

# Nonadherence to statins: individualized intervention strategies outside the pill box

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**Abstract:** Poor adherence to statin therapy is linked to significantly increased risk of cardiovascular events and death. Unfortunately, adherence to statins is far from optimal. This is an alarming concern for patients prescribed potentially life-saving cholesterol-lowering medication, especially for those at high risk of cardiovascular events. Research on statin adherence has only recently garnered broader attention; hence, major reasons unique to adherence to statin therapy need to be identified as well as suggestions for countermeasures. An integrated approach to minimizing barriers and enhancing facilitation at the levels of the patient, provider, and health system can help address adherence issues. Health care professionals including physicians, pharmacists, and nurses have an obligation to improve patient adherence, as routine care. In order to achieve sustained results, a multifaceted approach is indispensable.

**Keywords:** cardiovascular disease, nonadherence, placebo, myopathy, statins

## Nonadherence to statin therapy: a growing concern in prevention of cardiovascular disease

Cardiovascular disease (CVD) is the number one cause of death globally. About 17.7 million people died from CVD in 2015, representing 31% of global mortality.<sup>1</sup> Of these deaths, coronary heart disease (CHD) and stroke contributed to 7.4 and 6.7 million deaths, respectively.<sup>1</sup>

High cholesterol, especially elevated low-density lipoprotein cholesterol (LDL-C) levels, increases the risk of heart disease and stroke.<sup>2-5</sup> Globally, a third of ischemic heart disease is attributable to high cholesterol and responsible for 2.6 million deaths a year.<sup>6</sup>

More than three-quarters of deaths due to CVD occur in low- and middle-income countries.<sup>1</sup> It is predicted that CVD will be responsible for even more deaths in the developing world than the current common causes of diseases added together and will continue to dominate mortality trends in the foreseeable future.<sup>7-9</sup> Increased incidence and prevalence of CVD has seen an upsurge of health care expenditures in many countries due to rising number of patients and costs of preventive measures and treatment.<sup>8</sup>

The improved awareness and management of cardiovascular risk factors has resulted in a 50% decrease in deaths from CHD over the past 30 years.<sup>10</sup> Medical advances in the past decade, particularly the introduction of potent statins such as atorvastatin and rosuvastatin, have made achieving lower LDL-C levels within reach for most individuals at risk of CVD.<sup>11</sup> However, more and more patients are not at LDL-C target; nonadherence to medicines is said to be responsible for the failure to achieve, but more importantly, to retain LDL-C targets.<sup>11</sup> This prioritizes the need to identify problems with adherence in a clinical context.

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Adherence to prescribed medicines predicts outcomes, and better outcomes significantly lower associated health care costs.<sup>12–14</sup> In a cohort study of 59,000 new statin users in the Netherlands, compliance with statin therapy for at least 2 years was associated with a 30% reduction in risk of hospitalization for acute myocardial infarction with an increase in protective effect with higher doses.

Likewise, a systematic review of 19 studies reported a relative risk of statin discontinuation ranging from 1.22 to 5.26 for CVD and 1.25 to 2.54 for death.<sup>15</sup> Another retrospective cohort study conducted in >229,000 patients reported a direct association between survival and adherence to statin therapy.<sup>13</sup> Current estimates suggest that statin nonadherence generates US \$44 billion extra, but avoidable, health care costs in the USA.<sup>16</sup>

Despite the evidence of improved outcomes, adherence to guideline-recommended statin therapy is suboptimal, and almost 80% of high-risk patients do not reach guideline-recommended LDL-C targets.<sup>8,17,18</sup> Two key issues appear to be at play. First is the lack of high-intensity statin prescriptions in the appropriate dosage by physicians starting treatment,<sup>19</sup> resulting in a significant proportion of un(der)treated high-risk patients.<sup>18</sup> Second is the under-use of statins by patients.<sup>20</sup> A recent real-world evidence study assessing the effectiveness of lipid-lowering therapy on LDL-C in high CVD risk patients in a primary care setting in Italy found only 61% adherent to therapy 3 months after the initial statin prescription, and barely 55% were adherent after 6 months.<sup>21</sup> Approximately 50% of patients with CVD and/or its major risk factors demonstrate poor adherence to their prescribed medicines.<sup>22</sup> Even in the immediate period following acute coronary events, adherence is not optimal.<sup>23</sup> In a cohort study using linked population-based data from Ontario, 60% of patients with post-acute coronary syndrome (N=22,379) discontinued their statin therapy within 2 years of hospitalization.<sup>24</sup>

For a treatment with such well-documented CVD morbidity and mortality benefits, these rates are strikingly low.<sup>25</sup> Novel methods to help patients improve their adherence to existing evidence-based cardiovascular drug therapies have a powerful potential to improve patient outcomes and reduce associated health care expenditure.<sup>23</sup>

