event. The clinical events these lesions ultimately cause—the clinical events after age 65 years—were, in many or most cases, the outcome of processes underway for years and even decades before.[13] The fact that risk is increased in those who are older merely signals the maturation of these lesions over time. Thus, prevention of events that will occur after age 65 years should also begin much earlier in life. Further complicating the impact of age on cardiovascular risk is the fact that age is a risk factor generic to many chronic illnesses including chronic lower respiratory diseases, cancer, and dementia.[14] These 'competing risks' may limit the validity of risk scores in elderly populations and diminish the ability of preventive interventions to produce tangible health benefits in older populations.[15,16]

REFOCUSING PREVENTION STRATEGIES ON THE CAUSES OF ASCVD RATHER THAN THE RISK OF ASCVD

Very-low-density and low-density lipoprotein particles are the major classes of the atherogenic apoB particles.[17] Labeling them as *risk factors* for ASCVD was initially reasonable because the first evidence from prospective observational studies demonstrated an association between these factors and ASCVD, not a causal relation. However, the evidence from all sources including experimental, prospective observational, Mendelian randomization, and randomized clinical trials is now sufficient to prove that the apoB lipoproteins are *causal factors* for ASCVD.[17-19]

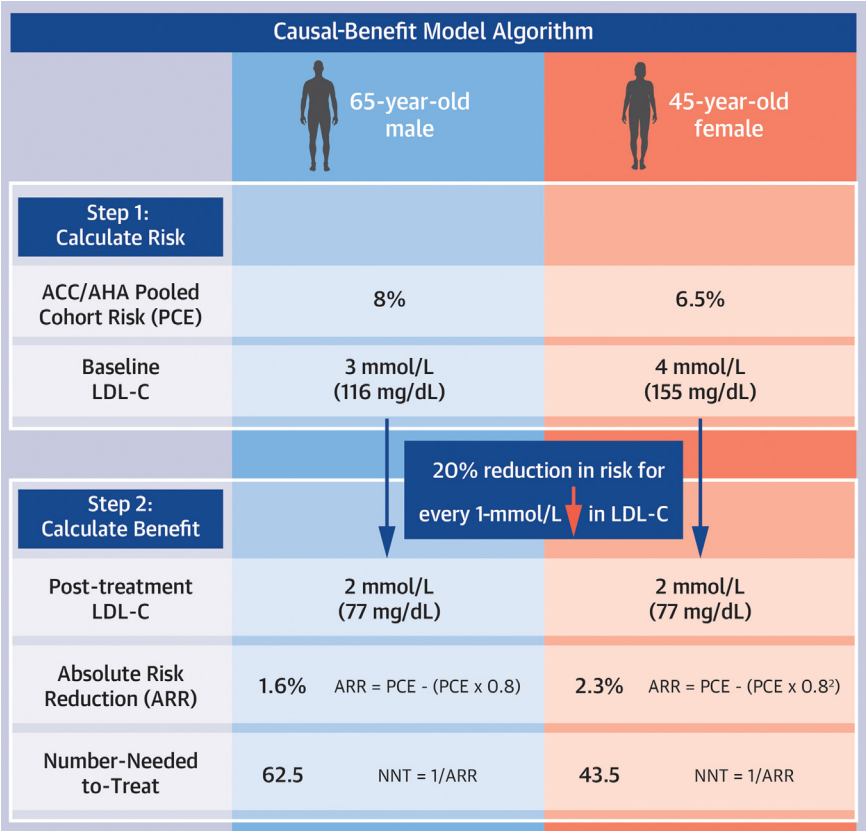
A NEW PARADIGM: THE CAUSAL-BENEFIT MODEL

DETERMINANTS OF BENEFIT. To improve selection for lipid-lowering therapy to prevent ASCVD, we must focus on treatment benefit as well as cardiovascular risk. Randomized clinical trials have demonstrated that the potential benefit from statin therapy is not uniform but is determined by 3 factors: baseline risk, absolute reduction in the level of the apoB lipoproteins with therapy, and when, in the natural history of the disease, prevention is initiated. Multiple meta-analyses of randomized clinical trials have established that every unit decrease in LDL-C produces a relatively consistent reduction in ASCVD risk. Specifically, lowering LDL-C by 1.0 mmol/L (38.5 mg/dL) reduces the risk of major adverse coronary events by approximately 20%. Therefore, the absolute risk reduction (ARR), which can be produced by lowering LDL-C, depends on an individual's baseline risk. Accordingly, in an individual with a 10-year risk of 10%, lowering LDL-C by 1 mmol/L will reduce absolute risk by 2%, whereas lowering LDL-C by 1 mmol/L in an individual with a 10-year risk of 5% will reduce absolute risk (ARR) by 1%. In both instances, the relative reduction in risk was the same (20%), but the ARR—the actual benefit from therapy—was greater for the first individual compared to the second.

