Nonfatal Outcomes in the Primary Prevention of Atherosclerotic Cardiovascular Disease
Is All-Cause Mortality Really All That Matters?

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There is considerable debate in the literature regarding appropriate end points for studies of primary prevention of atherosclerotic cardiovascular disease (ASCVD), most notably with regard to statin therapy for hypercholesterolemia. Some authors have argued that large clinical trials of primary prevention interventions must demonstrate an overall mortality benefit or a combined overall mortality and serious morbidity benefit. Others feel that such a high bar would lead to the erroneous dismissal of several beneficial strategies that can substantially decrease incident ASCVD.

Although several meta-analyses have now shown a modest mortality benefit of statins in primary prevention, the debate will undoubtedly be rekindled with the recent revision of the American College of Cardiology Foundation/American Heart Association (ACC/AHA) guidelines for the treatment of hypercholesterolemia. In this article, we advocate for the importance of nonfatal cardiovascular outcomes (nonfatal myocardial infarction [MI], nonfatal stroke, and peripheral arterial disease) in the assessment of ASCVD primary prevention strategies, illustrate this principle already in use in the management of hypertension, and advocate for the relevance of both nonfatal and fatal ASCVD events in the treatment of hypercholesterolemia in the primary prevention setting.

Defining Benefit

The definition of benefit in the primary prevention of clinical ASCVD has recently been debated. Some authors suggest that an improvement in total mortality, of which cardiac death is only one part, is the only relevant benefit. Prasad and Vandross refer to examples of medications that improve surrogate end points but subsequently fail to improve overall survival, such as fibrates and niacin in certain patient populations. Importantly, no distinction is made between clinical, nonmortality end points (eg, nonfatal MI and stroke) and surrogate markers of clinical ASCVD risk (eg, low-density lipoprotein-cholesterol). This line of reasoning suggests that nonmortality end points are simply surrogates and should not be used to guide clinical decision making. In addition, others have argued that a lack of a clear effect on all-cause mortality is enough evidence that there is no meaningful benefit on vascular events.

A distinction should be made between outcomes that are risk factors for nonfatal clinical outcomes and the clinical outcomes themselves (see the Table). Low-density lipoprotein-cholesterol in isolation falls into the first group because a reduction in low-density lipoprotein-cholesterol that does not correlate with improvement in clinical events, such as nonfatal MI or stroke, would not be an appropriate surrogate end point. However, nonfatal MI, nonfatal stroke, and peripheral arterial disease are nonmortality clinical outcomes that greatly impact patients. For this reason, these disease states merit prevention in and of themselves and, therefore, are distinct from surrogate outcomes that do not have value without the clinical correlation.

Indeed, some of these important end points lie along a spectrum in terms of morbidity and impact on quality of life. Although some MIs and strokes will be relatively minor in severity, many will dramatically impact their victims. The concept of quality-adjusted life years was introduced to help solve this problem in part, but it is fraught with difficulties including the inaccuracies and subjective variability of having healthy people anticipate the impact of an event on their lives. However, the wide spectrum of severity of these outcomes and the difficulty in quantifying their impact on individual lives should not lead us to discount them entirely.

Regardless of the severity of events for individual patients, however, the morbidity of incident clinical ASCVD on the population as a whole is great. According to the AHA, each year an estimated 635,000 Americans will have a new MI or coronary heart disease death, and 610,000 will suffer a new stroke, for a total of >1.2 million incident ASCVD events.

Imagine that a medication can prevent these new ASCVD events but does not result in improved all-cause mortality. A medication could have this property if the middle- to older-age people who would have suffered the ASCVD events died instead from a competing risk from another, unrelated cause (eg, cancer, pulmonary disease, accident, etc) before the time the downstream effects of the avoided ASCVD event...
Although both all-cause mortality and serious morbidities are important, utilizing a summary measure such as the serious adverse event confuses the fundamental risk–benefit principle. A serious adverse event counts every event as equal, and death, hospitalization, nonfatal MI, and incident diabetes are not equivalent events. Furthermore, rare side effects may occur in a few patients that are largely reversible by simply discontinuing the medication or intervention, such as severe myopathy or rhabdomyolysis with statin use. These events need not affect the overall balance of the benefit of the intervention for the target population as a whole. The balance between benefits and harms is what needs to be assessed, so combining them into a summary measure and weighing each equally ignores the careful evaluation of each component that is necessary to make an educated, reasoned decision as to the value of an intervention.

