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A Look at Statin Cost-Effectiveness in View of the 2013 ACC/AHA Cholesterol Management Guidelines

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Abstract The 2013 cholesterol management guidelines presented a major shift in recommendations on which patients at risk of cardiovascular disease should be treated and how to treat them. Implementation of the guidelines is estimated to increase substantially the number of people who would be eligible for statin therapy. As the medical community considers the broad population impact of the new cholesterol guidelines, the issue of cost-effectiveness plays a role. This review covers the basic fundamentals of cost-effectiveness analysis and summarizes the key cost-effectiveness studies that relate to the new cholesterol guidelines.

Keywords Cholesterol · Guidelines · Cardiovascular disease · Risk · Cost-effectiveness

Introduction

The American College of Cardiology/American Heart Association (ACC/AHA) recently released practice guidelines on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults [1••]. These new guidelines presented a marked shift from the previous National Cholesterol Education Program Adult Treatment Panel III (ATP III) guidelines, with treatment determinations based on atherosclerotic cardiovascular disease (ASCVD) risk and with medication recommendations limited to statins. The guidelines incorporated a new 10-year ASCVD risk calculator to help determine if a patient would benefit from a statin if that patient is at moderate risk (5–7.5 %) or high risk (greater than 7.5 %) [1••, 2], and made no recommendation for or against specific LDL cholesterol (LDL-C) targets for primary or secondary prevention of ASCVD [1••]. The guidelines estimated that approximately 33 million people would have a high 10-year ASCVD risk that would qualify for a high-intensity statin therapy, and an additional 13 million people would have a moderate risk for which statins could be considered [1••, 3]. An analysis of National Health and Nutrition Examination Survey (NHANES) data from 2005 to 2010 estimated that an additional 12.8 million people would be eligible for statin therapy, with the increase seen mostly among older adults without cardiovascular disease [4]. Moreover, the NHANES study estimated that almost 50 % (56 million) of all people between the ages of 40 and 75 years without cardiovascular disease would be eligible for statin therapy [4]. As these new guidelines are implemented nationally, the public health and health care cost implications could be quite profound. The aim of this article is to review the most pertinent current literature regarding the cost-effectiveness of statins in relation to the guidelines and to discuss the policy implications.

Cholesterol Guidelines

The previous ATP III cholesterol guidelines recommended specific targeted LDL-C thresholds if patients had coronary heart disease (CHD) or CHD-risk equivalents (LDL-C level below 100 mg/dL), had two or more risk factors with a 10-year incident CHD risk less than 20 % (LDL-C level below 130 mg/dL), or had zero risk factors or one risk factor (LDL-C level below 160 mg/dL) [2]. The 2013 ACC/AHA cholesterol guidelines abandon the LDL-C targets and establish four statin

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benefit categories: (1) individuals with clinical ASCVD, (2) individuals with primary elevations of LDL-C level (190 mg/dL or above), (3) individuals with diabetes mellitus (DM) and aged 40–75 years without clinical evidence of ASCVD and LDL-C levels of 70–189 mg/dL, and (4) individuals with without DM and without ASCVD and aged 40–75 years, whose LDL-C level is between 70 and 189 mg/dL and who have an estimated 10-year ASCVD risk of 7.5 % or higher [1••]. ASCVD includes CHD, stroke or transient ischemic attack, and peripheral arterial disease presumed to be of atherosclerotic origin [1••]. The major changes from the previous guidelines were the inclusion of stroke and exclusion of treat-to-target LDL-C, with the rationale that randomized controlled trials show reductions in incident ASCVD events by specific statin dosing targets rather than LDL-C targets [1••]. A point emphasized by the ACC/AHA is that these guidelines were developed to aid the clinician in everyday treatment [1••], and LDL-C levels could still be used as a marker of adherence to statin therapy.