But the benefit of therapy also depends on an individual's baseline LDL-C. Consider the potential benefit of treating a patient with an LDL-C of 4 mmol/L vs the potential benefit of treating a patient with an LDL-C of 2 mmol/L. Assume that the baseline risk is the same for both individuals—10% over 10 years—and their achieved level with therapy is the same—an LDL-C of 1 mmol/L. For the first individual, the 10-year risk of ASCVD is reduced to about 5%, whereas for the second, it is reduced to only 8%. Moreover, a given dose of a given statin tends to produce a relatively constant percent reduction in LDL-C rather than a constant absolute reduction in LDL-C. This means that the decrease in risk with a given dose of a given statin will be greater in those with a higher baseline LDL-C. It is important to note that all these relations will apply to non-HDL-C and apoB. However, the changes in apoB relate more closely to the benefit of therapy than the changes in LDL-C or non-HDL-C. Thus, the mean relative risk reductions per SD change in lipid marker in 7 randomized clinical trials were 20.1% (95% CI: 15.6%-24.3%) for LDL-C; 20.0% (95% CI: 15.2%-24.7%) for non-HDL-C; and 24.4% (95% CI: 19.2%-29.2%) for apoB.[19]

THE CAUSAL-BENEFIT MODEL OF CARDIOVASCULAR PREVENTION. The causal-benefit model extends the risk model by including the benefit obtained by treatment of a causal factor—reduction of the levels in plasma of the atherogenic lipoproteins. Benefit is estimated by the ARR, a measure that combines an individual's ASCVD risk and their expected risk reduction from a treatment as mediated by their baseline cholesterol or apoB level.[1] The absolute reduction in risk over 10 years (ARR_{10}) can be calculated for each individual based on their calculated 10-year risk and the reduction in risk with statin therapy that produces a 40% reduction in LDL-C, a value that approximates the average result in

CENTRAL ILLUSTRATION How Is Benefit Calculated for 2 Individuals Based on Their Baseline Risk and Baseline LDL-C?



Kohli-Lynch C, et al. JACC Adv. 2024;3(3):100825.

This figure illustrates the calculation of benefit in 2 subjects: one is a 65-year-old man with a 10-year pooled cohorts equation (PCE) risk of 8.0%, and the other is a 45-year-old woman with a 10-year PCE risk of 6.5%. Based on PCE risk, the man would be eligible for preventive therapy; the woman would not. However, the man has an LDL-C of 3 mmol/L, while the woman has an LDL-C of 4 mmol/L. For each 1 mmol/L reduction in LDL-C, absolute risk is reduced by 20%. With a target LDL-C of 2 mmol/L for both, lowering LDL-C by 1 mmol/L in the man would produce an ARR of 1.6%, whereas lowering LDL-C by 2 mmol/L would produce an absolute reduction of 2.3%. The result is that the number needed to treat would be lower in the woman than in the man (43.5 vs 62.5). By incorporating the benefit of treatment, preventive therapy becomes even more positive for women than for men.

multiple large-scale statin trials. A threshold ARR_{10} of 2.3% is the value, which would produce equivalent minimum benefit with statin therapy in individuals with a 10-year ASCVD risk of ≥7.5% over 10 years. Application of the causal-benefit model allows subjects with lower calculated risk but higher measured LDL-C to become eligible for statin preventive therapy.

The practical impact of applying a causal-benefit model as opposed to the conventional risk model is outlined in our **Central Illustration**. Patient A is a 65-year-old male with a calculated pooled cohorts equation 10-year risk of 8% and an LDL-C of 116 mg/dL. Patient A is above the 7.5% threshold at which preventive statin therapy is recommended. Patient B is younger, 45 years old and female. Based on her 10-year pooled cohorts equation calculated risk of 6.5%, she would not be eligible for statin preventive therapy. However, her LDL-C is 155 mg/dL. Based on the causal-benefit model, her ARR would be greater than his (2.3% vs 1.6%). Accordingly, her number-needed-to-treat would be 43.5, whereas his would be 62.5. Thus, the lower-risk patient in this example would get greater benefit from therapy than the higher-risk patient.