To summarize, short-term all-cause mortality is not the only relevant end point in a large-scale strategy for the prevention of clinical ASCVD. To focus on all-cause mortality is to miss the significant impact of incident MIs, strokes, and peripheral arterial disease on the daily existence of patients affected by 1 of these life-altering diseases. Furthermore, to focus on only short-term mortality misses the modifications to risk trajectory that result in long-term mortality benefits that are difficult to demonstrate in typical clinical trials with 5 or 10 years of follow-up. These principles are already at work in our management of hypertension, and the treatment of hyperlipidemia must be held to the same standard.

**Principles in Practice: Treatment of Hypertension**

As an illustration, hypertension is an excellent example. Hypertension is a major risk factor for clinical ASCVD, and the treatment of systolic blood pressures of ≤160 mm Hg has never been definitively shown in a randomized controlled trial to result in a decrease in all-cause mortality. More than a decade ago, a reanalysis of Framingham data by Port et al suggested that instead of being a continuous risk factor, blood pressure had a threshold that was age- and sex-dependent, below which there was no increased risk of ASCVD. The authors noted no mortality benefit of treating systolic pressures ≤160 mm Hg and concluded that the existing guidelines needed to be changed because treatment of stage I hypertension (a systolic blood pressure of 140–160 mm Hg or diastolic blood pressure of 80–90 mm Hg) had no value. However, the analysis of Port et al focused solely on the initial 18-year follow-up of Framingham data, which had many fewer cardiovascular events than the 30-year data.

Although we do not have a randomized clinical trial that looks specifically at the effect of treatment of baseline systolic blood pressure between 140 and 160 mm Hg, the Systolic Hypertension in the Elderly Program (SHEP) and the Systolic Hypertension in Europe (Syst-Eur) trials are informative. In SHEP, the mean follow-up systolic blood pressure was 143 mm Hg in the intervention group and 155 mm Hg in the control group, and in Syst-Eur, the mean systolic pressure in the intervention and control groups was ≤151 and 161 mm Hg, respectively. Both SHEP and Syst-Eur showed convincing
decreases in both coronary heart disease and stroke in the intervention groups.

Subsequent to the analysis of Port et al, an analysis of the Cardiovascular Health Study did indeed demonstrate a direct relationship between systolic and diastolic blood pressure and incident MI and stroke and between systolic blood pressure and total mortality. Furthermore, the National Heart, Lung, and Blood Institute issued a review stating that based on the totality of the evidence, there was indeed a critically important, strong, continuous, and graded relationship among systolic blood pressure, diastolic blood pressure, and cardiovascular risk. Systolic and diastolic blood pressures were also predictive for those with and without coronary heart disease.

Hypertension experts agree that the presence of other risk factors for ASCVD and the presence of known atherosclerosis, target organ damage, and diabetes mellitus need to be considered when deciding which patients with hypertension should receive pharmacological therapy. Many observational studies have shown a direct relationship of stage I hypertension with heart failure, nonfatal stroke, nonfatal MI, and chronic kidney disease. By focusing solely on total mortality, Port et al neglected the majority of cardiovascular events. In addition, their focus on short-term outcomes caused them to miss the significant benefit in lifetime risk trajectory that was evident at 30 years. The subsequent Joint National Committee guidelines and European Society of Hypertension/European Society of Cardiology guidelines did indeed recommend pharmacological therapy for systolic pressures between 140 and 159 mm Hg.

**A Double Standard: Treatment of Hypercholesterolemia**

In a similar fashion, the treatment of hypercholesterolemia with 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitors (statins) in patients without clinically evident ASCVD but at increased 10-year risk of incident ASCVD has come under fire in recent years. Some argue that clinical trials of statin therapy in this population have not shown an all-cause mortality benefit, and that in this setting statins do not reduce suffering. They conclude that statins should not be used in this population. This is reminiscent of the viewpoint that Port et al took over a decade ago with regard to the treatment of hypertension in primary prevention and falls short for similar reasons.

