

## Medication Adherence: WHO Cares?

MARIE T. BROWN, MD, AND JENNIFER K. BUSSELL, MD

The treatment of chronic illnesses commonly includes the long-term use of pharmacotherapy. Although these medications are effective in combating disease, their full benefits are often not realized because approximately 50% of patients do not take their medications as prescribed. Factors contributing to poor medication adherence are myriad and include those that are related to patients (eg, suboptimal health literacy and lack of involvement in the treatment decision-making process), those that are related to physicians (eg, prescription of complex drug regimens, communication barriers, ineffective communication of information about adverse effects, and provision of care by multiple physicians), and those that are related to health care systems (eg, office visit time limitations, limited access to care, and lack of health information technology). Because barriers to medication adherence are complex and varied, solutions to improve adherence must be multifactorial. To assess general aspects of medication adherence using cardiovascular disease as an example, a MEDLINE-based literature search (January 1, 1990, through March 31, 2010) was conducted using the following search terms: *cardiovascular disease*, *health literacy*, *medication adherence*, and *pharmacotherapy*. Manual sorting of the 405 retrieved articles to exclude those that did not address cardiovascular disease, medication adherence, or health literacy in the abstract yielded 127 articles for review. Additional references were obtained from citations within the retrieved articles. This review surveys the findings of the identified articles and presents various strategies and resources for improving medication adherence.

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BP = blood pressure; CVD = cardiovascular disease; MI = myocardial infarction; MTMS = medication therapy management services; WHO = World Health Organization

*Keep a watch...on the faults of the patients, which often make them lie about the taking of things prescribed. For through not taking disagreeable drinks, purgative or other, they sometimes die.*

Hippocrates, *Decorum*

In its 2003 report on medication adherence,<sup>1</sup> the World Health Organization (WHO) quoted the statement by Haynes et al that “increasing the effectiveness of adherence interventions may have a far greater impact on the health of the population than any improvement in specific medical treatments.” Among patients with chronic illness, approximately 50% do not take medications as prescribed.<sup>1,2</sup> This poor adherence to medication leads to increased morbidity and death and is estimated to incur costs of approximately \$100 billion per year.<sup>3</sup> Thus, Hippocrates’ exhortation to the physician to “not only be prepared to do what is right himself, but also to make the patient...cooperate”<sup>4</sup> has consistently failed for more than 2000 years. Today’s ever more complicated medical regimens make it even less likely that physicians will be able to compel compliance and more im-

portant that they partner with patients in doing what is right together.

This review will discuss general aspects of medication adherence, using cardiovascular disease (CVD) as an example, and provide the physician with various practical strategies and resources for improving medication adherence among their patients.

### METHODS

We conducted a MEDLINE database literature search limited to English- and non-English-language articles published between January 1, 1990, and March 31, 2010, using the following search terms: *cardiovascular disease*, *health literacy*, *medication adherence*, and *pharmacotherapy*. Of the 405 articles retrieved, those that did not address CVD, medication adherence, or health literacy in the abstract were excluded, leaving 127 for inclusion in the review. Additional references were obtained from citations within the retrieved articles.

**For editorial comment, see page 268**

### GENERAL ASPECTS OF MEDICATION ADHERENCE

Medication-taking behavior is extremely complex and individual, requiring numerous multifactorial strategies to improve adherence. An enormous amount of research has resulted in the development of medications with proven efficacy and positive benefit-to-risk profiles. This millennium has seen a new and greater focus on outcomes. However, we seem to have forgotten that between the former and the latter lies medication adherence:

Treatment → **Adherence** → Outcomes

The WHO defines adherence to long-term therapy as “the extent to which a person’s behavior—taking medication, following a diet, and/or executing lifestyle changes—

From the Department of Internal Medicine, Rush University Medical Center, Chicago, IL (M.T.B.); and Department of Medicine, University of Chicago Pritzker School of Medicine, Chicago, IL, and Department of Medicine, MacNeal Hospital, Berwyn, IL (J.K.B.).

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Address reprint requests and correspondence to Marie T. Brown, MD, 6326 W Roosevelt Rd, Oak Park, IL 60304 (mariebrown@drsbrownforbes.com).

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## ARTICLE HIGHLIGHTS

- Approximately 50% of patients do not take medications as prescribed
- Medication adherence is not exclusively the responsibility of the patient
- Increasing adherence may have a greater effect on health than improvements in specific medical therapy
- Medication-taking behavior is complex and involves patient, physician, and process components
- Identification of nonadherence is challenging and requires specific interviewing skills
- Solutions include encouraging a “blame-free” environment, opting for less frequent dosing, improving patient education, assessing health literacy, and paying attention to rational nonadherence
- Many helpful Web-based resources are available

corresponds with agreed recommendations from a health care provider.”<sup>1</sup> Often, the terms *adherence* and *compliance* are used interchangeably. However, their connotations are somewhat different: *adherence* presumes the patient’s agreement with the recommendations, whereas *compliance* implies patient passivity. As described by Steiner and Earnest,<sup>5</sup> both terms are problematic in describing medication-taking behavior because they “exaggerate the physician’s control over the process of taking medications.” The complex issues surrounding the taking of medication for chronic disease cannot easily be distilled into one word. Recognition of this complexity will help avoid assigning blame exclusively to the patient and assist in identifying effective solutions.

Measurement of medication adherence is challenging because adherence is an individual patient behavior. The following are some of the approaches that have been used: (1) subjective measurements obtained by asking patients, family members, caregivers, and physicians about the patient’s medication use; (2) objective measurements obtained by counting pills, examining pharmacy refill records, or using electronic medication event monitoring systems; and (3) biochemical measurements obtained by adding a nontoxic marker to the medication and detecting its presence in blood or urine or measurement of serum drug levels. Currently, a combination of these measures is used to assess adherence behavior. Along with the monitoring of outcome, these tools assist investigators in studying medication adherence.

Patients are generally considered adherent to their medication if their medication adherence percentage, defined as the number of pills absent in a given time period (“X”) divided by the number of pills prescribed by the physician in that same time period, is greater than 80%.<sup>3,6</sup>:

$$\frac{\text{No. of Pills Absent in Time X}}{\text{No. of Pills Prescribed for Time X}} \times 100 \geq 80\%$$

One limitation to calculating adherence using this method is that it assumes that the number of pills absent were actually taken by the patients. In addition, this method may not be representative of long-term adherence patterns because patients may exhibit *white-coat adherence*, or improved medication-taking behavior in the 5 days before and 5 days after a health care encounter.<sup>3</sup>

## INCIDENCE OF NONADHERENCE

According to a 2003 report published by the WHO, adherence rates in developed countries average only about 50%.<sup>1</sup> Adherence is a key factor associated with the effectiveness of all pharmacological therapies but is particularly critical for medications prescribed for chronic conditions. Of all medication-related hospitalizations that occur in the United States, between one-third and two-thirds are the result of poor medication adherence.<sup>3</sup> A fair amount of data is available regarding medication adherence in CVD because, for many of the risk factors, adherence can be roughly approximated via the measurement of surrogate markers. For example, adherence to antihypertensive therapy can be approximated by measuring blood pressure (BP) control, and adherence to lipid-lowering therapy can be approximated by measuring lipid levels. Because most research is disease-specific and not focused on medication adherence alone, this review will focus on medication adherence as it relates to CVD. Examining adherence in patients with CVD is a useful model for helping physicians understand medication adherence in other chronic conditions.