## Role of statins in the prevention of CVD

### Standard of care

Since their introduction in 1987, statins have been considered one of the key interventions associated with the decline of

cardiovascular morbidity and mortality.<sup>25</sup> By lowering LDL-C, statins have significantly decreased cardiovascular events in both primary and secondary CVD prevention trials.<sup>14</sup> Statins also help stabilize arterial plaques present in the blood vessels of the brain and heart, reducing the risk of stroke and CHD-related events.<sup>26</sup>

The use of statins has increased as a result of expanding indications, guidelines emphasizing intensification of LDL-C lowering goals, rising number of generics, as well as recommendations on earlier screening and treatment.<sup>14</sup> Clearly, statins have now become the universally accepted standard of atherosclerotic cardiovascular disease care, to the extent that clinical trials of new lipid-lowering drugs are being conducted as add-ons to statins rather than as novel stand-alone therapies.<sup>14,27</sup>

The benefits of statin therapy observed in randomized clinical trials can only be realized if patients adhere to the prescribed treatment regimens.<sup>14</sup> For those who discontinue statin treatment, the number needed to harm (NNH) based on mortality is 1 excess death for every 83 patients.<sup>25</sup> The NNH with reference to CVD is 59 per year.<sup>25</sup>

### Medicine-related adverse events

Statins are generally very well tolerated with three major documented side effects linked to their use. Serious adverse events (AEs) associated with statin therapy include myopathy, new-onset diabetes mellitus (NODM), and hemorrhagic stroke.<sup>28</sup> Five cases of myopathy may be seen when 10,000 patients are treated for 5 years with statins as recommended by guidelines; 50–100 new cases of diabetes or 5–10 cases of hemorrhagic strokes may result as well.<sup>28</sup>

### Statin-associated muscle symptoms

Statin-associated muscle symptoms (SAMS) can be myalgia, myopathy, or rhabdomyolysis (Table 1). Rhabdomyolysis is the most severe manifestation and can lead to further complications such as renal failure.<sup>28,29</sup> In very rare cases, an autoimmune myopathy develops in patients treated with statins; this autoimmune disorder is characterized by muscle symptoms, evidence of muscle-cell necrosis on biopsy, and the presence of autoantibodies against 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase. This is estimated to occur in ~2 or 3 of every 100,000 patients treated with statins.<sup>30</sup> In most cases, patients exhibit only mild-to-moderate muscle weakness. Some patients may have progressive weakness that may require immunosuppressive therapy (Table 1).<sup>30</sup> If creatinine kinase levels persist  $\geq 10$  times the upper limit of normal for 8 weeks after discon-

**Table 1** Classification of SAMS

Category	Definition
Myalgia	Muscle pain or weakness only
Myopathy	Muscle symptoms with a raised CK <10×ULN
Rhabdomyolysis	Muscle symptoms with a raised CK >10×ULN
Autoimmune myopathy	Muscle symptoms with muscle cell necrosis and presence of HMG-CoA reductase autoantibodies. CK levels persist ≥10 times the ULN 8 weeks after discontinuation of the statin.

**Notes:** Data compiled from Collins et al, Sathasivam and Lecky, Mammen, and Sweidan et al.<sup>28-31</sup>

**Abbreviations:** CK, creatinine kinase; HMG-CoA, 3-hydroxy-3-methyl-glutaryl-coenzyme A; SAMS, statin-associated muscle symptoms; ULN, upper limit of normal.

tinuation of the statin or if symptoms progress after statin discontinuation, autoantibodies for HMG-CoA reductase should be tested.<sup>31</sup>

The development of SAMS does not always suggest intolerance to statins. Not all reported muscle complaints are caused by statins per se. With aging, muscular-skeletal pathology can manifest and be misinterpreted as statin related.<sup>32</sup> Some patients are able to tolerate SAMS at a lower dose, with a longer dosing interval, or with an alternative statin.<sup>33</sup> Rechallenged patients who discontinued statin therapy as a result of reported statin-associated effects were able to tolerate statins for a long term.<sup>34</sup> It is therefore vital for health providers to determine if an individual is truly intolerant to statins or not.

### New-onset diabetes mellitus

There is a reported 10%–12% increase in NODM among patients receiving statins; this risk increases with more intensive treatment and in patients with prediabetes.<sup>35</sup> Earlier and more persistent use of high-dose, high-intensity statins appears to correlate with a greater increase in the risk of NODM. This, however, is offset by the proportionally larger reduction in cardiovascular events and death.<sup>36</sup>

Statins are prescribed on the basis of CVD risk and individual patient characteristics; diet and lifestyle interventions should be emphasized to help mitigate the risk of NODM.<sup>35</sup> For instance, weight control has been recommended to prevent statin-related NODM.<sup>36</sup>