Statins used for primary prevention in intermediate and high-risk patients (5% to 20% and >20% 10-year Framingham risk, respectively) have conclusively been shown to decrease cardiac death and ASCVD and have recently also been found to have a modest all-cause mortality benefit. Multiple large, randomized, controlled clinical trials have demonstrated significant improvements in incident MI, stroke, and coronary death, and the JUPITER trial showed a reduction in all-cause mortality (hazard ratio, 0.80, 95% confidence interval, 0.67–0.97). Furthermore, a recently updated Cochrane meta-analysis of 18 randomized clinical trials including 56934 patients without clinically apparent ASCVD demonstrated a 14% improvement in all-cause mortality, a 27% reduction in fatal and nonfatal coronary events, and a 22% reduction in fatal and nonfatal stroke.

Another meta-analysis included data from 27 trials with a total of 174 149 patients and found a 19% to 38% reduction in major vascular events per 1.0 mmol/L (39 mg/dL) decrease in low-density lipoprotein-cholesterol across a spectrum of 5-year major vascular event risk ranging from <5% to >30%. Lastly, an all-cause mortality benefit from statins in primary prevention was not conclusive but was strongly suggested in the frequently cited meta-analysis by Ray et al (relative risk, 0.91, 95% confidence interval, 0.83–1.01).

Critics of statin therapy for the primary prevention of ASCVD also focus on the side effects associated with statin therapy, including rhabdomyolysis, myalgias, cognitive dysfunction, cancer, and new-onset diabetes mellitus. However, several large meta-analyses have shown that statins are generally safe with no increased incidence of cancer, cancer mortality, myalgias, or rhabdomyolysis (which was quite rare). Furthermore, myalgias are not specific for statin-induced myopathy, and frequently patients can tolerate rechallenge of the same statin. Finally, a recent review found no evidence to support short-term adverse cognitive effects in patients without baseline cognitive dysfunction and suggested a possible long-term benefit on dementia.

It is important to note that the Cochrane meta-analysis reported a small increase in incident diabetes mellitus, although only 2 trials provided data, and the finding was largely driven by the Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) trial, which was enriched with metabolic syndrome. Further analysis of the JUPITER data found that those with ≥1 risk factors for diabetes mellitus were at higher risk of developing diabetes mellitus while on statin therapy, but that 134 vascular events or deaths were avoided for every 54 incident diabetes mellitus cases. In addition, they estimated that statin therapy accelerated the time to the diagnosis of diabetes mellitus by only 5.4 weeks. The authors concluded that the benefits of statins in terms of ASCVD event and mortality prevention exceed the risk of incident diabetes mellitus.

There is convincing evidence that the benefits of statin therapy added to diet and lifestyle interventions outweigh the harms in patients at intermediate to high risk for the development of ASCVD. As the preceding discussion shows, statins can prevent 20% to 40% of incident ASCVD in this population; the increased risk of diabetes mellitus conferred by statin therapy is more than offset by the reduction in ASCVD; and the other side effects (myalgias, rhabdomyolysis, etc) are easily detectable with close follow-up and reversible with cessation of statin therapy. Importantly, the direction and magnitude of effect sizes for outcomes other than total mortality for statins in primary prevention are commensurate with those demonstrated in the well-accepted and better-powered secondary prevention trials of statins, in which a total mortality benefit has been convincingly demonstrated. To require that clinical trials of statins in primary prevention redemonstrate this benefit when there is no suggestion (let alone evidence) that statins are somehow a different medication with different effects in the primary as compared with secondary prevention setting would be unnecessary and, perhaps, unethical. Therefore, statin therapy should be strongly considered for...
intermediate to high-risk patients after a discussion about the potential benefits and side effects has taken place.

Conclusions
If the medical community accepted the conclusions of Port et al and ignored the totality of evidence linking stage I hypertension to the development of cardiovascular morbidity, many patients would have missed out on proven preventive therapies, and the epidemics of end-stage renal disease and heart failure would likely have accelerated. The same is true if we ignore the evidence of the benefit of statins in the primary prevention of ASCVD for individuals at intermediate and high risk over the next decade. Relying on short-term all-cause mortality as the sole relevant end point does not take into account reductions in very morbid conditions including MI, disabling stroke, and lifestyle-limiting peripheral arterial disease over the lifetime. These end points matter in and of themselves, and therefore a reduction in these can and should be enough benefit to recommend evidence of benefit to statin and antihypertensive therapy for the millions of individuals who stand to benefit. Because of this, the revised ACC/AHA guidelines for the reduction of cardiovascular events include nonmortality outcomes as relevant end points when deciding whether to initiate statin therapy.

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References


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