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Editorial

Should We Up the Intensity of Statin Therapy After Placing a Drug-eluting Stent?

¿Se debería intensificar el tratamiento hipolipemiante tras la implantación de un *stent* farmacoactivo?

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Statins, which act by inhibiting HMG-CoA reductase, have become one of the most integral components for the prevention and treatment of atherosclerotic cardiovascular disease (ASCVD). The benefits of statins are due not only to their ability to lower low-density lipoprotein (LDL) cholesterol, but also to other benefits that include improving endothelial function, reducing vascular inflammation, and reducing platelet adhesion and thrombus formation.10.1016/j.rec.2017.06.008

Statin use has consistently been shown to reduce ASCVD risk in both primary[1,2] and secondary[3–5] prevention trials. The efficacy of statin therapy across the spectrum of ASCVD has been linked to the magnitude of LDL reduction provided by these agents. As a result, in prior trials, statin dose has mattered, and higher-intensity statin therapy has been demonstrated to provide even more benefits than lower-intensity statin therapy. Higher-intensity statin therapy can more aggressively reduce the progression of atherosclerotic plaque.[6] In the Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22) trial, intensive therapy achieved results superior to those of standard therapy in reducing clinical events in patients with a previous acute coronary event.[7] Similarly, the Treating to New Targets (TNT) trial demonstrated fewer major adverse cardiac events in stable patients treated with 80 mg of atorvastatin compared with those treated with 10 mg of atorvastatin.[8]

Although statin therapy has been found to be beneficial for a broad range of indications, lower than expected numbers of patients are actually treated with these drugs. For example, prior studies have demonstrated that only a minority (only 18%-28%) of patients with acute coronary syndromes are given statins at discharge,[9,10] and in patients with stable or unstable angina undergoing either stenting or bypass, only 35% were treated with statins after the intervention.[11] Despite advances in guideline implementation and adherence, patients undergoing contemporary drug-eluting stent (DES) placement may also be undertreated with statin therapies and lifestyle modification more generally.

In a recent article published in *Revista Española de Cardiología*, Im et al. detail the results of a modest- to large-sized randomized trial assessing the ability of high-intensity statin therapy (compared with a lower-intensity statin therapy) to reduce late adverse events following DES implantation. While some might question the potential equipoise in randomizing the treatment of patients with established ASCVD to high- vs low-intensity statin therapy, the study investigators nevertheless randomized 2000 clinically stable patients who were on aspirin monotherapy and free of clinical events for 12 months following DES implantation.[12] Study participants were assigned to receive either high-intensity (atorvastatin 40 mg) or low-intensity (pravastatin 20 mg) statin treatment and were then followed up for adverse events over the following year.

The primary endpoint of the study was a somewhat unconventional composite of death, myocardial infarction, stroke, stent thrombosis, repeat revascularization, deterioration of renal function, intervention for peripheral artery disease, and readmission for "significant cardiac events". Despite the combination of a number of endpoints in the overall composite (presumably to increase study power), the primary endpoint occurred in only 65 patients: 25 (2.5%) treated with high-intensity statin therapy and 40 (4.1%) treated with low-intensity statin therapy. While the study authors list specific endpoints that drove the difference between groups, it is challenging to reach such clear conclusions given the myriad of endpoints included in the composite and the relatively low rate of events for each endpoint. Ideally, this trial would have followed up patients for a longer period, during which the likely benefits of higher-intensity statin therapy would have become more manifest.

The strength of the study lies in the considerable work done by the study investigators in executing a randomized trial examining an important area of secondary prevention among patients with established ASCVD. This has some degree of novelty as there are limited studies on the benefit of statins specifically after newer-generation DES implantation. The trial highlights the importance of statin therapy, particularly high-intensity statins, after DES implantation. Although 11 287 patients were excluded from the initial patient set of 13 287, with only 15% meeting the inclusion criteria, it is notable that the authors were still able to randomize 2000 patients to this trial.

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Given overwhelming evidence supporting the benefit of statins in preventing and treating cardiovascular disease, the question warranting further examination are the reasons why they might be underused in actual clinical practice.[13] The reasons for low use of established therapies such as statins may be multifactorial, including logistic, environmental, social, and cultural issues. For example, cost barriers, transitions in health care between inpatient and outpatient settings, loss of follow-up, concern about adverse effects, and cultural beliefs can all impact uptake of these therapies. Specific subgroups of patients–including the very elderly, those with chronic kidney disease, and patients undergoing dialysis–have been hypothesized to have lower benefits from intensive statin therapies.[14,15] Nonetheless, current guidelines support the use of high-intensity statins for patients with established ASCVD, such as those patients who have undergone percutaneous coronary intervention. Furthermore, serious complications from statin therapy are rare. The rate of liver toxicity is overall less than 1% but is slightly higher with higher intensity of statins: in the TNT trial, this complication occurred in only 0.2% of patients receiving 10 mg of atorvastatin and in 1.2% of those receiving 80 mg.[16] Rhabdomyolysis is also rare, although rates can be increased if statins are concomitantly used with other medications that affect the cytochrome P450 3A4 system.

Perhaps the greatest barrier to the use of statin therapies is the perception of other adverse effects, including muscle-related complaints or even cognitive dysfunction. Despite trials suggesting the limited effects of statins in these areas, the perception of a potential harmful or "nocebo" effect with statins may be profound. In the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm, the authors used the sequential blinded vs unblinded phases of the trial to study this effect.[17] In the blinded phase of the trial, most adverse effects were reported at a similar rate by participants treated with statins or placebo. In the nonblinded phase, muscle-related events were reported at a significantly higher rate among the statin therapy group than in the group not receiving statins, with no differences observed in other adverse events.

Ultimately this phenomenon might represent the greatest barrier to the more effective use of statin therapies. It remains to be determined whether further awareness and education of the overall benefits (and limited risks) of higher-intensity statin therapy could offset this perception. Efforts that lead to increased use of higher-intensity statin therapies for patients at highest risk–those with established ASCVD–are a public health imperative, particularly given the burgeoning growth of ASCVD worldwide.

CONFLICTS OF INTEREST

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