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How Do We Improve Patient Compliance and Adherence to Long-Term Statin Therapy?

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Abstract

Statins are highly effective drugs prescribed to millions of people to lower LDL-cholesterol and decrease cardiovascular risk. The benefits of statin therapy seen in randomized clinical trials will only be replicated in real-life if patients adhere to the prescribed treatment regimen. But, about half of patients discontinue statin therapy within the first year, and adherence decreases with time. Patient, physician and healthcare system-related factors play a role in this problem. Recent studies have focused more on the patients' perspectives on non-adherence. Adverse events are cited as the most common cause of statin discontinuation; thus, the healthcare provider must be willing to ally and dialogue with patients to address concerns and assess the risks and benefits of continued statin therapy.

Keywords

Statin; Adherence; Compliance; Patient–physician communication; Adverse events; Lipid-lowering

Introduction

Cardiovascular (CV) disease is the leading cause of death in the United States, accounting for about one in three overall deaths per year [1]. Treatments that lower LDL-cholesterol (LDL-C) decrease the risk for CV disease and 3-Hydroxy-3-methylglutaryl-Coenzyme A (HMG-CoA) reductase inhibitors, more commonly known as statins, are the most frequently prescribed medications to lower LDL-C levels. Despite the benefits shown for primary and secondary prevention of CV disease, adherence to statin therapy remains suboptimal [2, 3]. Improving adherence to statins has been a priority in recent years, with modest success. In this review, we report on recent studies on statin adherence [4••], the role of biomarkers and pharmacogenetic testing for increasing adherence [5], the importance of patient–physician communication to improve adherence, and types of interventions that may increase statin adherence [6•].

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The Role of Statins in CV Disease

By lowering LDL-C, statins have been shown to decrease CV events in both primary and secondary CV disease prevention trials [7-13]. The Cholesterol Treatment Trialists' (CTT) Collaboration showed that lowering LDL-C by 1 mmol/L reduced the incidence of CV events by around 20 %, and that further reductions in LDL cholesterol with more intensive statin regimens yielded further reductions in CV risk [14•, 15]. The Adult Treatment Panel (ATP) III guidelines set targets for LDL-C based on a patient's estimated 10-year risk of developing coronary artery disease (CAD). LDL-C levels above a specific number are considered to reflect increased risk, and are thus deserving of treatment [16]. Achieving the goal of LDL-C lowering involves lifestyle modification, and when warranted, pharmacologic therapy [17]. Combination therapies of statins with other lipid-lowering therapies (LLT) may be necessary for those at highest risk.

In the United States, the age-adjusted prevalence of high LDL-C in adults is 25.3 %, based on National Health and Nutrition Examination Survey (NHANES) data from 1999 to 2004 [1]. About 24 million Americans received statin treatment in 2003–2004, almost double the number in 1999–2000 [18], while an estimated 29.7 million filled 173.7 million statin prescriptions in 2005 [19]. The proportion of adults with high LDL-C who were on treatment increased from 28.4 % during 1999–2002 to 48.1 % during 2005–2008 [20]. The prevalence of LDL-C treated to goals increased in parallel, from 14.6 % to 33.2 % between the periods [20].

Clearly, the use of statins has increased, and it is expected to further increase because of intensification of LDL-C lowering goals, new indications for treatment (e.g. increased CRP; Apo B and LDL particle number (LDL-P),which are potential markers particularly for subsets of patients with cholesterol-poor LDL) [12, 21, 22], branded statins going generic, as well as recommendation of earlier age of lipid screening and treatment [23]. Statins have now become standard of care, so much so that clinical trials of new lipid lowering therapies are being done on top of statins rather than as stand-alone drugs [24-27]. Moreover, a recent meta-analysis of the CTT Collaboration reported that individuals even at low-risk for major vascular events (< 10 % in 5 years) benefit from LDL-C reduction, with a reduction in major vascular events of about 11 per 1,000 over 5 years for each 1mmol/L reduction in LDL-C [14•]. This population typically would not be treated with statins under present guidelines, but adoption of a lower (≥ 10 %) CV risk threshold for starting statin therapy would classify 83 % of men older than 50 years and 56 % of women older than 60 years in the UK as needing a statin [28].

The prevalence of elevated LDL cholesterol levels in adults > 20 years of age has decreased by ~33 % likely due to increased statin use [29]. Nevertheless, failure to prescribe statins properly or non-adherence to statins continues to prevent the maximal public health benefit from this effective drug class [18].

