Medication Adherence
Its Importance in Cardiovascular Outcomes

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Abstract—Medication adherence usually refers to whether patients take their medications as prescribed (eg, twice daily), as well as whether they continue to take a prescribed medication. Medication nonadherence is a growing concern to clinicians, healthcare systems, and other stakeholders (eg, payers) because of mounting evidence that it is prevalent and associated with adverse outcomes and higher costs of care. To date, measurement of patient medication adherence and use of interventions to improve adherence are rare in routine clinical practice. The goals of the present report are to address (1) different methods of measuring adherence, (2) the prevalence of medication nonadherence, (3) the association between nonadherence and outcomes, (4) the reasons for nonadherence, and finally, (5) interventions to improve medication adherence. (Circulation. 2009;119:3028-3035.)

Key Words: cardiovascular diseases ▪ healthcare quality assessment ▪ medication adherence ▪ outcomes research

“Drugs don’t work in patients who don’t take them.”
—C. Everett Koop, MD

Adherence has been defined as the “active, voluntary, and collaborative involvement of the patient in a mutually acceptable course of behavior to produce a therapeutic result.”1,2 This definition implies that the patient has a choice and that both patients and providers mutually establish treatment goals and the medical regimen.1 Medication adherence usually refers to whether patients take their medications as prescribed (eg, twice daily), as well as whether they continue to take a prescribed medication. Medication adherence behavior has thus been divided into 2 main concepts, namely, adherence and persistence. Although conceptually similar, adherence refers to the intensity of drug use during the duration of therapy, whereas persistence refers to the overall duration of drug therapy.3,4

Medication adherence is a growing concern to clinicians, healthcare systems, and other stakeholders (eg, payers) because of mounting evidence that nonadherence is prevalent and associated with adverse outcomes and higher costs of care.5 Medication nonadherence is likely to grow as the US population ages and as patients take more medications to treat chronic conditions.6 Moreover, the rise of performance measures that reward quality based on the attainment of treatment targets such as blood pressure and low-density lipoprotein (LDL) levels or outcomes such as 1-year mortality after hospitalization for conditions like acute myocardial infarction reinforces the import of longitudinal medication adherence. Unlike other quality measures that are under more direct control of care providers and healthcare systems (eg, prescribing medications at discharge), the achievement of longer-term therapeutic and outcome goals requires a partnership with patients.

To date, measurement of patient medication adherence and use of interventions to improve adherence are rare in routine clinical practice. For this reason, medication adherence has been called the “next frontier in quality improvement” and is an important part of cardiovascular outcomes research.7 The goals of the present report are to address (1) different methods of measuring adherence, (2) the prevalence of medication nonadherence, (3) the association between nonadherence and outcomes, (4) the reasons for nonadherence, and finally, (5) interventions to improve medication adherence.

Methodology of Assessing Medication Adherence

There are many different methods for assessing adherence to medications. Osterberg et al5 categorized these methods as either direct or indirect. Direct methods include directly observed therapy, measurement of the level of medicine or metabolite in blood, and measurement of the biological marker in blood.5 Although these direct methods are considered to be more robust than indirect methods, there are also limitations to these direct methods of adherence assessment. For example, patients may hide pills in their mouth and discard them later, or there may be variations in metabolism that can affect serum levels. Furthermore, these direct methods are not practical for routine clinical use.
Indirect methods of adherence assessment include patient questionnaires, self-reports, pill counts, rate of prescription refills, assessment of the patient’s clinical response, electronic medication monitors, measurement of physiological markers, and patient diaries. The most commonly used indirect methods include patient self-report, pill counts, and pharmacy refills. The Morisky scale is a commonly used, validated, 4-item self-reported adherence measure that has been shown to be predictive of adherence to cardiovascular medications and blood pressure control.8,9 In addition, Gehi et al10 found that patient self-report of medication nonadherence was strongly associated with adverse cardiac events, including coronary heart disease death, myocardial infarction, and stroke, on the basis of a single screening question (“In the past month, how often did you take your medications as the doctor prescribed?”) among patients with known coronary artery disease. However, self-report measures can be biased by inaccurate patient recall or by social desirability, whereby patients report an overly optimistic estimation of adherence to their healthcare providers. Pill counts are easy to perform, have been correlated with electronic medication monitors, and are frequently used in randomized, controlled clinical trials to assess medication adherence.11–13 Although simple to measure, pill counts do not accurately capture the exact timing of medication taking, and the data can be manipulated by patients (eg, pill dumping). Each of these methods has advantages and disadvantages, and the use of a specific method to measure adherence will depend on the clinical scenario and availability of the data.

