Utilization of Statins: Guiding Principles and the New United States Guidelines

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Despite remarkable declines in mortality, cardiovascular disease (CVD) will remain the major cause of premature death in the United States and is becoming the major cause of premature deaths worldwide [1]. The small-to-moderate net benefits of statins in the treatment and prevention of CVD are statistically significant and clinically important for this common and serious disease [2]. There is a large, robust, and consistent totality of evidence that includes cogent findings from basic research, descriptive and observational analytic epidemiological studies as well as large-scale randomized trials [3]. For the reliable detection of small-to-moderate effects, randomized evidence is crucial because the amount of uncontrolled and uncontrollable confounding inherent in all nonrandomized design strategies may be as big as the effect sizes [4]. Randomized evidence is necessary to develop guidelines which have recently been revised and widely disseminated throughout the USA [5]. We believe that such guidelines are necessary but not sufficient for astute clinical judgments. In this manuscript we prefer general guiding principles to further aid the clinician to making the best individual judgment after weighing the benefits and risks of a statin in light of the entire risk profile of the patient. The benefits and risks of statins have recently been updated in comprehensive worldwide meta-analyses of large-scale randomized trials designed a priori to test the hypothesis in secondary prevention patients as well as high-risk primary prevention subjects [6].

The meta-analyses include individual participant data from 26 randomized trials of about 170,000 secondary prevention patients and high-risk primary prevention subjects. Those assigned at random to a statin had statistically significant and clinically important reductions in myocardial infarction of about 30%, stroke of 15%, the need for stents

and coronary artery bypass grafts of 25% and coronary death of 22% [6]. In subsequent analyses of an additional 40,000 patients randomized to more or less intensive statin therapy, those assigned to more intensive statin therapy achieved greater benefits. A more recent subgroup analysis was conducted among the randomized subjects with a 5-year risk lower than 10%. Their mean risks were 2.6% for major coronary events plus 3% for other major vascular events, even in those with no previous history of vascular disease, diabetes mellitus, or chronic kidney disease. Thus, these low-risk subjects had a 10-year risk of vascular events of less than 20%, which corresponds to a 10-year risk of coronary events of less than 10%. The results in these low-risk subjects were markedly consistent with secondary prevention patients and high-risk primary prevention subjects [7]. The hypothesis that statins are effective and safe for such subjects is being tested in a large-scale trial designed a priori to test the hypothesis [8]. Meanwhile, however, these findings add importantly relevant information to any individual judgment by the clinician as to whether to prescribe the drug to any such low-risk subjects [9].

In patients and subjects in every risk category, the size of the proportional reduction in major vascular events is directly proportional to the absolute reduction in low-density lipoprotein (LDL) cholesterol that is achieved. In addition, there is no threshold for LDL cholesterol below which there are no further benefits. These findings suggest that the primary goals for patients at high and moderate risk of occlusive vascular events should be to achieve the largest LDL cholesterol reduction possible. Further, the data show that this can be achieved without any material increases in the risk of myopathy. Finally, they also indicate that greater reductions in LDL cholesterol produce

additional benefits on CVD events without any increases in risks of cancer or nonvascular mortality [6, 7, 9].

In the new US guidelines [5], the algorithm used to calculate risk is based on a pooled cohort which included participants from several large racially and geographically diverse US National Heart Lung and Blood Institute-sponsored cohort studies including the Atherosclerosis Risk in Communities Study, the Cardiovascular Health Study, and the Coronary Artery Risk Development in Young Adults Study combined with applicable data from the Framingham original and offspring study cohorts. Nobody would disagree that any such risk calculator can be extremely valuable to any clinician to allow him or her to discern between high, moderate, and low risk. With regard to the precise quantification of risk, however, it is also important to note that the final decision about whether to prescribe a statin should be based upon the astute judgment of the clinician following a review of the totality of evidence. For example, obesity and physical inactivity are major risk factors for CVD but are not included in the risk algorithm. The clinical importance of this issue relates to the fact that about 40% of the US population over the age 40 has metabolic syndrome, a constellation of obesity associated with dyslipidemia, hypertension, and insulin resistance. In addition, subjects with metabolic syndrome have a 10-year risk of a first coronary event of 16–18% so statin therapy should be an integral component of a multifactorial approach to their management which should include therapeutic lifestyle changes (TLC) [2].

We believe that the current totality of evidence provides clinicians with challenges and opportunities to more widely prescribe statins in the treatment and prevention of CVD [8]. In secondary prevention and high-risk primary prevention, the challenge is to more widely prescribe statins as the first-line drug of choice. In low-

risk primary prevention subjects previously considered ineligible, the data provide clinicians with the opportunity to consider statin therapy. The current large, robust, and consistent totality of evidence suggests that more widespread and appropriate utilization of statins, as adjuncts, not alternatives to TLCs, will yield net benefits even in low-risk primary prevention subjects unwilling or unable to adopt TLCs. We also believe that any decision to prescribe statin therapy should be an individual clinical judgment that includes all the risk factors of the patient, not just those in any risk algorithm. Finally, we believe that utilization of these guiding principles should lead to greater and more appropriate utilization of statins. This, in turn, will lead to even greater net clinical and public health benefits in the treatment and prevention of CVD.

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