Curr Atheroscler Rep (2015) 17:471
DOI 10.1007/s11883-014-0471-8

STATIN DRUGS (BS WIGGINS, SECTION EDITOR)

When Compliance Is an Issue—How to Enhance Statin Adherence and Address Adverse Effects

Kim Birtcher

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Abstract Cardiovascular disease is prevalent and costly. Interventions and therapies that reduce morbidity and mortality associated with cardiovascular disease could have an enormous impact on clinical and economic outcomes. Statins reduce atherosclerotic cardiovascular disease-related morbidity and mortality; however, adherence to statins is less than optimal. It is important for clinicians as well as health plan managers to be aware of the patient- and insurance plan-specific factors that have been shown to influence adherence. Perceived statin-related side effects may also decrease adherence. Statin-related myalgia may be difficult to distinguish from myalgia caused by other conditions, and statin therapy may be discontinued unnecessarily in patients who would otherwise benefit. It is imperative that clinicians work closely with patients to improve adherence to statin therapy and be knowledgable in managing potential statin-related side effects.

Keywords Cardiovascular risk reduction · Primary prevention · Secondary prevention · Statin · Adherence · Compliance · Persistence · Copay · Cost sharing · Insurance benefits · Manufacturer coupon · Brand · Generic · Therapeutic substitution · Intolerance · Myalgia · Intermittent dosing · Alternative day dosing · Statin-related side effects

Introduction

The clinical and economic burden of cardiovascular disease (CVD) is tremendous. Although the mortality rate from CVD has declined in recent years, CVD remains the leading cause of death in the USA. Each year, approximately 915,000 Americans have a new or recurrent coronary event and approximately795,000 have a new or recurrent ischemic or hemorrhagic stroke. In 2010, the direct and indirect costs of CVD and stroke are estimated to be a staggering $315.4 billion [1]. Interventions and therapies that reduce CVD morbidity and mortality could have an enormous impact on clinical and economic outcomes.

Statins reduce morbidity and mortality associated with both the primary and secondary prevention of atherosclerotic cardiovascular disease (ASCVD) [2]. Because of the wealth of data on the benefits of statin therapy, the 2013 ACC/AHA cholesterol guidelines preferentially recommend statins over other lipid-lowering therapy for reducing ASCVD risk [3]. Pencina et al. estimated that approximately12.8 million more people will be eligible for statin therapy based on the new guidelines, and most of these individuals do not have known ASCVD [4]. These estimates are concerning because, historically, adherence to statins has been poor [5–9]. Chowdhury et al. estimated that statin adherence may be as low as 54 % [10]. There is also ample data suggesting that patients without ASCVD have higher rates of nonadherence than patients with known ASCVD [11, 12]. In addition, new statin users have high rates of nonadherence [12, 13], with at least 50 % of new statin users discontinuing therapy within 1 year [13]. It is important for the clinician to understand what influences statin adherence and consider ways to improve statin adherence. This paper will discuss recent research on and interventions to improve statin adherence.

Impact of Statin Adherence on LDL-C

A few recently published studies demonstrated an association with statin adherence and attainment of lower low-density

This article is part of the Topical Collection on *Statin Drugs*

K. Birtcher (✉)
University of Houston College of Pharmacy, 1441 Moursund St., Houston, TX 77030, USA
e-mail: kbirtcher@uh.edu

Published online: 20 November 2014

lipoprotein cholesterol (LDL-C) levels. New statin users with a medication possession ratio (MPR) ≥80 % at 1-year follow-up had greater reductions in LDL-C (20.98 mg/dL, $p<0.0001$) compared with nonadherent patients [14]. Statin adherence (MPR ≥80 % at ~1-year follow-up) was also associated with lower LDL-C values and greater LDL-C goal attainment (<100 mg/dL; optional <70 mg/dL) in patients with CVD. Overall, 79.8 % were adherent with statin therapy. Patients at goal had higher adherence rates (LDL-C <100 mg/dL 82.1 vs 66.0 %; LDL-C <70 mg/dL 84.3 vs 77.7 %) and lower mean LDL-C values (LDL-C <100 mg/dL 73.4 vs 121.0 mg/dL; LDL-C <70 mg/dL 57.3 vs 91.1 mg/dL) compared with those not at goal [15]. However, usability of the results of these studies is limited, as both used surrogate endpoints and the study duration was only 1 year. In addition, the new cholesterol guidelines do not advocate the use of goals for LDL-C [3]. However, there is evidence that reducing LDL-C by approximately 39 mg/dL over 4 years in patients with diabetes has been associated with a 13 % reduction in all-cause mortality [16].

