

# Not Getting to Goal: The Clinical Costs of Noncompliance

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## ABSTRACT

**BACKGROUND:** Cardiovascular disease is characterized by significant prevalence and cost in the managed care setting. Despite overwhelming evidence in favor of statin use for lowering low-density lipoprotein cholesterol (LDL-C), medication compliance to these agents remains suboptimal, as it does in other disease states.

**OBJECTIVE:** To establish the benefits of statin therapy in cardiovascular disease, demonstrate the current lack of compliance to lipid-lowering agents, and present potential interventions to improve medication compliance.

**SUMMARY:** As evidenced by a consistent body of clinical trial data, intensive LDL-C reduction plays a critical role in the mitigation of cardiovascular risk. Yet, the effectiveness of lipid-lowering strategies is offset to a significant degree by both physician and patient factors that limit goal attainment. Despite extensive evidence demonstrating the benefits of lipid-lowering therapy, many patients are still not getting to goal because the transition from physician awareness to clinical practice is lagging. Patient noncompliance to therapy also limits goal attainment, thus resulting in poor health outcomes and increasing managed care costs.

**CONCLUSION:** To overcome the issues surrounding LDL-C goal attainment, interventions designed to increase goal attainment should be based not only on the conclusions of clinical trials but also on successful patient- and provider-focused behavioral strategies. Interventions for improving adherence to lipid-lowering medication will provide an opportunity to decrease morbidity, mortality, and hospitalization associated with cardiovascular disease.

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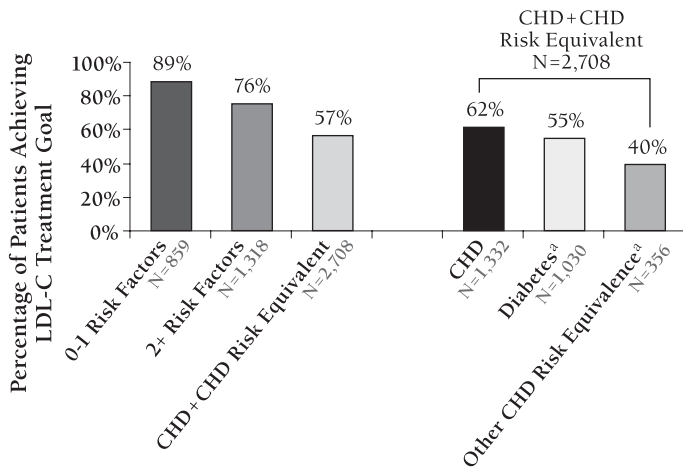
As a result of its prevalence and cost, cardiovascular disease demands significant attention by managed care stakeholders. Collectively, heart disease and stroke are the leading cause of death among American men and women, resulting in approximately \$400 billion in direct medical expenditures and lost productivity.<sup>1</sup> In managed care, plans are graded on their performance in the treatment of cardiovascular disease in terms of Healthcare Effectiveness Data and Information Set (HEDIS) attainment. Despite a collective awareness of the impact of cardiovascular disease, as well as effective therapies for treating these conditions, a disparity exists between the health care community's knowledge of how to prevent and manage cardiovascular disease and the implementation of practice and management strategies to bridge the gap. Specifically, there is a wealth of knowledge regarding risk factors that contribute to cardiovascular disease, such as dyslipidemia and hypertension, yet there is relatively poor adherence to proper therapy for these chronic conditions.

In particular, the benefits of lowering low-density lipoprotein cholesterol (LDL-C) have been well established.<sup>2-4</sup> Since the advent of modern pharmacotherapy, statin use has been proven to lower LDL-C. A meta-analysis of >90,000 patients demonstrated a 17%-26% reduction in risk of coronary events with statin use versus placebo.<sup>3</sup> Despite the overwhelming evidence in favor of statin use, medication compliance to these agents remains suboptimal, as it does in other disease states. Data have demonstrated that medication compliance rates for various chronic disease states drop to <50% 12 months after the initial prescription; statin compliance may be even less in some demographic groups (i.e., the elderly, those with low income, those prescribed a statin for preventive purposes).<sup>5,6</sup>