Cost-Effectiveness Analysis

Cost-effectiveness analysis determines the best way to optimize health gains from a health system or societal perspective, particularly when there are limited health care resources [5]. The first and most important part of any cost-effectiveness analysis is to demonstrate that the intervention benefits patients. Quantifying health benefits is often done through estimating quality-adjusted life years (QALYs) gained, which attempts to quantify both the numbers of years gained and the quality of life for those years. QALYs serve as a standard that may be compared across different intervention and treatment options [6]. The second part of cost-effectiveness analysis is to estimate the costs of a treatment, such as statin therapy, and the costs associated with clinical events, such as a hospitalization or procedure, that are hopefully avoided by the treatment. The third part is to generate some relationship between the health benefit and the cost, such as an incremental cost-effectiveness ratio (ICER) reported in terms of cost per QALY. A commonly used willingness to pay for health estimate in the USA is $50,000 to $100,000 per QALY gained—a somewhat arbitrary value that was established on the basis of the annual cost that Medicare pays for a dialysis patient in the USA [6], and some willingness-to-pay analyses have suggested that a higher cost-effectiveness threshold ($100,000 to $300,000 per QALY) should be used [7].

In cost-effectiveness analysis, there are two key aspects to consider. First, the results of all cost-effectiveness analyses are highly dependent on the benefit and cost assumptions that are put into the models. Cost-effectiveness studies generally take estimates of health benefit from randomized controlled trials; however, different trials produce different results. Cost-effectiveness researchers must select the best health benefit estimate, often with more conservative and more liberal estimates for sensitivity analyses. Similar assumptions must be made about the cost of drugs or procedures, and the cost savings from preventing future adverse events, such as myocardial infarctions (MIs). Moreover, both the health benefits and the costs are based on the estimates of baseline patient risk. For example, a patient at higher ASCVD risk would have greater absolute risk reduction with statin therapy, and would also potentially have greater costs or cost-saving. Second, and more importantly, is that cost-effectiveness analysis is most useful at a population level for policy decision-making. In treating an individual patient, physicians must consider the benefits and risks for that patient, along with the patient's preferences, to arrive at a shared decision on a particular medical issue.

Given the potential cost implications associated with the increased number of people eligible to start statin therapy, the following section reviews statin cost-effectiveness studies for the prevention of ASCVD in US patients. We categorized the research by the study populations: all risk profiles, clinical ASCVD, those with diabetes, and those with intermediate risk or LDL-C levels above 190 mg/dL. For the purposes of this review, we use the common cost-effectiveness threshold of $50,000 per QALY to interpret the findings from these studies, recognizing, however, that this threshold is subjective and depends on societal values.

All Risk Profiles

Since the 2013 ACC/AHA cholesterol guidelines provide recommendations targeted for specific populations, there are no recommendations that can be generally applied to patients. However, since multiple cost-effectiveness studies have looked at broad populations at all levels of cardiovascular risk, the review of these analyses is informative.

Prosser et al. (2000)

Using a computer simulation modeling program in a virtual group of adults aged 35–84 years with high LDL-C levels (at least 160 mg/dL), Prosser et al. [8] estimated the effects and costs of cholesterol-lowering strategies in 240 risk subgroups according to age, sex, and the presence of four CHD risk factors—smoking, hypertension, high LDL-C level, and low HDL cholesterol (HDL-C) level. The medication costs for statins were the average wholesale prices of pravastatin and simvastatin at the time of the study. All costs were adjusted to 1997 US dollars using the consumer price index. Notably, at a cost-effectiveness threshold of $50,000 per QALY, statins were not cost-effective for any of the 240 risk subgroups involved for primary prevention. For secondary prevention,

the ICER was less than $45,000 per QALY for all 240 risk subgroups and thus cost-effective. In fact, for certain high-risk subgroups (middle-aged smokers), addition of statins was found to be cost-saving.