In a 2016 analysis, Thanassoulis et al compared the effect of risk and causal-benefit approaches to statin prioritization in the U.S. They calculated that

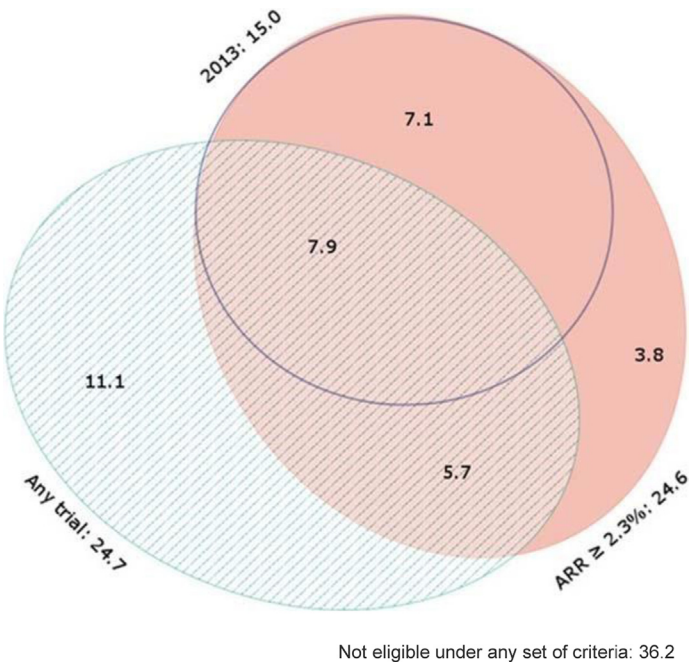
15 million individuals with an average age of 62.5 years were eligible for statin therapy based on the risk model (Figure 3). The average ARR in this population was 4.8%, with a minimum ARR of 2.3%. If a causal-benefit model were applied whereby all individuals selected for treatment could achieve an ARR_{10} ≥2.3%, then 24.6 million Americans—average age 55.2 years—would be eligible for preventive statin therapy.[1] A risk-based approach would prevent 728,572 ASCVD events over 10 years, while an individualized causal-benefit approach would prevent 995,080 ASCVD events over 10 years. Treatment of the 9.5 million individuals at lower risk but acceptable benefit identified by the individualized benefit-based approach would contribute to an additional 266,508 ASCVD events prevented over 10 years, corresponding to an increase in prevented ASCVD events by 36.6%. The corresponding numbers needed to be treated would be 21 and 25 for the risk and causal-benefit models, respectively. The superiority of the causal-benefit model has been confirmed and extended in subsequent analyses.[2,20]

An almost identical number of Americans—24.7 million—would be eligible for preventive therapy based on the criteria for randomized clinical trials. Of these, 7.9 million would also have been eligible based on high risk, while 11.1 million would not have been selected based on either the risk factor model or the causal-benefit model. It would not be unreasonable to argue that these patients should also be eligible for statin prevention.

Why must the benefit model be the mathematically optimal model for prevention? If everyone with an ARR_{10} equal to or >2.3% is eligible for therapy, any strategy that selects the same number to be eligible for preventive therapy but creates a different composition of individuals must necessarily replace some of the original cohort with individuals with an ARR_{10} <2.3%. It follows that the potential reduction of events in the new group, by definition, will be less than in the original group selected based on benefit.[21]

However, our fundamental objective is to improve prevention in younger individuals. Accordingly, we have also compared the outcomes produced by risk model and the causal-benefit model in younger individuals—those between 40 and 60 years of age—over a period of 10 years. With a 10-year ASCVD risk threshold of 7.5%, the risk model would select 5.4 million Americans (9.5% of the population) for preventive therapy, whereas the causal-benefit model using an ARR_{10} threshold of 2.3% would select 7.3 million (13% of the population). Over 10 years, application of the risk model would prevent 204,000 events, whereas application of the causal-benefit model would prevent 264,000 events, a 29% gain in events prevented. More subjects would be treated with the causal-benefit model than with the risk model. However, the number needed to be treated was 17.5 for the risk model vs 14.5 for the causal-benefit model. Thus, there was clear superiority in effective prevention of ASCVD events for the causal-benefit model compared to the risk model. Nevertheless, even though the target group was younger—40 to 60 years of age—little has been gained with the causal-benefit model in terms of age of onset of treatment with the median age of onset of therapy with the risk model being 54, whereas the median age of onset with the causal-benefit model was only slightly younger at 52 years. We, therefore, re-examined the potential for prevention in terms of the pathological evolution of atherosclerosis.

FIGURE 3 Millions of Americans Who Might Be Eligible for Statin Prevention Depending on How the Selection Is Made



Estimated millions of primary risk-based candidates by eligibility for statin therapy under the 2013 American College of Cardiology/American Heart Association cholesterol treatment guideline risk-based approach (2013), a trials-based approach (trials), and a benefit-based approach (ie, estimated absolute risk reduction [ARR] from treatment ≥2.5%). Approximately 71.8 million Americans are represented by 2,134 National Health and Nutrition Examination Survey (NHANES) 2005 to 2010 subjects.

