



REVIEW

Real-world Evidence for Adherence and Persistence with Atorvastatin Therapy

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ABSTRACT

Atorvastatin, which has been approved by regulatory agencies for primary- and secondary-prevention patients with dyslipidemia, has historically been the most commonly prescribed statin and is now widely available in generic formulations. Despite widespread statin usage, many patients fail to attain recommended

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(LDL-C) targets. While several factors impact the successful treatment of dyslipidemia, sub-optimal patient adherence is a major limiting factor to medication effectiveness. In this narrative review we sought to investigate patient adherence and persistence with atorvastatin in a real-world setting and to identify barriers to LDL-C goal attainment and therapy outcomes beyond the realm of clinical trials. Moreover, in light of growing generic usage, we carried out targeted literature searches to investigate the impact of generic atorvastatin availability on patient adherence/persistence, and on lipid and efficacy outcomes, compared with branded formulations. Unsurprisingly, real-world data suggest that patient adherence/persistence to atorvastatin is suboptimal, but few studies have attempted to address factors impacting adherence. Data from studies comparing adherence/persistence in patients prescribed branded or generic atorvastatin are limited and show no clear evidence that initiation of a specific preparation of atorvastatin impacts adherence/persistence. Furthermore, results from studies comparing adherence/persistence of patients who switched from the branded to the generic drug are conflicting, although they do suggest that switching may negatively impact adherence over the long term. Additional real-world studies are clearly required to understand potential differences in adherence and persistence between patients initiating treatment with branded versus generic atorvastatin and,

moreover, the factors that influence adherence. Targeted education initiatives and additional research are needed to understand and improve patient adherence in a real-world setting.

Keywords: Statin; Atorvastatin; Real-world data; Adherence; Lipids; Cardiovascular

Key Summary Points

Why carry out this study?

The lipid-lowering efficacy of atorvastatin is well studied in clinical trials, yet many patients fail to meet their prescribed low-density lipoprotein-cholesterol (LDL-C) goals when atorvastatin is taken in a real-world setting.

The availability of atorvastatin as a generic formulation has facilitated widespread prescribing, increasing the need to understand medication-taking behavior of patients in the non-clinical setting.

The aim of this review was to identify literature that discussed: (1) patient adherence/persistence to atorvastatin in the real-world setting and the impact of adherence on lipid and efficacy outcomes; and (2) the influence of generic atorvastatin utilization on adherence/persistence and efficacy outcomes.

What was learned from the study?

Adherence to atorvastatin remains suboptimal; patients fail to achieve their LDL-C goals, leading to increased risk of cardiovascular events.

Adherence may be impacted by switching between generic and branded atorvastatin, but further long-term studies are required to confirm the real impact of generic atorvastatin usage on medication-taking behaviors.

Several gaps in the literature exist regarding factors responsible for poor adherence to atorvastatin and their impact on efficacy outcomes, and further studies and training initiatives are required to resolve these issues.

INTRODUCTION

Atorvastatin was first introduced to the market in 1996 and has been approved by regulatory agencies for use as a moderate-to-high intensity statin therapy (10–80 mg/day, respectively). The lipid-lowering efficacy of atorvastatin is well established, and patients receiving 10–80 mg/day generally experience dose-dependent reductions in low-density lipoprotein cholesterol (LDL-C) and total cholesterol, and small reductions in triglycerides [1, 2]. In addition, the long-term benefit and safety of atorvastatin for lowering cardiovascular (CV) risk have been demonstrated in > 80,000 patients across 11 CV clinical outcomes trials for both primary- and secondary-prevention patients, with and without comorbidities [3–13]. The landmark Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm (ASCOT-LLA) trial was terminated early after hypertensive patients with at least three additional CV risk factors demonstrated a 36% reduction in non-fatal myocardial infarction (MI) and fatal coronary heart disease (CHD) when atorvastatin (10 mg) was added to blood pressure-lowering regimens, versus patients receiving placebo [7]. Similarly, the Collaborative Atorvastatin Diabetes Study (CARDS) in patients with dyslipidemia and type 2 diabetes was terminated approximately 2 years early because patients treated with atorvastatin (10 mg) experienced a 37% reduction in the incidence of major CV events compared with those treated with placebo [11]. The benefits of more intensive atorvastatin therapy were later demonstrated in studies such as the Treatment to New Targets (TNT) study, where patients with clinical evidence of CHD receiving 80 mg atorvastatin experienced a 25% reduction in major CV

events versus those receiving 10 mg atorvastatin [4]. Collectively, outcomes data have contributed to the development of clinical management guidelines for cardiovascular disease (CVD) [14–16] and resulted in > 400 subsequent clinical trials, accruing over 250 million patient-years of experience.

The patent for branded atorvastatin expired globally in November 2011, although the generic formulation was available as early as 2008 in South Korea [17]. Generic products are approved on the premise that they contain the same active compound as the branded product, their inactive ingredients are safe, they are pharmacokinetically bioequivalent (i.e. equivalent rate and extent of exposure) and they display no significant differences in efficacy or safety, when administered at the same dose under the same conditions as branded drugs [18]. Generic products are deemed bioequivalent if the mean (and 95% confidence intervals) of maximum serum concentration (C_{max}) and/or area under the curve (AUC) are contained within 80 to 125% range of the proprietary values [18]. The most commonly prescribed statins, namely atorvastatin, rosuvastatin and simvastatin, are all now available as generic products. It has been shown that the availability of generic statins directly influences prescription trends [19–22]. For example, in the UK, branded atorvastatin was the most prescribed statin formulation but was outcompeted by generic simvastatin introduced to the market in 2003, in accordance with National Institute for Health and Care Excellence (NICE) guidelines recommending usage of the statins with the lowest cost and highest efficacy [21]. With expiration of the global patent for branded atorvastatin and marketing of its generic formulation with cheaper acquisition costs, atorvastatin once again became the most frequently prescribed statin by healthcare professionals [21]. Similarly, in the USA and Korea, the availability of generic atorvastatin led to widespread prescribing [19, 22], and atorvastatin has remained the most frequently prescribed lipid-lowering drug worldwide.

The Problem of Adherence

‘Adherence’ is a crucial factor associated with gaining full therapeutic benefit from a medication regimen [23]. Patients are enrolled into randomized controlled trials (RCTs) under strict inclusion/exclusion criteria, and they remain closely monitored by medical staff responsible for ensuring protocol adherence. With a focus on outcomes, RCTs do not always report adherence (only 85% according to some reports [24]), and investigators often utilize different adherence assessments, which may preclude comparison between RCTs and/or with real-world observations [24, 25]. The 2016 European guidelines on CVD prevention recommend an LDL-C target of < 70 mg/dL for very high-risk patients, < 100 mg/dL for high-risk patients and < 115 mg/dL for remaining patients [26]. However, the EUROASPIRE V (2016–2017) survey that used these guidelines found that most patients had LDL-C levels ≥ 1.8 mmol/L (≥ 70 mg/dL) and that more than one-third (37%) had LDL-C levels ≥ 2.5 mmol/L (≥ 100 mg/dL), despite being classified as very high risk, 1 year after acute MI and/or acute myocardial ischemia [27]. Decades of clinical evidence with statin therapy is now available in electronic databases, enabling researchers to link real-world adherence with efficacy and outcomes [28, 29]. As such, there is now potential to determine the impact of non-adherence with atorvastatin therapy in the real-world setting by studying these reports.

The aim of this targeted review of the literature was to identify studies that report patient adherence to atorvastatin therapy in the real-world setting (i.e. non-clinical trial). Specifically, we sought to investigate reported barriers to LDL-C goal attainment and how adherence to atorvastatin therapy has been related to efficacy outcomes, in an attempt to better understand medication-taking behavior of patients prescribed atorvastatin. Specifically, in the advent of widespread prescribing of generic atorvastatin, we sought evidence reporting the impact that generic atorvastatin has had on adherence and (where available) other efficacy outcomes.