Pignone et al. (2006)

Pignone et al. [9] developed a Markov decision-analytic model, which is a commonly used simulation approach, to perform the cost-effectiveness analysis of the effects of aspirin therapy alone, statin therapy alone, combination therapy, or no primary prevention therapy in middle-aged men (modeled on a 45-year-old) without history of cardiovascular disease at various levels of 10-year Framingham risk of incident CHD (2.5–25 %). Drug costs were based on the average 2003 wholesale price of simvastatin and lovastatin, and the researchers assumed 100 % medication adherence unless there were adverse side effects. All other costs were converted to 2003 US dollars via the consumer price index. On the basis of previous population studies, the researchers used a statin treatment relative risk of 0.7 (0.62–0.79) for primary prevention of incident CHD events [9]. Their model demonstrated that the addition of a statin to aspirin therapy was cost-effective, at $42,500 per QALY for individuals at 10 % risk and $33,600 per QALY for those at 15 % risk. For people at 7.5 % risk, adding a statin had an ICER of approximately $56,200 per QALY. This study was highly dependent on the cost assumption for statins because for an annual cost of statins of less than $632, adding a statin to aspirin therapy produced an ICER of less than $50,000 per QALY for all risk groups.

Pletcher et al. (2009)

To assess the cost-effectiveness and impact of the ATP III guidelines, the CHD Policy Model (a Markov-type cost-effectiveness model) was developed using national surveys (US Census, NHANES, National Health Interview survey, and National Hospital Discharge Survey) and the Framingham Heart Study to determine the incremental cost-effectiveness of statin therapy initiation in the US population aged 35–85 years [10]. This study estimated that implementing the ATP III guidelines would result in 11 million people either needing to start or intensifying statin therapy, and that 20,000 MIs and 10,000 CHD events would be prevented. These health gains came at an annual cost of $3.6 billion, resulting in an ICER of approximately $42,000 per QALY [10]. Compared with previous studies, this study categorized statin drugs on the basis of the estimated LDL-C-lowering capability into low intensity (27 % mean decrease in LDL-C level) and high intensity (55 % mean decrease in LDL-C level) [10]. The statin costs were also estimated as the lowest average wholesale price reported in the 2006 National Drug Data file, and were approximately $2.11 per low-intensity statin therapy pill and $2.81 per high-intensity statin therapy pill. The results demonstrated initiating statin therapy according to the ATP III guidelines would be cost-effective, with an ICER of $42,000 per QALY. However, if the Framingham Offspring Cohort estimated CHD risk were lower at 0–5 %, the ICER would range from $56,000 to $93,000 per QALY. Interestingly, if the estimated CHD risk were greater than 7.5 %, similar to that in the current guidelines minus the inclusion of stroke, the ICER would be $50,000 per QALY and would be cost-effective even at 2006 wholesale statin prices.

Hayward et al. (2010)

Hayward et al. [11] simulated a more tailored treatment approach to statin therapy, somewhat similar to the current ACC/AHA guidelines, in which moderate statin doses were given for a 5-year CHD risk between 5 and 15 %, and high statin doses were given for a 5-year CHD risk greater than 15 %. This treatment approach was compared with the previous model of treat-to-target LDL-C per the ATP III guidelines. The study used statin trial data from 1994 to 2009 and defined the target population as US individuals aged 30–75 years with no MI history. The main outcome was QALYs. The tailored treatment approach resulted in 15 million more people being treated, but a gain of 570,000 more QALYs over a period of 5 years. No calculations or data were given regarding the cost per QALY.