THE NATURAL HISTORY OF ATHEROSCLEROSIS AND THE BENEFIT FROM PREVENTIVE THERAPY. The benefit of preventive therapy is determined not only by its duration but also by the stage in the natural

history of the disease at which it is initiated. Thus, Wang et al,[22] in a meta-analysis of 327,037 subjects who participated in primary and secondary prevention RCTs confirmed that the benefit of therapy was inversely related to the baseline ASCVD 10-year risk. That is, the lower the baseline risk, the greater the benefit. For all included studies, there was a 3% greater benefit for every 10% lower baseline risk. When the analysis was restricted to primary prevention studies, there was a 27% reduction in risk for every 10% lower baseline risk. Moreover, when benefit was considered as a function of baseline age, the relative reduction in major vascular events increased by 8% for each 10-year-old younger age per 1 mmol/L reduction in LDL cholesterol.

Why is therapy earlier in the course of the disease more successful than therapy later in the course of the disease? Because the causes of atherosclerosis—the apoB lipoproteins, blood pressure, diabetes, and smoking—injure arteries over time. Time or the natural history of atherosclerosis can be divided into 2 phases. With limited exceptions, such as familial hypercholesterolemia or premature diabetes mellitus, both of which accelerate the timeline of the natural history of the disease, the initial phase of atherosclerosis usually lasts 3 to 4 decades, during which apoB particles become trapped within the arterial wall and provoke a myriad of inflammatory adaptive and maladaptive responses.[17,23,24] Toward the end of this period, complex, advanced lesions with thin-walled cholesterol-rich plaques are formed. Over the next decades, the disease spreads further through the arterial tree with the appearance of more and more complex high-risk lesions, lesions that are capable of abruptly, and without warning, causing a clinical event by plaque rupture, endothelial erosion, or intramural hemorrhage. The risk of a cardiovascular event parallels the anatomic progression of the disease.[13]

Statins, ezetimibe, and PCSK9 inhibitors prevent cardiovascular events in 2 different ways. The first is the most effective: preventing new atherosclerotic lesions. This is the most effective because the lesion that never happens can never cause a clinical event. The second is less effective, but is still a major mechanism of benefit: healing of established lesions. Medications that lower the apoB particle number in plasma reduce trapping of apoB particles within the arterial lumen. This reduces the delivery of cholesterol and the other atherogenic components of apoB particles to the arterial wall. This allows the processes that do remove cholesterol from the arterial wall, which very likely involve nascent HDL particles, to operate with greater efficiency.[25] Because the cholesterol within atherosclerotic lesions is extracellular, this likely explains why a cell-free high-density-specific phospholipid efflux assay correlates more closely with cardiovascular risk than conventional cell-based assays of reverse cholesterol transport.[26] Over time, this results in a decrease in the number of vulnerable lipid-rich plaques and a reciprocal increase in fibrous tissue and calcification.[27-30] The result is stabilization of lesions such that acute events are less likely.

We believe this positive interaction between pharmacological intervention and physiological peripheral transport of cholesterol largely accounts for the reduction in the cholesterol content of atherogenic lesions and the associated decrease in cardiovascular risk that has been documented with statin and PCSK9 inhibitor therapy. Nevertheless, however effective this linked positive effect may be, the normal anatomy of the artery cannot be restored, and a residual risk of a clinical event persists. It follows that the earlier the intervention, the greater the potential to prevent the development of the complex lesions that cause the clinical events. Unfortunately, because selection of subjects by the conventional 10-year risk model is dominated by age and sex and because 10-year risk in younger individuals is low, this approach will never succeed in preventing premature cardiovascular events. Indeed, a 10-year risk is not even calculable until age 40 years.

Accordingly, we calculated the 30-year event rates at successive decades, beginning with those aged 30 to 39 in groups with different levels of non-HDL-C.[3] Two different models were used: Model A assumes a constant benefit over time of statin therapy of a 22% reduction in risk per mmol/L decrease in LDL-C, whereas Model B combines this estimate as suggested by Ference et al[18] with a 54% reduction in risk over 40 years based on Mendelian randomization. With either model, the benefit is greater, the earlier the therapy begins, whereas with the second model, the benefit of therapy almost doubles if begun at the earliest time period. These analyses demonstrate the utility of incorporating cause as well as risk in developing a model of cardiovascular prevention. In summary, a long-term causal-benefit model would offer the option of prevention to younger adults and women, a potential for care that is not possible with the conventional risk model.[31]

HYPERTENSION AND BENEFITS. The contrast between the hypertension and the lipid guidelines illustrates how guidelines are a product of the attitude to evidence as well as the evidence itself. Just as there has been controversy about the role of

cholesterol as a risk factor for ASCVD, there has been certainty about the role of hypertension as a cause for ASCVD. As a result, except for extreme elevations of LDL-C, the decision to lower LDL-C has been based on a calculated probability of a clinical event, a calculation that incorporates all the known determinants of cardiovascular risk,[32] whereas the decision to lower blood pressure is based just on blood pressure.[33] Because a causal role for blood pressure was virtually unchallenged from the beginning, although the quality of the evidence was no different than for cholesterol, the necessity to treat elevated blood pressure has been virtually unchallenged from the beginning. This contrast in approaches has persisted notwithstanding the differences in the risks and benefits associated with therapy. Therapies that lower LDL-C and, even more so apoB, with the exception of patients with end-stage renal disease[34,35] and aortic stenosis,[36,37] have been almost uniformly successful: the lower the apoB, the greater the reduction in risk.[38] By contrast, while there is no doubt that lowering markedly elevated blood pressure is beneficial, there continues to be some uncertainty about how low the targets for therapy should be, primarily because there are significant risks with antihypertensive therapy.