Electronic pharmacy data are becoming more widely available, and this is one of the more frequently used methods in the literature. The act of obtaining refills and the frequency with which the refills are acquired reflect different aspects of a patient’s adherence behavior, and adherence based on pharmacy refill data has been correlated with a broad range of patient outcomes.14 Currently, the 2 most commonly used measures of medication adherence based on pharmacy data are the medication possession ratio and the proportion of days covered methods, which essentially are defined by the number of doses dispensed in relation to a dispensing period. The main difference between these 2 measures is that the maximum proportion of days covered is 1.0, which indicates full adherence, whereas the medication possession ratio accounts for oversupplies and can have a value >1.0.15–19 The use of pharmacy prescription refill data, however, requires that patients obtain their medications within a closed pharmacy system. In addition, the medication possession ratio and proportion of days covered measures of medication adherence correlate well with the quantity of doses taken but not the timing of the doses, and the assessment of adherence with these measures is more difficult when the length of follow-up varies between patients.12

For medication persistence, there are also multiple commonly used measures. These measures can be related to a specific medication (medication persistence) or a set of medications (regimen or therapy persistence).18 In addition, there have been many proposed definitions for medication persistence, including the anniversary, minimum refills, refill sequence, or proportion of days covered methods.3 Although each measure has its strengths and limitations, there is currently no general consensus as to the best measure to use to define adherence or persistence. These studies highlight the challenges of measuring medication adherence in routine clinical practice and in research studies given the lack of a “gold standard” criterion.

On the basis of pharmacy refill data, patients with medications available 80% of the time have generally been categorized as adherent in the literature. This dichotomous cutoff is somewhat arbitrary; however, it has been used for a majority of the studies in the literature on medication adherence, with data from both observational and randomized, controlled clinical trials. In addition, adherence based on this cut point has been associated with both intermediate and hard outcomes. However, a more recent analysis suggests that there continues to be reductions in LDL cholesterol and blood pressure with adherence levels beyond 80% (eg, 80% to 100%), which suggests that the optimal level of adherence may be higher than current cutoffs.20 Certainly for conditions such as human immunodeficiency virus or medications such as oral contraceptives, the 80% cutoff may be too low. Although the current 80% cutoff appears reasonable for cardiovascular medications, future studies focused on medication adherence using pharmacy refill data should report both continuous measures of adherence and the distribution of adherent patients based on different dichotomous cutoffs. The appropriate cutoff will depend on the specific medication, its formulation (eg, once daily versus twice daily), and the specific disease condition.

Prevalence of Medication Nonadherence
Nonadherence to medications is common for patients with cardiovascular diseases. After acute myocardial infarction hospitalization, Jackevicius et al21 found that almost one fourth of patients (~24%) did not even fill their cardiac medications by day 7 of discharge. Among patients discharged with prescriptions for aspirin, statin, and β-blockers after acute myocardial infarction, 1 study found that ~34% of patients stopped at least 1 medication and 12% stopped all 3 medications within 1 month of hospital discharge.22 Beyond the early discharge period, there appears to be a progressive decline in adherence to prescribed cardioprotective medications (eg, statins, β-blockers) over time. Newby et al23 found that patient self-report of consistent use of cardiac medications over 6 to 12 months was low, with approximately three fourths of patients reporting persistent aspirin use (71%), whereas less than half reported persistent use of β-blockers (46%), lipid-lowering agents (44%), and all 3 medications (21%) after diagnosis of coronary artery disease by coronary angiography. Another study demonstrated that only ~40% of patients were still taking statin medications 2 years after hospitalization for acute coronary syndrome, and adherence was even lower for patients taking statins for chronic coronary artery disease.24 Although the transition period from hospital discharge to the outpatient setting appears to be a particularly high-risk period, medication nonadherence continues to decline during the long-term follow-up phase for coronary artery disease.
For other cardiovascular conditions, the prevalence of medication nonadherence varies tremendously depending on the population studied and the specific medications assessed. For example, Vrijens et al.\textsuperscript{23} using medication event monitor (MEMS) data, found that about half of all patients prescribed antihypertensive medications stopped taking them within 1 year of the initial prescription. They also found that on any 1 day, patients omitted \( \approx 10\% \) of the scheduled doses of medications.\textsuperscript{25} In contrast, Bramley et al.\textsuperscript{26} found that \( \approx 75\% \) of patients on monotherapy for hypertension were highly adherent, defined as a medication possession ratio of 80\% to 100\%. Among heart failure patients, studies of medication adherence have also found widely differing rates of nonadherence. For example, 1 study reported persistence rates of 79\% for renin-angiotensin inhibitors, 65\% for \( \beta \)-blockers, 56\% for spironolactone, and 83\% for statins 5 years after an index heart failure hospitalization.\textsuperscript{27} In contrast, the rate of nonadherence based on pill counts was much lower in the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) randomized, controlled trial of patients with heart failure, with 11\% of patients taking fewer than 80\% of the prescribed pills.\textsuperscript{28} Although nonadherence to medications is prevalent in cardiovascular populations, the variability of the methods for assessment of medication use (eg, self-report or pharmacy refill data) makes comparisons across studies and across cardiovascular conditions difficult.