METHODS

Targeted literature searches of the PubMed (www.ncbi.nlm.nih.gov/pubmed) database were performed, with a focus on the years following the introduction of generic atorvastatin (1 January 2009 to 1 January 2020). A search of available meeting abstracts was also conducted using the Web of Science (<http://apps.webofknowledge.com/>) database. Meeting abstract data were only available from the Web of Science database from 2010 onwards; therefore searches were conducted between 1 January 2010 and 1 January 2020. The patent for atorvastatin expired globally in November 2011, although some countries did produce generic products prior to this date (as early as March 2008 in South Korea). These date ranges selected for our targeted searches aimed to cover the period just before and after global patent expiration.

Relevant publications and congress materials were identified using a combination of key search terms in different strings (atorvastatin; Lipitor; adherence; compliance; persistence; generic; brand; cardiovascular outcome or event; low-density lipoprotein cholesterol/LDL/lipid; mortality; treatment satisfaction). Relevant literature was supplemented by the inclusion of published evidence identified from screening of the reference lists of identified literature at the time of publication. Literature from these targeted searches was first assessed for relevance in order to provide context for the background of the narrative review. Targeted searches were also carried out to specifically identify literature discussing adherence with branded versus generic atorvastatin. Titles and abstracts of all literature were screened. These articles were then taken forward for full-text screening to confirm relevance. Literature that focused on prescription trends, switching to a different statin (non-atorvastatin) therapy, genetic conditions, atorvastatin use in children or health economic outcomes were not included.

This article is based on previously conducted studies and does not contain any new studies

with human participants or animals performed by any of the authors.

DEFINING MEDICATION ADHERENCE

Medication adherence and compliance have historically been used synonymously to describe ‘the extent to which the patient follows medical instructions’ [30]; however, in 2003 the World Health Organization expanded this definition to incorporate dietary and lifestyle factors, and to further distinguish adherence from compliance by emphasizing that agreement to the recommendations is required by the patient [30, 31]. Medication persistence refers to the duration of medication use, from initiation to discontinuation, for the prescribed duration [32]. These terms are used by medical professionals and other healthcare providers to give a comparative ‘guide’ to assess whether patients are taking their medication as prescribed. Although different methods for assessing adherence and persistence are still used in the medical literature [33–36] (see Electronic Supplementary Material [ESM] Table S1), taking medication in accordance with 100% of the prescribed regimen is rarely achieved in the real-world setting [30, 37]. Consequently, patients will not receive the full therapeutic benefit from their medications, which in CVD means they remain at higher risk for major CV events than if they took their medications as prescribed [38].

ATORVASTATIN: REAL-WORLD ADHERENCE, LDL-C GOAL ATTAINMENT AND OUTCOMES

While the efficacy of atorvastatin has been demonstrated in several RCTs and meta-analyses [3–13, 39, 40], LDL-C goal attainment remains inadequate in a real-world setting [41–54]. For example, a cross-sectional, observational study of 1849 outpatients from across Croatia who were receiving statins reported that although nearly half of patients were taking atorvastatin (43%), LDL-C goal attainment was low (39%), especially among those at high CV

risk (37%) [51]. The authors also reported that adherence was suboptimal overall, with only 35% of patients compliant with > 70% of their prescribed dose and just half (51%) being fully compliant [51].

Observations from the IDEAL study demonstrate how poor adherence to atorvastatin may be linked to increased CV risk. Although conducted in the clinical trial arena, IDEAL was a non-blinded, open-label study of atorvastatin (80 mg/day) versus simvastatin (40 mg/day), the results of which demonstrated high patient adherence (total study medication exposure as a percentage of follow-up time) of 89%, and a low discontinuation rate (14%) [5]. However, a subanalysis of IDEAL that adjusted for categorical adherence (above and below 80%, within each treatment arm) and censoring of the first occurrence of a CV event demonstrated a significant lowering of CV risk by 6% in patients with > 80% adherence [52].

Primary- and secondary-prevention patients have been compared to determine if a previous history of CV events drives better adherence in a real-world setting [53, 54]. For example, an analysis of 94,287 patients with dyslipidemia demonstrated that approximately 50% of patients were non-persistent with atorvastatin after the first year of treatment, with CV events occurring in approximately 2 and 9% of primary- and secondary-prevention patients, respectively [53]. Across both cohorts, patients who remained ‘adherent’ with their medication (taking a relatively conservative $\geq 60\%$ proportion of days covered [PDC; ESM Table S1] in the year after initiation) were significantly less likely to experience CV events versus non-adherent patients, and the relative risk was 8% lower for secondary-prevention patients [53]. Similarly, a study of 500 patients newly prescribed atorvastatin found that those with a prior CV event or history of diabetes were significantly more adherent and persistent throughout the 6-month study period compared with patients without a history of comorbidities [54]. These results are consistent with observations from studies of other statins which demonstrate that secondary-prevention patients appear to appreciate the importance of managing CVD risk and are more likely to be

adherent and persistent to these measures after experiencing CVD complications, as reviewed elsewhere [55]. There is a clear need to fully understand factors associated with poor adherence in order to help optimize adherence and CV risk factor management [56]. More recently, in an era where generic formulations have contributed to the increased utilization of statins [21], the influence of cheaper, generic statins on patients’ medication-taking behavior has become an additional consideration. Therefore, we specifically sought out literature that compared adherence and efficacy outcomes following use and/or switching to generic or non-generic atorvastatin therapy.

COMPARING ADHERENCE AND PERSISTENCE WITH BRANDED VERSUS GENERIC ATORVASTATIN

Studies of adherence among patients prescribed atorvastatin have demonstrated that the switch from branded to generic atorvastatin had a mixed impact on adherence [57–61]. For example, a 6-month retrospective study analyzed adherence in 3417 patients on statin therapy (atorvastatin, fluvastatin, lovastatin, pravastatin, simvastatin) who switched from a branded to a generic formulation [57]. Patients with a medication possession ratio (MPR; ESM Table S1) $\geq 80\%$ were considered to be ‘adherent.’ Of those who switched from a branded to generic formulation, the majority (52.3% [$n = 1786/3417$]) switched from branded to generic atorvastatin. While this study did not record adherence data for each specific type of statin, combined data showed that adherence was below optimal for one in four statin users who switched from branded to generic formulations (75.4% with MPR $\geq 80\%$) [57]. Many factors were identified that affected adherence, such as previous compliance with statin therapy [57].

Studies of patients who switched from branded to generic atorvastatin have also shown that switching may change patients’ adherence [57–61] (Table 1). For example, an 18-month non-interventional real-world study conducted in Greece by Tsioufis et al. compared

the adherence of patients who continued taking branded atorvastatin with those who switched to generic atorvastatin [58]. In this study, patients remaining on branded atorvastatin therapy were more persistent than those switched to generic atorvastatin (76.4 vs. 90.1%; $p = 0.1627$) and significantly more adherent using both PDC (73.0 vs. 79.1; $p < 0.001$) and the Morisky Medication Adherence Scale-4 (MMAS-4; 73.7 vs. 26.3%; $p < 0.001$), although adherence remained suboptimal ($< 80\%$ across both the PDC and MMAS-4) (Table 1; ESM Table S1) [58]. Conversely, a shorter observational study (180 days) by Mano et al. in Japanese patients showed higher adherence, albeit non-significant (92.2 vs. 89.4%; $p = 0.058$) and persistence (75.6 vs. 67.3%; $p = 0.097$) in patients who switched to generic atorvastatin [59] (Table 1). Mano et al. also reported a higher overall adherence in both cohorts than seen in the longer-term study by Tsioufis et al. It appears that the first 180 days of follow-up is the most critical period in determining whether patients become non-adherent or discontinue treatment [62, 63], which reflects the observation that patient adherence decreases as time progresses [23]. Why switching to a generic medication could impact adherence and/or persistence may be a consequence of changes to medication appearance (tablet color, shape and packaging) throughout treatment, leading to patient confusion [64]. Therefore, it is important to consider how adherence is impacted in patients who were not switched, but rather initiated on either branded or generic atorvastatin [60, 61] (Table 1). Results from a Korean study utilizing insurance claims data of 747 patients showed that those who were newly prescribed generic atorvastatin had a significantly lower coverage ratio than those prescribed branded atorvastatin (Table 1) [61]. These results are consistent with those from another study of Spanish patients who were prescribed either a branded or generic statin, and further highlighted the impact of poor adherence with a generic formulation on lipid and CV outcomes [65].

