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Perspective on Trends in Statin Use

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Since their introduction in the 1990s, statins have become the most common class of prescription medications in the United States.[1] Statins work by blocking the critical pathway in the synthesis of cholesterol in the liver. This leads to increased expression of the low-density lipoprotein (LDL) receptor and a significant reduction in LDL cholesterol. Elevated LDL cholesterol level can be considered a true surrogate for downstream development of cardiovascular events.[2] Multiple agents have been shown to reduce events in proportion to LDL reduction.[3] Multiple clinical trials and meta-analyses have conclusively demonstrated that therapy with statins in appropriate patients will reduce cardiovascular events.[4] The patients appropriate for statin therapy have been broadened from secondary prevention in patients with prior cardiovascular events to primary prevention in patients at elevated risk.[5] While there have been some concerns over myalgias and a slight increase in the incidence of type 2 diabetes, statins have proven to be safe and effective.[6] Statins also have proven to be cost-effective in appropriate patients (ie, providing good value), using generally accepted willingness-to-pay thresholds.[7] The most recent guidelines for lipid-lowering therapy would also increase the number of patients considered appropriate for statin therapy.[5] Nonetheless, there has been concern about the cost to society of prescribing a medication so widely.

The article in this issue of *JAMA Cardiology* by Salami et al[8] provides additional perspective on this issue. The authors examined trends in statin use, as well as total and out-of-pocket expenditures associated with statin prescriptions from 2002 to 2013 in US adults. Demographic, medical conditions, and prescription information for adults older than age 40 years were obtained from the Medical Expenditure Panel Survey database. The authors estimated trends in statin use and total and out-of-pocket expenditures in the general adult population, those with established and at risk for atherosclerotic cardiovascular disease. Costs were adjusted to 2013 dollars using the Gross Domestic Product Index. Statin use increased 79% from 21.8 million individuals (17.9%) in 2002–2003 (134 million prescriptions) to 39.2 million individuals (27.8%) in 2012–2013 (221 million prescriptions). Among patients with established atherosclerotic vascular disease, statin use was at 49.8% and 58.1% in 2002–2003 and 2012–2013, respectively, although less than one-third was prescribed a high-intensity statin. Of import, statin use was significantly lower in women, racial/ethnic minorities, and the uninsured. However, the proportion of generic statin use increased substantially from 8.4% in 2002–2003 to 81.8% in 2012–2013. Furthermore, the

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gross domestic product–adjusted total cost for statins decreased from $17.2 billion (out of pocket cost, $6.9 billion) in 2002–2003 to $16.9 billion (out of pocket cost, $3.3 billion) in 2012–2013. The mean annual out-of-pocket costs for patients decreased from$280 to $94. The authors are to be congratulated for this clear, succinct, and timely evaluation of statin use in the United States.

Overall, these are welcome data revealing that millions of patients are being treated with life-prolonging therapy and that the costs are decreasing. Overall, mortality from cardiovascular disease has fallen some 70%fromits peak in the late 1960s.[9] Undoubtedly, statins have played an important role in this development. Nonetheless, there are concerning issues raised in this article. In particular, the lower use of statins across subgroups in women, racial/ethnic minorities, and the uninsured reflects unacceptable health care disparities in our society. Also, it is clear that not all appropriate patients are being treated with statins, such that just a bare majority of patients with established atherosclerotic vascular disease are taking therapy. The data in this article reflect a set of cross-sectional analyses, and thus cannot address the issue of adherence, a well-known problem with statins.[10] Whether adherence has improved over time is uncertain.

There also are patients who are statin intolerant. Now, many of these patients who have myalgias while taking statins have no difference in myalgia incidence when taking placebo. Nonetheless, there are patients who will not or cannot take statins. There are also patients who will not achieve an adequate response of the LDL cholesterol level while taking statins. Ezetimibe, which prevents the intestinal reabsorption of cholesterol, is an effective medication, shown to decrease cardiovascular events in a secondary prevention population taking statins.[11] Ezetimibe as monotherapy is the only LDL-lowering medication that has not been shown to decrease events, and its effect on LDL cholesterol is modest compared with statins. The newest drugs in the arsenal are the PCSK9 inhibitors. They function by inhibiting PSCK9, which causes degradation of the LDL receptor on the hepatocyte. These parenteral medications, taken approximately every 2 weeks, will have a profound effect on LDL cholesterol either alone or in combination with statins. Preliminary data from randomized trials also suggest that PCSK9 inhibitors will reduce events, and definitive trial data are expected in the next several years.[12] Simulation data suggest the PSCK9 inhibitors, which cost $12000 to $14000 a year in the United States, are unlikely to be found cost-effective at societally acceptable willing-to-pay thresholds.[12] The PSCK9 inhibitors story is just beginning, and their place will depend on further developments.

At present, statins will remain the dominant form of pharmacotherapy for elevated LDL cholesterol levels. A major issue will be when to test asymptomatic patients and when to begin therapy. A critical concept is lifetime exposure to elevated LDL cholesterol. Mendelian randomization data suggest that patients have risk proportional to genetically determined LDL exposure.[13] This suggests that early intervention with statin therapy may be appropriate, although the details in young people of when and in whom to treat are not clear. In any case, increasing use of generic statins will lower overall societal costs compared with patent-protected prices.

A major issue is the large and increasing burden of cardiovascular disease in the developing world. Cardiovascular disease is now the number 1 cause of death in most of the world, and the higher incidence of cardiovascular disease in developing countries also occurs at an earlier age than in developed countries.[14] Generic statins will have a critical role in the developing world, but even with generics, there will be concern over cost, and the public health infrastructure to screen populations and make statins widely available generally does not exist.[15] Here is a major worldwide health care issue, currently receiving insufficient attention.

The article by Salami et al[8] provides good news concerning increasing use of statins, movement from patent protected to generic statins, and decreasing costs. However, much needs to be done to achieve higher use in appropriate populations, increase adherence, reduce disparities, appropriately incorporate new therapies, address appropriateness of therapy in young people, and address how to provide care to all people around the world.

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