### Hemorrhagic stroke

In observational studies, blood cholesterol concentrations have been negatively associated with rates of hemorrhagic stroke.<sup>28</sup> Conversely, in a meta-analysis of large statin trials, no increased risk of intracerebral hemorrhage (ICH) was found, most likely as a consequence of a low absolute risk of ICH.<sup>37</sup> Based on the SPARCL trial, an increased risk of ICH may only be associated with elderly patients who have a history of ICH and poorly controlled hypertension particularly while using high-dose statins.<sup>38</sup>

Acute memory loss has also been reported with the use of statins. However, these findings have been inconsistent, and studies of long-term statin use have found either improved memory or no effect.<sup>28,39</sup>

### Statin intolerance

Statin intolerance can be defined as the occurrence of muscle symptoms or other AEs that lead to the discontinuation of statin therapy.<sup>40</sup> Although muscle-related AEs may occur with statins, “true” statin intolerance is uncommon.<sup>41</sup> Statin intolerance may prevent a large proportion of patients from continuing statin therapy for a long term. Placebo-controlled randomized trials show that most AEs that are attributed to statin therapy in routine practice are not actually caused by it.<sup>28</sup> These claims of AEs are based on nonrandomized observational studies and are not supported by the evidence from randomized-controlled trials.<sup>29</sup> It is vital, but challenging, to differentiate between individuals who are truly intolerant to statins and those who can actually tolerate them.<sup>40</sup> This is because management of “true” statin intolerance requires a totally different approach. “True” statin intolerance is suggested if a patient has unacceptable muscle-related symptoms that resolve with discontinuation of therapy and occur with rechallenge on at least two to three statins and one of which is prescribed at the lowest approved dose.<sup>41</sup> Most guidelines recommend restarting at a lower dose and/or a different statin (maximally tolerated statin dose) after symptoms subside combined with non-statin lipid-lowering therapies to attain recommended LDL targets.<sup>42-44</sup> In 2017, the Expert Consensus Decision Pathway writing committee of the American College of Cardiology (ACC) provided updated recommendations on the use of non-statins. Addition of a non-statin cholesterol-lowering therapy (either ezetimibe or a proprotein convertase subtilisin/kexin 9 [PCSK9] inhibitor) is recommended for high-risk patients who are statin intolerant. Bile acid sequestrants are recommended only in patients intolerant to ezetimibe.<sup>41</sup>

The lipid-lowering capability of the two recommended non-statin medications, ezetimibe and evolocumab (a PCSK9 inhibitor), was compared in the GAUSS-3 (Goal

Achievement After Utilizing an Anti-PCSK9 Antibody in Statin Intolerant Subjects 3) trial in patients with documented clinical statin intolerance.<sup>45</sup> Evolocumab resulted in significantly greater reduction in LDL-C after 24 weeks compared with ezetimibe. Subcutaneously administered PCSK9 inhibitors have demonstrated marked reduction in LDL-C both as a monotherapy and when combined with statin and/or ezetimibe therapy.<sup>46</sup> National Lipid Association 2017 Expert Panel on treatment with PCSK9 inhibitors recommend these agents in selected very-high-risk statin-intolerant patients.<sup>46</sup> A recent meta-analysis has also concluded their efficacy, safety, and tolerability in statin-intolerant patients.<sup>47</sup>

However, there are several arguments against treating statin-intolerant patients with PCSK9 inhibitors.<sup>48</sup> First, PCSK9 inhibitors are not approved for this indication.<sup>48</sup> Second, these agents do not have successful long-term outcomes like statins yet. Third, some statin-intolerant patients still may report muscle-related adverse effects as seen in GAUSS-3 trial, and lastly, they are very expensive, and pharmacoeconomic analysis is required to identify patient sub-groups where “value for money” can be clearly demonstrated.<sup>45</sup>

Hence, it is vital for physicians to ensure that their patients are aware of the possible statin-associated side effects when prescribing the medicine. This should be done without raising any unnecessary negative expectations and at the same time encouraging patients’ understanding of benefits of statin treatment to promote adherence to therapy.<sup>33</sup>

### Interracial variation and statin intolerance

It has been reported that Asians respond differently to statins than Western populations.<sup>49</sup> Several studies have demonstrated an increased systemic exposure with rosuvastatin in Asians.<sup>50–52</sup> Data indicate that polymorphisms in the *SLCO1B1* and *ABCG2* genes contribute to this difference.<sup>49,53,54</sup> However, this phenomenon is not a class effect among other high-intensity statins and should not be seen as a barrier to prescription of higher doses of other statins. No difference has been identified in systemic exposure with atorvastatin between Asians and Caucasians.<sup>55</sup> Atorvastatin (10–80 mg) has been found to be equally efficacious and safe in Asian and Western populations.<sup>56,57</sup> Therefore, there is no regulatory warning about the dose of atorvastatin in Asians.<sup>57</sup>

### The nocebo response

In patients presenting with only mild myalgia, a nocebo response should be considered.<sup>58</sup> A nocebo response refers to the induction or worsening of symptoms induced by patients’ expectations of administered therapies.<sup>59</sup> This can affect the

outcome of a given therapy in a negative way, similar to how placebo affects outcome in a positive way.<sup>60</sup>