COMPARING EFFICACY AND SAFETY OBSERVATIONS WITH BRANDED VERSUS GENERIC ATORVASTATIN

Our literature searches identified studies reporting patient adherence and persistence with branded or generic atorvastatin, but these rarely included data on changes in lipid levels [2, 66, 67] (Table 2). Two observational studies provided lipid data for patients who switched from branded to generic atorvastatin over a period of 1–3 months, with the authors reporting no significant difference in LDL-C or triglyceride levels after switching to generic atorvastatin (Table 2) [2, 67].

While it is not clear why adverse events (AEs) may occur upon switching in some patients, differences in excipients may cause adverse reactions [68]. Four RCTs comparing branded versus generic atorvastatin reported myalgia as an AE, with a slightly higher prevalence in the generic cohort, although no formal analyses were conducted [69–72]. Historically, patients may report concerns around AEs as a factor impacting adherence [73], although we did not identify any studies that included patient perspectives of generic versus branded atorvastatin. The so-called ‘nocebo’ effect may negatively impact how patients or physicians perceive branded or generic treatment. In a non-blinded extension phase of the ASCOT-LLA trial, wherein patients knew they were receiving atorvastatin, trialists observed increased reporting of muscle-related AEs versus when patients were in the blinded phase and did not know if they were receiving a placebo or statin therapy [74]. The authors attributed this to the nocebo effect, as during the blinded phase of ASCOT-LLA, muscle symptoms, as well as other AEs such as sleep disturbance, cognitive impairment and erectile dysfunction, were reported at a similar rate in both the placebo and atorvastatin arm [74]. The nocebo effect has also been documented in patients who switch from other branded to generic medications, resulting in reduced effectiveness and increased reported AEs as a consequence of a negative bias toward generic products [75, 76].

Table 1 Studies reporting data on adherence, persistence or compliance in patients taking branded or generic atorvastatin

First author of study (year) [reference], study type	Sample size, <i>N</i>	Treatment regimen (generic or brand), <i>n</i>	Dose (mg)/prevention type	Measure of adherence/persistence/compliance	Adherent/persistent/compliant	<i>p</i> value	Follow-up period
Adherence							
Tsioufis (2017) [58], observational	190	ATO (continued brand), 95	NA	Adherence: PDC (%)	79.1	< 0.001	18 months
		ATO (switched to generic), 95			73.0		
		ATO (continued brand), 95		Compliance: high adherence (%; rate, MMAS-4)	73.7	< 0.001	
		ATO (switched to generic), 95			26.3		
Mano (2015) [59], observational	282	ATO (continued brand), 147	5–30	Adherence: median % PDC (% change pre- to post-index)	89.4 (– 10.3)	0.058	180 days
		ATO (switched to generic), 135	2.5–10		92.2 (– 8.6)	(0.443 ^d)	
		ATO (continued brand), 147		Patients achieving ‘adherence’: PDC ≥ 80%, <i>n</i> (%)	93 (63.3)	0.162	
		ATO (switched to generic), 135			96 (71.1)		
Jackevicius (2016) [60] ^a , observational	15,726	ATO (prescribed brand), 7863	Mean dose: 47.7/secondary	Adherence: MPR (%)	88.4		1 year
		ATO (prescribed generic), 7863	Mean dose: 47.2/secondary		88.4		

Table 1 continued

First author of study (year) [reference], study type	Sample size, <i>N</i>	Treatment regimen (generic or brand), <i>n</i>	Dose (mg)/prevention type	Measure of adherence/persistence/compliance	Adherent/persistent/compliant	<i>p</i> value	Follow-up period
Romanelli (2014) [57] ^b , observational	3417	ATO (switched to generic): 1786 Other statins (switched to generic): 1631		'Adherent' patients: MPR $\geq 80\%$, <i>n</i> (%)	2575 (75.4)		6 months
Kwon (2016) [61], observational	747	ATO (prescribed brand), NA ATO (prescribed generic), NA	NA	Coverage ratio (< 1 indicates missed ≥ 1 dose)	0.9 \pm 2.1 0.6 \pm 0.9	< 0.0001	24 months
Persistence							
Tsioufis (2017) [58], observational	190	ATO (continued brand), 95 ATO (switched to generic), 95	NA	Persistence rate (%)	90.1 76.4	0.1627	18 months
Mano (2015) [59], observational	282	ATO (continued brand), 147 ATO (switched to generic), 135	5–30 2.5–10	Persistence rate (%)	67.3 75.6 ^c	0.097	180 days

ATO Atorvastatin, MMAS-4 4-Item Morisky Medication Adherence Scale, MPR medication possession ratio, NA not available, PDC proportion of days covered

^a Patients who switched from branded to generic formulations, or vice versa, were censored

^b Includes other statins in addition to atorvastatin. Of those receiving branded atorvastatin, 57% were switched to generic atorvastatin

^c No significant difference after Cox proportional-hazards regression model analysis (adjusted hazard ratio 0.97; 95% confidence interval 0.61–1.55)

^d Parentheses indicate comparison of % change pre- to post-index

Table 2 Studies reporting lipid outcomes in patients taking branded or generic atorvastatin

First author of study (year) [reference], study type	Sample size, <i>N</i>	Treatment regimen (generic or brand), <i>n</i>	Dose (mg)/prevention type	LDL-C goal attainment, %	Change in LDL-C, mg/dL	Change in LDL-C, (%)	Change in TGs, mg/dL (%)	Change in HDL-C, mg/dL (%)	Change in CK (U/L)	Follow-up period
Loch (2017) [2], observational	629	ATO (switched to generic)	NA	NA	- 0.4 ^a	0 ^a	0.4 [*]	NS	NS	3 months ^c
Rahalkar (2013) [67], observational	85	ATO (switched to generic)	10–80/primary	NA	0.3 (0.32) ^a	10.9 (6.54) ^a	1.9 (4.45)**	0.88 (0.62%)		1 month ^d
Awoniyi (2013) [66], case report	1	ATO (brand before switch)	10/primary	NA	67	108	34	182		8 years
		ATO (generic after switch)	10/primary		73	71	40	1397		7 months
		ATO (brand switch back)	10/primary		58 ^b	52 ^b	35 ^b	144 ^b		5 months ^c

Lipid levels reported as mmol/L were converted to mg/dL: HDL and LDL = mmol/L × 38.67; TG = mmol/L × 88.57
 CK Creatine kinase, HDL-C high-density lipoprotein-cholesterol, LDL-C low-density lipoprotein-cholesterol, NS not significant, TG triglyceride
^{*}*p* < 0.01 (median change in HDL-C); ^{**}*p* < 0.01 (mean change in HDL-C)

^a No significant intergroup differences found

^b *p* values not reported

^c Patients had to be taking generic atorvastatin for at least 3 months to be included (after switching); blood test taken at least 3 months after transition date

^d Patients had to be taking generic atorvastatin for at least 1 month to be included (after switching)

^e Period of time for taking of each type of treatment

When looking at longer-term outcomes, a single study by Jackevicius et al. [60] that enrolled patients aged ≥ 65 years with acute coronary syndrome and prescribed either branded or generic atorvastatin upon discharge from hospital showed that both cohorts remained adherent with their medications, with an identical MPR of 88.4% [60] (Table 1). Patients taking branded or generic atorvastatin had an equivalent rate of MI/angina (17.7% for both), heart failure (6.3 vs. 6.6%), stroke (1.6 vs. 1.9%) or overall mortality (11.6%), which might be anticipated given the similar MPR [60]. No other articles were identified that monitored the long-term CV outcomes of branded versus generic atorvastatin. However, similar to the conclusions drawn by Jackevicius et al., a study by Corrao et al. [77] that followed 13,799 patients newly prescribed generic or branded simvastatin showed no difference in persistence or CV outcomes over a 3-year period. It has been shown that patients are more likely to adhere to their statin treatment regimen following a cardiac event [56, 78, 79] and that statin patients following an MI are approximately 10% more adherent than primary treatment patients [80].