Cardiovascular complications resulting from hypertension, hyperlipidemia, and diabetes lead to substantial disability, morbidity, and mortality. For example, for every increase of 20 mm Hg in systolic BP and every increase of 10 mm Hg in diastolic BP, the risk of stroke and ischemic heart disease doubles.<sup>7</sup> Because of this increased risk, comprehensive treatment plans for patients with established CVD include antidiabetes, antihypertensive, and lipid-lowering (typically statin-based) therapies for patients who present with diabetes, hypertension, and dyslipidemia, respectively.<sup>8</sup>

Although it is well known that antidiabetes, antihypertensive, and lipid-lowering therapies significantly reduce the risk of ischemic events,<sup>9-11</sup> long-term adherence to these medications is poor even among patients who have already experienced a cardiovascular event (Figure 1).<sup>12</sup> For example, despite the fact that pharmacological antihypertensive therapy has a positive safety and tolerability profile and reduces the risk of stroke by approximately 30% and myocardial infarction (MI) by approximately 15%,<sup>11</sup> evidence from a number of studies suggests that as many as 50% to 80% of patients treated for hypertension are nonadherent to their treatment regimen.<sup>13-15</sup> According to the WHO,

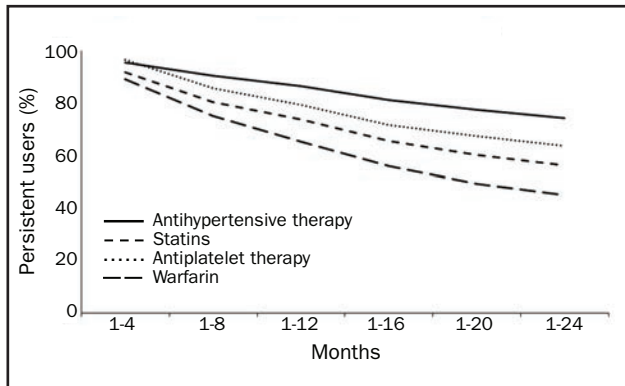


FIGURE 1. Persistence with secondary prevention medication in the 24 months after ischemic stroke in Sweden. Persistent use of secondary preventive drugs declines rapidly during the first 2 years after stroke. From *Stroke*,<sup>12</sup> with permission.

this lack of adherence is the most important cause of failure to achieve BP control.<sup>1</sup> Failure to achieve BP control significantly increases the risk of MI, stroke, and hospitalization.<sup>16,17</sup> As expected, adherence to antihypertensive therapy reduces the risk of these events.<sup>18</sup>

Comprehensive treatment plans for patients with CVD also include indefinite use of antiplatelet therapy.<sup>8</sup> For patients with heart disease, ischemic cerebrovascular disease, or peripheral artery disease, aspirin or clopidogrel monotherapy has a favorable benefit-to-risk profile; for patients who experience an ischemic cerebrovascular event, therapy with aspirin plus extended-release dipyridamole is an additional treatment option.<sup>19</sup> For patients who experience acute coronary syndrome or undergo percutaneous coronary intervention with stent implantation, dual antiplatelet therapy with aspirin and either clopidogrel or prasugrel is recommended for at least 12 months for those not at a high risk of bleeding.<sup>20</sup>

Like adherence to antihypertensive therapy, adherence to statins and antiplatelet agents is poor, as are the outcomes associated with nonadherence. Within 6 months to 1 year after having been prescribed statins, approximately 25% to 50% of patients discontinue them<sup>21-24</sup>; at the end of 2 years, nonadherence is as high as 75%.<sup>25,26</sup> Achievement of the treatment goals recommended by the National Cholesterol Education Program is also poor.<sup>27,28</sup> With regard to antiplatelet therapy, studies that assessed long-term aspirin use found that rates of adherence beyond 1 year ranged from 71% to 84%.<sup>29-32</sup> For dual antiplatelet therapy recipients, premature discontinuation of clopidogrel rates has been reported to occur in 12% to 14% of patients within 1 to 3 months of initiation<sup>33,34</sup> and in up to 20% of patients beyond 6 months.<sup>35,36</sup>

Nonadherence to lipid-lowering and antiplatelet therapies is associated with an increased risk of adverse cardio-

vascular outcomes.<sup>16,32,34,36-41</sup> Aside from the increased risk of MI, stroke, and death, stent recipients who prematurely discontinue clopidogrel also have an increased rate of stent thrombosis.<sup>34,36,42-45</sup> For example, in an analysis of 3021 drug-eluting stent recipients, discontinuation of clopidogrel within 6 months of stent implantation was the strongest predictor of 6-month stent thrombosis (hazard ratio, 13.74; 95% confidence interval, 4.04-46.68;  $P < .001$ ).<sup>43</sup> In a study of 500 drug-eluting stent recipients, 13.6% of patients discontinued thienopyridine therapy within 30 days.<sup>34</sup> These patients had a 10-fold greater mortality rate at 1 year than those who continued thienopyridine therapy (7.5% vs 0.7%).<sup>34</sup>

### CAUSES OF POOR MEDICATION ADHERENCE

Poor adherence to medical treatment severely compromises patient outcomes and increases patient mortality. According to the WHO, improving adherence to medical therapy for conditions of hypertension, hyperlipidemia, and diabetes would yield very substantial health and economic benefits.<sup>1</sup> To improve medication adherence, the multifactorial causes of decreased adherence must be understood. The WHO classifies these factors into 5 categories: socioeconomic factors, factors associated with the health care team and system in place, disease-related factors, therapy-related factors, and patient-related factors.<sup>1</sup> In broader terms, these factors fall into the categories of patient-related factors, physician-related factors, and health system/team building-related factors.

#### PATIENT-RELATED FACTORS

Several patient-related factors, including lack of understanding of their disease,<sup>46</sup> lack of involvement in the treatment decision-making process,<sup>47</sup> and suboptimal medical literacy,<sup>48</sup> contribute to medication nonadherence. In the United States alone, an estimated 90 million adults have inadequate health literacy,<sup>49</sup> placing them at risk for increased rates of hospitalization and poorer clinical outcomes.<sup>50,51</sup> The patient's health beliefs and attitudes concerning the effectiveness of the treatment, their previous experiences with pharmacological therapies, and lack of motivation also affect the degree of medication adherence.<sup>3,52,53</sup> Medication adherence continues to decline even after a catastrophic event such as a stroke (Figure 1)<sup>12</sup>; thus, it is not surprising that treating asymptomatic conditions to prevent the possible occurrence of adverse events years later presents an even greater challenge. Specific factors identified as barriers to medication adherence among inner city patients with low socioeconomic status were high medication costs, lack of transportation, poor understanding of medication instructions, and long wait

times at the pharmacy.<sup>55</sup> A lack of family or social support is also predictive of nonadherence,<sup>52,56,57</sup> as is poor mental health.<sup>3,53,58</sup> These findings are clinically relevant for patients with CVD because studies have shown that depression and anxiety are common in patients with coronary artery disease or stroke.<sup>59-61</sup> Indeed, the poorer outcomes experienced by patients with depression and CVD may be due, at least in part, to poorer medication adherence by depressed patients.<sup>62,63</sup>

#### PHYSICIAN-RELATED FACTORS

Not only do physicians often fail to recognize medication nonadherence in their patients, they may also contribute to it by prescribing complex drug regimens, failing to explain the benefits and adverse effects of a medication effectively, and inadequately considering the financial burden to the patient.<sup>3,55</sup> Ineffective communication between the primary care physician and the patient with a chronic disease such as CVD further compromises the patient's understanding of his or her disease, its potential complications, and the importance of medication adherence.<sup>5</sup> Failing to elicit a history of alternative, herbal, or supplemental therapies from patients is another source of ineffective communication.