Beyond the obvious clinical implications of noncompliance to pharmacotherapy, such as higher LDL-C levels and an increased rate of coronary events in patients who are noncompliant to statin therapy, noncompliance can result in a poor quality of life and increased medical expenditures in managed care. In cardiovascular disease as well as in other conditions, noncompliance has been linked to increased morbidity in the form of drug resistance, disease-related complications, hospitalizations, and disability, as well as increased mortality.<sup>7</sup> The economic ramifications of these adverse health outcomes are significant, with analyses demonstrating a distinct correlation between medication compliance and medical costs. For example, in one analysis, Sokol et al. reported that, as compliance to therapy decreases, overall cost of care increases.<sup>8</sup> The result is that hundreds of billions of dollars are being attributed to medication noncompliance annually.<sup>9</sup>

Several measures may be used by managed care stakeholders to overcome patient noncompliance to medication therapy. Specifically, educational and behavioral interventions have demonstrated promise in improving compliance, thereby positively

**FIGURE 1** Percentage of Patients Achieving LDL-C Treatment Goal in the NEPTUNE II Survey

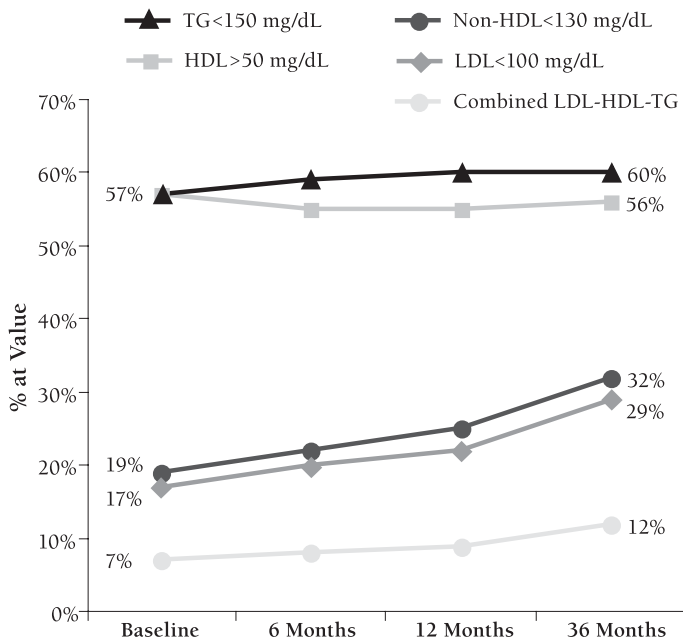


Adapted from Davidson et al.<sup>11</sup>

<sup>a</sup> No CHD.

CHD=coronary heart disease; LDL-C=low-density lipoprotein cholesterol; NEPTUNE II=National Evaluation Project Utilizing Novel E-Technology.

**FIGURE 2** Attainment of Treatment Goals in Clinical Practice Over a Three-Year Period in Women at High Risk for CHD



Adapted from Mosca L et al.<sup>13</sup>

CHD=coronary heart disease; HDL=high-density lipoprotein; LDL=low-density lipoprotein; TG=triglyceride.

effecting treatment outcomes and reducing overall health care costs.<sup>10</sup> These interventions may be applied to a myriad of disease states, including cardiovascular disease.

### Current State of Care for Cardiovascular Disease

Despite clinical evidence demonstrating the benefits of lipid lowering in averting coronary events and improving health outcomes, many patients fail to achieve LDL-C goals. In addition, there appears to be a gender disparity in cardiovascular care in that women are less likely to achieve LDL-C goals. The National Evaluation Project Utilizing Novel E-Technology (NEPTUNE II) Survey, for example, demonstrated a lack of patients who attained their LDL-C goal even in a best-case scenario for compliance to therapy.<sup>11</sup> NEPTUNE II researchers surveyed a sample of the top decile of statin prescribers across the United States and assessed the equivalent of a “day in the life” of their practice by observing 20 consecutive patients.<sup>11</sup> By reviewing the LDL-C goals of these patients according to National Cholesterol Education Program Adult Treatment Panel (NCEP ATP) III guidelines and then evaluating patient status in relation to their goals, the researchers assessed guideline attainment.<sup>11</sup>

In NEPTUNE II patients who were at relatively low coronary heart disease (CHD) risk and, therefore, had a relatively high LDL-C level target, 89% were at LDL-C goals (Figure 1).<sup>11</sup> In moderate-risk patients with  $\geq 2$  risk factors, 76% were at goal. Finally, in patients with the most significant disease and arguably the most at stake, only 57% actually attained their LDL-C treatment goal. NEPTUNE II researchers also reported that the more severe a patient’s disease state, the more likely they were to be at their LDL-C goal (Figure 1).<sup>11</sup> For example, patients with established CHD are more likely to get to goal compared with diabetic patients or patients with other coronary risk equivalents.<sup>11</sup>