Impact of Statin Adherence on Clinical Outcomes

There is tremendous evidence that statin adherence has also been associated with improved clinical outcomes [17], including fewer emergency room visits [18], hospitalizations, lower health care costs [19, 20], and nonfatal CVD events [21]. Low statin adherence for primary prevention was associated with a higher risk of CVD (odds ratio (OR) 1.07; 95 % confidence interval (CI), 1.01–1.13), cerebrovascular disease (OR 1.13; 95 % CI 1.03–1.25), and chronic heart failure (OR 1.13; 95 % CI 1.01–1.26) within the 3-year follow-up period [22]. A recent meta-analysis demonstrated an association with statin adherence (≥80 %) and lower relative risk (0.85, 95 % CI 0.81–0.89) of developing CVD and all-cause mortality (0.55, 95 % CI 0.46–0.67) [10].

Pittman et al. observed similar results. This retrospective cohort study of 381,422 patients used an integrated pharmacy and medical claim database to evaluate the association between MPR for 12 months and the health care costs and CVD-related hospitalizations during the subsequent 18 months. Adherence was defined as having a MPR ≥80 %. Of those individuals studied, 67.6 % were adherent, 17.3 % had a MPR of 60–79 %, and 15.1 % had a MPR 60 %. The mean level of adherence at year 1 was 94.5 % in the MPR ≥80 % group, 71.3 % in the 60–79 % adherence group, and 43.1 % in the MPR <60 % group. Older age, more total medications, presence of CV diagnosis, and lower copayments were associated with MPR ≥80 %. The adjusted mean all-cause total health care costs were lowest in adherent group at $10,198 ±$39.4 versus $10,609±$77.7 ($p<0.001$) for a MPR of 60–79 %, and $11,102±$84.3 ($p<0.001$) for a MPR <60 %. The adjusted total health care costs were lowest for the MPR ≥90 % group ($p<0.001$). A 10 % increase in the MPR was associated with a decreased risk of CVD-related hospitalizations (OR 0.95, 95 % CI 0.95–0.96) [23•]. These results emphasize the importance and benefits of statin adherence during the first year of statin therapy.

Patients who are initially adherent to statin therapy may not demonstrate long-term adherence. Slejko et al. evaluated yearly changes in adherence for 3 years and the subsequent risk of CV events among 11,126 individuals being treated for primary prevention of ASCVD and were adherent to statin therapy during the first year of therapy. Adherence was defined as proportion of days covered (PDC) ≥0.80, and only patients who were adherent for the first year of therapy were included in the study. For subsequent years, patients were grouped into three levels: PDC ≥0.80, 0.20≤PDC<0.80, and PDC <0.20. Patients were excluded if they experienced an ASCVD event in their first year of statin exposure. ASCVD outcomes were identified using claims data up to 5 years following the index statin or until the patient had a gap in health plan enrollment. Only 70 % remained adherent (PDC >0.80) in year 2. Of those in this level during year 2, 73 % remained adherent (PDC >0.80) in year 3. The mean follow-up time was 42 months. The mean time to ASCVD event was 3.3 years, and 828 (7.44 %) experienced an ASCVD event. The second-year adherence level was found to be a significant predictor of CV event hazard ($p<0.001$). Compared with the highest level of adherence, patients with PDC <0.20 had more ASCVD events in year 2 (hazard ratio (HR) 2.26, 95 % CI 1.801–2.828; $p<0.0001$) and year 3 (HR 2.71, 95 % CI 2.089–3.527; $p<0.0001$). The authors concluded that adherence levels tend to decline over time even if the patient is adherent during the first year of therapy, and a transition to adherence levels <80 % was associated with increased risk of CV events [24••]. These findings emphasize the importance of continued adherence to therapy. They also emphasize that patient's adherence behavior can change over time and assessments of adherence may be needed throughout the time the patient is on statin therapy.