Lazar et al. (2011)

Lazar et al. [12•] used the CHD Policy Model used by Pletcher et al. [10] to project the cost-effectiveness of an expanded statin strategy in light of the increased availability of low-cost generic statins at about $4 per month from discount retailers. The study examined a US population over the age of 35 years and stratified the individuals into four risk groups: moderately high risk (greater than two risk factors with 10–20 % 10-year risk of incident CHD), moderate risk (greater than two risk factors with 0–10 % 10-year risk of incident CHD), lower risk (one risk factor), and lowest risk (zero risk factors). The risk factors in this model were consistent with the ATP III guidelines—cigarette smoking, hypertension, low HDL-C level, family history of premature CHD, and age [2, 12•]. The model tested a low-intensity statin therapy that reduced the relative risk of incident CHD events by 8–34 % depending on age. The study found primary prevention statins to be cost-effective for all patients of the moderate ($37,000 per QALY) and moderately high ($23,000 per QALY) risk groups. Furthermore, statin treatment was cost-effective for those at lower risk if their LDL-C level was greater than 100 mg/dL ($35,000 per QALY) and for those at the lowest risk if their LDL-C level was greater than 130 mg/dL ($47,000 per QALY), with

both of these LDL-C values being more aggressive than the ATP III guideline recommendations.

Clinical ASCVD

For patients with a history of ASCVD, the 2013 ACC/AHA guidelines recommend a high-intensity statin therapy for patients younger than 75 years and a moderate-intensity statin therapy for patients younger than 75 years if they cannot tolerate a high-intensity statin therapy [1••]. Extensive evidence demonstrates that the use of high-intensity statin therapy over moderate-intensity statin therapy will decrease incident ASCVD events in patients with a history of ASCVD [1••, 13–15]. For patients older than 75 years with a history of ASCVD, moderate-intensity statin therapies have shown benefit in the reduction of incident ASCVD events, but for higher-dose statins the evidence for additional risk reduction is less clear. Therefore, the ACC/AHA guidelines recommend initiating a moderate-intensity statin therapy in this cohort [1••, 16].

Ganz et al. (2000)

Ganz et al. [17] developed a Markov model to determine the cost-effectiveness of adding statin therapy in patients aged 75–84 years with a history of MI. Statin costs were based on average wholesale prices and costs of care were adjusted to 1998 US dollars by using the medical care component of the consumer price index. Clinical data came from the available cohort studies at the time (Multicenter Diltiazem Postinfarction Trial Research Group, Oxfordshire Community Stoke Project, and Cholesterol and Recurrent Events trial), rather than from randomized controlled trials [17–19]. This simulation estimated that the statin therapy was cost-effective, with an ICER of $18,880 per QALY.

Chan et al. (2007)

Chan et al. [20] used a Markov model to determine if high-dose statin therapy compared with conventional-dose statin therapy in patients with stable CHD and a history of an acute coronary syndrome (ACS) was cost-effective [20]. They used both ACS and stable CHD trials for their clinical data and developed pooled estimates of clinical events. Notably, the ACS group receiving high-dose statin therapy had a relative risk of 0.76 (0.62–0.94, $p=0.01$) for all-cause mortality and 0.88 (0.79–0.99, $p=0.04$) for revascularization, but no significant difference in relative risk for incident MI, stroke, or rehospitalization [20]. The stable CHD group receiving high-dose statin therapy had a relative risk of 0.81 (0.73–0.91, $p<0.001$) for incident MI, 0.82 (0.70–0.96, $p=0.01$) for stroke, and 0.78 (0.71–0.86, $p<0.001$) for revascularization, but no significant difference in relative risk for all-cause mortality or rehospitalization [20]. Costs were standardized to 2005 US dollars and the prices for high-dose statin therapy (80 mg of atorvastatin) and conventional-dose statin therapy (20 mg of simvastatin) were obtained from the 2005 listed wholesale costs. This study demonstrated a net benefit of 0.35 QALYs in patients with a history of ACS and 0.1 QALYs in patients with stable CHD with a high-dose statin therapy strategy. The ICER was $31,000 per QALY for ACS and $33,400 per QALY for stable CHD.