Communication among physicians is often insufficient and may contribute to medication nonadherence. Direct communication between hospitalists and primary care physicians occurs in less than 20% of hospitalizations, and discharge summaries are available at less than 34% of first postdischarge visits.<sup>64</sup> Inadequate communication between physicians, hospitalists, primary care physicians, and consultants also contributes to medication errors and potentially avoidable hospital readmissions.<sup>64,65</sup>

#### HEALTH SYSTEM/TEAM BUILDING-RELATED FACTORS

Fragmented health care systems create barriers to medication adherence by limiting the health care coordination and the patient's access to care.<sup>66</sup> Prohibitive drug costs or copayments also contribute to poor medication adherence.<sup>35,67</sup> Health information technology is not widely available, preventing physicians from easily accessing information from different patient care-related venues, which in turn compromises patient care, timely medication refills, and patient-physician communication. In an overtaxed health care system in which clinicians see a large volume of patients without resources to meet individual patient needs, the amount of time a clinician spends with patients may be insufficient to properly assess and understand their medication-taking behaviors. This lack of time may preclude engaging the patient in a discussion on the importance of medication adherence and strategies to achieve success.

## STRATEGIES TO IMPROVE MEDICATION ADHERENCE

Between 2000 and 2002, the typical Medicare beneficiary saw a median of 7 physicians per year: 2 primary care physicians and 5 specialists.<sup>68</sup> This finding highlights the need for coordinated, multifactorial strategies to improve medication adherence. However, given the enormous complexities involved in medication adherence, research on improving adherence has been challenging and generally focused on single disease states. A recent Cochrane review of 78 randomized trials found no one simple intervention and relatively few complex ones to be effective at improving long-term medication adherence and health outcomes,<sup>69</sup> underscoring the difficulty of improving medication adherence.

Although improving medication adherence is challenging, clinicians can take several steps to assist patients' medication-taking behavior, and subsequently, outcomes. The ensuing discussion will focus on strategies to improve medication adherence related to the areas of patient-, physician-, and health system/team building-related factors. A summary of available resources that can be used to implement these strategies is found in Table 1.

#### PATIENT-RELATED FACTORS

Medication adherence is primarily in the domain of the patient.<sup>1</sup> Because patients recall as little as 50% of what is discussed during the typical medical encounter,<sup>70</sup> effective patient education must be multifactorial, individualized, and delivered in a variety of methods and settings outside of the examining room. A key component of any adherence-improving plan is patient education. In one recent prospective study of 1341 patients with hypertension, education of both the patient and physician was associated with improved BP control vs education of the physician alone.<sup>71</sup> Formal health education programs, such as diabetes self-management education, have been shown to be effective<sup>72</sup>; however, access to similar non-disease-specific programs is limited. In the absence of a formal program, physicians would do well to emphasize the availability of other educational resources, including but not limited to pharmacists, community health programs, and interactive Web-based materials such as those found at [www.medlineplus.gov](http://www.medlineplus.gov) (Table 1). It might also be beneficial to recommend to patients that they engage local librarians to help them access the Internet.

The more empowered patients feel, the more likely they are to be motivated to manage their disease and adhere to their medications. Thus, another key factor that can improve patient-related medication adherence is actively involving patients in treatment decisions when possible. One simple way to involve patients is to ask what time of day

TABLE 1. **Strategies and No-Cost Resources Aimed at Overcoming Barriers to Medication Adherence**

<i>Patient-related factors</i>	
Health literacy	
Teach-back method (video of real patients)	<a href="http://www.acpfoundation.org">http://www.acpfoundation.org</a>
Empowering patients to ask questions	<a href="http://www.npsf.org/askme3/">http://www.npsf.org/askme3/</a>
Visual, interactive video medical education	<a href="http://medlineplus.gov">http://medlineplus.gov</a>
Providing a pictorial medication schedule	<a href="http://www.ahrq.gov/qual/pillcard/pillcard.htm">http://www.ahrq.gov/qual/pillcard/pillcard.htm</a>
Audio information: podcasts/radiocasts	<a href="http://healthcare411.ahrq.gov/">http://healthcare411.ahrq.gov/</a>
Health literacy universal precautions toolkit	<a href="http://www.ahrq.gov/qual/literacy/">http://www.ahrq.gov/qual/literacy/</a>
Medication list for patients	<a href="http://www.safemedication.com">http://www.safemedication.com</a>
Mental health issues	
Videos from the National Institutes of Mental Health	<a href="http://www.nimh.nih.gov">http://www.nimh.nih.gov</a>
Helpline of the National Alliance for the Mentally Ill	<a href="http://www.nami.org/">http://www.nami.org/</a>
Patient participation	
Developing a patient-centered medical home	<a href="http://www.aafp.org/online/en/home/membership/initiatives/pcmh.html">http://www.aafp.org/online/en/home/membership/initiatives/pcmh.html</a> <a href="http://www.acponline.org/running_practice/pcmh/">http://www.acponline.org/running_practice/pcmh/</a>
Financial issues/access to care	
Prescription medicine financial assistance	<a href="http://www.needymeds.org/">http://www.needymeds.org/</a> <a href="http://rxassist.org/">http://rxassist.org/</a> <a href="http://www.pparx.org/">http://www.pparx.org/</a> <a href="http://www.togetherrxaccess.org/Tx/jsp/home.jsp">http://www.togetherrxaccess.org/Tx/jsp/home.jsp</a> <a href="http://www.benefitscheckup.org/">http://www.benefitscheckup.org/</a> <a href="http://www.medicare.gov/">http://www.medicare.gov/</a>
National Council on Aging	
Medicare plans	<a href="http://www.medicare.gov/">http://www.medicare.gov/</a>
<i>Physician-related factors</i>	
Awareness	
Identification and useful tools	<a href="http://www.ethnomed.org">http://www.ethnomed.org</a>
Rapid estimate of adult health literacy	<a href="http://www.ahrq.gov/populations/sahlsatool.htm">http://www.ahrq.gov/populations/sahlsatool.htm</a>
Rapid test of literacy	<a href="http://www.adultmeducation.com/">http://www.adultmeducation.com/</a>
Health literacy video of physician interviews with patients	<a href="http://www.acpfoundation.org">http://www.acpfoundation.org</a>
Communication	
Video vignettes relating to cultural competency	<a href="https://cccm.thinkculturalhealth.org/videos/index.htm">https://cccm.thinkculturalhealth.org/videos/index.htm</a>
National Council on Patient Information and Education	<a href="http://www.talkaboutrx.org/">http://www.talkaboutrx.org/</a>
American Academy on Communication in Healthcare	<a href="http://www.aachonline.org/">http://www.aachonline.org/</a>
Complexity of dosing	
Medication list and helpful questions	<a href="http://www.learnaboutrxsafety.org/">http://www.learnaboutrxsafety.org/</a>
<i>Health system/team building–related factors</i>	
Time constraints	
Patient-centered medical home	<a href="http://www.acponline.org/running_practice/pcmh/">http://www.acponline.org/running_practice/pcmh/</a>
American Association of Family Practice medical home	
Web site	<a href="http://www.medicalhomeinfo.org/">http://www.medicalhomeinfo.org/</a>
Patient-Centered Primary Care Collaborative	<a href="http://www.pcpc.net/">http://www.pcpc.net/</a>
Lack of care coordination (“fumbled hand offs”)	
Coordinating care among all physicians	<a href="http://www.ihl.org/ihl">http://www.ihl.org/ihl</a>
Medication reconciliation	<a href="http://www.psnet.ahrq.gov/primer.aspx?primerID=1">http://www.psnet.ahrq.gov/primer.aspx?primerID=1</a>
Lack of automation	
American EHR Partners (ACP-sponsored)	<a href="http://www.americanehr.com">http://www.americanehr.com</a>
Electronic Prescribing Readiness Assessment	<a href="http://getrxconnected.org">http://getrxconnected.org</a>
Health information technology	<a href="http://healthit.ahrq.gov/">http://healthit.ahrq.gov/</a>
Introduction to electronic health records	<a href="http://www.centerforhit.org/">http://www.centerforhit.org/</a> <a href="http://www.thecimm.org/">http://www.thecimm.org/</a>

ACP = American College of Physicians.

they would prefer to take their medications. One patient may be more likely to adhere to his or her medications if they were taken in the evening, whereas for another, the morning may be preferred. Only the patient can make this decision. Ascertaining how quickly patients would like to achieve the desired medical outcome also engages the patients in their care. For patients with CVD, this would include how quickly they would like to achieve controlled BP and lipid levels. Patients’ answer to this question can help the physician determine how quickly medication may need to be

titrated and how often patients will need to be seen in the office or undergo laboratory testing. If a number of alternative treatment options are recommended, offering patients choices encourages active participation in their treatment. For example, once adherence to one medication or treatment is realized and a sense of accomplishment attained, moving to the next recommendation and treatment goal is more achievable. Similarly, the physician should avoid prescribing numerous medications and behavioral modifications at any one visit because this may overwhelm the patient and induce

a sense of futility. If it is necessary to prescribe more than one drug or intervention during a given visit, a rationale should be provided for which are most important because it will help ensure that, if patients decide to stop taking their medications for any reason, they will discontinue the most important medications last. It is also hoped that providing a rationale would encourage patients to inform their physicians of any plans to change medications, allowing for discussion.