The common side effects of statin therapy—muscle aches and stiffness—are relatively minor and can usually be dealt with easily. Statin therapy is associated with an increased risk of diabetes mellitus, but the risk is low and almost all confined to those who are already at high risk of diabetes mellitus.[39] Rhabdomyolysis, including statin-induced autoimmune myopathy, is a serious complication of statin therapy but is fortunately rare.[40]

By contrast, the consequences of medication-induced hypotension, which is not uncommon, can be clinically significant and, on occasion, even disastrous. Increasing the intensity of lipid therapy does not substantially multiply the risk of significant adverse effects, whereas increasing the intensity of antihypertensive therapy does. Given the wide range over which reductions in LDL-C or apoB have been proven to be beneficial, benefit is easy to calculate for lipid therapy. Given the minimal differences in risk, a clinical judgment as to net benefit is also straightforward. By contrast, calculating net benefit for an individual for intensive hypertensive therapy is more challenging.

Nevertheless, a comprehensive scheme to calculate benefit and risk from multiple interventions in the U.S. Medicare population—the Million Hearts Longitudinal ASCVD Risk Assessment Tool—has been developed.[41] How helpful this approach will be clinically is not certain. The reality is that most clinicians do not base their therapeutic decisions on mathematical calculations. Time is a factor. The more detailed the calculation, the more data is needed for the calculation, and the more time is required to input the data needed for the calculation. Additionally, most of the output of such calculations is not intuitively meaningful for either the clinician or the patient. A 10-year risk of 7.5% may be defined as high, but this still means there is a 92.5% likelihood no event will occur.

But different diseases have different time lines. An important, although infrequently noted, difference between elevated levels of the atherogenic lipoproteins and elevated blood pressure is that the former generally precedes the latter. Hyperlipidemia, which represents a maladaptive response of our lipid transport systems to our metabolic environment, often presents earlier in life than hypertension, which, we suspect, is more commonly a degenerative process than a metabolic disease. Thus, in terms of prevention of premature ASCVD, the decision to reduce risk from elevated apoB lipoproteins generally comes before the decision to reduce risk due to elevated blood pressure. This difference in natural history can be a welcome simplification in the prevention decision-making process.

HEALTH ECONOMIC CONSIDERATIONS

Originally, cost was a major reason for the implementation of the risk model. Before 2003, no low-priced generic statin formulations were available and, accordingly, statins were very expensive (eg, annual price >$800 in the United States).[42] It was therefore not possible to recommend widespread use of statins for ASCVD prevention. Moreover, early trials were conducted in patients with very high cholesterol levels or established ASCVD. Statins were prioritized for these high-risk patients, for whom there was the greatest degree of certainty regarding treatment benefit. The introduction of generic simvastatin substantially lowered the price of statin therapy and was followed by a large increase in the number of patients receiving statins.[43-45]

As patents for simvastatin, pravastatin, fluvastatin, atorvastatin, and rosuvastatin expired, the price of generic statin therapy continued to fall. As prices fell, so too did the 10-year risk thresholds that guided statin prioritization. Studies showed that falling prices rendered statins cost-effective for individuals with 10-year risk ≥7.5% in the United States, when considered against the standard benchmarks of cost-effectiveness (ie, incremental cost-effectiveness

ratio <$50,000/QALY).[46-48] In England and Wales, researchers at the National Institute for Health and Care Excellence found that a threshold of 10% would be optimal.[49,50] Guidelines from the ACC/AHA and National Institute for Health and Care Excellence reflected this new evidence by reducing their respective risk thresholds for statin initiation.[50,51] While expanding treatment eligibility was a logical step, these guidelines retained the risk factor approach to prevention.