Heart Protection Study Collaborative Group (2009)

This study used Heart Protection Study (HPS) clinical outcomes from the UK and US estimated health care costs to estimate the cost-effectiveness of initiating statin therapy in those with various levels of incident ASCVD risk ranging from 12 to 42 % (or from 8 to 39 %, Framingham risk score) [21]. The 20,536 HPS study participants had an LDL-C level of at least 135 mg/dL and a medical history of CHD, stroke, or other occlusive arterial disease, type 2 DM, or treated hypertension, and were randomized to receive either simvastatin (40 mg) or placebo. Although the 2006 wholesale average US price was approximately $5.25 per day, this study used a daily price of simvastatin of $1 to estimate future costs when simvastatin would become generic [21]. The HPS demonstrated that statin therapy produced a highly significant 25 % reduction in incident major vascular events, with similar effects observed across the risk subgroups. For all subgroups, the initiation of statin therapy was cost-effective using cost per QALY. Further analysis and extrapolation suggested that initiation of statin therapy for those with 5 % risk of a major vascular event was also cost-effective, with an estimated ICER of $20,220 per QALY [21].

Mullins et al. (2008)

Mullins et al. [22] created a 7-year cost model incorporating data from the Aggressive Lipid-Lowering Initiation Abates New Cardiac Events (ALLIANCE) study to determine the cost-effectiveness of a more intensive lipid-lowering therapy for patients with cardiovascular disease. The ALLIANCE study was a randomized controlled but open-label multicenter trial of 2,442 patients with established CHD who were treated to an aggressive LDL-C target with 80 mg of atorvastatin versus a usual care arm. Usual care was defined as any treatment deemed appropriate by their regular physicians, and the primary end point of cardiovascular events included cardiac death, nonfatal MI, resuscitated cardiac arrest, cardiac revascularization, and unstable angina requiring hospitalization [23]. ALLIANCE showed that the higher-intensity statin treatment resulted in fewer cardiovascular events (hazard ratio

0.83; 0.71–0.97, p=0.02), with a number needed to treat of 11 to prevent a cardiovascular event over a 7-year period [23]. In the cost-effectiveness analysis, drug costs were estimated using the 2007 wholesale average price minus 15 %. This analysis estimated an incremental cost-effectiveness ratio of $10,344 per event avoided. This study was unique since it reported cost-effectiveness in terms of cost per event avoided as opposed to the more typical cost per QALY ratio.

Diabetes Mellitus

For type 1 or type 2 diabetic patients aged 40–75 years, the new ACC/AHA cholesterol guidelines recommend a moderate-intensity or high-intensity statin therapy for primary prevention if the estimated 10-year ASCVD risk is greater than 7.5 % [1••]. The use of moderate-intensity statin therapy in this group was given a level of evidence of IA, and the use of high-intensity statin therapy was given a level of evidence of IIA, mainly driven by the expert consensus [1••]. Studies have shown that statin therapy in patients with type 2 DM with normal LDL-C levels has reduced the risk of incident ASCVD [24, 25].

Ramsey et al. (2008)

To estimate the cost-effectiveness of atorvastatin as primary prevention against cardiovascular disease, a Markov model was developed using clinical data from the Collaborative Atorvastatin Diabetes Study (CARDS), a study that demonstrated atorvastatin reduces incident CHD and stroke in patients with type 2 DM and normal LDL-C levels [24]. The clinical costs were valued at 2005 US prices, and the cost of atorvastatin was based on the wholesale acquisition cost. Ramsey et al. [26] found that in patients with type 2 DM and one additional risk factor (retinopathy, albuminuria, current smoking, or hypertension), atorvastatin was cost-effective at 10 years ($3,640 per QALY) and cost-saving at 25 years, but provided less value in the short term ($137,276 per QALY at 5 years) [26].

Intermediate Risk

The 2013 ACC/AHA guidelines recommend initiating a moderate-dose to high-dose statin therapy if a patient's estimated 10-year risk of ASCVD is greater than 7.5 %, as estimated by the new pooled cohort equations including the risk factors of age, gender, ethnicity, total cholesterol, HDL, systolic blood pressure, diabetes, smoking, and hypertension treatment [1••].