Inadequate health literacy is often underrecognized and therefore not addressed by physicians.<sup>73</sup> According to data from the first National Assessment of Adult Literacy, conducted in 2003, 77 million US adults (35%) have basic or below basic health literacy, whereas only 26.4 million (12%) have proficient health literacy.<sup>74</sup> Many patients with basic or below basic health literacy may be unable to read a medicine bottle or poison warning.<sup>75</sup> In another study, almost half of patients with low literacy admitted shame, which prevented them from seeking needed help.<sup>76</sup> Of patients who admitted having reading problems and being ashamed, more than 85% hid their limited literacy from co-workers or supervisors, and approximately 50% hid it from their children.<sup>76</sup> The economic consequences of low health literacy skills are exemplified in a 1992 study conducted by the University of Arizona that showed that total annual health care costs for patients enrolled in Medicare with low health literacy were 4 times greater than costs for patients with high health literacy.<sup>75</sup> Comments such as “I’ll read this when I get home” or “I forgot my glasses, can you read this to me?” are clues that the patient may have poor literacy. Simple tools to help the clinician are presented in Table 1.

To help combat poor health literacy and its negative effect on medication adherence, a “shame-free” environment must be created. Possible solutions to poor patient literacy include providing the patient with pictorial and audiovisual educational material instead of written instructions. Given that less than 60% of the US population has English as their first language,<sup>75</sup> providing information in the patient’s native language may also lessen the burden of poor health literacy. For example, the Web site [www.medlineplus.gov](http://www.medlineplus.gov) provides simple audiovisual education in more than 40 languages and 250 topics. The topics available in multiple languages include several related to CVD, such as cholesterol, coronary artery disease, diabetes, heart attack, hypertension, peripheral artery disease, and stroke.

Recognizing and treating mental illness must be a priority when treating patients for other chronic conditions such as CVD. Often, successful treatment of patients’ coexisting illnesses depends on first treating any underlying mental illness.

Consideration of patients’ economic status is of paramount importance. Recognizing that patients’ economic constraints will limit their ability to adhere to their medi-

cation, the physician may direct patients to programs that provide financial assistance. Such programs include pharmaceutical company–based assistance plans, state-based assistance plans, and pharmacies that provide 30-day supplies of widely prescribed medications, including many of those often prescribed for patients with CVD, for less than \$5 (Table 1). A hospital social worker, practice champion, or community center volunteer may offer the time and resources necessary to assist individual patients.

### PHYSICIAN-RELATED FACTORS

The substantially improved adherence of patients who report a good relationship with their physician highlights the important role of physicians in the medication adherence equation.<sup>3</sup> Similar to any relationship, one key to a good physician-patient relationship is effective communication. Thus, perhaps the foremost strategy physicians can use to increase medication adherence is to follow a patient-centered approach to care that promotes active patient involvement in the medical decision-making process. As part of such a patient-centered approach, the physician should consider patients’ cultural beliefs and attitudes. For instance, a common cultural attitude held by many patients is a preference for herbal remedies. Reassuring such a patient with diabetes that metformin is derived from the French lilac might improve his or her acceptance of the therapy.

A recent article by Reach<sup>54</sup> addressed the behavior of people who have a “taste for the present rather than the future” and proposed that these “impatient patients” are unlikely to adhere to medications that require long-term use. In it, he proposes that, if an “impatience genotype” exists, assessing these patients’ view of the future while stressing immediate advantages of adherence may improve adherence rates more than emphasizing potentially distant complications. Reach<sup>54</sup> suggests that rather than attempt to change the character of those who are “impatient,” it may be wise to ascertain the patient’s individual priorities, particularly as they relate to immediate vs long-term gains. For example, while advising an “impatient” patient with diabetes, stressing improvement in visual acuity rather than avoidance of retinopathy may result in greater medication adherence rates. Additionally, linking the cost of frequently changing prescription lenses because visual acuity fluctuates with glycemic levels may provide insight to the patient and an immediate financial motivation for improving adherence.

Overall, by acknowledging the presence of cultural beliefs and attitudes, physicians can build trust with their patients and proactively address any culture- or belief-related adherence barriers.<sup>77</sup> An essential component of effective physician-patient relationships is the creation of an encouraging, “blame-free” environment, in which patients are praised for achieving treatment goals and are given “per-

**TABLE 2. Questions a Clinician Can Ask to Assess a Patient's Medication Adherence**

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I know it must be difficult to take all your medications regularly. How often do you miss taking them?<sup>3</sup>

Of the medications prescribed to you, which ones are you taking?

Of the medications you listed, which ones are you taking?

Have you had to stop any of your medications for any reason?

How often do you not take medication X? (address each medication individually)

When was the last time you took medication X? (address each medication individually)

Have you noticed any adverse effects from your medications?

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mission” to honestly answer any questions related to their treatment.

By asking the appropriate questions, physicians can accurately assess which medications patients are taking and how they are taking them. At a routine visit, patients may be asked twice to list their medications (eg, on a form while waiting to be seen and again when the nurse escorts them to the examination room). However, simply listing medications does not address whether they are actually being taken. Thus, if the physician assumes that the medications listed are being taken, the scene for miscommunication is set. Assessment of medication-taking patterns may be more efficiently obtained by asking a number of direct questions in a nonjudgmental way (Table 2).

Inquiring whether patients plan on “rationing” or “sharing” their medication for financial or other reasons is essential because this is a common practice often kept from physicians. If physicians are aware that patients plan to ration their medication, they will be able to discuss the importance of taking the medication as directed or to prescribe a different medication that is more “forgiving.” Forgiving drugs are defined as those for which a missed dose

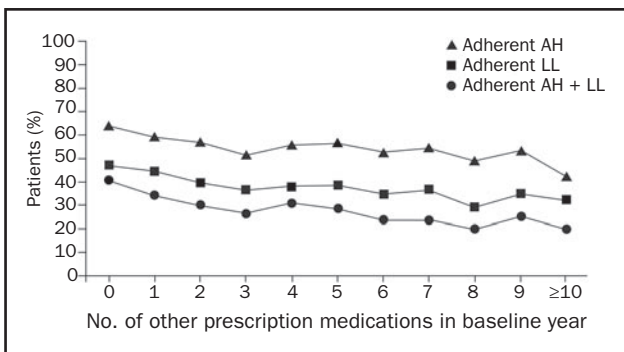


FIGURE 2. Percentage of patients adherent (proportion of days covered  $\geq 80\%$ ) to antihypertensive (AH) and lipid-lowering (LL) therapy, by prescription burden. From *Am J Health Syst Pharm*.<sup>81</sup> with permission. ©2009, American Society of Health System Pharmacists, Inc. All rights reserved.

is less detrimental to long-term outcomes.<sup>78</sup> Alternatively, physicians might prescribe a drug taken on a monthly basis or administered by depot or transdermally.