A separate study of NEPTUNE II patients according to gender revealed poorer LDL-C goal attainment among females than males.<sup>12</sup> Although goal attainment was not exceptional among high-risk male patients, attainment was significantly worse among high-risk female patients (60% vs. 50%, respectively;  $P < 0.001$ ).<sup>12</sup> Interestingly, the providers’ gender did not have an effect on outcomes; results were similar for both male and female providers.<sup>12</sup>

Women at high risk for CHD have also demonstrated slow attainment of treatment goals for LDL-C and other cardiovascular clinical markers, such as high-density lipoprotein cholesterol (HDL-C) and triglycerides (TGs).<sup>13</sup> Patients with CHD or risk equivalent should arguably be started on lipid-lowering therapy at the first visit following detection or diagnosis; however, there is often a lag in the initiation of therapy in clinical practice as well as an extended delay in actually getting patients treated to goal (Figure 2).<sup>13</sup> One study demonstrated this lag in attaining goals over a 3-year period for LDL-C, HDL-C, TGs, and non-HDL-C.<sup>13</sup> Furthermore, by the end of the study, only 29% of high-risk female patients attained the LDL-C goal of  $< 100$  mg per dL, and

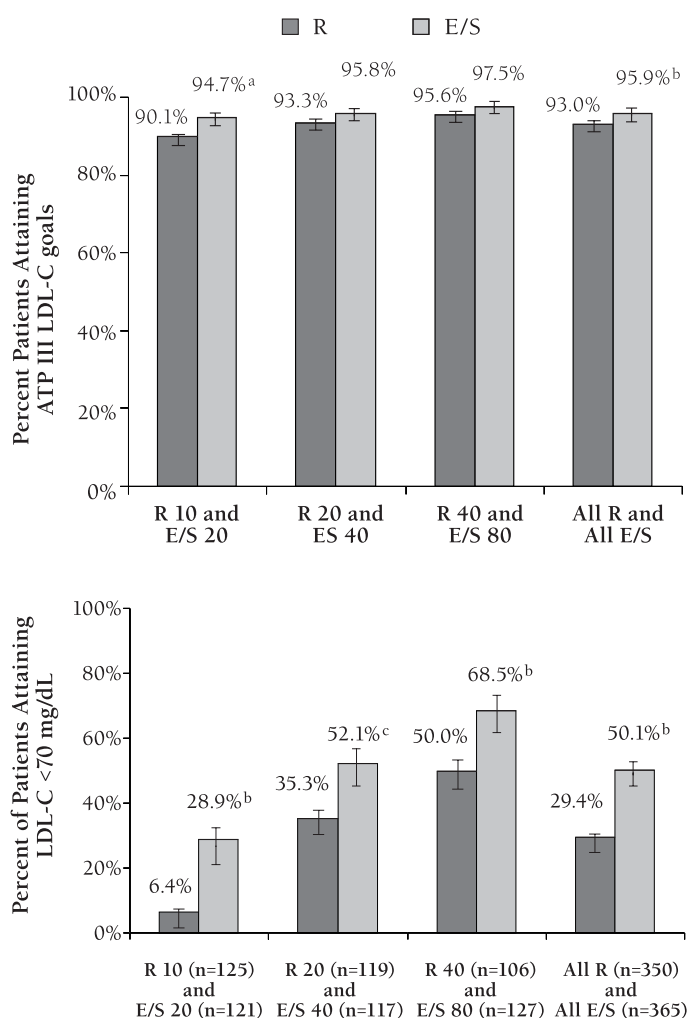
only 32% attained the non-HDL-C secondary target of <130 mg per dL for CHD prevention.<sup>13</sup> As a result, the percentage of high-risk female patients attaining combined goals for LDL-C/HDL-C/TGs after 3 years was even lower at 12% (Figure 2).<sup>13</sup>

This study also demonstrated that gender-based disparity in LDL-C goal attainment may be the result of suboptimal pharmacotherapeutic treatment.<sup>13</sup> Study researchers reviewed the attainment of Class I pharmacotherapy recommendations among high-risk women in a managed care setting and reported that only 32% of high-risk women with LDL-C levels  $\geq 100$  mg per dL were receiving statin therapy.<sup>13</sup> Similarly, only 10% of high-risk women with LDL-C levels <100 mg per dL were receiving a statin.<sup>13</sup> These results are startling considering that all high-risk women beyond childbearing age should arguably be receiving statin therapy.