Ohsfeldt et al. (2010)

Ohsfeldt et al. [27] used a probabilistic Monte Carlo simulation model to estimate the long-term cost-effectiveness of rosuvastatin therapy in a hypothetical cohort of 100,000 patients with an estimated Framingham risk greater than 10 % versus no treatment. The clinical data were estimated from the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) clinical results. Prescription drug costs were estimated on the basis of the wholesale average cost as of 2009 for rosuvastatin—approximately $3.59 per pill. All treatment cost estimates were standardized to 2008-equivalent dollars. Per this model, approximately 12,073 cardiovascular events were avoided over the lifetime of patients, including 6,146 nonfatal MIs, 2,905 nonfatal strokes, and 4,030 cardiovascular disease deaths avoided. The model had a 1-year fixed time frame advance and the patients remained in the model/stage until they had an event, died, or reached 100 years of age [27]. With use of the 2009 branded drug prices, the ICER was $11,030 per QALY over the lifetime, and $15,502 per QALY over a 20-year period [27]. The researchers also ran a simulation assuming that rosuvastatin would eventually become generic after 9 years with an 80 % price reduction. With use of this assumption, rosuvastatin in primary prevention for an intermediate-risk individual had an ICER of $7,062 per QALY.

High LDL Level

The 2013 ACC/AHA guidelines recommend initiating statin therapy for adults older than 21 years with an LDL-C level greater than 190 mg/dL. Genetic screening and investigation of secondary causes are recommended. This group was often not included as part of the trials, and there are no cost-effectiveness data to review.

Policy Implications

Assuming a 25 % relative risk reduction with statin therapy in primary prevention, approximately 475,000 cardiovascular events would be prevented, with more than 90 % of the benefit occurring among older adults [4, 28]. That being said, there will certainly be added costs to the health care system and, per a systematic review on statin cost-effectiveness, drug price seems to be the primary determinant of statin cost-effectiveness [29]. As more statins become generic and less costly,

expanded treatment may become more cost-effective [29]. Furthermore, the general increases in medical costs as technology advances [30] may further tilt the cost-effectiveness analyses toward favoring primary and secondary prevention statin therapy. If at least half the gain in life expectancy is due to improved medical care [30], then perhaps a higher "willingness-to-pay" estimate for health is needed for our cost-effectiveness models. With a higher cost-effectiveness threshold such as $100,000 per QALY, treatments such as statins for primary prevention to prevent incident ASCVD risk would be more convincingly cost-effective.

The recent expansion in health insurance coverage through the Affordable Care Act provides more people with access to care and cardiovascular disease prevention. With the new ACC/AHA cholesterol management guidelines, the population treated with statins could rise dramatically and, given the benefits and risks of statin therapy initiation, patient-centered decision-making will be key [31, 32]. At a patient level, the ACC/AHA guidelines are clear about the primary and secondary prevention benefits of statins for patients at higher cardiovascular risk. At a population level, the cost-effectiveness analyses show that for primary prevention, and clearly for secondary prevention, treatment with statins is consistent with other health technologies that our society values and deems appropriate. Thus, the question of whether to initiate statin therapy sits, as it should be, with the patient and the patient's physician, weighing benefits, risks, and preferences for that individual patient.

Conclusions

With use of the recommendations from the 2013 ACC/AHA guidelines on the treatment of blood cholesterol, statins for secondary prevention and the four primary prevention statin benefit groups generally meet societal acceptable levels of cost-effectiveness. In the evolving health care environment, cost-effectiveness studies will need to be reassessed as risk factor profiles change, more statins become generic, and new cardiovascular treatments become available.

Compliance with Ethics Guidelines

Conflict of Interest Roderick C. Deaño, Ankur Pandya, Erica C. Jones, and William B. Borden declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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