Physicians have several opportunities to improve medication adherence when prescribing drugs. Prescribing the maximum number of doses possible at one time, thereby limiting the frequency of pharmacy visits, and acknowledging the patient’s economic status by adhering to their formulary improve adherence by minimizing economic barriers. An increased number of pills ingested per day may also decrease adherence.<sup>29,79-81</sup> A recent study by Benner et al<sup>81</sup> of approximately 6000 patients enrolled in a managed care setting focused on the effect of previous prescription burden on future adherence rates when antihypertensive or lipid-lowering therapy were added. Adherence rates decreased to 41%, 35%, and 30% in patients who received 0, 1, and 2 previous medications, respectively; among patients with 10 or more previous medications, adherence was 20% (Figure 2). It is interesting to note that adherence rates were increased by initiating antihypertensive and lipid-lowering therapies concurrently. To help combat the decreased adherence associated with polypharmacy, physicians should consider prescribing fixed-dose combination pills when possible. Indeed, data suggest that adherence to multidrug antihypertensive and lipid-lowering therapy regimens is improved when single- vs multiple-pill regimens are used.<sup>82-84</sup> For example, a meta-analysis of fixed-dose vs free-drug regimens in more than 20,000 patients identified a 26% decrease in the risk of nonadherence associated with a fixed-dose combination.<sup>82</sup>

Medications with once-daily dosing may be preferable to medications with multiple doses per day because minimizing the frequency of dosing has been shown to improve adherence.<sup>85</sup> In a meta-analysis, adherence  $\pm$  SD to once-daily dosing was found to be 79% $\pm$ 14%; to twice-daily dosing, 69% $\pm$ 15%; to dosing 3 times per day, 65% $\pm$ 16% ( $P=.008$  vs once-daily); and to dosing 4 times per day, 51% $\pm$ 20% ( $P<.001$  vs once-daily;  $P=.001$  vs twice-daily dosing) (Figure 3).<sup>3,86</sup> These data suggest that a 10% decrease in adherence will occur with each additional daily dose. Because complex treatment regimens are associated with decreased adherence,<sup>79</sup> physicians would be wise to prescribe drugs that can be taken at the same time of day. If complex treatment regimens cannot be avoided, open acknowledgement of this by the physician may improve the physician-patient relationship, thus increasing adherence.

When prescribing a new medication, the physician should provide the patient with all necessary and important information, including the name of the medication; its purpose (eg, to lower BP); the rationale for choosing it (eg, other drugs are available to lower your BP, but this one is equally effective and is available on your insurance plan’s

formulary list); the frequency of dosing (eg, once daily); when it should be taken (eg, in the morning with your other medications); how long it should be taken (eg, for 1 year or lifelong); and any potential adverse effects, their likelihood of occurring, whether they will resolve without intervention, and how the treatment plan may change if they do not resolve. Unfortunately, physicians frequently fail to communicate all of this information to their patients. In one study, Tarn et al<sup>87</sup> found that in more than 65% of audiotaped cases they analyzed, physicians had omitted at least one piece of critical information when discussing a new medication with a patient.<sup>87</sup> Education regarding the duration of medication use was lowest (17%) for cardiovascular medications.<sup>87</sup>

Patients' perceptions of adverse effects contribute significantly to decisions regarding medication adherence. In a study of patients with hypertension, adverse effects were listed as the most common concern among patients who were not adherent to their antihypertensive medication.<sup>88</sup> Nonadherence to medications secondary to adverse effects is termed *rational nonadherence*, which Garner<sup>89</sup> defines as "the cessation of a prescribed therapy because of concern for, or the presence of, medication side effects." Garner further states that rational nonadherence "is nearly impossible to circumvent if a patient's specific side-effect concerns are not substantially addressed." Therefore, it is critical that adverse effect profiles are considered when prescribing a medication and discussed with the patient before the initial prescription and at every visit thereafter.

Using the teach-back approach (ie, asking patients to repeat the important points) and asking patients to read and interpret the medication label are ways in which the physician can confirm that patients understand all aspects of their new medication, which in turn increases adherence. Patient medication lists with pictograms are helpful and are available at sites listed in Table 1. Use of motivational interviewing is another effective communication tool. Motivational interviewing, a counseling technique originally developed to help treat addiction, is designed to help patients identify and overcome reasons they may be reluctant to change their behavior.<sup>90</sup> A meta-analysis of 72 randomized controlled trials showed significant benefit for motivational interviewing in achieving cholesterol and BP control, with psychologists and physicians able to achieve an effect in 80% of the studies.<sup>91</sup> A randomized trial conducted in 190 African Americans with hypertension showed that the addition of motivational interviewing led to steady maintenance of adherence during a 1-year period, in contrast to the control group, in which adherence rates declined significantly.<sup>92</sup>

#### HEALTH SYSTEM/TEAM BUILDING-RELATED FACTORS

The health system in which a physician practices is integral to achieving the ultimate goal of improved patient health.

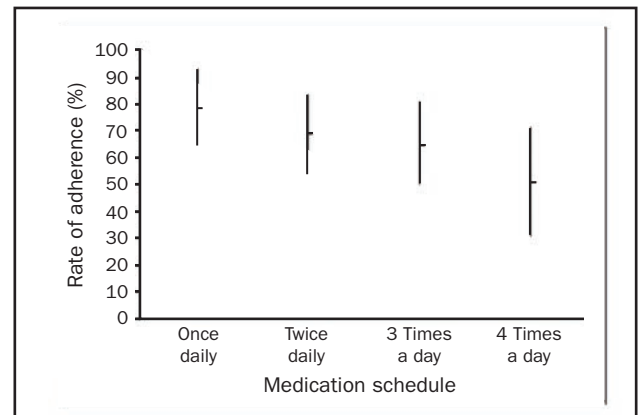


FIGURE 3. Adherence to medication according to frequency of doses. Vertical lines represent 1 SD on either side of the mean rate of adherence (horizontal bars).

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Because medication adherence is an important contributor to improved patient health, health care systems must evolve in a way that emphasizes its importance. Health system changes are necessary to ensure that sufficient time is allotted to discussing aspects of medication adherence.<sup>93</sup> Time constraints may be addressed by developing a team-based approach to health care (Table 1). The team-based approach includes training nonphysician staff to perform duties traditionally completed by physicians, thus allowing the physician more time to discuss the patient's medication adherence patterns. For example, during a telephone reminder for an upcoming appointment, clerical staff might remind patients to bring in all their medications and pill boxes for review at the office appointment. Other aspects of a team-based approach to health care include assessment of nonadherence by office staff and pharmacists, pharmacist-based patient education, phone call reminders, Web-based tools, and assignment of a case manager. Because these activities occur outside of the physician-patient encounter, they will not lengthen the visit and may increase efficiency. The importance of a team-based approach to managing medication use is highlighted by the medication therapy management services (MTMS) mandated by the 2003 Medicare Prescription Drug Improvement and Modernization Act.<sup>94</sup> Medication therapy management services, which are provided by insurers mainly through community-based pharmacists, are designed to provide education and counseling to improve patient understanding of their medications, improve medication adherence, and detect adverse drug reactions. Preliminary studies suggest that patient participation in MTMS programs improves medication adherence and patient outcomes<sup>95-97</sup>; thus, physicians should encourage eligible patients to participate in MTMS programs.



Increased implementation of electronic medical records and electronic prescribing has the potential to increase adherence by identifying patients at risk of nonadherence and targeting them for intervention. A large US study showed that a greater than 30-day delay in filling an initial prescription for a statin independently predicted medication nonadherence.<sup>98</sup> However, increased use of electronic records would allow for the implementation of systems that could identify delayed filling on an initial prescription, thus allowing the physician to intervene and perhaps prevent poor adherence. Some pharmacies already use automated reminders to alert patients that their prescriptions should be refilled and remind physicians to contact their patients who do not refill their prescriptions.