WHAT EVIDENCE IS NEEDED TO HELP IMPROVE ADHERENCE IN THE REAL-WORLD SETTING: GAPS IN THE LITERATURE

In this review we highlight that many barriers to adherence occur throughout the initiation, execution and persistence stages of treatment [30, 81, 82]. These factors have been reviewed extensively elsewhere and have been broadly characterized into five interacting factors [30]: patient-related (lifestyle, perceptions), socio-economic (demographics, costs, family, country, conflict), therapy-related (side effects, treatment regimen/concomitant medications, type of statin [formulation, branded, generic], dose), condition-related (disabilities, disease severity, comorbidities, access to treatment) and healthcare-related factors (patient interactions, physician perceptions of therapy effectiveness, clinical inertia) [23, 30, 55, 83, 84].

However, we also highlight a paucity of data directly comparing real-world adherence with atorvastatin to longer-term lipid and CV outcomes and, in addition, whether the introduction and use of generic formulations has impacted CV morbidity and mortality. The conclusions reported here are drawn from mixed sources depending on available studies, but we highlight a number of gaps in the literature that could be addressed by future studies in this area (Table 3).

The literature on outcomes in patients who initiated or switched between branded atorvastatin and its generic version was also sparse; instead, we frequently found studies focusing on therapeutic substitution (switching between different types of statin) [85–94]. Studies that saw improved adherence with switching therapies highlighted associations with increasing age, prior CVD and polypharmacy, with the authors suggesting that patients who are switched may receive more attention at the pharmacy [95]. In patients initiated on generic statins, lower out-of-pocket expenses have been associated with improved adherence and persistence [88, 96]. Conversely, variability in excipients and co-payment effects are potential hurdles to compliance upon switching statin therapy [65]. Real-world observational studies are needed which monitor adherence and persistence alongside lipid outcomes and therapeutic goal attainment, but also factor in these barriers to adherence (Table 3).

HOW CAN HEALTHCARE PROVIDERS WORK TO IMPROVE ADHERENCE IN THE REAL-WORLD SETTING? PRACTICAL ADVICE FOR IMPROVING STATIN THERAPY ADHERENCE

Although physicians are aware of the importance of treatment optimization, additional factors more specific to lipid-lowering therapies should be considered. For example, patients with dyslipidemia do not have immediate ‘feedback’ to recognize/feel improvements in their condition associated with lipid-lowering

Table 3 Barriers to adherence with atorvastatin therapy: gaps in the current literature

Dimension of adherence^a	Barrier to adherence with atorvastatin therapy	Possible resolution?	Gap in literature?
Therapy-related; condition-related	Medication regimen (too many pills)	Simplify medication regimen	Supports use of SPC therapy (where possible) to lower pill burden
Therapy-related	Generic formulation	Medication appearance	Supports use of uniform medication appearance (packaging and pills) across formulations (generic, branded)
Healthcare-related	Generic formulation	Physician education around bioequivalence	Use of training materials for healthcare providers to improve confidence when prescribing generics
Healthcare-related	Generic formulation	Patient reassurance when switching	The impact on adherence and cost-effectiveness of patient education and regular consultations
Healthcare-related	Medication regimen (dose intensity)	Lower dose	
Healthcare-related; patient-related	Generic formulation	Regular follow-up	
Healthcare-related; patient-related	Medication regimen; patient satisfaction with long-term usage	Regular follow-up and discussion concerning treatment goals	The impact of atorvastatin use in a real-world setting over the long term. Support regular follow-ups to facilitate adherence and testing to provide evidence of benefit
Healthcare-related; patient-related	Inadequate patient–physician relationship	Healthcare provider education	Creating a strong relationship improves adherence by improving trust in efficacy of drug/treatment regimen
Healthcare-related; patient-related	The nocebo effect	Healthcare provider and patient education	Perceptions of generic or branded treatments impact adherence; education can improve confidence and, in turn, improve adherence
Patient-related	Generic formulation	Patient consent	Adherence in patients who approved switching to a new formulation vs those who did not

Table 3 continued

Dimension of adherence^a	Barrier to adherence with atorvastatin therapy	Possible resolution?	Gap in literature?
Patient-related	Patient preference and satisfaction	Patient preference is honored (where possible)	Patients who are satisfied with their treatment regimen are more likely to remain adherent with therapy
Patient-related; socio-economic	Socio-demographics—pill rationing or sharing	Maximally tolerated dose	Increasing dosage for low-income patients reduces refills/pharmacy visits and reduces incidence of sharing
Patient-related; socio-economic; Healthcare-related	Patient age and the role of carers	Medication palatability and follow-up with carers	Improving palatability of medication. The impact of carers with children on adherence
Condition-related; patient-related	No direct biofeedback	Patient education to ensure they understand and are invested in lipid measurements	Patients who return to receive their lipid measurements are more likely to remain adherent with therapy
Condition-related; healthcare-related	Different formulations of statins are not bioequivalent	Healthcare provider education	Physician education of statin dose equivalency upon switching to avoid inappropriate dosing
Condition-related; healthcare-related	Out-of-date understanding of clinical practice targets	Educational materials for general practitioners who are not up-to-date with current prescribing guidelines preventing on-target treatment	Targeted primary care education improves knowledge of current treatment practices

SPC Single-pill combination

^a Based on the 5-dimensions of adherence, as outlined by the World Health Organization [30]

therapy. This lack of perceived benefit may negatively impact adherence [63, 97]; therefore, a blood test and follow-up assessment are required to confirm if patients are taking medications as prescribed [16]. Subsequent appointments may be needed to further allow healthcare providers to consult patients about their medication adherence and to discuss reasons for non-adherence, all of which require active benefit on the part of both patient and prescriber. A patient–physician interaction

provides the physician with an opportunity to consider changes to the treatment regimen (e.g. up-titration, concomitant therapy, monitoring of AEs) or, if needed, to provide further support (e.g. counseling, reminders, support group sessions, involving family) to ensure adherence to achieve recommended treatment targets [16, 98]. The relationship between patient and physician should be based on both verbal and non-verbal communication (‘body language’) aimed at increasing patient understanding of

their disease and the risks and benefits of the chosen treatment [99]. Mutual collaboration between patient and healthcare provider can not only reduce the risks of non-adherence, but also improve patient satisfaction with therapy and, ultimately, patients' healthcare outcomes [99]. Healthcare providers should also consider the demographics of their patients. For instance, while statins are increasingly used in some children (aged > 10 years), particularly those with genetic lipid disorders [100], limited data are available on adherence in this patient population. Considerations of age-appropriate formulations, weight-appropriate dosing, acceptability, palatability and the role of their parents/carers are critical for improving adherence in the pediatric population, and further studies are required to understand their influence with real-world statin usage [101, 102]. This trust is especially important for statin patients, as chronic medication regimens, fear of AEs and polypharmacy are all factors linked to poor adherence [103].