Data from the European Action on Secondary and Primary Intervention to Prevent Events (EUROASPIRE) II Survey demonstrate that the problem of patient failure to achieve lipid goals is not confined to the United States and may be the result of inadequate titration of statin therapy to LDL-C goals.<sup>14</sup> In EUROASPIRE II, Kotseva et al. reviewed the medical records of 8,181 patients with CHD in 15 European countries.<sup>14</sup> Researchers reported that 58.3% of patients did not reach the European Society of Cardiology total cholesterol goal of <5.0 mmol per L despite the fact that 60.6% of patients were being treated with statin therapy.<sup>14</sup> Similar to gender-based disparities in the United States, a higher percentage of female patients failed to achieve goal than did male patients (63.6% vs. 57.3%;  $P=0.007$ ) in this European study.<sup>14</sup> While these percentages are of interest to clinicians in the United States and Europe alike, perhaps the most compelling data extracted from EUROASPIRE II are the distribution of doses of the various statins used with respect to achieving cholesterol goals.<sup>14</sup> It becomes apparent from the data that a vast number of patients included in the survey were on low-dose statin therapy, were not at goal, and were seemingly maintained on that same low dose.<sup>14</sup> A failure to titrate the statins to effective doses was ultimately the common denominator; this was not simply an issue of the statins not working adequately. The underlying message is that, with rare exceptions, clinicians have the ability to bring nearly every patient toward their NCEP goals by using conventional pharmacotherapy, which is also demonstrated in U.S. clinical trials.<sup>15</sup>

One such trial by Catapano et al. illustrates the success that clinicians can achieve in treating patients to NCEP goals.<sup>15</sup> Using ATP III LDL-C goals and, specifically, the goal of <70 mg per dL as the endpoint, researchers in this study established robust rates of goal attainment among patients via appropriate titration of rosuvastatin and ezetimibe/simvastatin. Escalating doses of rosuvastatin (i.e., 10 mg, 20 mg, 40 mg) resulted in ATP III LDL-C goal achievement in 90.1%, 93.3%, and 95.6% of patients, respectively, with 93.0% of patients achieving goal on all doses of rosuvastatin (Figure 3).<sup>15</sup> Similarly, escalating doses of

**FIGURE 3** Patients Reaching LDL-C Goals on Rosuvastatin (R) and Ezetimibe/Simvastatin (E/S)



Adapted from Catapano et al. *Current Med Res Opin.* 2006;22:2041.

Proportion of patients attaining NCEP ATP III LDL-C goals for low (<160 mg/dL), moderate (<130 mg/dL) and high (<100 mg/dL) risk patients.

<sup>a</sup> $P=0.009$ .

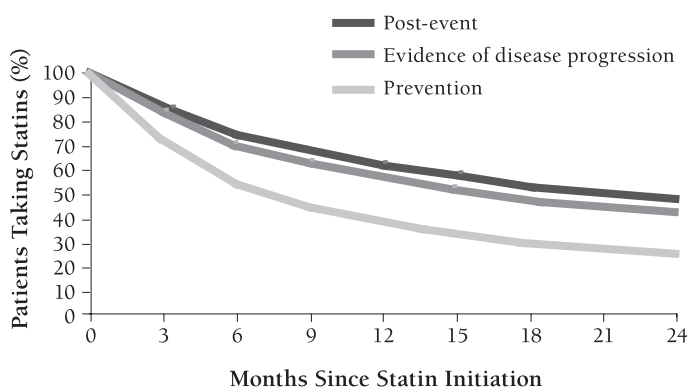
<sup>b</sup> $P\leq 0.001$  for treatment comparison between rosuvastatin and ezetimibe/simvastatin at specified doses and across doses.

<sup>c</sup> $P=0.005$ .