Initiating long-term medications during hospitalization for an acute event, rather than beginning therapy after discharge, may improve adherence. In a post hoc analysis of the EPILOG (Evaluation of PTCA to Improve Long-term Outcome) trial of patients undergoing percutaneous coronary intervention, those prescribed lipid-lowering therapy while hospitalized were 3 times more likely than those prescribed therapy after hospital release to be adherent at 6 months.<sup>99</sup> Initiating therapy while patients are hospitalized is thought to improve adherence because patients and their caregivers are focused on cardiovascular risk and how it can be reduced during this “teachable moment.”<sup>100</sup> Many patients perceive that medications initiated while they are in the hospital are essential for their health.<sup>100</sup>

A critically important health system–related factor that improves medication adherence, as well as patient safety, is appropriate medication reconciliation. Medication reconciliation is the process of creating the most accurate list possible of all medications a patient is taking, including drug name, dosage, frequency, and route, and comparing that list against admission, transfer, and/or discharge orders. The goal of medication reconciliation, a national priority of the Joint Commission on Accreditation of Healthcare Organizations, is to ensure provision of correct medications to patients at all transition points and avoid medication duplication and errors.<sup>101</sup> On the basis of the observation that primary care physicians do not receive the hospital discharge summary before the patient’s next contact or treatment 66% of the time,<sup>68</sup> much greater emphasis on medication reconciliation is needed if medication adherence and patient safety are to improve. An important component of the reconciliation process is the use of a personalized, up-to-date medication list for patients to keep with them at all times (for sources of downloadable medication lists, see Table 1). These personalized medication lists are particularly important for patients with chronic conditions such as CVD, which typically necessitate the use of multiple medications. By reviewing medication lists at every visit, physi-

cians can ensure that other physicians have not prescribed new medications without their knowledge. For example, if a patient is seeing his or her primary care physician for the first time after an MI, an updated medication list will help ensure that the primary care physician is aware of any new medications. Furthermore, the list can serve as a basis to discuss actual medication usage patterns with the patient.

## CONCLUSION

Strong evidence shows that many patients with chronic illnesses have difficulty adhering to their recommended medication regimen. Believing that medication nonadherence is the “fault” of the patient is an uninformed and destructive model that is best abandoned. As the former Surgeon General C. Everett Koop reminded us, “Drugs don’t work in patients who don’t take them.”<sup>3</sup> Thus, physicians must recognize that poor medication adherence contributes to suboptimal clinical benefits, particularly in light of the WHO’s statement that increasing adherence may have a greater effect on health than any improvement in specific medical treatments.<sup>1</sup> The multifactorial nature of poor medication adherence implies that only a sustained, coordinated effort will ensure optimal medication adherence and realization of the full benefits of current therapies. Current recognition of the importance of medication adherence has resulted in the development of many useful Web-based resources.

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## REFERENCES

1. Sabaté E, ed. *Adherence to Long-Term Therapies: Evidence for Action*. Geneva, Switzerland: World Health Organization; 2003.
2. Lee JK, Grace KA, Taylor AJ. Effect of a pharmacy care program on medication adherence and persistence, blood pressure, and low-density lipoprotein cholesterol: a randomized controlled trial. *JAMA*. 2006;296(21):2563-2571.
3. Osterberg L, Blaschke T. Adherence to medication. *N Engl J Med*. 2005;353(5):487-497.
4. Huth EJ, Murray TJ, eds. *Medicine in Quotations: Views of Health and Disease Through the Ages*. 2nd ed. Philadelphia, PA: American College of Physicians; 2006.
5. Steiner JF, Earnest MA. The language of medication-taking. *Ann Intern Med*. 2000;132(11):926-930.
6. Winkler A, Teuscher AU, Mueller B, Diem P. Monitoring adherence to prescribed medication in type 2 diabetic patients treated with sulfonylureas. *Swiss Med Wkly*. 2002;132(27-28):379-385.

7. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet*. 2002;360(9349):1903-1913.
8. Smith SC Jr, Allen J, Blair SN, et al. AHA/ACC guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease: 2006 update: endorsed by the National Heart, Lung, and Blood Institute. *Circulation*. 2006;113(19):2363-2372.
9. Amarenco P, Labreuche J. Lipid management in the prevention of stroke: review and updated meta-analysis of statins for stroke prevention. *Lancet Neurol*. 2009;8(5):453-463.
10. Baigent C, Keech A, Kearney PM, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet*. 2005;366(9493):1267-1278.
11. Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. *BMJ*. 2009;338:b1665. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2684577/>. Published May 19, 2009. Accessed November 12, 2009.
12. Glader EL, Sjölander M, Eriksson M, Lundberg M. Persistent use of secondary preventive drugs declines rapidly during the first 2 years after stroke. *Stroke*. 2010;41(2):397-401.
13. Costa FV. Compliance with antihypertensive treatment. *Clin Exp Hypertens*. 1996;18(3-4):463-472.
14. Cramer JA, Benedict A, Muszbek N, Keskinaslan A, Khan ZM. The significance of compliance and persistence in the treatment of diabetes, hypertension and dyslipidaemia: a review. *Int J Clin Pract*. 2008;62(1):76-87.
15. Elliott WJ. What factors contribute to the inadequate control of elevated blood pressure? *J Clin Hypertens (Greenwich)*. 2008;10(1, suppl 1):20-26.
16. Ho PM, Magid DJ, Shetterly SM, et al. Medication nonadherence is associated with a broad range of adverse outcomes in patients with coronary artery disease. *Am Heart J*. 2008;155(4):772-779.
17. Kettani FZ, Dragomir A, Cote R, et al. Impact of a better adherence to antihypertensive agents on cerebrovascular disease for primary prevention. *Stroke*. 2009;40(1):213-220.
18. Mazzaglia G, Ambrosioni E, Alacqua M, et al. Adherence to antihypertensive medications and cardiovascular morbidity among newly diagnosed hypertensive patients. *Circulation*. 2009;120(16):1598-1605.
19. Adams RJ, Albers G, Alberts MJ, et al. Update to the AHA/ASA recommendations for the prevention of stroke in patients with stroke and transient ischemic attack. *Stroke*. 2008;39(5):1647-1652.
20. Kushner FG, Hand M, Smith SC Jr, et al. 2009 Focused Updates: ACC/AHA Guidelines for the management of patients with ST-elevation myocardial infarction (updating the 2004 Guideline and 2007 Focused Update) and ACC/AHA/SCAI Guidelines on percutaneous coronary intervention (Updating the 2005 Guideline and 2007 Focused Update): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2009;120(22):2271-2306.
21. Mann DM, Allegante JP, Natarajan S, Halm EA, Charlson M. Predictors of adherence to statins for primary prevention. *Cardiovasc Drugs Ther*. 2007;21(4):311-316.
22. Deambrosio P, Saramin C, Terrazzani G, et al. Evaluation of the prescription and utilization patterns of statins in an Italian local health unit during the period 1994-2003. *Eur J Clin Pharmacol*. 2007;63(2):197-203.
23. Perreault S, Dragomir A, Blais L, et al. Impact of better adherence to statin agents in the primary prevention of coronary artery disease. *Eur J Clin Pharmacol*. 2009;65(10):1013-1024.
24. Poluzzi E, Strahinja P, Lanzoni M, et al. Adherence to statin therapy and patients' cardiovascular risk: a pharmacoepidemiological study in Italy. *Eur J Clin Pharmacol*. 2008;64(4):425-432.
25. Chodick G, Shalev V, Gerber Y, et al. Long-term persistence with statin treatment in a not-for-profit health maintenance organization: a population-based retrospective cohort study in Israel. *Clin Ther*. 2008;30(11):2167-2179.
26. Evans CD, Eurich DT, Lamb DA, et al. Retrospective observational assessment of statin adherence among subjects patronizing different types of community pharmacies in Canada. *J Manag Care Pharm*. 2009;15(6):476-484.
27. National Cholesterol Education Program (NCEP) Expert Panel. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation*. 2002;106(25):3143-3421.
28. Waters DD, Brotons C, Chiang CW, et al. Lipid treatment assessment project 2: a multinational survey to evaluate the proportion of patients achieving low-density lipoprotein cholesterol goals. *Circulation*. 2009;120(1):28-34.
29. Kulkarni SP, Alexander KP, Lytle B, Heiss G, Peterson ED. Long-term adherence with cardiovascular drug regimens. *Am Heart J*. 2006;151(1):185-191.
30. Newby LK, LaPointe NM, Chen AY, et al. Long-term adherence to evidence-based secondary prevention therapies in coronary artery disease. *Circulation*. 2006;113(2):203-212.
31. Hamann GF, Weimar C, Glahn J, Busse O, Diener HC. Adherence to secondary stroke prevention strategies: results from the German Stroke Data Bank. *Cerebrovasc Dis*. 2003;15(4):282-288.
32. Ho PM, Spertus JA, Masoudi FA, et al. Impact of medication therapy discontinuation on mortality after myocardial infarction. *Arch Intern Med*. 2006;166(17):1842-1847.
33. Melloni C, Alexander KP, Ou FS, et al. Predictors of early discontinuation of evidence-based medicine after acute coronary syndrome. *Am J Cardiol*. 2009;104(2):175-181.
34. Spertus JA, Kettelkamp R, Vance C, et al. Prevalence, predictors, and outcomes of premature discontinuation of thienopyridine therapy after drug-eluting stent placement: results from the PREMIER registry. *Circulation*. 2006;113(24):2803-2809.
35. Pallares MJ, Powers ER, Zwerner PL, Fowler A, Reeves R, Nappi JM. Barriers to clopidogrel adherence following placement of drug-eluting stents. *Ann Pharmacother*. 2009;43(2):259-267.
36. Roy P, Bonello L, Torguson R, et al. Temporal relation between clopidogrel cessation and stent thrombosis after drug-eluting stent implantation. *Am J Cardiol*. 2009;103(6):801-805.
37. Lesaffre E, Kocmanova D, Lemos PA, Disco CM, Serruys PW. A retrospective analysis of the effect of noncompliance on time to first major adverse cardiac event in LIPS. *Clin Ther*. 2003;25(9):2431-2447.
38. Perreault S, Ellia L, Dragomir A, et al. Effect of statin adherence on cerebrovascular disease in primary prevention. *Am J Med*. 2009;122(7):647-655.
39. Dragomir A, Côté R, White M, et al. Relationship between adherence level to statins, clinical issues and health-care costs in real-life clinical setting. *Value Health*. 2010;13(1):87-94.
40. Wiederkehr D, Ogbonnaya A, Casciano R, Makenbaeva D, Mozaffari E, Corbelli J. Clinical impact of early clopidogrel discontinuation following acute myocardial infarction hospitalization or stent implantation: analysis in a nationally representative managed-care population. *Curr Med Res Opin*. 2009;25(9):2327-2334.
41. Biondi-Zoccai GG, Lotrionte M, Agostoni P, et al. A systematic review and meta-analysis on the hazards of discontinuing or not adhering to aspirin among 50,279 patients at risk for coronary artery disease. *Eur Heart J*. 2006;27(22):2667-2674.
42. Eisenstein EL, Anstrom KJ, Kong DF, et al. Clopidogrel use and long-term clinical outcomes after drug-eluting stent implantation. *JAMA*. 2007;297(2):159-168.
43. Airolidi F, Colombo A, Morici N, et al. Incidence and predictors of drug-eluting stent thrombosis during and after discontinuation of thienopyridine treatment. *Circulation*. 2007;116(7):745-754.
44. Iakovou I, Schmidt T, Bonizzi E, et al. Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. *JAMA*. 2005;293(17):2126-2130.
45. van Werkum JW, Heestermaas AA, Zomer AC, et al. Predictors of coronary stent thrombosis: the Dutch Stent Thrombosis Registry. *J Am Coll Cardiol*. 2009;53(16):1399-1409.
46. Ryan AA. Medication compliance and older people: a review of the literature. *Int J Nurs Stud*. 1999;36(2):153-162.
47. Haynes RB, McDonald HP, Garg AX. Helping patients follow prescribed treatment: clinical applications. *JAMA*. 2002;288(22):2880-2883.
48. Raynor DK. Medication literacy is a 2-way street [editorial]. *Mayo Clin Proc*. 2008;83(5):520-522.
49. Kindig D, Affonso D, Chudler E, et al. *Health Literacy: a Prescription to End Confusion*. Washington, DC: Institute of Medicine of the National Academies; 2004.
50. Baker DW, Parker RM, Williams MV, Clark WS. Health literacy and the risk of hospital admission. *J Gen Intern Med*. 1998;13(12):791-798.
51. Mancuso CA, Rincon M. Impact of health literacy on longitudinal asthma outcomes. *J Gen Intern Med*. 2006;21(8):813-817.
52. Brunner R, Dunbar-Jacob J, Leboff MS, et al. Predictors of adherence in the Women's Health Initiative Calcium and Vitamin D Trial. *Behav Med*. 2009;34(4):145-155.
53. Joyner-Grantham J, Mount DL, McCorkle OD, Simmons DR, Ferrario CM, Cline DM. Self-reported influences of hopelessness, health literacy, life-

style action, and patient inertia on blood pressure control in a hypertensive emergency department population. *Am J Med Sci.* 2009;338(5):368-372.

54. Reach G. Is there an impatience genotype leading to non-adherence to long-term therapies? *Diabetologia.* 2010;53(8):1562-1567.

55. Kripalani S, Henderson LE, Jacobson TA, Vaccarino V. Medication use among inner-city patients after hospital discharge: patient-reported barriers and solutions. *Mayo Clin Proc.* 2008;83(5):529-535.

56. Molloy GJ, Perkins-Porras L, Bhattacharyya MR, Strike PC, Steptoe A. Practical support predicts medication adherence and attendance at cardiac rehabilitation following acute coronary syndrome. *J Psychosom Res.* 2008;65(6):581-586.

57. Molloy GJ, Perkins-Porras L, Strike PC, Steptoe A. Social networks and partner stress as predictors of adherence to medication, rehabilitation attendance, and quality of life following acute coronary syndrome. *Health Psychol.* 2008;27(1):52-58.

58. Kronish IM, Rieckmann N, Halm EA, et al. Persistent depression affects adherence to secondary prevention behaviors after acute coronary syndromes. *J Gen Intern Med.* 2006;21(11):1178-1183.

59. Sundel KL, Stain-Mahngren R, Andersson A, Aberg-Wistedt A, Schenck-Gustafsson K. High frequency of anxiety and angina pectoris in depressed women with coronary heart disease. *Gen Med.* 2007;4(2):146-156.

60. Amin AA, Jones AM, Nugent K, Rumsfeld JS, Spertus JA. The prevalence of unrecognized depression in patients with acute coronary syndrome. *Am Heart J.* 2006;152(5):928-934.

61. Dafer RM, Rao M, Shareef A, Sharma A. Poststroke depression. *Top Stroke Rehabil.* 2008;15(1):13-21.

62. Frasure-Smith N, Lespérance F. Depression and anxiety as predictors of 2-year cardiac events in patients with stable coronary artery disease. *Arch Gen Psychiatry.* 2008;65(1):62-71.

63. Jia H, Damush TM, Qin H, et al. The impact of poststroke depression on healthcare use by veterans with acute stroke. *Stroke.* 2006;37(11):2796-2801.