Predictors of Statin Adherence

Primary Adherence

Unfortunately, it is difficult to determine who will be adherent to statin therapy, and nonadherence may occur at any time. Lipid-lowering therapy has been associated with primary nonadherence [25]. Primary nonadherence to statin therapy is defined as the patient not picking up a new statin prescription from the pharmacy after the prescription is written. This can be studied by connecting e-prescribing and pharmacy claims data. Data reflect that 13 % of new statin prescriptions

were not filled within 30 days of the order date [26] and 34.1 % of new statin prescriptions were not filled within 60 days of the order date [27]. These statistics are consistent with the results from a recent study showing almost one in six patients (15.4 %) did not obtain their statin within 90 days from when it was prescribed. Compared to patients who picked up their initial statin prescription, the patients who didn't pick up their initial statin order tended to be younger (55 vs. 57 years, $p<0.001$), healthier, with fewer comorbid conditions (Charlson Comorbidity Index ≥1, 42.2 vs. 52.3 %, $p<0.001$), lower rates of hospitalizations (7.2 vs. 12.0 %, $p<0.001$), fewer clinic (4 vs. 5, $p<0.001$) and emergency department visits (18.2 vs. 24.6 %, $p<0.001$), and fewer concurrent prescriptions (3 vs. 4, $p<0.001$) in the prior year [28]. Keep in mind that these numbers may over-estimate primary nonadherence with statins, since data for patients who pay cash for their prescriptions or order their medications from the Internet will not get captured in the type of analysis done in these studies.

Longer-Term Adherence

Lower adherence (PDC <0.80) in the first 90 days of statin therapy was the strongest predictor for poor adherence at 1 year (OR 25.0, 95 % CI 23.7–26.5) in Medicare Part D beneficiaries initiating statin therapy. Predictions could be made as early as 40 days after statin initiation for individuals who receive 30-day supplies of medication and 100 days after statin initiation for individuals who receive 90-day supplies of medication [29•]. Medicare Part D plan administrators and pharmacy benefits managers could use an individualized surveillance model similar to the one used in this study to detect early on which beneficiaries will fall below the designated adherence threshold.

Many patient, physician, and health system-related factors are known to affect adherence to long-term statin therapy; however, there is no magic bullet to easily predict and resolve statin nonadherence [11, 12, 30]. Variables associated with nonadherence to statin medications include the following: primary prevention (rate ratio=1.52; 95 % CI, 1.50–1.53), new statin users (rate ratio=1.46; 95 % CI, 1.33–1.61), copayment (rate ratio=1.28; 95 % CI, 1.09–1.50), lower income status (rate ratio=1.26; 95 % CI, 1.16–1.37), fewer than two lipid tests performed (rate ratio=1.38; 95 % CI, 1.16–1.64), and not having hypertension (rate ratio=1.16; 95 % CI, 1.12–1.21) [12].

Specific Interventions That Influence Adherence

Switching Between Brand-Name and Generic Products

Switching from brand-name to generic statins may affect adherence. Romanelli used electronic health records and pharmacy claims data from an ambulatory-care medical network to identify patient characteristics associated with adherence to statin therapy after switching 5156 patients from brand-name to generic agents. Adherence was defined as MPR ≥0.80, and 73 % of patients were adherent in the 6 months after switching from brand-name to generic statin. Higher adherence was associated with each 10-year increase in age (OR 1.13; 95 % CI 1.07, 1.19; $p<0.001$), receipt of a generic statin equivalent in potency to the prior brand-name statin (OR 1.41; 95 % CI 1.16, 1.70; $p<0.001$), and adherence with prior brand-name statin (OR 4.68; 95 % CI 4.07, 5.39; $p<0.001$). Lower adherence was seen among Hispanic patients compared to non-Hispanic white patients (OR 0.68; 95 % CI 0.52, 0.91; $p=0.009$) and when there was a switch to a higher-potency generic statin (OR 0.87; 95 % CI 0.80, 0.94; $p=0.001$). The authors concluded that counseling and close monitoring for adherence are necessary when switching from brand-name to generic statin therapy [31].