Patient perceptions also influence adherence to statins and are intrinsically tied to treatment-related factors [23, 30, 83]. Studies are needed that link patient's perception and preference with their statin formulation to adherence. When focusing on generic versus branded atorvastatin therapy, we were unable to identify any studies that included a survey of patient preferences or perceptions of their atorvastatin medication (i.e. perceived benefit or need) (Table 3). In this review of the literature, only a single study by Tsioufis et al. was identified that reported both atorvastatin adherence and treatment satisfaction data [58]. In this study of 190 patients from Greece, the authors report that global patient satisfaction and perceived effectiveness, measured by the Treatment Satisfaction Questionnaire for Medication (TSQM), in those who did not switch to generic atorvastatin was significantly higher versus those who switched (mean score 68 vs. 58, respectively; $p < 0.001$) [58]. These observations support the association between patient treatment satisfaction and greater treatment adherence/persistence, an association that has been noted in other non-atorvastatin studies [104, 105]. While most physicians discuss statin treatment

with their patients, those patients who discontinue have reported being less satisfied with these discussions [106]. Thus, poor adherence as a consequence of patient perceptions is also closely tied to interactions with their physician and may be compounded by a non-perceived benefit and/or medical distrust [83]. On balance, it remains unclear whether the prescription of generic or branded atorvastatin influences adherence in a real-world setting. Studies investigating patient perceptions would help physicians understand this patient-related barrier to adherence with atorvastatin therapy (Table 3).

CONCLUSIONS

Adherence to atorvastatin remains suboptimal in the real-world setting, and the introduction of generic formulations adds further complexity to the multifaceted issues around poor adherence. There are clear gaps in the literature concerning the factors responsible for poor adherence and their impact on efficacy outcomes, including data on cost, long-term usage, patient perspectives and polypharmacy. Furthermore, we highlight a paucity of real-world data from comparisons between initiation with branded or generic atorvastatin and the impact on adherence/persistence and lipid/CV outcomes. However, healthcare providers should consider the potential impact on adherence of switching patients between branded and generic medications. Targeted education initiatives and additional research are still needed with the aim to improve adherence to atorvastatin in the clinical setting.

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REFERENCES

1. Adams SP, Tsang M, Wright JM. Lipid lowering efficacy of atorvastatin. *Cochrane Database Syst Rev.* 2012;12: CD008226. <https://doi.org/10.1002/14651858.CD008226.pub2>.
2. Loch A, Bewersdorf JP, Kofink D, Ismail D, Abidin IZ, Veriah RS. Generic atorvastatin is as effective as the brand-name drug Lipitor® in lowering cholesterol levels: a cross-sectional retrospective cohort study. *BMC Res Notes.* 2017;10:291. <https://doi.org/10.1186/s13104-017-2617-6>.
3. Amarenco P, Bogousslavsky J, Callahan A 3rd, et al. High-dose atorvastatin after stroke or transient ischemic attack. *N Engl J Med.* 2006;355:549–59. <https://doi.org/10.1056/NEJMoa061894>.
4. LaRosa JC, Grundy SM, Waters DD, et al. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *N Engl J Med.* 2005;352: 1425–35. <https://doi.org/10.1056/NEJMoa050461>.
5. Pedersen TR, Faergeman O, Kastelein JJ, et al. High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction: the IDEAL study: a randomized controlled trial. *JAMA.* 2005;294:2437–45. <https://doi.org/10.1001/jama.294.19.2437>.
6. Cannon CP, Braunwald E, McCabe CH, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med.* 2004;350:1495–504. <https://doi.org/10.1056/NEJMoa040583>.
7. Sever PS, Dahlof B, Poulter NR, et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA): a multicentre

- randomised controlled trial. *Lancet*. 2003;361:1149–58. [https://doi.org/10.1016/S0140-6736\(03\)12948-0](https://doi.org/10.1016/S0140-6736(03)12948-0).
8. Koren MJ, Hunninghake DB, ALLIANCE Investigators. Clinical outcomes in managed-care patients with coronary heart disease treated aggressively in lipid-lowering disease management clinics: the alliance study. *J Am Coll Cardiol*. 2004;44:1772–9. <https://doi.org/10.1016/j.jacc.2004.07.053>.
 9. Knopp RH, d’Emden M, Smilde JG, Pocock SJ. Efficacy and safety of atorvastatin in the prevention of cardiovascular end points in subjects with type 2 diabetes: the Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in non-insulin-dependent diabetes mellitus (ASPEN). *Diabetes Care*. 2006;29:1478–85. <https://doi.org/10.2337/dc05-2415>.
 10. Pitt B, Waters D, Brown WV, et al. Aggressive lipid-lowering therapy compared with angioplasty in stable coronary artery disease. Atorvastatin versus Revascularization Treatment Investigators. *N Engl J Med*. 1999;341:70–6. <https://doi.org/10.1056/NEJM199907083410202>.
 11. Colhoun HM, Betteridge DJ, Durrington PN, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *Lancet*. 2004;364:685–96. [https://doi.org/10.1016/S0140-6736\(04\)16895-5](https://doi.org/10.1016/S0140-6736(04)16895-5).
 12. Wanner C, Krane V, Marz W, et al. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. *N Engl J Med*. 2005;353:238–48. <https://doi.org/10.1056/NEJMoa043545>.
 13. Schwartz GG, Olsson AG, Ezekowitz MD, et al. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes: the MIRACL study: a randomized controlled trial. *JAMA*. 2001;285:1711–8. <https://doi.org/10.1001/jama.285.13.1711>.
 14. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. *J Am Coll Cardiol*. 2019;73:e285–350. <https://doi.org/10.1016/j.jacc.2018.11.003>.
 15. Ference BA, Ginsberg HN, Graham I, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. *Eur Heart J*. 2017;38:2459–72. <https://doi.org/10.1093/eurheartj/ehx144>.
 16. Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J*. 2020;41:111–88. <https://doi.org/10.1093/eurheartj/ehz455>.
 17. Roughead EE, Kim DS, Ong B, Kemp-Casey A. Pricing policies for generic medicines in Australia, New Zealand, the Republic of Korea and Singapore: patent expiry and influence on atorvastatin price. *WHO South East Asia J Public Health*. 2018;7:99–106. <https://doi.org/10.4103/2224-3151.239421>.
 18. Andrade C. Bioequivalence of generic drugs: a simple explanation for a US Food and Drug Administration requirement. *J Clin Psychiatry*. 2015;76:e742–744. <https://doi.org/10.4088/JCP.15f10094>.
 19. Rosenson RS, Farkouh ME, Mefford M, et al. Trends in use of high-intensity statin therapy after myocardial infarction, 2011 to 2014. *J Am Coll Cardiol*. 2017;69:2696–706. <https://doi.org/10.1016/j.jacc.2017.03.585>.
 20. Minard LV, Corkum A, Sketris I, Fisher J, Zhang Y, Saleh A. Trends in statin use in seniors 1999 to 2013: time series analysis. *PLoS One*. 2016;11:e0158608. <https://doi.org/10.1371/journal.pone.0158608>.
 21. Chapman SR, Fitzpatrick RW, Aladul MI. Has cost inhibited the uptake of more potent statins in England? *Pharmacoepidemiol Drug Saf*. 2017;26:984–91. <https://doi.org/10.1002/pds.4231>.
 22. Son KB, Bae S. Patterns of statin utilisation for new users and market dynamics in South Korea: a 13-year retrospective cohort study. *BMJ Open*. 2019;9:e026603. <https://doi.org/10.1136/bmjopen-2018-026603>.
 23. Maningat P, Gordon BR, Breslow JL. How do we improve patient compliance and adherence to long-term statin therapy? *Curr Atheroscler Rep*. 2013;15:291. <https://doi.org/10.1007/s11883-012-0291-7>.
 24. Beintner I, Vollert B, Zarski AC, et al. Adherence reporting in randomized controlled trials examining manualized multisession online interventions: systematic review of practices and proposal for reporting standards. *J Med Internet Res*. 2019;21:e14181. <https://doi.org/10.2196/14181>.
 25. Eliasson L, Clifford S, Mulick A, Jackson C, Vrijens B. How the EMERGE guideline on medication adherence can improve the quality of clinical trials.