LDL-C=low-density lipoprotein cholesterol; NCEP ATP III=National Cholesterol Education Program Adult Treatment Panel III.

combination ezetimibe/simvastatin (i.e., 10/20 mg, 10/40 mg, 10/80 mg) resulted in ATP III LDL-C goal achievement in 94.7%, 95.8%, and 97.5% of patients, respectively, with 95.9% of

**FIGURE 4** Medication Compliance Over Time as Related to the Nature of Therapy



Adapted from Jackevicius et al.<sup>5</sup>  
Cohort study using linked population-based administration data from Ontario, Canada (N=143,505).

patients achieving goal on all doses of ezetimibe/simvastatin. Similar but more modest improvement was reported with dose escalation of both rosuvastatin and ezetimibe/simvastatin in the rates of patients achieving the more aggressive LDL-C goal of <70 mg per dL (Figure 3).<sup>15</sup> Appropriate utilization of pharmacotherapy puts LDL-C goal attainment within the reach of both the clinician and patient. Taking these data into consideration, the strategy of using more aggressive statin therapy at initial dosing and introducing combination therapy earlier to get patients to goal may indeed be the optimum treatment decision.<sup>15</sup>

Given the wealth of data supporting the appropriate use of lipid-lowering pharmacotherapy in the treatment and prevention of cardiovascular disease, it is tragic that managed care fails to treat more patients to goal. Unfortunately, when dealing with chronic asymptomatic diseases, patient and, to some extent, provider behaviors must be altered to actually transition the information from clinical trials into clinical practice. In addition, clinical trials represent the very best-case scenarios in terms of compliance because patient care is followed up, drugs are provided at no cost, and some level of patient education is often associated with the trials. Therefore, the problem of poor goal attainment is likely even more significant than it appears in much of the literature.

The extent to which a person's behavior parallels provider recommendations when they take medications or comply with diet and exercise regimens (i.e., compliance) is perhaps the greatest challenge in the practice in medicine. Clearly, many factors are involved in noncompliance. In addition to patient issues, provider issues include managed care, formulary, and economic challenges that can contribute to noncompliance. Furthermore,

providers may contribute to noncompliance by not sharing decision-making with patients and failing to assess the individual patient's goals for treatment. However, regardless of the mechanisms by which poor compliance and goal attainment occur, the costs cannot be ignored, especially for patients at highest risk. While clinical goals are a component of the solution that managed care can grasp fairly easily, attainment of those goals requires a more complex understanding of people and their behaviors. All of these factors must be discussed to effectively address noncompliance.

### Noncompliance to Therapy

The World Health Organization defines adherence (i.e., compliance) as "the extent to which a person's behaviour—taking medication, following a diet, and/or executing lifestyle changes—corresponds with agreed recommendations from a health care provider."<sup>16</sup> In terms of compliance to pharmacotherapy, the patient must complete a certain process before any particular treatment can actually be used, let alone used effectively. The patient must fill the prescription, take the medication as recommended, renew the prescription, potentially adjust the dosage, and potentially discontinue the medication. As medications are added or changed over time, the patient must recycle this process. If a patient decides not to fill a prescription, not to take it as recommended, or not to refill the prescription, these decisions will obviously impact compliance.

While some small degree of noncompliant behavior is likely expected by managed care stakeholders, many do not realize that noncompliance is more often the rule than the exception. In fact, two thirds of all Americans on prescription medication fail to take either any or all of the prescription.<sup>17</sup> Breaking down this noncompliant behavior even further, 29% stop taking their medication before the prescription runs out, 22% take less than the prescribed amount on the label, and 12% never even fill the prescription.<sup>17</sup> Polypharmacy further compounds the problem, with 59% of people with ≥5 medications taking them improperly, irrespective of age.<sup>17</sup>

As previously mentioned, statin therapy appears to consistently have the poorest compliance among the cardiovascular therapies, which is likely due to the demographics of the statin-treated population.<sup>6</sup> Income may be lower in these often elderly patients, thereby making the therapies less affordable. In a study of a Medicaid population of enrollees in a pharmaceutical assistance program aged ≥65 years, compliance at baseline was only 60% because 40% did not initially fill their prescriptions.<sup>6</sup> After 5 years, compliance dropped to 30% as the remaining compliant population stopped taking their prescription medication over the long term.<sup>6</sup>