Cost-Sharing Strategies

Cost-sharing strategies may unintentionally impact adherence to medications for chronic diseases [32]. Higher copayments have been associated with lower adherence rates to medications in general [12, 25, 33, 34]. Higher out-of-pocket costs have also been associated with lower statin adherence rates [19, 25, 35, 36]. Gibson et al. found that a $10 increase in copayment resulted in a 1.8 % reduction in the probability of adherence for new users and a 3 % reduction in the probability of adherence for continuing users. For continuing users adherent to statins, total costs did not change [19]. Chen, et al. found the moving brand-name statins to a lower tier and copayment had a positive effect of adherence in a Medicare Part D population [37].

Elimination of Copayments

Two studies evaluated the impact of not having copayments on adherence of statins. Watanabe et al. observed better adherence with statins for new statin users in the Veterans Administration who did not have a copayment versus patients who did have a copayment [38•]. Choudhry et al. evaluated the impact of providing full prescription coverage (eliminating copayments) on medication adherence and ASCVD outcomes in patients discharged post-AMI. Rates of adherence to statins, beta-blockers, ACE inhibitors, and ARBs were higher in the full-coverage group. There was no difference in the rate of the first major vascular event or revascularization between the two groups (HR, 0.93; 95 % CI, 0.82–1.04). The rates of total major vascular events or revascularization (21.5 vs. 23.3; HR, 0.89; 95 % CI, 0.90–0.99) and the rate of first major vascular event (11 vs. 12.8; HR, 0.86; 95 % CI, 0.74–0.99) were reduced in the full-coverage group. Total spending did not

increase; although, patient costs were reduced [39••]. It will be important for insurance benefits managers to evaluate total health care costs of eliminating or reducing copayments for prescriptions medications. In the long-run, the plan may benefit from less expenditures and better clinical outcomes.

Manufacturer Coupons

Pharmaceutical manufacturers use coupons as a promotional activity to encourage initiation and continuing use of brand-name medications [40]. Daugherty et al. evaluated the impact of coupons on brand-name statin (i.e., atorvastatin and rosuvastatin) use and expenditures 1 year after initiation of statin therapy in patients with commercial insurance. The investigators identified three groups initiating statin use: coupon users of atorvastatin or rosuvastatin (n=9638, 2.8 %), noncoupon users of atorvastatin or rosuvastatin (n=87,123, 25.6 %), and users of a generic statin (i.e., lovastatin, pravastatin, or simvastatin) (n=243,589 or 71.6 %). Coupon users had the highest number of statin fills in the 12 months following initiation, and the noncoupon brand-name statin users had the lowest number (7.1 vs. 5.8; p<0.001). Medication adherence rates were 61.1, 60.1, and 53.8 % (p<0.001) for the coupon users, generic statin users, and brand-name statin users, respectively. Statin prescription costs were $798, $92, and $675 ($p$<0.001) for the coupon users, generic statin users, and brand-name statin users, respectively. Health plan costs for statins excluding rebates were lower for coupon users than noncoupon users ($460 vs. $508; p<0.001), but higher when compared with generic statin users ($460 vs. $39; p<0.001). For patients initiating statin therapy, manufacturer coupons lowered out-of-pocket costs and improved adherence rates during the first year of statin therapy [41]. It would be interesting to see if the adherence rates and overall costs change after 1 year, since most manufacturer coupons only lower the cost of the prescriptions for the first 12 months. Health plans should evaluate the long-term costs for patients who use a manufacturer coupon or other means to lower prescription copayments.