Adherence/Compliance/Persistence

The World Health Organization defines adherence as the degree to which the person's behavior corresponds with the agreed recommendations from a healthcare provider. Compliance is defined as the degree to which a patient correctly follows medical advice. Although related, "compliance" suggests that the patient is passively following the physician's orders, while "adherence" acknowledges that the patient is part of the decision-making process, making this the preferred term. Another frequently encountered word is "persistence," defined as the duration of time over which a patient continues to fill the prescription.

Adherence is a key factor associated with all pharmacological therapies. The CV benefits shown by statin treatment in randomized controlled trials (RCTs) can only be expected to provide similar clinical benefits in patients who follow the prescribed treatment regimen for a prolonged period, possibly even for a lifetime. However, 50% or more of patients discontinue statins within 1 year of treatment initiation, and more do so over longer time periods [30-32]. Among adults > 65 years, adherence to statins for primary prevention after two years was a dismal 25.4 %, while it was only slightly better at 36.1 % and 40.1 % for patients with chronic CAD and acute coronary syndrome (secondary prevention), respectively [3]. The situation might not be quite as bad as these numbers suggest, since some users only temporarily discontinue statin therapy. In one study, 53.8 % of new statin users had at least one extended period (at least 90 days) of non-adherence, but about 60 % returned to regular statin use within 2 years [33].

Non-adherence to medications is widely recognized as a major public health concern and contributes to patient morbidity, mortality and healthcare costs [34-36]. Compliance with statin therapy in the first 2 years of prescription may reduce hospitalization rates and direct medical costs in the subsequent year [37]. Shroufi and Powles [38•] recently performed a simulation study showing that improving adherence to statins by 50 % (from 50 % to 75 %) would prevent twice as many additional deaths compared to a strategy of lowering the CV threshold (from 20 % to 15.5 % 10-yr risk of CVD) for statin therapy. Therefore, improving adherence to statin therapy would be beneficial for patients and other healthcare stakeholders.

Is Adherence To Statins Different From Adherence To Other Medications?

In patients with documented CAD, Duke University researchers showed that consistent use of aspirin was 71 %, β-blockers 46 %, and statins 44 %, while adherence to all three therapies was only 21 % [39]. In diabetics, another study found statins were discontinued at a higher rate than oral anti-diabetic medications, particularly when statins were initiated after the anti-diabetic medications [40]. In this group, the more frequent checking of blood sugar compared to cholesterol levels may lead to better adherence to the anti-diabetes medications, especially if the value of statin therapy is not adequately explained.

Measuring Adherence

There is no recognized gold-standard method to measure adherence. There are direct and indirect ways to measure adherence, and a combination of these may be needed to accurately quantify adherence in actual practice. Direct methods include directly observing treatment, or measuring the concentration of the drug or metabolite or a biological marker added to the drug in blood or urine. However, these methods tend to be costly and burdensome [41, 42]. Indirect methods include questionnaires, pill counts, prescription refill rates, measurement of physiological markers (e.g. LDL-C levels), filling out a medication diary and electronic medication monitoring [41, 42]. These methods are thought to be less burdensome, but subject to distortion by the patient, which may result in overestimation of adherence. The prescription refill rate is a commonly used measure of adherence in a closed pharmacy system using insurance provider databases, but does not reflect actual medication intake [42]. Electronic medication monitors track patterns of medication intake by recording times when the medication bottle is opened, but this method also does not document actual ingestion of the pill or taking the correct dose. Two commonly used measures of medication adherence based on administrative claims data are the medication possession ratio (MPR) and proportion of days covered (PDC), which are defined by the number of doses dispensed in relation to a dispensing period [43]. A MPR or PDC ≥ 80 % generally corresponds to

good adherence for statin therapy [38•], but may not be appropriate for therapies of other conditions.

Causes of Non-Adherence

Adherence to medication for treatment of a symptomless condition, such as high LDL-C levels, is a challenge to both doctor and patient. Causes of non-adherence are complex and can be broadly classified into three categories: patient-related, physician-related and health system-related [44]. Among these, patient-related factors may be the strongest [45].