When considering the diseases confronting Americans as they age, a preventive model presents even greater challenges in overcoming the underlying reasons for noncompliant behavior. Basically, the more asymptomatic the patient or the more

improvement a patient begins to feel, the less likely the patient is to take a medication.<sup>5</sup> For example, a cohort study using linked population-based administration data from Ontario, Canada (N=143,505), revealed that patients taking a statin post-event were likely to remain compliant longer than patients taking a statin who demonstrated evidence of disease progression and were even more likely to remain compliant than patients taking a statin for preventive reasons who were likely asymptomatic (Figure 4).<sup>5</sup> Post-event patients and patients with evidence of disease progression do relatively well in the short term, with compliance declining over time, but patients who are only taking a statin for preventive ideological reasons without necessarily feeling better as a result are the least likely to maintain adherence in the long run.<sup>5</sup> This decline in compliance over time is not confined to therapy for cardiovascular disease.<sup>6</sup> Specific compliance rates vary by therapeutic class but demonstrate similar discontinuation patterns, with the most dramatic decline occurring between months 1 and 4 of therapy.<sup>6</sup>

Sokol et al. demonstrated the impact of medication non-compliance on total diabetes medical cost in a study of 3,260 patients.<sup>8</sup> For patients at 80%-100% adherence, total medical costs were approximately \$4,000 compared with approximately \$9,000 for patients at 1%-19% adherence (Figure 5).<sup>8</sup> Although drug costs escalated, as expected, in the increasingly compliant groups, medical costs decreased, thus reducing the total cost of care in more compliant groups.<sup>8</sup>

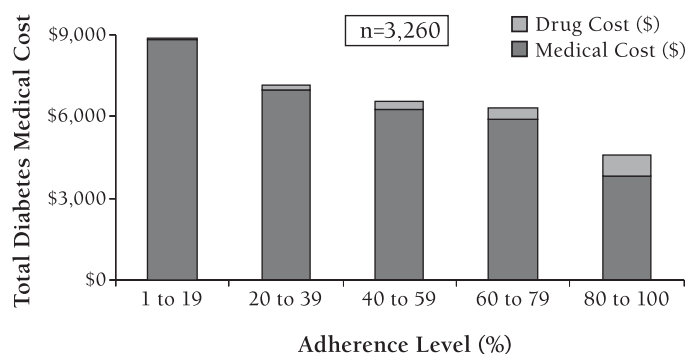
Noncompliance involves a myriad of economic and provider/health care-related factors beyond the patient-related factors discussed previously. Patient out-of-pocket cost is certainly one of these factors, which is impacted most significantly by copayments. One study demonstrated that compliance was greatest and declined less rapidly among patients with copays from \$0 to <\$10 compared with patients with copays from \$10 to <\$20.<sup>18</sup> In this analysis, researchers reported that compliance was lowest and declined most rapidly among patients with copays ≥\$20.

Using cardiovascular disease as a model, one study demonstrated the impact of provider-related factors on patient compliance.<sup>19</sup> In this study, surveyed providers cited the time constraints of a “typical” office visit as well as the use of multiple guidelines with different recommendations (e.g., different recommendations for female patients) as barriers to providing patient education and obtaining improved compliance to therapies.<sup>19</sup> Regarding health care-related factors, another study reported that fragmented care negatively impacts compliance.<sup>20</sup> In this study (N=21,011), patients who patronized ≥2 pharmacies or who had ≥3 prescribing physicians had approximately twice the rate of nonadherence over a 1-year period.<sup>20</sup>

### Interventions for Improving Compliance

A multidimensional approach is necessary to effectively address the diverse and varying factors contributing to noncompliance in managed care. The literature supports this approach, with

**FIGURE 5** Medical and Drug Costs as Related to Medication Compliance Levels



Adapted from Sokol MC et al.<sup>8</sup>

As adherence to medication decreases, the overall cost of care increases. Diabetes-Related Health Care Costs.

some studies citing the integration of multiple components as the key toward a successful approach to improving adherence.<sup>16,21</sup> Furthermore, follow-up visits or multiple interventions should improve attempts to enhance compliance.

Due to the various contributors to the problem of noncompliance, a need arises to focus on educational, behavioral, and combination strategies to implement evidence-based treatment plans.<sup>10</sup> Clearly, education is critical. Education starts with the provider, who is typically the physician supplemented by the support of nurses and pharmacists.<sup>10</sup> In addition, written materials and Web sites can be helpful in bolstering educational interventions. Behavioral efforts center on follow-up with high-risk patients via telephone or mail to ensure that they come in for scheduled visits and/or take their medications.<sup>10</sup> Behavioral interventions may also entail including the patient as a partner in treatment decision making and enlisting the social support of family members and significant others.<sup>21,22</sup> Additional behavioral factors shown to positively impact compliance include an insight into the disease state, a belief that the medication will cure or control the disease, a feeling of being threatened by the disease, and a good relationship with the health care provider.<sup>23</sup> The positive effect of this latter factor was demonstrated in a study by Piette et al. in which patients with “high trust” in their physician demonstrated reduced cost-related underuse of medication compared with patients with “low trust,” despite increasing out-of-pocket costs.<sup>24</sup> Obviously, combining behavioral and educational efforts can be quite effective in preventing nonadherence.<sup>10</sup>