Evaluating and Managing Reports of Statin Intolerance

Many patients stop taking their statin therapy due to side effects [13]. Zhang et al. demonstrated that most patients who receive statin therapy after reporting a statin-related event can tolerate longer-term statin therapy. Electronic medical records were used to identify patients with a documented statin-related event and to determine the reasons for statin discontinuation and their impact on long-term statin discontinuation (≥12 months). Statin rechallenge was defined as any documentation of statin therapy during the 12 months after the statin-related event. Statin-related events were documented for 18,778 (17.4 %) patients, and the statin therapy was discontinued in 11,124 (59.2 %) of these patients. More than half (6579 out of 11,124) of the patients were rechallenged with a statin sometime in the subsequent 12 months, and 92.2 % of the patients who were rechallenged were taking a statin 12 months after the original statin-related event. The authors concluded that a statin rechallenge is a viable option, recognizing that many reported statin-related events may be due to other causes, are tolerable, or may be specific to individual statins rather than the entire drug class [42••].

Many studies have used medical and prescription databases to identify patient characteristics that might be associated with statin intolerance; however, very little is known from the patients' point of view. Cohen et al. used an internet-based survey to assess the characteristics and behaviors of 10,138 adult patients in the USA with a self-reported diagnosis of a high cholesterol level made by a health care provider and self-reported current or former statin use. Of the patients currently taking statins, 70 % reported not missing any doses in the last month. The primary reason former statin users stopped taking their statin was side effects (62 %). Muscle-related side effects were reported by 60 and 25 % of former and current users, respectively (p<0.05). Former statin users were less satisfied than current statin users with their physicians' explanation of the importance of cholesterol levels for their health (65 vs. 83 %, p<0.05). It is interesting to note that 28 % of current statin users switched statins at some point due to statin-related side effects [13].

Mampuya et al. performed a retrospective analysis of medical records of patients referred to the cardiology clinic for statin intolerance to determine subsequent treatment strategies. Patients were included if there was documented intolerance to at least two statins. Patients were divided into three groups based on their statin regimen at the time of their last follow-up visit: no statin, intermittent statin dosing (i.e., not taking daily statin), or daily statin dosing. During the median follow-up time (31 months), most of the patients (1163 or 72.5 %) remained on statin therapy, with 63.2 % (n=1014) on a daily regimen and 9.3 % (n=149) on an intermittent statin regimen. Statins were completely discontinued in 27.5 % (n=442) of patients. Rosuvastatin was used most frequently in the intermittent-dosing group (75.2 %). Atorvastatin (21.5 %), pravastatin (18.0 %), rosuvastatin (38.3 %), and orsimvastatin (20.1 %) were used in the daily dosing group. Patients on daily statin or intermittent statin dosing achieved greater LDL-C reduction compared with those who discontinued statin (27.7 ±1.4 vs 21.3±4.0 vs 8.3±2.2 %, p<0.001) Patients on intermittent statin dosing achieved a LDL-C reductions similar to patients on daily statin dosing (21.3±4.0 vs 27.7±1.4 %, p=.04). The authors concluded that most patients with documented statin intolerance can tolerate subsequent trial of statin, and intermittent statin dosing can be an effective therapeutic option in some patients [43••]. These results and conclusions are consistent with the findings of a recent literature

review that demonstrated at least 70 % of patients with prior statin-related side effects were able to tolerate intermittent statin dosing, ranging from every-other-day to once-weekly dosing, without a recurrence of previous statin-related adverse effects [44•].

Statin-related myalgia is difficult to distinguish from myalgia caused by other conditions, and statin therapy may be discontinued unnecessarily in patients who would otherwise benefit. Joy et al. used a creative method to evaluate reported statin-related myalgia in eight patients. Each of the patients had reported statin-related myalgia within 3 weeks of starting therapy. The investigators wanted to compare the side effects associated with rechallenging these patients with the same statin and dose or placebo. Each patient's trial period lasted up to 33 weeks, and the trial included up to three double-blind, cross over comparisons with the previously used statin and dose or placebo, separated by 3-week washout periods. The patients' visual analogue scale (VAS) myalgia score and symptom specific VAS score, pain interference scores, and pain severity scores were recorded during the 3-week periods when the patients were receiving placebo or statin. Patients who developed symptoms were offered the option of discontinuing a treatment period early and crossing over to the other treatment period after a washout period. Eight women participated in the trials, seven patients completed the three treatment pairs, and one completed only two treatment pairs. For each trial, no statistically significant differences were seen between statin and placebo in the VAS myalgia score, symptom-specific VAS score, pain interference score, and pain severity score. Five patients of the eight patients resumed statin treatment, with a median post-trial follow-up of 10 months [45••]. Though the investigators and patients in this study used matching statin and placebo doses, the other methodology used to discern the difference in side effects to statin and placebo could be used in other clinical settings.