- Br J Clin Pharmacol. 2020;86:687–97. <https://doi.org/10.1111/bcp.14240>.
26. Piepoli MF, Hoes AW, Agewall S, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: the Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J*. 2016;37:2315–81. <https://doi.org/10.1093/eurheartj/ehw106>.
 27. Kotseva K, De Backer G, De Bacquer D, et al. Lifestyle and impact on cardiovascular risk factor control in coronary patients across 27 countries: results from the European Society of Cardiology ESC-EORP EUROASPIRE V registry. *Eur J Prev Cardiol*. 2019;26:824–35. <https://doi.org/10.1177/2047487318825350>.
 28. Blonde L, Khunti K, Harris SB, Meizinger C, Skolnik NS. Interpretation and impact of real-world clinical data for the practicing clinician. *Adv Ther*. 2018;35:1763–74. <https://doi.org/10.1007/s12325-018-0805-y>.
 29. Bartlett VL, Dhruva SS, Shah ND, Ryan P, Ross JS. Feasibility of using real-world data to replicate clinical trial evidence. *JAMA Netw Open*. 2019;2:e1912869. <https://doi.org/10.1001/jamanetworkopen.2019.12869>.
 30. World Health Organization (WHO). Adherence to long-term therapies. Evidence for action. 2003. <https://apps.who.int/iris/bitstream/handle/10665/42682/9241545992.pdf>. Accessed 22 Jul 2021.
 31. Anghel LA, Farcas AM, Oprean RN. Medication adherence and persistence in patients with autoimmune rheumatic diseases: a narrative review. *Patient Prefer Adherence*. 2018;12:1151–66. <https://doi.org/10.2147/PPA.S165101>.
 32. Cramer JA, Roy A, Burrell A, et al. Medication compliance and persistence: terminology and definitions. *Value Health*. 2008;11:44–7. <https://doi.org/10.1111/j.1524-4733.2007.00213.x>.
 33. Anghel LA, Farcas AM, Oprean RN. An overview of the common methods used to measure treatment adherence. *Med Pharm Rep*. 2019;92:117–22. <https://doi.org/10.15386/mpr-1201>.
 34. Pednekar PP, Agh T, Malmenas M, et al. Methods for measuring multiple medication adherence: a systematic review-report of the ISPOR medication adherence and persistence special interest group. *Value Health*. 2019;22:139–56. <https://doi.org/10.1016/j.jval.2018.08.006>.
 35. Raebel MA, Schmittiel J, Karter AJ, Konieczny JL, Steiner JF. Standardizing terminology and definitions of medication adherence and persistence in research employing electronic databases. *Med Care*. 2013;51:S11–21. <https://doi.org/10.1097/MLR.0b013e31829b1d2a>.
 36. Al-Hassany L, Kloosterboer SM, Dierckx B, Koch BC. Assessing methods of measuring medication adherence in chronically ill children—a narrative review. *Patient Prefer Adherence*. 2019;13:1175–89. <https://doi.org/10.2147/PPA.S200058>.
 37. Brown MT, Bussell JK. Medication adherence: WHO cares? *Mayo Clin Proc*. 2011;86:304–14. <https://doi.org/10.4065/mcp.2010.0575>.
 38. Meier R, Rachamin Y, Rosemann T, Markun S. The impact of the 2019 European guideline for cardiovascular risk management: a cross-sectional study in general practice. *J Clin Med*. 2020;9:2140. <https://doi.org/10.3390/jcm9072140>.
 39. Sever PS, Chang CL, Gupta AK, Whitehouse A, Poulter NR, Investigators A. The Anglo-Scandinavian Cardiac Outcomes Trial: 11-year mortality follow-up of the lipid-lowering arm in the UK. *Eur Heart J*. 2011;32:2525–32. <https://doi.org/10.1093/eurheartj/ehr333>.
 40. Taylor F, Huffman MD, Macedo AF, et al. Statins for the primary prevention of cardiovascular disease. *Cochrane Database Syst Rev*. 2013;2013(1):CD004816. <https://doi.org/10.1002/14651858.CD004816.pub5>.
 41. Danchin N, Almahmeed W, Al-Rasadi K, et al. Achievement of low-density lipoprotein cholesterol goals in 18 countries outside Western Europe: the International Cholesterol management Practice Study (ICLPS). *Eur J Prev Cardiol*. 2018;25:1087–94. <https://doi.org/10.1177/2047487318777079>.
 42. Arca M, Ansell D, Averna M, et al. Statin utilization and lipid goal attainment in high or very-high cardiovascular risk patients: insights from Italian general practice. *Atherosclerosis*. 2018;271:120–7. <https://doi.org/10.1016/j.atherosclerosis.2018.02.024>.
 43. Presta V, Figliuzzi I, Miceli F, et al. Achievement of low density lipoprotein (LDL) cholesterol targets in primary and secondary prevention: analysis of a large real practice database in Italy. *Atherosclerosis*. 2019;285:40–8. <https://doi.org/10.1016/j.atherosclerosis.2019.03.017>.
 44. Degli Esposti L, Saragoni S, Batacchi P, et al. Adherence to statin treatment and health outcomes in an Italian cohort of newly treated patients: results from an administrative database analysis.