Providers play an integral role in ensuring the success of compliance interventions, beginning with a strategy of improved

communication with patients.<sup>25</sup> To improve compliance, providers should discuss compliance with their patients at every visit in a nonjudgmental manner and should also communicate their respect for the patient's perspective on his/her condition.<sup>25</sup> Furthermore, providers must divulge a rationale for any recommended treatment and negotiate a plan that anticipates and addresses any problems that may arise.<sup>25</sup> Ultimately, a collaborative process for problem solving should be established with patients to ensure that they take an active role in their treatment, thereby increasing the likelihood that compliance-improving interventions will be successful.<sup>25</sup>

The aforementioned noncompliance-targeted activities have been applied in some form to clinical practice with noticeable success. For example, the University of California Los Angeles Comprehensive Hospital-Based Atherosclerosis Management Program (CHAMP) instituted a discharge protocol 15 years ago for patients hospitalized for myocardial infarction (MI) to improve utilization of and adherence to evidence-based therapies.<sup>26</sup> Prior to implementation of the CHAMP protocol, persistence rates for aspirin, beta-blocker, and statin therapy in patients 1 year postdischarge for MI were modest at 68%, 18%, and 10%, respectively.<sup>26</sup> Post-CHAMP persistence rates at 1 year after discharge for these therapies improved to 94%, 57%, and 91%, respectively.<sup>26</sup> These improved persistence rates resulted in significantly reduced rates of coronary events such as recurrent MI, hospitalization, and cardiac mortality ( $P < 0.05$ ).<sup>26</sup>

Similar results have been demonstrated in outpatients with cardiovascular disease. At Walter Reed Army Medical Center, a study of 200 ambulatory patients aged  $> 65$  years with coronary risk factors introduced 3 phases to examine an intervention for medication noncompliance. The first phase constituted a 2-month observational period to determine patient compliance with blood pressure- and lipid-lowering treatments. The second phase involved a 6-month intervention in which all patients received aggressive disease management in the form of medication dispensed in a time-specific blister pack. The final phase consisted of a follow-up period in which half of the patients were maintained on blister pack medication dispensing for 6 months while the other half resumed medication dispensed in conventional bottles.<sup>27</sup> Patients selected for the trial were deemed at risk for noncompliance due to their age and to the prescription of  $\geq 4$  chronic medications.<sup>27</sup> Relative to baseline compliance (approximately 60%), most patients improved to nearly 100% compliance.<sup>27</sup> Following Phase 2 of the study, patients who resumed their usual care also returned to their baseline levels of compliance compared with those who were maintained on intensive pharmacy oversight with time-specific blister pack dispensing.<sup>27</sup> While this intervention had relatively little impact on LDL-C lowering in terms of outcomes, blood pressure was significantly reduced in patients receiving more careful administration of the time-specific blister pack ( $P = 0.04$ ).<sup>27</sup>

### Conclusions

Intensive LDL-C reduction plays a critical role in the mitigation of cardiovascular risk. Still, the effectiveness of lipid-lowering strategies is offset to a significant degree by both physician and patient factors that limit goal attainment. Despite extensive evidence demonstrating the benefits of lipid-lowering therapy, many patients are still not getting to goal because the transition from physician awareness to clinical practice is lagging. Additionally, patient noncompliance to therapy also contributes to poor health outcomes and increasing costs in managed care.

To overcome the issues surrounding LDL-C goal attainment, interventions used to attain these goals should be based not only on the conclusions of clinical trials but also on successful behavioral strategies from both the patient and provider perspective. Interventions for improving adherence to lipid-lowering medication will provide an opportunity to decrease cardiovascular disease morbidity, mortality, and hospitalization, as well as improve the quality of life for patients and reduce costs for managed care.

### DISCLOSURE

Author Benjamin J. Ansell has received honoraria as a speaker and consultant for AstraZeneca, Pfizer, and Merck. Ansell was responsible for the entire study concept and design of this article. He performed all of the data collection, data interpretation, writing, and revision of this article.

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