In a recent study by Gupta et al, AEs reported with atorvastatin therapy during a blinded, randomized, placebo-controlled phase were compared with those during an unblinded, nonrandomized phase when open-labeled treatment with atorvastatin was continued.<sup>61</sup> The study found an excess rate of muscle-related AEs when patients and their doctors knew that they were on statin therapy in comparison to when they were blinded.<sup>61</sup> These observations should provide assurance to both physicians and patients that most AEs linked with statins do not actually have a causal relationship.<sup>61</sup>

Patients who commonly experience these adverse reactions (the nocebo response) either challenge their physician about the risks of treatment or simply stop the treatment.<sup>58</sup> Although patients do experience statin-associated side effects, the majority of these complaints may represent the nocebo response.<sup>25</sup> Physicians should evaluate patients’ existing knowledge or perceptions of statin therapy and try to counter the negative perception of exaggerated claims about statin-related side effects.<sup>33</sup> With the nocebo response being so prominent, and yet underrecognized in clinical practice, physicians need to be informed on how to detect and handle this effect.<sup>62</sup>

## Why is nonadherence to statins unique?

Cholesterol-lowering medicines as a class are associated primarily with nonadherence.<sup>8</sup> Furthermore, adherence to medicines for treatment of a symptomless condition, such as high lipid levels, is a challenge to both doctor and patient.<sup>14</sup> It follows that statins may be discontinued at rates higher than for other oral medicines used for chronic therapy. For example, the more frequent screening of blood glucose levels compared with cholesterol levels encourages patients to be more adherent to their diabetic medication than to statins.<sup>14</sup>

Patients’ beliefs about medicines or how recent the treatment was initiated were also found to be significant predictors of adherence.<sup>11</sup> Correspondingly, the nocebo response reflects alterations in human psychobiology (brain, body, and behavior) rather than the effect of the medicine.<sup>58</sup> For example, reporting of SAMS can be a consequence of negative media reports about statins or an improper understanding by patients of possible statin-associated adverse effects.<sup>33</sup>

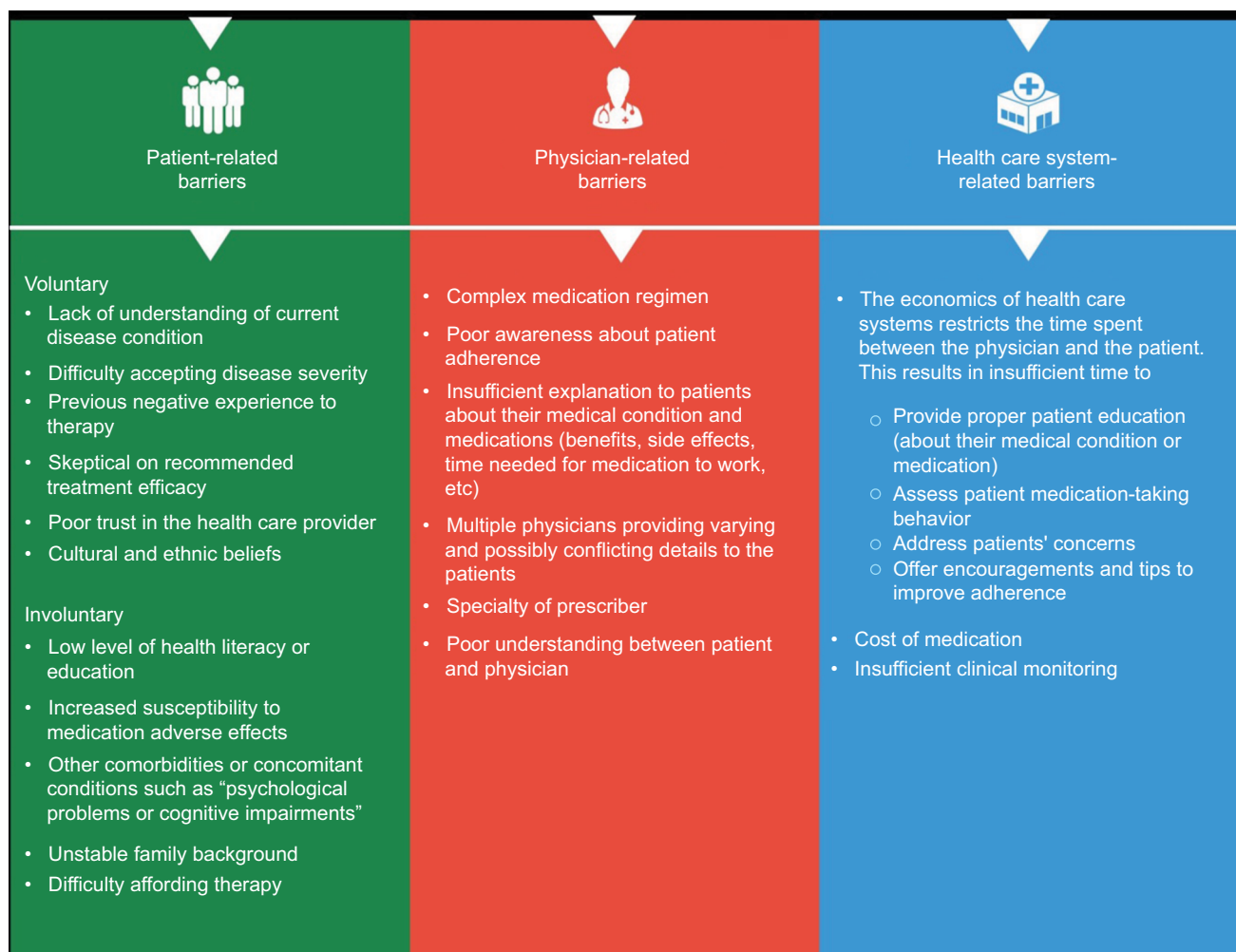
AEs are cited as the most frequent cause of statin discontinuation.<sup>14</sup> In a focus group of 18 participants, nonadherence was primarily due to concerns about experiencing AEs.<sup>63</sup>