- Clin Ther. 2012;34:190–9. <https://doi.org/10.1016/j.clinthera.2011.12.011>.
45. Zhang W, Ji F, Yu X, Wang X. Factors associated with unattained LDL-cholesterol goals in Chinese patients with acute coronary syndrome one year after percutaneous coronary intervention. *Medicine (Baltimore)*. 2017;96:e5469. <https://doi.org/10.1097/MD.0000000000005469>.
46. Martin SS, Gosch K, Kulkarni KR, et al. Modifiable factors associated with failure to attain low-density lipoprotein cholesterol goal at 6 months after acute myocardial infarction. *Am Heart J*. 2013;165(26–33):e23. <https://doi.org/10.1016/j.ahj.2012.10.005>.
47. De Vera MA, Bhole V, Burns LC, Lacaille D. Impact of statin adherence on cardiovascular disease and mortality outcomes: a systematic review. *Br J Clin Pharmacol*. 2014;78:684–98. <https://doi.org/10.1111/bcp.12339>.
48. Deshpande S, Quek RG, Forbes CA, et al. A systematic review to assess adherence and persistence with statins. *Curr Med Res Opin*. 2017;33:769–78. <https://doi.org/10.1080/03007995.2017.1281109>.
49. Zhu JR, Tomlinson B, Ro YM, Sim KH, Lee YT, Sri-ratanasathavorn C. A randomised study comparing the efficacy and safety of rosuvastatin with atorvastatin for achieving lipid goals in clinical practice in Asian patients at high risk of cardiovascular disease (DISCOVERY-Asia study). *Curr Med Res Opin*. 2007;23:3055–68. <https://doi.org/10.1185/030079907x242809>.
50. Ohsfeldt RL, Gandhi SK, Fox KM, Stacy TA, McKenney JM. Effectiveness and cost-effectiveness of rosuvastatin, atorvastatin, and simvastatin among high-risk patients in usual clinical practice. *Am J Manag Care*. 2006;12:S412–423.
51. Reiner Z, Tedeschi-Reiner E. Prevalence and types of persistent dyslipidemia in patients treated with statins. *Croat Med J*. 2013;54:339–45. <https://doi.org/10.3325/cmj.2013.54.339>.
52. Holme I, Szarek M, Cater NB, et al. Adherence-adjusted efficacy with intensive versus standard statin therapy in patients with acute myocardial infarction in the IDEAL study. *Eur J Cardiovasc Prev Rehabil*. 2009;16:315–20. <https://doi.org/10.1097/HJR.0b013e32832130f5>.
53. Rublee DA, Chen SY, Mardekian J, Wu N, Rao P, Boulanger L. Evaluation of cardiovascular morbidity associated with adherence to atorvastatin therapy. *Am J Ther*. 2012;19:24–32. <https://doi.org/10.1097/MJT.0b013e3181ee707e>.
54. Goswami NJ, Dekoven M, Kuznik A, et al. Impact of an integrated intervention program on atorvastatin adherence: a randomized controlled trial. *Int J Gen Med*. 2013;6:647–55. <https://doi.org/10.2147/IJGM.S47518>.
55. Casula M, Tragni E, Catapano AL. Adherence to lipid-lowering treatment: the patient perspective. *Patient Prefer Adherence*. 2012;6:805–14. <https://doi.org/10.2147/PPA.S29092>.
56. Kolandaivelu K, Leiden BB, O’Gara PT, Bhatt DL. Non-adherence to cardiovascular medications. *Eur Heart J*. 2014;35:3267–76. <https://doi.org/10.1093/eurheartj/ehu364>.
57. Romanelli RJ, Segal JB. Predictors of statin compliance after switching from branded to generic agents among managed-care beneficiaries. *J Gen Intern Med*. 2014;29:1372–8. <https://doi.org/10.1007/s11606-014-2933-7>.
58. Tsioufis C, Kasiakogias A, Kyriazopoulos K, et al. The impact of switching from prototype to generic atorvastatin on persistence and compliance in Greece: the lipid study. *J Hypertens*. 2017;35:E124–E124. <https://doi.org/10.1097/01.hjh.0000523317.25842.54>.
59. Mano Y, Fukushima S, Kuroda H, et al. Adherence to changing from brand-name to generic atorvastatin in newly treated patients: a retrospective cohort study using health insurance claims. *J Pharm Health Care Sci*. 2015;1:12. <https://doi.org/10.1186/s40780-015-0013-8>.
60. Jackevicius CA, Tu JV, Krumholz HM, et al. Comparative effectiveness of generic atorvastatin and Lipitor® in patients hospitalized with an acute coronary syndrome. *J Am Heart Assoc*. 2016;5:e003350. <https://doi.org/10.1161/JAHA.116.003350>.
61. Kwon HY, Godman B. Do newly marketed generic medicines expand markets using descriptive time series analysis and mixed logit models? Korea as an exemplar and its implications. *BMC Health Serv Res*. 2016;16:130. <https://doi.org/10.1186/s12913-016-1356-z>.
62. Jimmy B, Jose J. Patient medication adherence: measures in daily practice. *Oman Med J*. 2011;26:155–9. <https://doi.org/10.5001/omj.2011.38>.
63. Ofori-Asenso R, Jakhu A, Zomer E, et al. Adherence and persistence among statin users aged 65 years and over: a systematic review and meta-analysis. *J Gerontol A Biol Sci Med Sci*. 2018;73:813–9. <https://doi.org/10.1093/gerona/glx169>.
64. Lumbreras B, Lopez-Pintor E. Impact of changes in pill appearance in the adherence to angiotensin

- receptor blockers and in the blood pressure levels: a retrospective cohort study. *BMJ Open*. 2017;7:e012586. <https://doi.org/10.1136/bmjopen-2016-012586>.
65. Sicras-Mainar A, Sanchez-Alvarez L, Navarro-Artieda R, Darba J. Treatment persistence and adherence and their consequences on patient outcomes of generic versus brand-name statins routinely used to treat high cholesterol levels in Spain: a retrospective cost-consequences analysis. *Lipids Health Dis*. 2018;17(1):277. <https://doi.org/10.1186/s12944-018-0918-y>.
66. Awoniyi O, Gosmanov AR. Myopathy after switching from brand to generic atorvastatin. *J Am Geriatr Soc*. 2013;61:2254–5. <https://doi.org/10.1111/jgs.12559>.
67. Rahalkar AR, Ban MR, Hegele RA. Clinical equivalence of proprietary and generic atorvastatin in lipid clinic patients. *Can J Cardiol*. 2013;29:418–22. <https://doi.org/10.1016/j.cjca.2012.05.010>.
68. Reker D, Blum SM, Steiger C, et al. “Inactive” ingredients in oral medications. *Sci Transl Med*. 2019;11:eaau6753. <https://doi.org/10.1126/scitranslmed.aau6753>.
69. Boh M, Opolski G, Poredos P, Ceska R, Jezovnik M. Therapeutic equivalence of the generic and the reference atorvastatin in patients with increased coronary risk. *Int Angiol*. 2011;30:366–74.
70. Kim SH, Park K, Hong SJ, et al. Efficacy and tolerability of a generic and a branded formulation of atorvastatin 20 mg/d in hypercholesterolemic Korean adults at high risk for cardiovascular disease: a multicenter, prospective, randomized, double-blind, double-dummy clinical trial. *Clin Ther*. 2010;32:1896–905. <https://doi.org/10.1016/j.clinthera.2010.10.004>.
71. Kim SH, Seo MK, Yoon MH, Choi DH, Hong TJ, Kim HS. Assessment of the efficacy and tolerability of 2 formulations of atorvastatin in Korean adults with hypercholesterolemia: a multicenter, prospective, open-label, randomized trial. *Clin Ther*. 2013;35:77–86. <https://doi.org/10.1016/j.clinthera.2012.11.009>.
72. Lee JH, Kim SH, Choi DJ, et al. Efficacy and tolerability of two different formulations of atorvastatin in Korean patients with hypercholesterolemia: a multicenter, prospective, randomized clinical trial. *Drug Des Devel Ther*. 2017;11:2277–85. <https://doi.org/10.2147/DDDT.S112241>.
73. Colgan S, Faasse K, Martin LR, Stephens MH, Grey A, Petrie KJ. Perceptions of generic medication in the general population, doctors and pharmacists: a systematic review. *BMJ Open*. 2015;5:e008915. <https://doi.org/10.1136/bmjopen-2015-008915>.
74. Gupta A, Thompson D, Whitehouse A, et al. Adverse events associated with unblinded, but not with blinded, statin therapy in the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid-Lowering Arm (ASCOT-LLA): a randomised double-blind placebo-controlled trial and its non-randomised non-blind extension phase. *Lancet*. 2017;389:2473–81. [https://doi.org/10.1016/S0140-6736\(17\)31075-9](https://doi.org/10.1016/S0140-6736(17)31075-9).
75. Faasse K, Cundy T, Gamble G, Petrie KJ. The effect of an apparent change to a branded or generic medication on drug effectiveness and side effects. *Psychosom Med*. 2013;75:90–6. <https://doi.org/10.1097/PSY.0b013e3182738826>.
76. Desai RJ, Sarpatwari A, Dejene S, et al. Comparative effectiveness of generic and brand-name medication use: a database study of US health insurance claims. *PLoS Med*. 2019;16:e1002763. <https://doi.org/10.1371/journal.pmed.1002763>.
77. Corrao G, Soranna D, Arfe A, et al. Are generic and brand-name statins clinically equivalent? Evidence from a real data-base. *Eur J Intern Med*. 2014;25:745–50. <https://doi.org/10.1016/j.ejim.2014.08.002>.
78. Kronish IM, Ross JS, Zhao H, Muntner P. Impact of hospitalization for acute myocardial infarction on adherence to statins among older adults. *Circ Cardiovasc Qual Outcomes*. 2016;9:364–71. <https://doi.org/10.1161/CIRCOUTCOMES.115.002418>.
79. Hickson RP, Robinson JG, Annis IE, Killeya-Jones LA, Fang G. It’s not too late to improve statin adherence: association between changes in statin adherence from before to after acute myocardial infarction and all-cause mortality. *J Am Heart Assoc*. 2019;8:e011378. <https://doi.org/10.1161/JAHA.118.011378>.
80. Colantonio LD, Rosenson RS, Deng L, et al. Adherence to statin therapy among US adults between 2007 and 2014. *J Am Heart Assoc*. 2019;8:e010376. <https://doi.org/10.1161/JAHA.118.010376>.
81. Drexel H, Coats AJS, Spoletini I, et al. ESC position paper on statins adherence and implementation of new lipid-lowering medications: barriers to be overcome. *Eur Heart J Cardiovasc Pharmacother*. 2020;6:115–21. <https://doi.org/10.1093/ehjcvp/pvz079>.
82. Vonbank A, Agewall S, Kjeldsen KP, et al. Comprehensive efforts to increase adherence to statin therapy. *Eur Heart J*. 2017;38:2473–9. <https://doi.org/10.1093/eurheartj/ehw628>.