Patient-Related

Patient-related factors leading to non-adherence include low health literacy, lack of understanding of the disease being treated, attitudes concerning the effectiveness of the treatment, negative previous experience with pharmacological therapies, presence of psychological problems, and/or cognitive impairment [42, 44]. Forgetfulness plays a role, but underlying reasons often contribute to forgetfulness, including lack of prioritization of the importance of medication intake, medication as a reminder of the patients' condition, having to take medications making the patient feel old or bad about themselves, or simply not liking the idea of taking a pill. The shared decision-making between physician and patient that might improve adherence is often compromised by the latter's reluctance to disagree with the authority figure physician, and hence engage in a true dialogue of his/her concerns [46].

Statin non-adherence has been independently associated with younger patient age, female gender, lower incomes, and non-Caucasian race [30, 47], but these demographic predictors are not always reliable [32]. A meta-analysis showed that age as a predictor of non-adherence follows a U shaped curve, with the youngest (< 50 years) and oldest (≥ 70 years) showing lower adherence than those between 50–69 years [30, 31]. Not surprisingly, adherence to statins is better when patients have a history of CV disease and possess a number of CV risk factors other than elevated LDL-C [30, 48], but even in patients who have been diagnosed with CV disease, adherence to statin therapy remains poor [43]. Coexisting illnesses such as diabetes and hypertension may predict better adherence [30].

Because the patient ultimately makes the decision whether or not to take the medication, it is important to understand their perspectives on non-adherence to statin therapy. In a focus group of 18 participants, non-adherence was primarily due to concerns about or experiences with adverse events (AEs). Some of the concerns about statin AEs were due to information from the internet. Other concerns included uncertainty about the benefits or importance of statins, the inconvenience of taking a medication and getting laboratory tests done, wanting to drink grapefruit juice, which they were instructed to avoid, and preferring to take brand name statins instead of the prescribed generic statin [49]. A recently published study, the Understanding Statin Use in America and Gaps in Patient Education (USAGE) [4••], provided further insight into reasons for switching or discontinuing statins through an internet-based survey of 10,138 respondents. At the time of the survey, 88 % of respondents were statin users and 12 % were former users. Although 70 % of respondents reported their physicians explained the importance of lowering cholesterol levels for their heart health, former users were less satisfied than current users with their physician-provided information. Most importantly, the majority (67 %) of patients who stopped statins did so because of AEs.

AEs associated with statin treatment are dose-related and range from muscle-related side effects, cognitive and memory problems, and new-onset diabetes [50-52]. As the LDL-cholesterol-lowering goals of therapy become more stringent, larger doses of statins,

sometimes accompanied by other lipid-lowering therapies, will be required and as a result, the frequency of statin-associated AEs may increase. Recently, the Food and Drug Administration (FDA) added safety warnings of memory loss and cognition problems related to statin use, but stated that these are generally nonserious and reversible with discontinuation [53]. Also, the FDA has limited the use of the highest dose of simvastatin (80 mg) because of increased risk of muscle damage [54]. The JUPITER study found statin treatment associated with increased incidence of new-onset diabetes, especially in the high-risk subgroup with impaired glucose tolerance [55•]. The American Diabetes Association recommends yearly diabetes screening for patients with pre-diabetes [56], and whether those on statin treatment should be screened more frequently has not been determined. These recent warnings by the FDA about statin AEs and the recognition of new-onset diabetes associated with statin treatment may influence statin adherence.

Physician-Related

Complex drug regimens prescribed by physicians, lack of adequate explanation about the disease and the benefits and potential AEs of medications, and multiple physicians with inconsistent messages all contribute to medication non-adherence, and this is true for statins as well. Based on an administrative claims database, certain types of physician prescribers were associated with greater rates of statin adherence among their patients. The writing of the initial statin prescription by the patients' primary care physician, a cardiologist or a US medical graduate was noted as a predictor of improved adherence [45].

Healthcare-Related

The economics of the health care market place severely limits the time a physician can spend with an individual patient. This can interfere with adequate patient education about medications, assessment of medication-taking behaviors and encouragement of adherence to prescribed medication regimens. The involvement of several physicians and the necessity of multiple visits to pharmacies to fill/refill different prescriptions, including different refill dates for patients' prescriptions, predict worse medication adherence [57]. In the USAGE study, nearly half switched statins because of cost [4••]. Higher copayments are negatively correlated with adherence [45, 58], but this may become less of an issue as both simvastatin and atorvastatin have become available as generic drugs.