Concerns were raised from information on the Internet, uncertainty about the benefits or importance of statins, the inconvenience of taking a medicine, and obtaining lipid profile tests on a routine basis.<sup>63</sup> In general, unfavorable reports found on both social and professional media are a major cause for discontinuation of statin therapy. This is because the AEs of statins are frequently reported and mostly overstated.<sup>8</sup> The proliferation of absurd and unscientific but seemingly persuasive criticism of statins on the Internet has created a bad reputation for statins in the public eye.<sup>25</sup> Information on the Internet can be made available by anyone with little or no scientific expertise, and usually promotes statin denial, the proposition that cholesterol is not related to heart disease, and statin fear, which is the notion that lowering serum cholesterol levels will cause serious AEs, such as muscle or liver toxicity.<sup>25</sup> A study of 6,74,900 patients revealed that early statin discontinuation was associated with negative media attention on statins.<sup>64</sup>

The adherence problem is exacerbated by hesitation among doctors to discuss and prescribe statins when there are harmful media reports, and compounded by reduced patient compliance as a result of increased awareness of perceived side effects.<sup>65</sup> Failure to correct misleading claims about side effects quickly and completely leads patients to stop their statin therapy even though they are at high risk of cardiovascular events.<sup>64,66</sup>

## Predictors for statin nonadherence

The causes of nonadherence are certainly complex and can be broadly classified into three categories: patient related, physician related, and health care system related (Figure 1). Among these, patient-related factors may be the strongest and may be further differentiated into voluntary and involuntary factors.<sup>14</sup> Treatment burden (requirement of daily medication), lack of symptomatic benefit, large time lag to benefit, and perceived or real AEs are perhaps the key causes of nonadherence.



**Figure 1** Factors associated with statin nonadherence.

Several factors such as copayment, statin use for either primary or secondary prevention, female gender, age, and belonging to a minority race are also predictive of nonadherence and statin discontinuation. The number of appointments with cardiologists, frequency of LDL tests performed, and the simplicity of the medication regimen are linked with improved statin adherence.<sup>20</sup>

A meta-analysis showed that age as a predictor of nonadherence follows a U-shaped curve, with the youngest (<50 years) and oldest ( $\geq 70$  years) showing lower adherence than those in between.<sup>14,67,68</sup> Existing comorbidities such as diabetes and hypertension are associated with improved adherence.<sup>14</sup> Persistence with statin therapy in older patients declines substantially over time, with the greatest drop occurring in the first 6 months of treatment.<sup>68</sup> Forgetfulness is a common reason but there are many factors that can lead up to it, such as insufficient prioritization of the importance of medication intake or simply disliking the need to swallow a pill.<sup>14</sup>

Overall, nonadherence is influenced by an interaction between various factors, such as patient education, communication between patients and physicians, medication regimen, as well as access to health care.<sup>69</sup>

## Measuring adherence

Adherence is defined as the percentage of pills a patient takes as prescribed. By convention, a cutoff point of 80% is used to categorize adherence to cardiovascular medications into good and poor adherence groups.<sup>70</sup> Patients are also categorized as nonadherent if they discontinue a medication before a certain time period. In primary nonadherence, a patient “discontinues” a medication even before filling a prescription once.<sup>23</sup>

While there is no recognized gold standard method to measure adherence, a combination of direct and indirect methods can be used to get an accurate measurement of adherence in actual practice (Table 2).<sup>14</sup>

