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The 2013 cholesterol guideline controversy: Would better evidence prevent pharmaceuticalization?☆

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ABSTRACT

Cardiovascular disease (CVD) remains the leading cause of death globally. A class of medications, known as statins, lowers low-density lipoprotein cholesterol levels, which are associated with CVD. The newest 2013 U.S. cholesterol guideline contains an assessment of risk that greatly expands the number of individuals without CVD for whom statins are recommended. Other countries are also moving in this direction. This article examines the controversy surrounding these guidelines using the 2013 cholesterol guidelines as a case study of broader trends in clinical guidelines to use a narrow evidence base, expand the boundaries of disease and overemphasize pharmaceutical treatment.

We find that the recommendation in the 2013 cholesterol guidelines to initiate statins in individuals with a lower risk of CVD is controversial and there is much disagreement on whether there is evidence for the guideline change. We note that, in general, clinical guidelines may use evidence that has a number of biases, are subject to conflicts of interest at multiple levels, and often do not include unpublished research. Further, guidelines may contribute to the "medicalization" or "pharmaceuticalization" of healthcare.

Specific policy recommendations to improve clinical guidelines are indicated: these include improving the evidence base, establishing a public registry of all results, including unpublished ones, and freeing the research process from pharmaceutical sector control.

Cardiovascular disease (CVD) remains the leading cause of death globally, and prevention of CVD is a priority in world health systems. Prevention focuses on the reduction of risk factors such as an unhealthy diet, inadequate exercise, obesity, and smoking, as well as reduction in total blood cholesterol and the low density lipoprotein (LDL) portion of cholesterol.

Several decades ago a class of pharmaceuticals, HMG-CoA reductase inhibitors – commonly known as statins – were found to have a significant impact on cholesterol, particularly LDL. Statins have been recommended for both

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secondary prevention of CVD (individuals with known CVD, so prevention focuses on reducing further development of the disease and complications), and primary prevention (those without CVD but with risk factors for the disease, including certain levels of cholesterol or LDL). Since their entry into the U.S. market in 1987, the utilization of statins has skyrocketed. Between 2007 and 2010 statins were the most commonly prescribed therapeutic class in the U.S. [143]. According to the U.S. Centers for Disease Control and Prevention, in the last two decades statin use in the U.S. increased seven-fold among adults age 45–64 [1].

Statin utilization has been guided by clinical protocols. In the U.S., the National Cholesterol Education Program issued Adult Treatment Protocol (ATP) reports in 1988, 1993 and 2001, each one recommending a successively broader application of statins to the population [2]. The newest guidelines in the U.S., issued in 2013 by the American College of Cardiology and the American Heart Association (ACC/AHA), simplified some of the older guidelines and added risk categories [3]. More importantly, however, they contain a controversial new threshold and calculation of risk that would greatly expand the number of individuals that should be placed on statins [4].

A thorough understanding of this controversy has become even more important given two new lipid-lowering medications, Repatha (Evolocumab) and Praluent (Alirocumab), approved by the U.S. Food and Drug Administration (FDA) for marketing. Medications in this new class (PCSK-9 inhibitors) appear to be capable of lowering LDL below even that of statins, and (in a post hoc study) of reducing the incidence of cardiovascular disease [5]. They are being promoted for the care of patients whose LDLs are not adequately lowered by statins, and for those who do not stay on statins due to their side effects. However, to date, the effects of the new medications are based on just a few trial studies with surrogate outcomes [5], and the medications are far more expensive than statins [6]. If the 2013 guidelines become widely accepted and lipid-lowering continues to be called for in low-risk individuals, it is very possible that the new class of medications will be necessary to achieve that lowering and could become part of the next generation of lipid-lowering guidelines.

This article examines the controversy surrounding the 2013 cholesterol guidelines. We use cholesterol guidelines as a case study to address the broader issues of clinical guideline development, including the quality of evidence and conflicts of interest embedded in guideline recommendations. The evidence presented suggests a link between the clinical guideline evidence-base and the expansion of disease categories, "medicalization" and "pharmaceuticalization" of health and illness in the U.S. and other countries. Policies are recommended for future clinical guideline development.

1. 2013 U.S. guideline controversy

The 2013 ACC/AHA cholesterol guidelines recommend statins for both secondary and primary prevention of CVD. For secondary prevention the guidelines recommend statin use in anyone who has had heart or peripheral vascular disease, angina, heart bypass or angioplasty, and stroke or transient stroke (TIA) [3]. Statins are recommended for primary prevention for those: between 40 and 75 years of age with type 1 or 2 diabetes; over 21 years of age with LDL of 190 mg/dl or more; and 40–75 years of age with a 7.5 percent or higher risk of developing CVD (heart attack or stroke) within 10 years. The risk calculator is based on age, gender, race, total cholesterol, High Density Lipoprotein (HDL), systolic blood pressure level, and current blood pressure medication status [3].

It is mainly the calculation of risk and the recommendation for starting statin therapy for primary prevention at ≥7.5 per cent risk of CVD within 10 years that has been controversial. Several studies show that the risk calculator overestimates the risk of CVD by 50% or more [7–10]. As far as the threshold, some consider it to be "aggressive," and point out that guidelines in other countries have higher thresholds, as for example the most recent ones in the U.K. and Australia, which are set at 10% over 10 years and 10–15% over 5 years respectively [11]. Estimates indicate that this aspect of the U.S. guidelines would broaden the use of statins for those between the ages of 40 and 75 by 25–30% [4,12,13]. In practical terms, it is estimated that the new guidelines would recommend statin therapy for nearly all men > 60, women > 69 years [7,14], and all African American men over the age of 65 with *normal* blood pressure and cholesterol levels [15].

Proponents of the 2013 guidelines point out that the recommendations for statin use in lower risk populations are based on randomized controlled trials (RCTs) of statin efficacy. Two large meta-analyses of statin RCTs, both before [16] and after [17] the guideline change, also support the change. The first review, published in 2012 by the Cholesterol Treatment Trialists' Group (CTT), found that in low risk individuals (five-year risk of major vascular events <10%) a reduction in LDL due to statins was associated with an absolute reduction in the risk of major vascular events and all-cause mortality. The second review, published in 2014 in the Cochrane Collection of Systematic Analyses, used study-level results, including those from the CTT analysis, and found that non-fatal CVD events and all-cause mortality were reduced with the use of statins in individuals with no prior history of CVD. Some post-guideline studies have found the new guidelines to be better at predicting indicators of CVD such as blood vessel plaque [18,19] and coronary artery calcification [20], and to be more accurate in identifying increased risk of CVD incidents, particularly in intermediate-risk participants [20].

These studies represent a degree of support for the new guidelines, but critics of the guidelines charge that there are a number of issues with this evidence. First, the risk categories in the 2013 guidelines are not the same as those studied in RCTs, including the meta-analyses, so it is impossible to apply outcomes in the studies to individuals under the new guidelines. Second, while RCTs have found statins to be efficacious for those with CVD or high risk of CVD, there is less evidence that they are effective in lower risk populations, especially older adults [2,21–24]. This is especially true for the most important outcomes of statin therapy – lower all-cause mortality, few side effects or adverse events, and positive patient-reported outcomes such as good quality of life [22,25]. CTT claims of