Interventions to Improve Adherence

Medication-taking behavior is complex. In general, about 33 % will be adherent to therapy just by being given a prescription and asked to take it by their physicians, while about 15–25 % will be non-adherent despite any intervention [32]. Thus, interventions to improve adherence are aimed at the middle 50 % of individuals who may adhere if given support and encouragement. The interventions to improve adherence are also divided into three groups focused on: the patient, health professionals, and the health delivery system. Strategies with some degree of success are multifaceted combinations of patient education, patient–physician communication enhancement, extended care through ancillary health care providers, simplification of drug regimens, and increased patient monitoring and follow-up, but these are labor intensive and expensive [38•, 42, 57]. More practical interventions are needed for use in routine clinical practice.

Interventions Focused on the Patient

In a recent review on improving adherence to lipid-lowering therapies, Schedlbauer, et al. [6•] found that the most promising interventions involved reinforcement and reminders to patients, which increased adherence by up to 24 %. Improving patient information and

education increased adherence by 13 % [6•]. In another study, patients suggested additional information about statins (reasons for prescription, benefits, risks), additional time for discussion with the clinician, and being provided written information about statin risks, side effects, and drug interactions would improve adherence to therapy. Again, reminders through the mail and telephone, as well as clarifying the need for follow-up, were also suggested [6•, 49]. A promising tool is the use of audio booklets (in English and Spanish), which were shown to increase patients' knowledge and understanding of statin medication, and is hoped to result in increased adherence [59].

In another study, it was hypothesized that the use of phytosterols in the diet, which lower LDL-C, might promote healthy behaviors, such as adherence to prescribed statins. However, users compared to non-users of phytosterol-enriched margarines were up to 2.5-fold more likely to discontinue statin therapy [60]. It is possible that patients who used phytosterols thought statins no longer necessary. In a follow-up study, when users of phytosterols-enriched margarines were educated about the importance of statin therapy, users and non-users of phytosterol-enriched margarines had comparable adherence to statin therapy [61]. Thus, healthcare providers must educate patients that functional foods should be adjuncts to and not replace their prescribed medications.

Pharmacogenetics and coronary artery calcium scores (CAC) are being examined for a possible role in adherence to statin therapy. The kinesin-like protein 6 (KIF6) 719Arg allele has been associated with increased risk of CV disease, and carriers of this polymorphism receive greater CV risk reductions from statin therapy than non-carriers [62-64]. The Additional KIF6 Risk Offers Better Adherence to Statins (AKROBATS) study was a prospective, nonrandomized interventional trial of the effect of KIF6 carrier status knowledge on statin adherence, based on PDC at 6 months. Two abstracts showed that providing the patient with KIF6 genetic information improves adherence to statin therapy, with 63 % of informed patients vs. 45 % uninformed patients remaining adherent to therapy [5, 65•]. A retrospective study showed that allowing patients to see calcium lining their arteries on CT scans may motivate them to adhere to statin treatment [66••]. Despite LDL-C lowering, residual CV risk remains and new biomarkers to improve CV risk prediction and as potential novel targets of therapy are being studied. Apart from CRP, other CV disease risk biomarkers such as Apo-B and LDL-P may become part of routine testing, and potentially provide increased motivation for statin adherence [22]. The cost/benefit of such additional tests would need to be determined.

Interventions Focused on Healthcare Delivery

Programs that have found success leverage information technology and patient data and tailor interventions towards patients' attributes. These programs also offer follow-up and patient support by healthcare professionals trained to work closely with patients to improve adherence [2]. Extended care by nurses through counseling on CV risk factors improved adherence to statin therapy in the Netherlands [67•]. Interventions that enlist ancillary healthcare providers, such as pharmacists and behavioral specialists, may provide additional motivation to patients. Pharmacists are uniquely positioned to interact at more frequent intervals with patients than other healthcare providers and can promote better medication-taking behaviors. They also have immediate access to medication refill information to ascertain medication adherence [35].

Healthcare providers can improve adherence by simplifying the process of filling prescriptions, by using a "pharmacy home" and by synchronizing refill dates to lessen the number of pharmacy visits [57]. Another approach is to mail medication refills to the patient at the appropriate time [49]. However, one study found that restricting pharmacy choice and

providing mandatory medication refills was associated with discontinuation of therapy compared to patients who chose voluntary mail service [68]. Another approach is to simplify the medication regimen by using once daily dosing, and in those with comorbidities, taking several medications using combination pills. The latter was associated with better adherence, higher persistence, lower cost and greater response compared to prescribing multiple individual medications [69, 70]. Simplification of the drug regimen increased adherence by 11 % in one study [6•]. Other strategies to improve adherence are using pillboxes to organize daily doses and cues to remind patients to take their medications.