## Interventions to improve medication-taking behaviors

Generally, about 33% of patients will be adherent to therapy just by being given a prescription and asked to take it by their physicians, while about 15%–25% will be nonadherent despite any intervention.<sup>71</sup> Interventions to improve adherence are aimed at the middle 50% of patients who may adhere if given support and encouragement.<sup>14</sup>

Identifying specific barriers for each patient and adopting suitable techniques to overcome them are necessary to improve medication adherence.<sup>22</sup> However, individual interventions, as distinct from a shared responsibility between the clinician and patient, tend to be associated with poor improvements in adherence. Alternatively, multifaceted approaches designed for individual patients are more likely to improve long-term adherence to medication.<sup>69</sup>

A personalized, patient-focused program involving frequent interactions with a health care professional or a combination of techniques that make use of physician communication and pharmacist involvement have shown to improve medication adherence and ultimately, better health outcomes.<sup>72</sup> Figure 2 summarizes various interventions to improve medication adherence.

We have not analyzed the cost-effectiveness of individual strategies. Comparing costs of different adherence strategies or technologies would be a relevant topic for a costs-effectiveness analysis, but this is beyond the scope of this review.

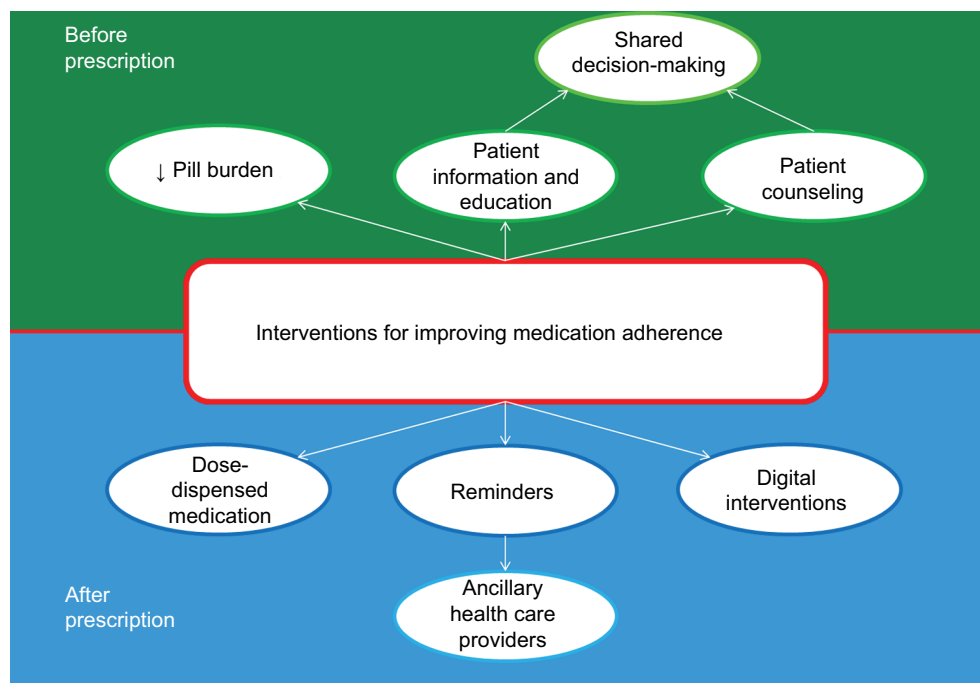
## Shared decision-making

Current evidence-based clinical guidelines often do not take into account specific individual issues. Values, goals, and preferences need to be taken into account. Clinical decisions should be made based on the concept of “shared decision-making”.<sup>73</sup> Providing positive reassurances that the patient is making a good effort to lower risk of a cardiovascular

**Table 2** Measures to quantify medication adherence

Direct methods	Indirect methods
<ul style="list-style-type: none"> <li>• Direct observation by health care provider</li> <li>• Measuring blood levels to yield quantitative data               <ul style="list-style-type: none"> <li>– Costly and time consuming</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• Patient education/adherence scale</li> <li>• Pill counts</li> <li>• Statistics on repeated prescriptions</li> <li>• Electronic monitoring systems in blister packs               <ul style="list-style-type: none"> <li>– Does not assure if the patient actually ingests the medication or whether patient takes the correct dose</li> </ul> </li> <li>• Patient diaries</li> <li>• Combined electronic opening, pill counts, and interviews               <ul style="list-style-type: none"> <li>+ Minimize patient manipulation by revealing openings without pill intake</li> </ul> </li> </ul>

**Note:** Data compiled from Laufs et al, Maningat et al, and Gagnon et al.<sup>13,14,92</sup>



**Figure 2** Interventions for improving medication adherence.

**Notes:** Overall, the interventions can be differentiated as “before” and “after” prescription interventions. The strategies are multimodal varying from “patient education/counseling” to “adopting team-based” approaches. Effective approaches must involve strong partnerships between patients and health providers.

event has neither been assessed nor addressed in existing guidelines.<sup>73</sup> Understanding the patient’s apprehensions about therapy is vital to improve adherence. Patient-specific factors such as perceptions about their condition, perceived efficacy of treatment, and other elements that have been associated with nonadherence need to be discussed to avoid poor adherence and adverse treatment outcomes. Health care providers need to come up with an educational strategy, tailored to each patient’s needs.