The ACC/AHA issued an update to their cholesterol management guidelines in 2018, which identified elevated cholesterol as a 'risk-enhancing factor' and recommended statins for borderline-risk individuals (ASCVD Risk Score 5.0%-7.4%) and LDL-C ≥160 mg/dL. This signaled a willingness to complement the risk model with causal-benefit information, acknowledging that high LDL-C not only contributes to overall ASCVD risk but is a predictor of statin benefit. We used a decision-analytic model to predict the cost-effectiveness of statins in 4 subgroups that would incrementally expand statin eligibility in the U.S. population: all patients with ASCVD Risk Score ≥7.5%, diabetes, or LDL-C ≥190 mg/dL (2013 ACC/AHA guideline), adding treatment for borderline risk and LDL-C 160 to 189 mg/dL (2018 ACC/AHA guideline), adding treatment for borderline risk and LDL-C 130 to 159 mg/dL, and adding treatment for all borderline risk patients.[52] Expanding treatment to borderline-risk individuals with LDL-C ≥130 mg/dL was 'cost-saving', indicating a net reduction in costs due to prevented ASCVD events under this strategy. Further expanding treatment to all individuals with borderline risk would be highly cost-effective (incremental cost effectiveness ratio [ICER]: $33,600/QALY).

A second analysis, set in the Scottish National Health Service, provides additional health and economic evidence in favor of the causal-benefit model.[20] Currently, preventive statin eligibility in Scotland is largely limited to individuals with a 10-year cardiovascular disease (CVD) risk ≥20%.[53] We estimated the cost-effectiveness of expanding eligibility by reducing this risk threshold to 10%, bringing Scotland in line with guidelines for England and Wales. Next, we considered the cost-effectiveness of ARR-guided statin therapy. Treatments were considered cost-effective if their ICER was <£20,000/QALY. We found that expanding eligibility to all individuals with 10-year risk ≥10% would be cost-effective (ICER: £12,300/QALY) and lead to around 642,000 new people becoming eligible for statins. Using ARR, rather than 10-year risk, to distribute statins to 642,000 new individuals would produce around 8,000 QALYs and would be cost-effective compared to treating 10-year risk ≥10% (ICER: £11,700/QALY).

The findings from these 2 studies are clear. Generic price statins are highly cost-effective for many CVD-free adults, and apoB lipoproteins are an important marker of statin benefit. Ultimately, complementing the current standard Risk model with a causal-benefit model is a cost-effective approach to statin prioritization that maximizes treatment benefit.

IMPLEMENTATION CONSIDERATIONS

Statins are a highly cost-effective measure to prevent ASCVD for large numbers of CVD-free adults in high-income countries. Health and economic evidence justifies expanded statin coverage, yet <50% of eligible individuals currently receive statins.[54] Guidelines bodies and clinicians should prioritize treating eligible patients with elevated cholesterol who have the greatest capacity to benefit from treatment. Adopting the causal-benefit model paradigm will lead to a reconsideration of how elevated cholesterol is treated, especially in young adults.

Exposure to atherogenic apoB lipoprotein particles cumulatively increases the risk of ASCVD events throughout the life course.[55] About 26 million U.S. young adults have an LDL-C ≥130 mg/dL, but few are screened for high cholesterol, let alone treated for it. We estimated that commencing statin therapy in young adulthood would be highly cost-effective for men (ICER: $31,000/QALY) and intermediately cost-effective for women (ICER: $106,000/QALY).[37,56] PCSK9 inhibitors are an innovative and highly effective alternative to statins for CVD prevention through LDL-C-lowering, and long-acting PCSK9 inhibitors requiring only annual administration may be more patient-centered and lead to expanded treatment coverage. While PCSK9 inhibitors and other novel lipid-lowering agents are currently priced far too high to justify wide clinical recommendation,[57,58] the causal-benefit model could help to guide the next generation of cholesterol treatment guidelines when cheaper, very long-acting PCSK9 inhibitors and other novel lipid-lowering therapies are more affordable and accessible.

ApoB VS LDL-C

LDL-C is not the most effective tool to guide selection by the causal-benefit model. ApoB is a more accurate marker of cardiovascular risk and the adequacy of lipid-lowering therapy than LDL-C or

non-high-density lipoprotein cholesterol.[17,38,59] The clinical evidence in favor of apoB is now definitive. Johannesen et al[60] used discordance analysis to demonstrate that apoB was a more accurate marker of the risk of death and myocardial infarction than non-HDL-C or LDL-C in a large Danish cohort treated with statins. Marston et al[61] demonstrated that apoB was a more accurate marker of residual cardiovascular risk than LDL-C or non-HDL-C in patients treated with statins and ezetimibe in the IMPROVE-IT trial, as well as statins and a PCSK9 inhibitor in the FOURIER trial. Finally, Hagstrom et al[62] have reported not only that apoB is superior to LDL-C and non-HDL-C in the ODYSSEY trial, a test of a statin and a PCSK9 inhibitor in patients who have suffered an acute coronary syndrome, but that there was a linear relation between residual risk and plasma apoB to as low as apoB could be measured. Since clinical decisions regarding PCSK9 therapy are based in large part on the measured levels of the apoB lipoproteins, the fact that apoB can be measured more accurately, more precisely, and more selectively than LDL-C or non-HDL-C, particularly at low concentrations, is a critical advantage for apoB.[63] Introducing patient apoB information into the causal-benefit model will further improve its performance and can be achieved at a low cost.[64]