A multifaceted randomized intervention study was undertaken in CAD patients to improve post-hospital discharge adherence to aspirin, β-blockers and statins. Of the 143 patients enrolled, half were randomized to usual care, and half to the intervention, which included patient education, adherence aids, and expanded communication links between hospital and community pharmacists, physicians and patients. Although there was no significant difference between usual care and intervention in adherence based on self-reporting, there was a trend toward increased adherence in the intervention group for β-blockers and statins based on prescription refill records [35]. The authors concluded that the trend toward increased adherence provided encouraging evidence to support further testing of multifaceted, combined hospital and community-based strategies to improve medication adherence.

Interventions Focused on the Physician and the Physician–Patient Relationship

The physician and patient must be partners in achieving the goals of therapy, and a key strategy is enhancing the dialogue between the physician and patient in order to better educate patients and clear up any misconceptions [71]. There is evidence that providing patients with comprehensive knowledge about statins, even to those who have already been on statin therapy, improves adherence and increases the number of people reaching LDL-C lowering goals [72]. Even brief CV risk counseling followed by mailings to continue patient education have been found useful [73, 74].

There is enormous potential to increase adherence by improving patient–physician communication. O'Malley [75] has criticized the trend towards excessive reliance on technologies at the expense of cultivating communication-based and relationship-based skills, which he argues are likely to be more effective in the psychosocial domains of care, such as enhancing adherence. Practically, the physician should ask questions in a nonjudgmental way to determine if there are problems adhering to the treatment. If a patient admits to non-adherence, he/she is usually telling the truth, but if a patient denies non-adherence, he/she is telling the truth about half the time [32]. During follow-up, the healthcare provider should probe about whether patients know why they are taking their medication and the benefits they can expect from adhering to their medications. It is equally important during follow-up for the physician to inquire about the occurrence of AEs and to take such reports seriously. There is evidence that even for well-documented and commonly recognized statin AEs, such as muscular and neurological complains, physicians often dismiss these as statin-unrelated [76, 77]. The failure of physician–patient communication with regard to statin AEs prevents honest reassessment of the risk/benefit profile for statin treatment. Even in cases where the benefits of statins outweigh the risks, the denial of the patient's symptoms by the physician can lead to a lack of trust and may be a strong contributor to non-adherence.

Finally, physicians should be willing to acknowledge that some patients may be unable to tolerate statins, and must be willing to work with the patient to improve CV health. If a

patient is unable or unwilling to take a statin, other interventions must be tried. In the USAGE study, those who discontinued statins were found to be more willing to adopt therapeutic lifestyle changes (TLC) [4••]. TLC must be emphasized at every visit, and other lipid-lowering therapies may be necessary to achieve lipid goals. To this end, we have advocated the need for further studies to address the needs of the population of patients who are statin-intolerant [25]. Adams [46] wrote that "many healthcare decisions have multiple options and no correct choice. The optimal decision is one that takes into account patient preferences and values in a collaborative process with the physician, and is known as shared decision-making." Respecting a patient's preferences is vital to continue maintaining a good relationship with the patient or this may result in a missed opportunity to manage the patient adequately.

Conclusions

There are no simple solutions to motivating patients for increased adherence to long-term statin therapy. Thus far, the interventions employed in various studies have resulted in modest increases in adherence at best. The promise of modern technology and pharmacogenetics to increase medication adherence has yet to be realized. In our current state of knowledge, the physician and patient must form an alliance to more effectively communicate the importance of statin treatment, and establish goals for therapy. A brief discussion listening to patients' concerns and discussing potential AEs may make a big difference. Predictors of non-adherence should be used to identify those at high-risk for statin discontinuation for targeted counseling. Clinicians should emphasize non-pharmacological approaches in addition to statins for reducing cholesterol levels in all patients, no matter what risk stratification. The most important breakthrough for increasing statin adherence may not be new at all: remembering to involve the patient and making patients an active part of shared-decision making may in fact be the best way to achieve statin adherence.

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