The current cholesterol guidelines recommend proactively screening for muscle issues prior to initiating and during statin therapy and provide an approach for managing statin therapy if muscle symptoms occur. The clinician should ask the patient about muscle symptoms, including aching, pain, stiffness, tenderness, weakness, fatigue, or cramps or history of muscle disease before initiating statin therapy and at each follow-up visit. A baseline creatine kinase level may be measured in patients who are at increased risk for muscle symptoms (e.g., elderly; personal or family history of statin intolerance or muscle disease; comorbidities or medications which increase myopathy risk). Routine measurement of creatine kinase is not necessary; however, the creatine kinase may be measured in patients on statin therapy and complaining of muscle symptoms. If a patient reports muscle symptoms while on statin therapy, then the clinician should speak with the patient to determine the severity of the symptoms, if there appears to be an association with statin therapy, and investigate other possible causes of the myalgia (e.g., hypothyroidism, low vitamin D levels, recent exercise, alcohol or drug abuse). The patient may need to stop the statin therapy, at least temporarily, to see if symptoms subside. If the muscle symptoms resolve, the patient may resume the same or lower dose of the same statin to help determine a causal relationship between the statin therapy and the muscle symptoms. If a causal relationship is established, the patient may be able to tolerate a different statin given daily or intermittently (e.g., ranging from every-other-day to once-weekly dosing) The guidelines emphasize the importance for the clinician to thoroughly evaluate the patient's muscle symptoms before permanently discontinuing statin therapy, especially in patients with clinical ASCVD, LDL-C ≥190 mg/dL, or diabetes [3]. Though it would be nice to have the benefit of large-scale clinical trials to determine the exact strategy for handling reports of statin-related myalgia, those will not be completed any time soon. The take-home message for the clinicians is that many patients who report statin intolerance or statin-related muscle side effects can tolerate subsequent statin therapy.

Statins may increase the risk of hyperglycemia and type 2 diabetes in some patients. In 100 individuals treated with statin therapy for 1 year, the risk of diabetes is ~0.1 and ~0.3 excess cases with a moderate-intensity and high-intensity statin, respectively; however, the benefits of ASCVD risk reduction outweigh the risk of developing diabetes except for in the lowest-risk patients [46, 47]. The A1c should be measured at baseline if it is not known if the patient has diabetes. If the patient develops diabetes while on statin therapy, the diabetes should be managed according to current recommendations [3].

The expert panel for the current cholesterol guidelines expert did not find evidence that statins adversely affect cognition. If patient complains of confusion or memory impairment while on statin therapy, consider all possible causes, including other drugs (e.g., sleep aides, analgesics, OTC antihistamines) and medical conditions (e.g., depression, anxiety, sleep apnea) that affect memory [3].

Tool to Increase Statin Adherence

The National Lipid Association developed the *Clinician's Toolkit: A Guide to Medication and Lifestyle Adherence*. The toolkit challenges clinicians to view adherence as a disease, which will require an understanding of what represents adherence and how to "diagnose" it in patients. It identifies barriers to medication and lifestyle adherence, and it provides ways that the health care team members may help prevent, identify, and manage nonadherence. The toolkit provides a tear-out quick guide that may be posted in the office as a reference. The quick guide provides information on how to identify patients at risk for nonadherence, start a dialogue with patients

about nonadherence, and assess adherence or medication taking behavior. It also lists evidence-based interventions that have been successful at improving patient adherence. The toolkit may be used to improve adherence to any medication, including statin therapy [48••].

Conclusion

The clinical and economic impact of CVD is tremendous. Statins reduce atherosclerotic CVD disease-related morbidity and mortality; however, adherence to statins is suboptimal. Clinicians must work closely with patients to improve adherence and manage potential side effects. Many patients who have reported statin-related myalgia will be able to continue some form of statin therapy.

Compliance with Ethics Guidelines

Conflict of Interest Kim Birtcher declares no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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