LIMITATIONS OF ALL PREDICTIVE MODELS

In reality, all estimates of individual risk are estimates of the frequencies of events in groups to which the individual has been assigned.[65] Indeed, the validity of an algorithm to estimate risk can only be tested by examining the frequency of events in a group. Except for the prediction that it is impossible for an event to occur, all that can be determined in an individual is whether the event occurred, not whether the likelihood predicted of its occurring was correct. If 1 algorithm predicted a likelihood in an individual of an ASCVD event of 10%, whereas another predicted a likelihood of 5%, the validity of the 2 models cannot be compared in the same individual, only in groups of individuals with these predicted risks. As well, prediction of the likelihood of cardiovascular events is based on a small number of variables. The list is incomplete, and therefore the capacity to predict risk is incomplete.[12] Adding more information, such as coronary artery calcification, to a validated risk algorithm results in significant reclassification, evidence of the limited individual accuracy of the initial algorithm.[65]

But coronary artery calcification cannot be the last step in the process. Other major causes must exist. Moreover, little is known about the determinants of the events themselves. Thin-walled lipid-rich plaques are prone to rupture, but the determinants of plaque structure are not known and therefore cannot be factored into a prediction. Healing with removal of cholesterol from the wall and increase of fibrous tissue content can occur, but the natural determinants of this process are not known with any precision. Therefore, at the moment and for the foreseeable future, the process of prediction is incomplete. These limitations apply to the causal-benefit model as well as to the risk model since both include an estimate of risk derived from an accepted algorithm. However, the imprecision in prediction and the uncertainty of the results do not invalidate the utility of all algorithms. Estimates of risk provide reasonable guides, not precise estimates, to decisions; the higher the estimate, the more meaningful it will be. Thus, a risk of 8% over 10 years means, on average, 8 out of 100 individuals will suffer an event, whereas 92 will not. By contrast, a risk of 30% over 30 years means almost 1 in 3 will suffer an event. The period of life with its opportunities and responsibilities between the ages of 35 and 65 is as easy to imagine as the period of 35 to 45. But a risk of 30% is a more substantial number, and therefore, possibly a more persuasive number than a risk of 8%. Imprecision and uncertainty are ineradicable from the medical decision-making process. But the necessity to make informed and reasonable choices remains.

The levels of the apoB lipoproteins, particularly apoB, can be measured with considerable accuracy, precision, and selectivity in the individual,[63] and the relation between these levels and subsequent cardiovascular events is secure. Thus, the assignment of an individual to a group based on a cause should be more secure than assignment of an individual to a group based on risk. But the risk of disease and the benefit from therapy are based not just on what the level has been but on what it will be in the future. If the population is divided into groups based on the level, the trajectory over time is reasonably predictable, particularly at the extremes. Individual uncertainty, of course, will remain.[66,67] The greater the deviation from the norm, the more likely the deviance is to remain; nevertheless, regression to the mean will occur. Physiological and lifestyle changes will, undoubtedly, affect the levels of the apoB lipoproteins in individuals. Except with extreme elevations, serial testing will be necessary to establish stability, but if serial surveillance begins at early age—say in the third decade—this challenge can be met. Moreover, this allows time for non-pharmacological measures to be implemented and their success assessed.

TABLE 1 The Risk Model vs the Causal Benefit Model of Cardiovascular Prevention

Advantages of the Risk Model for Primary Prevention of ASCVD	Advantages of the Causal Benefit Model for Primary Prevention of ASCVD
• Risk models integrate multiple factors that contribute to the development of ASCVD events. • Only those at high risk of a clinical event should be treated with medications by physicians. • Targets therapies with cost and risk to those who are most likely to suffer a clinical event. • Intuitively reasonable to physicians and patients. • Has been applied worldwide and therefore represents the current paradigm. • Multiple calculators exist to facilitate application.	• Acknowledges the progress of science: ◦ Trapping of apoB particles within the arterial wall is the primary cause of ASCVD. ◦ Elevated plasma levels of the plasma apoB lipoproteins are a primary determinant of trapping of apoB particles within the arterial wall. ◦ Therefore, elevated levels of the plasma apoB lipoproteins are a primary cause of ASCVD, not merely a risk factor for ASCVD. • Tailors the intensity of therapy to the individual: Because the relative reduction in risk is close to constant per unit reduction in the apoB lipoproteins, the higher the baseline level of the apoB lipoproteins, the greater the reduction in baseline risk that is achievable with treatment. • Coherent: Treatment should be prioritized for those who are at risk of a disease and who can benefit from the treatment • Improves identification and therefore treatment of those at risk of premature ASCVD. • Identifies individuals who could benefit from earlier treatment to prevent development and progression of disease that will create a high risk of ASCVD later in life. • Increase the total number of events prevented but remains cost-effective. • Has been shown to be optimal in maximizing the number of events prevented among treatment strategies.
Disadvantages of the Risk Model for Primary Prevention of ASCVD	**Disadvantages of the Causal Benefit Model for Primary Prevention of ASCVD**
• Because age is the primary determinant of short-term risk and risk is, with few exceptions, low in younger individuals, this approach is inefficient at identifying individuals who will suffer premature ASCVD. • Risk of ASCVD is only present when atherosclerotic disease is present. Disease develops over decades. If risk is the primary trigger for prevention, disease is allowed to develop and progress without treatment until risk increases beyond the threshold for intervention. The increase in risk reflects the increased likelihood of advanced complex disease, which can trigger clinical events. • Treating based on risk as an integrated measure rather than treating specific causes is harder to conceptualize.	• Requires another calculation on top of estimation of risk. • Expands the current paradigm requiring additional education.

