VIEWPOINT

More Than a Billion People Taking Statins? Potential Implications of the New Cardiovascular Guidelines

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The American College of Cardiology/American Heart Association (ACC/AHA) guidelines on assessment of cardiovascular risk[1] and on treatment of blood cholesterol, which included recommendations for primary prevention with statins,[2] came under intense criticism immediately with their release. Main concerns focused on flawed methods (problems with the risk calculation),[3] ethics (conflicts of interest),[4] and inferences (too many people offered treatment).

The ACC and the AHA are among the most experienced organizations in medicine that develop guidelines. Their processes are meticulous, including transparent reporting of conflicts. The work behind the guidelines' development was monumental. References to randomized trials and systematic reviews were continuous (the word "evidence" appears 346 times in the cardiovascular risk assessment report and 522 times in the treatment report alone). Panelists were highly qualified. Statins have been extensively evaluated in numerous randomized clinical trials. The guidelines focused on hard clinical outcomes such as myocardial infarction and stroke. Remaining caveats were explicitly acknowledged in documents covering hundreds of pages. However, this apparently seasoned integration of data and opinion eventually would lead to massive use of statins at the population level; ie, "statinization." It is uncertain whether this would be one of the greatest achievements or one of the worst disasters of medical history.

According to the ACC/AHA guidelines[1,2] of the 101 million people in the US population without cardiovascular disease and aged 40 to 79 years, 33 million are expected to have a 10-year predicted risk of cardiovascular disease of 7.5% or higher (ie, high-intensity statins are recommended) and another 13 million are expected to have a predicted risk between 5% and 7.4% (ie, statins should be considered). The US population is approximately one-twentieth of the global population in this age range. If crude distributions of risk profiles were similar, on average, around the globe, a rough estimate would suggest that (33 + 13) × 20 = 920 million people would be classified in the same risk categories. This is probably an underestimate. Accounting for population growth, an increasingly aging population in developed countries, and increasing prevalence of cardiovascular risk factors in developing countries resulting in risk profiles worse than that of the United States,[5] these risk categories may already exceed or could soon exceed 1 billion people. These projections do not even count the hundreds of millions of patients who already have cardiovascular disease or extremely high low-density lipoprotein cholesterol levels and for whom statins demonstrate even better effectiveness.

Risk profiles and the importance of risk factors may well differ in other populations, and the ACC/AHA guidelines are very careful in avoiding such extrapolations.[1] However, unavoidably, extrapolations will happen. Prior experience shows that previous efforts such as the Framingham risk score and the Third Adult Treatment Panel (ATP III) guidelines were adapted and adopted widely around the world. Authoritative guidelines of this sort carry such prestige that they influence global treatment and marketing. Moreover, several statins are available as generic products and are relatively inexpensive, contributing to further pressure to "statinize" the planet even in countries with modest health care budgets.

The core of the ACC/AHA guidelines depends on a new risk score that was explicitly developed for the sake of informing US-oriented recommendations. Problems with this score have been noted,[3] and even its developers largely acknowledged them up front.[1] Based on the evidence of overprediction derived even in the original validation of the risk calculator and subsequent independent validations, perhaps about half of statin candidates may actually have a true 10-year risk of less than 7.5%.[1,3] However, there is large uncertainty about the extent of any overprediction, and the cohorts in which the model was developed and validated may differ compared with current populations. Here, several important factors must be considered. First, after 30 years of work and hundreds of cardiovascular predictors and models,[6] when the time came, the expert panel considered (probably correctly) that none of the models previously developed was good enough and had to develop a new one. Second, despite a plethora of candidate emerging predictors of cardiovascular risk, the model ended up selecting risk factors known since the 1960s: age, sex, race, lipids, diabetes, smoking, and blood pressure. Third, when looking at the granularity of the predictors (eg, how lipids should be represented), high-density lipoprotein cholesterol was selected even though it is clearly noncausally related to coronary artery disease,[7] an example of how highly significant predictors may have little to do with how treatment works. Fourth, even the new model was acknowledged by its developers as having major limitations.[1] Performance in external validation cohorts is clearly disappointing. Areas under the curve range from 0.56 to 0.71 (except for African American women) and calibration metrics (χ^2 of 15 to 67) are worse than almost any previously published cardiovascular model.[6] The development of the new model most likely was rigorous, and these disappointing

numbers are an accurate reflection of its performance. But what does this say about the credibility of all the other previous models that seemingly have superior (published) performance? It is concerning that after thousands of articles on cardiovascular prediction, this is the best that can be expected. Fifth, even though many randomized trials on statins have been published, there is no randomized evidence that this particular risk model, rather than any of its predecessors built with the same, similar, or other predictors, would identify the patients who benefit most from statin therapy and that the optimal treatment threshold is 5%, 7.5%, or even 2.5% or 15%. Information on potential statin harms (myopathy, diabetes, and more) is accumulating and concerning but also less systematically collected and thus carries more uncertainty than the benefits. The exact incidence of harms could markedly affect the optimal risk threshold for treatment.

Eventually, a leap of trust is needed to interpret clinically this excellent but convoluted and problematic modeling effort and its management implications—this was left to the otherwise excellent content experts who made the influential treatment recommendations. So, here, critics point out that 8 of the 15 panelists had industry ties.[4] Perhaps this is an improvement because almost all panelists who participated in the prior ATP III guidelines had industry ties. Moreover, the new guidelines often recommend more inexpensive therapies. However, should the very best content experts be the ones writing recommendations, making that delicate leap from the often fragmented or uncertain evidence to the actual dicta? Can the very best content experts ever be conflict free?[8] Critics have justifiably pointed out[4] that severing ties with the industry while working on the guidelines and promising not to have any industry ties for at least 2 years after the guidelines are published does not abolish conflicts. Even if all expert panelists have no financial industry ties, the decisions they make may affect how many patients will visit preventive cardiology clinics and influence patient activity in these divisions. The debate over the ACC/AHA guidelines offers an opportunity to rethink the membership of these influential panels. As articulated by the American Cancer Society and as recommended by the Institute of Medicine, the American Cancer Society will separate the processes of specialty input and evidence synthesis from writing of the actual guideline.[9] Perhaps these panels should include knowledgeable patients who are well versed in understanding the scientific background (eg, predictive models), many methodologists (ideally working in different applied fields), and excellent clinicians/scientists from other specialties whose practice volume is not at stake. Content experts could serve as nonvoting members or advisors to such panels.

The ACC/AHA guidelines demonstrate that even in a topic area with extensive amounts of data and published clinical trials, crucial evidence is still missing. The definitive way to test the recommendations is to subject them to randomized experimentation. The new proposed model could be compared against other models or approaches in its ability not only to predict risk accurately but also affect patient outcomes.[8] The proposed strategy could also be compared against different strategies where treatment is recommended at different thresholds. With potentially more than 1 billion people caught in the statin dilemma, there should be hundreds of thousands of interested participants for such trials. With expanded target populations and more affordable generic prices, the cumulative global sales of statins may approach $1 trillion by 2020. Lipitor sales alone exceeded $120 billion between 1996 and 2011. Therefore, funding for trials to demonstrate the best predictive model and treatment threshold should be negligible compared with the accumulated profit from statins and the millions of lives and deaths at stake.

ARTICLE INFORMATION

Published Online: December 2, 2013. doi:10.1001/jama.2013.284657.

Conflict of Interest Disclosures: The author has completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

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