The development of shared decision-making tools will allow current clinical evidence to be portrayed in simple terms such that it allows physicians to help their patients make appropriate decisions related to medication use.<sup>73</sup>

## Counseling

Strategies such as hospital staff, other than the physician, conducting regular phone counseling on medication adherence, were shown to have an impact on patient survival.<sup>74</sup> Data strongly suggest medication adherence can be improved as a result of this method of weekly communication.<sup>13</sup> Predictors of nonadherence can also be used to identify those at high risk of statin discontinuation for targeted counseling.<sup>14</sup> Recent international guidelines such as those from the “American College of Cardiology/American Heart Association (2013)” and the “European Society of Cardiology (2016)” recommend

that physicians, and allied health care professionals, should regularly monitor patients’ adherence to statin therapy.<sup>75–77</sup>

Patients in whom knowledge and understanding of statins and CVD risk factors were improved, adherence to therapy was better and the number of people reaching their LDL-C goals increased.<sup>78</sup> Motivational interviewing techniques can help the patient develop a list of treatment goals.<sup>8</sup> Likewise, physicians can also advocate good practices by encouraging patients to set medication reminders, organize medicines in pill boxes, and maintain a medicine tracker sheet to help improve adherence.

## Patient information and education

Enhancing communication between physician and patient is crucial to improve patient education and allow patients to clarify and resolve any concerns or misconceptions.<sup>79</sup> It is important for physicians to empower patients to become informed medication consumers by educating patients as well as family members about their medical condition and medicines.<sup>8</sup> Educational videos, mobile apps, and audio books can help improve knowledge about their conditions.<sup>8,80</sup>

Suggested topics for patient education can highlight the importance of a medicine’s benefit, for example, long-term benefits in prevention of CVD with statins. Physicians must abandon commonly used fear tactics, as scaring the patient

will more likely result in decreased adherence.<sup>81</sup> Information about statins (reasons for prescription, benefits, risks, etc.), additional time for discussion with the clinician, and written or trustworthy online information about statin risks, side effects, and drug interactions, can also help improve adherence.<sup>14</sup>

Education on harmful pseudoscience will also prove useful. Products promoted on the Internet commonly imply benefits that have no evidence from formal clinical studies and could potentially be harmful as well.<sup>25</sup> For instance, patients are promised that adhering to a certain diet or taking exotic food supplements can result in a reversal of heart disease. These diets are aggressively promoted to patients as an alternative to statin medication, promising all the benefits without any risk, when in fact there is no scientific basis for these claims.

## Reminders

Medication reminders by pharmacists, nurses, or therapists can improve adherence.<sup>13</sup> Techniques commonly involve phone calls, SMS texts, mail, and the use of calendar reminders. Telephone reminders when used together with educational materials were shown to be the most effective strategies.<sup>16</sup>

A Cochrane database review by Schedlbauer et al concluded that “reminding” or “re-enforcement” appeared to be the most promising intervention tactic to improve adherence to lipid-lowering drugs.<sup>8,82</sup> In another study, Derose et al investigated statin adherence in 5,216 participants who had discontinued statin use within the previous year and found that the group that received periodic automated telephone calls had a significantly better adherence to statins within the year of the study.<sup>83</sup>

## Dose-dispensed medicine

Overall, the use of various types of pill box did not show any improvement in adherence by patients when compared to usual practices.<sup>84</sup> However, this method could be more effective when it is used in combination with other forms of intervention.<sup>84</sup> Multiple studies have reported significant improvement in adherence when a drug reminder packaging was used with results being much more distinct when it was part of a multifaceted approach compared with a single-faceted approach.<sup>85</sup>

Dose-dispensed medicines such as the time-specific blister packs contain the patient’s medication for each time point of the day.<sup>86</sup> Patient-specific multidose adherence packs also contain the medications required for a week and are labeled

with the day and time of drug administration. Their use maintains the ability for individual choice of drug and dose.<sup>13</sup>

Evidence suggests that the combination of weekly dose-dispensed blister packs with regular pharmacy counseling on adherence demonstrates an absolute increase in adherence of one-third when compared with the standard prepacked medication in blister cards.<sup>13</sup> One study showed that drug reminder packaging significantly reduced the mean hospitalization rate, a more relevant marker of adherence for patients on polypharmacy.<sup>85</sup>

