

Editorial

To Persist or Not to Persist: Learning From Precision Medicine to Optimize Statin Adherence



Cumplimiento terapéutico del tratamiento con estatinas: medicina de precisión para optimizar la adherencia

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It has become a truism to state that medication nonadherence is a major contributor to suboptimal health outcomes. In a recent review, failure to take medications as prescribed was estimated to cause 125 000 deaths and cost the health care system \$100 billion to \$289 billion US dollars annually.¹ Nonadherence to statin therapy is especially common, leading to increased cardiovascular morbidity and mortality.²⁻⁴ Despite growing recognition of the high prevalence and adverse impact of statin nonadherence, efforts to optimize statin adherence through interventions such as education, treatment support, and reminders have met with limited success.⁵

In a recent article published in *Revista Española de Cardiología*, Malo et al.⁶ demonstrate the high prevalence of nonadherence to statin therapy in a population of mostly young (average age 54.7 years), male Spanish factory workers without cardiovascular diseases. Of the 725 individuals in their sample who were newly started on primary prevention statin therapy, about 15% ceased statin therapy after just 1 prescription fill. Further, 70.5% had at least 1 major gap in statin refills at 1 year and, of those with a gap, about 42% represented true discontinuation without any reinitiation of statins for the remainder of the year-long observation period. The current manuscript expands our understanding of the scope of statin nonadherence by assessing the prevalence of nonadherence in a relatively understudied primary prevention population. Consistent with prior studies of correlates of nonadherence, younger age and lower comorbidity were associated with increased risk of nonadherence.⁷

The authors focused on “nonpersistence”, a specific form of nonadherence defined as a gap in statin prescription refills that is more than 56 days long (twice the period of a standard statin prescription in Spain). Their estimates did not include patients who did not fill their initial statin prescription. Prior studies have estimated that approximately 15% of patients newly prescribed statins never fill their prescription even once.⁸ In addition, their measure of nonadherence did not incorporate nonadherence due to intermittent discontinuation of shorter duration, often

measured through percent of days covered⁴ or cumulative multiple-refill gap.³ Furthermore, the authors were only describing 1 aspect of adherence behavior—obtaining medication refills. Their refill measure of adherence did not assess the extent to which pills were actually ingested, also known as implementation of the medication regimen.^{9,10} As such, there was likely underestimation of the full extent of nonadherence.

While the authors should be applauded for shining a light on the high prevalence of nonadherence to statins—a prevalence so high that clinicians should expect that a majority of their primary prevention patients will discontinue statins within the first year—we must not lose sight of the nuances of the specific patient context before deciding how to approach nonadherence. Nonadherence is commonly defined as the extent to which patients do not follow recommendations for prescribed treatments. For primary prevention statin therapy, there remains a tension between what guidelines recommend for treatment of a population vs what clinicians should do when applying these guidelines to individual patients. Although current guidelines specify categories of patients who may benefit from statins,^{11,12} the decision to start statin therapy at the point of care must take into account the heterogeneity of risks and benefits for individual patients. For instance, a 45-year-old woman with diabetes or a 60 year-old man with a Systematic Coronary Risk Evaluation (SCORE)-estimated 10-year cardiovascular mortality risk of 5% would both be eligible for statin therapy based on the 2011 European Society of Cardiology/European Atherosclerosis Society guideline for the management of dyslipidaemias,¹¹ but these patients may not consider themselves to be at high enough risk to outweigh the disutility they hold for taking a daily preventive medication.^{13,14} Furthermore, although statins are generally well-tolerated, adverse effects such as statin-induced diabetes and muscle or liver dysfunction may still occur.¹² Especially for primary prevention, development of such adverse effects can alter the risk-benefit calculus and lead to reconsideration of the appropriateness of persistence with statin therapy. In such scenarios, even when patients initially express willingness to try statin therapy, nonpersistence may actually reflect concordance with patient preferences and values. In other words, not all statin nonpersistence is inappropriate, and some statin nonpersistence may represent high-value patient-centered care.

Complicating the discussion of the relative costs and benefits of statin therapy, there is increasing evidence that patients may be

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arriving at a flawed understanding of the treatment effects. Most notably, adverse effects attributed to statins such as myalgia may not always be due to the biologic effect of statins. A recent, rigorously conducted N-of-1 trial¹⁵ as well as a secondary analysis of the Anglo-Scandinavian Cardiac Outcomes Trial¹⁶ both demonstrated that perceived muscle-related adverse effects frequently represent “nocebo” effects, ie, symptoms that are real but are due to expectation of harm. It is likely that this phenomenon, in part due to the frequent focus on adverse effects and treatment risk that accompany discussions of statins in the media, may inappropriately contribute to nonadherence. In these instances, patients may overestimate the “costs” of statin treatment, both before initiating and while taking statins. It is the role of a trusted clinician to help patients reach an accurate and balanced understanding of the risks of treatment.

To answer the central question of how we can address statin nonpersistence, it is worth considering the perspective of precision medicine, which advocates for “prevention and treatment strategies that take individual variability into account”.¹⁷ For statin therapy, the population-level risks and benefits as well as the science of cardiovascular risk estimation are well established. The imperative is now to apply patient-centered principles throughout the process of statin initiation and maintenance in which treatment recommendations are personalized to each patient, accounting for variability in patient values and preferences. For statin initiation, a shared decision-making approach that reviews the individual patient’s benefits and risks of statins and takes account of patient preferences is essential, and can potentially improve long-term adherence.¹⁸ Once statin therapy is initiated, assessment of adherence should be a routine part of follow-up care, through directly asking about day-to-day adherence in a nonjudgmental manner and by asking patients about medication concerns and adverse effects. As patients gain direct experience with statin medications, an iterative shared decision making process may be beneficial, since the risk-benefit profile of statins to individual patients as well as their understanding and perception of these issues can evolve over time. Health system approaches that involve flagging patients with a pattern of nonpersistent statin refills may be useful for identifying patients for adherence interventions. However, clinicians are encouraged to be mindful that not all nonpersistence represents inappropriate health behavior. The exploration of specific reasons for nonadherence can guide reassessment of the burden and benefits of statin therapy at the individual level, correct misperception of risk and misattribution of adverse effects symptoms, and address other factors such as cost and polypharmacy. Novel approaches, such as personalized (N-of-1) trials in which patients compare statins with placebo to disentangle nocebo effects from true adverse effects, have the potential to become powerful tools to provide objective data for guiding these discussions. Although much research remains to be done on how to standardize and implement these kinds of patient-centered approaches, we owe it to our patients to move beyond descriptive studies of nonadherence. It is time to embrace patient-centered perspectives that help us understand why patients stop taking medications and inform our efforts to support patients across the chronic disease management process.

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CONFLICTS OF INTEREST

None declared.

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