apoB = apolipoprotein B; ASCVD = atherosclerotic cardiovascular disease.

We also acknowledge that the calculations in the causal-benefit model are based on applying data on benefit from randomized clinical trials, many of which were secondary prevention, to estimates of risk from prospective observational studies. There does not, however, appear to be any substantial difference between benefit expressed as percent reduction in risk per mmol/L reduction in LDL-C or apoB between trials conducted in primary or secondary prevention.[68] However, there has been no primary prevention trial conducted in young adults, nor given the duration and size of the trial required is one likely in the foreseeable future. However, given the technical advances in coronary computed tomography angiography, demonstrating whether early therapy produces significant benefit based on quantitive changes in arterial wall disease would seem achievable.[69]

APPLICATION OF THE CLINICAL BENEFIT MODEL

Consensus groups create formal rules to guide clinical care. These may be simple and inclusive and based on clear-cut evidence from randomized clinical trials: all those with a history of myocardial infarction should be treated with a statin. These are straightforward to implement.

Alternatively, they may be more complex and require application of an algorithm, such as the calculation of the 10-year risk of a cardiovascular event, which produces a precise, but arbitrary, decisional threshold. How often these calculations are made in routine clinical care is not known, but we suspect they represent the exception more often than the rule. Indeed, as we have noted, age and sex dominate the calculation of risk; the calculation, certainly for males over 60 years, adds little.

How then would we apply the causal-benefit model given that the potential need for cardiovascular prevention should, in our view, be evaluated before 10-year risk can even be calculated before age 40 years? In adults, we would suggest that the levels of the plasma lipids apoB and Lp(a) be evaluated after age 25 years. Extreme elevations, consistent with familial hypercholesterolemia, should be further investigated and, if marked deviance is confirmed, appropriately treated. In those with levels >75th percentile, the levels should be repeated, and if

confirmed, nonpharmacological measures to lower LDL-C and apoB are recommended. Follow-up is essential, and if substantial elevations persist over the next few years, the option of pharmacological therapy could be considered. Longer estimates of risk—30-year risk scores—will be vital in clinical decision-making because they inform the patient of the likelihood of serious consequences during the years of their life when they are generally the most productive and the most depended on. These are individual discussions in which the patient needs to be informed of their options and that any decision, whether pro or con, can be revisited.

CONCLUSIONS

During the latter half of the twentieth century, ASCVD rates declined substantially in high-income countries.[70] Statin therapy, alongside other pharmacologic developments, played a decisive role in this decline. Typically, selection of lipid-lowering treatments for primary prevention has been based on the risk model of prevention. However, since 2010, ASCVD rates have plateaued.[4] This argues for a new approach to further improve population health. A blended approach combining the standard risk model with the new causal-benefit model can be introduced as part of guideline updates without disrupting current lipid screening and management practices. In places where clinicians use electronic medical records, patient selection based on baseline 10- or 30-year ASCVD risk can be combined with expected risk reduction from a statin in a single digital application that draws clinical data from the electronic medical record and selects patients based on national and local eligibility guidelines.

The advantages and disadvantages of both the risk model and the causal-benefit model are summarized in **Table 1**. The need to move beyond the risk model is driven by the need to improve prevention of premature ASCVD events and to prevent the development of disease, which causes the events later in life. This change in preventive strategy is driven by the now incontrovertible evidence that apoB lipoproteins play a causal role in the pathogenesis of atherosclerosis and its clinical complications and that therapy that lowers the level of apoB lipoproteins substantially reduces the risk of clinical cardiovascular events. Embracing this new approach to prevention, we submit, will help to further improve global cardiovascular outcomes.

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