Statin therapy: reduction in cardiovascular events still pays in new-onset diabetes

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With a few exceptions [1], in the past two decades the benefit of statin therapy has been reproducible irrespective of the individual drug, population subset or prevention strategy (i.e., primary or secondary) used [2]. In addition to the established benefits, the decision to use statin therapy has recently been reinforced by the introduction of generic formulation drugs (i.e., simvastatin, lovastatin and pravastatin) in the market. Accordingly, the need for expanding the indications was met in the 2011 European Society of Cardiology (ESC) guidelines for the management of dyslipidemia [3]. These guidelines confirm that patients with a risk score of ≥10%, those with established cardiovascular disease (CVD), type II or I diabetes or chronic kidney disease have a class I indication, level of evidence (LoE) A to receive aggressive statin treatment in order to achieve low density lipoprotein cholesterol (LDL-C) levels of less than 70 mg/dl. In these guidelines, it is also recommended that a drug therapy with statins be considered in patients with a risk score of <1% who have LDL-C levels of ≥190 mg/dl (Class IIa, LoE A), and in those patients with a risk score from 1 to 5% who have LDL-C levels of 100–190 mg/dl (Class IIa recommendation, LoE A), or ≥190 mg/dl (Class I recommendation and LoE A).

However, recent data suggest that statin therapy is associated with an increased incidence of new-onset diabetes. The incident finding in large clinical trials [4–6] of increased new-onset diabetes was in fact confirmed recently in two well-conducted metanalysis [7,8]. The first one [7], including 91,140 patients, showed that, as compared to patients receiving placebo, patients receiving statin therapy had a 9% increase in relative risk for developing diabetes (odds ratio [OR] 1.09, 95% confidence interval [CI] 1.02–1.17). More specifically, 1 out of 255 patients would develop diabetes during a 4-year period of statin therapy. The second metanalysis [8] assessed whether, among those patients receiving statins, an intensive-dose treatment regimen would further increase the incidence of new-onset diabetes. Data from five clinical trials including 32,752 patients showed that, as compared to moderate-dose therapy, an intensive treatment strategy was associated with a further 12% increase in relative risk for developing new-onset diabetes (OR 1.12, 95% CI 1.04-1.22). Therefore, during a year of statin treatment, one out of 498 patients would develop new-onset diabetes if in the intensive treatment arm. However, on the other hand, 1 out of 155 of the same patient population would experience less cardiovascular events because of the intensive treatment. Although no plausible biological effects can yet be identified, the dose-dependence relationship observed in the

latter study further confirmed that statin therapy is associated with an increased risk for new-onset diabetes.

The status quo of statin therapy can therefore be summarized as follows: on one hand, as supported also by the availability of generic formulations and establishment of new guidelines, there is a strong willingness to extend treatment indications; however, on the other hand, there is also an increasing concern regarding the incidence of new-onset diabetes, particularly for the low risk patient population.

Given such statements, how is the clinician supposed to weight the benefits and risks of statin treatment in the individual patient?

Following the recent meta-analysis, another, very elegant study, that might actually help answer this question was published [9]. This study used an established computer simulation model to project cost-effectiveness of statin therapy in an era where a more aggressive statin treatment is being sought, low cost generic formulations are available and side effects such as new-onset diabetes are better defined. The authors found that lowering LDL-C thresholds to <130 mg/dl for patients with no risk factors and to <100 mg/dl for patients with one risk factor and treating all moderate and moderately high risk patients regardless of LDL-C levels would provide additional health benefits. Most importantly, these benefits were not negatively affected by the inclusion in the analysis of statin-associated diabetes or other severe hypothetical side effects.

In conclusion, as outlined by the recently published ESC guidelines [3], broadening of the indications to statin therapy appears reasonable. With regards to the individual patient, one should keep in mind that the odds of developing diabetes from statin therapy are lower than those of reducing cardiovascular events. Therefore, if the former occurs, statin therapy is theoretically supposed to provide a payback by reducing the risk for cardiovascular events, one of the major complications of diabetes. •

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