64. Kripalani S, LeFevre F, Phillips CO, Williams MV, Basaviah P, Baker DW. Deficits in communication and information transfer between hospital-based and primary care physicians: implications for patient safety and continuity of care. *JAMA.* 2007;297(8):831-841.

65. Winterstein AG, Sauer BC, Hepler CD, Poole C. Preventable drug-related hospital admissions. *Ann Pharmacother.* 2002;36(7-8):1238-1248.

66. Gordon K, Smith F, Dhillon S. Effective chronic disease management: patients' perspectives on medication-related problems. *Patient Educ Couns.* 2007;65(3):407-415.

67. Kennedy J, Tuleu I, Mackay K. Unfilled prescriptions of medicare beneficiaries: prevalence, reasons, and types of medicines prescribed. *J Manag Care Pharm.* 2008;14(6):553-560.

68. Bodenheimer T. Coordinating care: a perilous journey through the health care system. *N Engl J Med.* 2008;358(10):1064-1071.

69. Haynes RB, Ackloo E, Sahota N, McDonald HP, Yao X. Interventions for enhancing medication adherence. *Cochrane Database Syst Rev.* 2008;(2):CD000011.

70. Schillinger D, Piette J, Grumbach K, et al. Closing the loop: physician communication with diabetic patients who have low health literacy. *Arch Intern Med.* 2003;163(1):83-90.

71. Roumie CL, Elasy TA, Greevy R, et al. Improving blood pressure control through provider education, provider alerts, and patient education: a cluster randomized trial. *Ann Intern Med.* 2006;145(3):165-175.

72. Balamurugan A, Ohsfeldt R, Hughes T, Phillips M. Diabetes self-management education program for Medicaid recipients: a continuous quality improvement process. *Diabetes Educ.* 2006;32(6):893-900.

73. Praska JL, Kripalani S, Seright AL, Jacobson TA. Identifying and assisting low-literacy patients with medication use: a survey of community pharmacies. *Ann Pharmacother.* 2005;39(9):1441-1445.

74. US Department of Health and Human Services, Office of Disease Prevention and Health Promotion. America's health literacy: why we need accessible health information. Bethesda, MD: US Dept of Health and Human Services; 2008. <http://www.health.gov/communication/literacy/issuebrief/>. Accessed November 15, 2010.

75. US Department of Health and Human Services, National Institutes of Health. Clear communication: an NIH health literacy initiative. Bethesda, MD: National Institutes of Health; 2010. <http://www.nih.gov/clearcommunication/>. Accessed November 15, 2010.

76. Parikh NS, Parker RM, Nurss JR, Baker DW, Williams MV. Shame and health literacy: the unspoken connection. *Patient Educ Couns.* 1996;27(1):33-39.

77. Perez-Stable EJ, Salazar R. Issues in achieving compliance with antihypertensive treatment in the Latino population. *Clin Cornerstone.* 2004;6(3):49-61.

78. Urquhart J. Patient non-compliance with drug regimens: measurement, clinical correlates, economic impact. *Eur Heart J.* 1996;17(suppl A):8-15.

79. Odegard PS, Capoccia K. Medication taking and diabetes: a systematic review of the literature. *Diabetes Educ.* 2007;33(6):1014-1029.

80. Chapman RH, Petrilla AA, Benner JS, Schwartz JS, Tang SS. Predictors of adherence to concomitant antihypertensive and lipid-lowering medications in older adults: a retrospective, cohort study. *Drugs Aging.* 2008;25(10):885-892.

81. Benner JS, Chapman RH, Petrilla AA, Tang SS, Rosenberg N, Schwartz JS. Association between prescription burden and medication adherence in patients initiating antihypertensive and lipid-lowering therapy. *Am J Health Syst Pharm.* 2009;66(16):1471-1477.

82. Bangalore S, Kamalakkannan G, Parkar S, Messerli FH. Fixed-dose combinations improve medication compliance: a meta-analysis. *Am J Med.* 2007;120(8):713-719.

83. Balu S, Simko RJ, Quimbo RM, Cziraky MJ. Impact of fixed-dose and multi-pill combination dyslipidemia therapies on medication adherence and the economic burden of sub-optimal adherence. *Curr Med Res Opin.* 2009;25(11):2765-2775.

84. Hussein MA, Chapman RH, Benner JS, et al. Does a single-pill antihypertensive/lipid-lowering regimen improve adherence in US managed care enrollees? A non-randomized, observational, retrospective study. *Am J Cardiovasc Drugs.* 2010;10(3):193-202.

85. Schroeder K, Fahey T, Ebrahim S. How can we improve adherence to blood pressure-lowering medication in ambulatory care? Systematic review of randomized controlled trials. *Arch Intern Med.* 2004;164(7):722-732.

86. Claxton AJ, Cramer J, Pierce C. A systematic review of the associations between dose regimens and medication compliance. *Clin Ther.* 2001;23(8):1296-1310.

87. Tarn DM, Heritage J, Paterniti DA, Hays RD, Kravitz RL, Wenger NS. Physician communication when prescribing new medications. *Arch Intern Med.* 2006;166(17):1855-1862.

88. Svensson S, Kjellgren KI, Ahlner J, Säljö R. Reasons for adherence with antihypertensive medication. *Int J Cardiol.* 2000;76(2-3):157-163.

89. Garner JB. Problems of nonadherence in cardiology and proposals to improve outcomes. *Am J Cardiol.* 2010;105(10):1495-1501.

90. Miller NH. Motivational interviewing as a prelude to coaching in health care settings. *J Cardiovasc Nurs.* 2010;25(3):247-251.

91. Rubak S, Sandbaek A, Lauritzen T, Christensen B. Motivational interviewing: a systematic review and meta-analysis. *Br J Gen Pract.* 2005;55(513):305-312.

92. Ogedegbe G, Chaplin W, Schoenthaler A, et al. A practice-based trial of motivational interviewing and adherence in hypertensive African Americans. *Am J Hypertens.* 2008;21(10):1137-1143.

93. Abbo ED, Zhang Q, Zelder M, Huang ES. The increasing number of clinical items addressed during the time of adult primary care visits. *J Gen Intern Med.* 2008;23(12):2058-2065.

94. Medicare Prescription Drug, Improvement, and Modernization Act of 2003. Pub L No. 108-173, 117 Stat 2066.

95. Pellegrino AN, Martin MT, Tilton JJ, Touchette DR. Medication therapy management services: definitions and outcomes. *Drugs.* 2009;69(4):393-406.

96. Fox D, Ried LD, Klein GE, Myers W, Foli K. A medication therapy management program's impact on low-density lipoprotein cholesterol goal attainment in Medicare Part D patients with diabetes. *J Am Pharm Assoc (2003).* 2009;49(2):192-199.

97. Planas LG, Crosby KM, Mitchell KD, Farmer KC. Evaluation of a hypertension medication therapy management program in patients with diabetes. *J Am Pharm Assoc (2003).* 2009;49(2):164-170.

98. Yu AP, Yu YF, Nichol MB, Gwadry-Sridhar F. Delay in filling the initial prescription for a statin: a potential early indicator of medication nonpersistence. *Clin Ther.* 2008;30(4):761-774, discussion 716.

99. Aronow HD, Novaro GM, Lauer MS, et al. In-hospital initiation of lipid-lowering therapy after coronary intervention as a predictor of long-term utilization: a propensity analysis. *Arch Intern Med.* 2003;163(21):2576-2582.

100. Fonarow GC. In-hospital initiation of statins: taking advantage of the 'teachable moment' [editorial]. *Cleve Clin J Med.* 2003;70(6):502, 504-506.

101. Joint Commission on Accreditation of Healthcare Organizations. Using medication reconciliation to prevent errors. *Sentinel Event Alert.* 2006;(35):1-4.