## Reducing pill burden or simplification of the drug regimen

A complex medication regimen and high pill burden can also lead to nonadherence. Careful reduction in the use of unnecessary or unsafe medications, and use of combination and once-daily formulations are effective strategies in managing polypharmacy and reducing pill burden.<sup>87</sup> One such strategy is the use of a polypill. Polypills are the combination of multiple classes of preventive medications in one pill. Their use has demonstrated significant improvement in adherence when used instead of usual care in patients with CVD.<sup>88</sup> Less-intensive strategies, such as prescribing products that simplify the medication regimen, achieve relatively smaller improvements in compliance.<sup>89</sup>

## Digital interventions

Digital interventions that involve the use of modern technology to develop approaches to improve adherence such as smartphone apps are novel solutions.<sup>69</sup> By incorporating physical physician–patient interactions with technology-driven medication adherence reminders, electronic medication reconciliation, and the usage of pharmaceutical databases, adherence to medicines may be improved as well.<sup>90</sup> A recent example is the ACC Statin Intolerance App, which was developed to guide physicians how to manage and treat patients who experience muscle symptoms while on statin therapy. Physicians would be able to determine if a patient is really intolerant to their statin medication, follow guidelines in managing and treating muscle symptoms while on statins, and compare between different statin characteristics or any potential drug interactions.<sup>91</sup>

Upcoming potential digital interventions also include technotherapeutics. Technologies are gradually expanding in the health care arena to capture previously unavailable data and to generate new knowledge about patients.<sup>92</sup> The use of new technological devices even allows for previously unavailable data to be recorded on a continuous basis and transmitted



via a tiny microchip inserted into the body. This information can then be transmitted to health care professionals.<sup>92</sup> They have the potential to track physiological responses and treatment adherence with exact precision. A prompt signal will be transmitted when there is nonadherence to a medication regimen.<sup>92</sup> This new technological device may be able to improve the therapeutic management of chronic conditions, maximize clinical outcomes, facilitate communication with health care providers, and individualize patient care.<sup>92</sup> Technotherapeutics is, however, expensive and complex. Also, its design has limitations as it places the responsibility of adherence primarily on the patient.

## Importance of combined pharmacist and/or nurse participation

Pharmacists are uniquely positioned to interact more frequently with patients than other health care providers. Pharmacists are better able to emphasize proper medication-taking behaviors and address issues about the patient's medication adherence by using their access to medication refill information.<sup>93</sup> By enlisting ancillary health care providers such as pharmacists, additional motivation to patients can be provided.

Some techniques include phone calls, counseling, medication review, home visits, and comprehensive pharmacy care focusing on patient education and the importance of adherence. Another technique can involve the implementation of a reward system by providing positive feedback whenever a treatment goal is attained according to the treatment plan.<sup>8</sup> Ultimately, this could even include reduced payments for health insurance schemes.

Based on multiple studies, integration of pharmacist and/or specialized nurse practitioner counseling with a focus on adherence demonstrated the most noteworthy improvements in medication habits.<sup>16</sup> The use of specialized nurse practitioners for follow-up has even led to a reduction in LDL-C of about 0.9 mmol/L from baseline.<sup>86</sup> Integration of a pharmacy/nurse program is likely to achieve substantial improvements in medication adherence and significant LDL-C reductions.

## Conclusion

Nonadherence to statins is exceptionally common and has been undervalued by the majority health care professionals as well as professional organizations responsible for formulating lipid management guidelines. Identifying at-risk patients and initiating treatment remains a priority, but if medication adherence is ignored, this will result in wasted efforts, resources and lives. We have to intensify our efforts to overcome this formidable barrier if our goal is to preserve our patients' health. We need to

empower our patients so they can recognize sham information found on the Internet that promote alternative remedies, created by people with little or no scientific expertise. The only way to address this challenge is allocating time to talk and interact with patients. This can be done by physicians or dedicated hospital staff on an individual basis or in groups. Support from health authorities for educating the public and enlisting media support should complement individualized strategies.

Specific guidelines to improve adherence are urgently needed. Evidence-based interventions to improve adherence are available and should be effectively integrated in patient management. Various health care providers including physicians, pharmacists, and nurses need to collaborate and communicate with patients to address concerns and discuss the risks and benefits of long-term statin therapy. Identification of relevant approaches and techniques by health care providers can improve adherence, but most importantly, physician and patient need to create a trusting alliance; this will promote statin adherence and ultimately reduce morbidity and increase life expectancy.

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## Author contributions

All authors were involved in conception, design, analysis, and interpretation of data. All authors were also involved in the preparation of the manuscript, revising it for important intellectual content, and final approval before submitting for publication.

## Disclosure

Dr Zhen-Vin Lee has received honoraria from Aspen, Astra Zeneca, Bayer, Boehringer Ingelheim, Merck Serono, Merck, Sharp & Dohme, and Pfizer. Mr Andre Lee underwent indirect patient care pharmacy training for 3 months at Pfizer, Singapore. Dr Sajita Setia and Dr Kannan Subramaniam are employees of Pfizer. Professor Lansberg has received consultancy and speaker honorarium payments from Pfizer and Sanofi. The authors report no other conflicts of interest in this work.

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