83. Ingersgaard MV, Helms Andersen T, Norgaard O, Grabowski D, Olesen K. Reasons for nonadherence to statins—a systematic review of reviews. *Patient Prefer Adherence*. 2020;14:675–91. <https://doi.org/10.2147/PPA.S245365>.
84. Vashitz G, Meyer J, Parmet Y, Henkin Y, Peleg R, Gilutz H. Physician adherence to the dyslipidemia guidelines is as challenging an issue as patient adherence. *Fam Pract*. 2011;28:524–31. <https://doi.org/10.1093/fampra/cm025>.
85. Folse H, Sternhufvud C, Andy Schuetz C, Rengarajan B, Gandhi S. Impact of switching treatment from rosuvastatin to atorvastatin on rates of cardiovascular events. *Clin Ther*. 2014;36:58–69. <https://doi.org/10.1016/j.clinthera.2013.12.003>.
86. O'Brien EC, McCoy LA, Thomas L, Peterson ED, Wang TY. Patient adherence to generic versus brand statin therapy after acute myocardial infarction: insights from the can rapid stratification of unstable angina patients suppress adverse outcomes with early implementation of the American College of Cardiology/American Heart Association Guidelines Registry. *Am Heart J*. 2015;170:55–61. <https://doi.org/10.1016/j.ahj.2015.04.011>.
87. Degli Esposti L, Sangiorgi D, Buda S, Degli Esposti E, Scaglione F. Therapy discontinuation or substitution in patients with cardiovascular disease, switching among different products of the same off-patent active substance: a “real-world” retrospective cohort study. *BMJ Open*. 2016;6:e012003. <https://doi.org/10.1136/bmjopen-2016-012003>.
88. Gagne JJ, Choudhry NK, Kesselheim AS, et al. Comparative effectiveness of generic and brand-name statins on patient outcomes: a cohort study. *Ann Intern Med*. 2014;161:400–7. <https://doi.org/10.7326/M13-2942>.
89. Gandhi SK, Jensen MM, Fox KM, Smolen L, Olsson AG, Paulsson T. Cost-effectiveness of rosuvastatin in comparison with generic atorvastatin and simvastatin in a Swedish population at high risk of cardiovascular events. *Clinicoecon Outcomes Res*. 2012;4:1–11. <https://doi.org/10.2147/CEOR.S26621>.
90. Kakavas PW, McManus JL, Wolfe TA, et al. The need for a systematic approach to statin switching: an analysis of real-world experience. *J Cardiovasc Nurs*. 2013;28:565–72. <https://doi.org/10.1097/JCN.0b013e31826fe89d>.
91. Liew D, Webb K, Meerding WJ, Buskens E, Jukema JW. Potential cardiovascular consequences of switching from atorvastatin to generic simvastatin in the Netherlands. *Neth Heart J*. 2012;20:197–201. <https://doi.org/10.1007/s12471-012-0243-4>.
92. Rublee DA, Burke JP. LDL-C goal attainment in patients who remain on atorvastatin or switch to equivalent or non-equivalent doses of simvastatin: a retrospective matched cohort study in clinical practice. *Postgrad Med*. 2010;122:16–24. <https://doi.org/10.3810/pgm.2010.03.2118>.
93. Simpson RJ Jr, Signorovitch J, Birnbaum H, et al. Cardiovascular and economic outcomes after initiation of lipid-lowering therapy with atorvastatin vs simvastatin in an employed population. *Mayo Clin Proc*. 2009;84:1065–72. <https://doi.org/10.4065/mcp.2009.0298>.
94. Cao X, Ejzykowicz F, Ramey DR, et al. Impact of switching from high-efficacy lipid-lowering therapies to generic simvastatin on LDL-C levels and LDL-C goal attainment among high-risk primary and secondary prevention populations in the United Kingdom. *Clin Ther*. 2015;37:804–15. <https://doi.org/10.1016/j.clinthera.2014.12.019>.
95. Trusell H, Sundell KA. Effects of generic substitution on refill adherence to statin therapy: a nationwide population-based study. *BMC Health Serv Res*. 2014;14:626. <https://doi.org/10.1186/s12913-014-0626-x>.
96. Helin-Salmivaara A, Korhonen MJ, Alanen T, Huupponen R. Impact of out-of-pocket expenses on discontinuation of statin therapy: a cohort study in Finland. *J Clin Pharm Ther*. 2012;37:58–64. <https://doi.org/10.1111/j.1365-2710.2011.01250.x>.
97. Chapman RH, Pelletier EM, Smith PJ, Roberts CS. Can adherence to antihypertensive therapy be used to promote adherence to statin therapy? *Patient Prefer Adherence*. 2009;3:265–75. <https://doi.org/10.2147/ppa.s5868>.
98. Haynes RB, McDonald HP, Garg AX. Helping patients follow prescribed treatment: clinical applications. *JAMA*. 2002;288:2880–3. <https://doi.org/10.1001/jama.288.22.2880>.
99. Martin LR, Williams SL, Haskard KB, Dimatteo MR. The challenge of patient adherence. *Ther Clin Risk Manag*. 2005;1:189–99.
100. Vuorio A, Kuoppala J, Kovanen PT, et al. Statins for children with familial hypercholesterolemia. *Cochrane Database Syst Rev*. 2019;2019(11):CD006401. <https://doi.org/10.1002/14651858.CD006401.pub5>.
101. Kearns GL, Abdel-Rahman SM, Alander SW, Blowey DL, Leeder JS, Kauffman RE. Developmental pharmacology—drug disposition, action, and therapy in infants and children. *N Engl J Med*. 2003;349:1157–67. <https://doi.org/10.1056/NEJMra035092>.

102. Ferro A. Paediatric prescribing: why children are not small adults. *Br J Clin Pharmacol*. 2015;79:351–3. <https://doi.org/10.1111/bcp.12540>.
103. Osterberg L, Blaschke T. Adherence to medication. *N Engl J Med*. 2005;353:487–97. <https://doi.org/10.1056/NEJMra050100>.
104. Jneid S, Jabbour H, Hajj A, et al. Quality of life and its association with treatment satisfaction, adherence to medication, and trust in physician among patients with hypertension: a cross-sectional designed study. *J Cardiovasc Pharmacol Ther*. 2018;23:532–42. <https://doi.org/10.1177/1074248418784292>.
105. Barbosa CD, Balp MM, Kulich K, Germain N, Rofail D. A literature review to explore the link between treatment satisfaction and adherence, compliance, and persistence. *Patient Prefer Adherence*. 2012;6:39–48. <https://doi.org/10.2147/PPA.S24752>.
106. Cohen JD, Brinton EA, Ito MK, Jacobson TA. Understanding Statin Use in America and Gaps in Patient Education (USAGE): an internet-based survey of 10,138 current and former statin users. *J Clin Lipidol*. 2012;6:208–15. <https://doi.org/10.1016/j.jacl.2012.03.003>.