**Association Between Medication Adherence and Outcomes**

Many observational studies have evaluated the association between medication adherence and outcomes. In general, these studies have focused on medications that have already been demonstrated in clinical trials to be efficacious and therefore are trying to assess the effectiveness of these medications in routine clinical practice. Pharmacy refill data and patient self-report are the mostly commonly used adherence assessment methods in these studies. High adherence (defined as medication possession ratio of 80\% to 100\%) to antihypertensive medications was associated with higher odds (odds ratio 1.45, 95\% confidence interval 1.04 to 2.02) of blood pressure control compared with those with medium or low levels of adherence.\textsuperscript{29} Similarly, each incremental 25\% increase in proportion of days covered for statin medications was associated with an \( \approx 3.8 \)-mg/dL reduction in LDL cholesterol.\textsuperscript{29} Furthermore, nonadherence to cardiovascular medications has been associated with increased risk of morbidity and mortality. For example, nonadherence to statins in the year after hospitalization for myocardial infarction was associated with \( \approx 12\% \) to 25\% increased relative hazard for mortality.\textsuperscript{30} In the chronic coronary artery disease setting, nonadherence to cardioprotective medications (\( \beta \)-blockers, statins, and/or angiotensin-converting enzyme inhibitors) was associated with a 10\% to 40\% relative increase in risk of cardiovascular hospitalizations and a 50\% to 80\% relative increase in risk of mortality.\textsuperscript{14} Another study demonstrated that patients discontinuing clopidogrel within 1 month after hospital discharge for acute myocardial infarction and drug-eluting stent placement were significantly more likely to have an adverse outcome, including rehospitalization and mortality, in the subsequent 11 months.\textsuperscript{31} In addition, poor adherence to heart failure drugs was associated with an increased number of cardiovascular-related emergency department visits.\textsuperscript{32} These effectiveness studies reinforce the benefits of cardiovascular medications in routine clinical practice and highlight the importance of taking these medication as prescribed to optimize patient outcomes.

**Healthy Adherer Effect**

Although the association between medication nonadherence and adverse outcomes has been demonstrated in many observational studies, some concern has been raised that this association may be, at least in part, related to a “healthy adherer” effect.\textsuperscript{33} The healthy adherer effect implies that the lower risk of adverse outcomes associated with adherence may be a surrogate marker for overall healthy behavior. This is supported by post hoc analyses of randomized, controlled clinical trials in which even adherence to placebo is associated with better outcomes than for patients who are nonadherent to active treatment. These findings were first noted over 25 years ago in the Coronary Drug Project, which involved clofibrate.\textsuperscript{34} In the \( \beta \)-blocker Heart Attack Trial, poor adherence was associated with higher mortality risk regardless of whether patients were randomized to propranolol or placebo.\textsuperscript{35} Similar findings were demonstrated in the Canadian Amiodarone Myocardial Infarction Arrhythmia Trial (CAMIAT) study for sudden death, total cardiac mortality, and all-cause mortality and in the CHARM program for all-cause mortality.\textsuperscript{28,36} It appears that patients who take their medication regularly are also more likely to perform other healthy behaviors, such as eating properly and exercising regularly.\textsuperscript{37,38} These behaviors are often not measured directly in prospective or retrospective studies.

However, there is also evidence against the healthy adherer effect being a major factor in observed associations between medication adherence and outcomes. For example, in a study of post–myocardial infarction patients by Rasmussen et al.,\textsuperscript{30} the association between adherence to cardiovascular medications and outcomes in which neither clinical evidence nor biological plausibility existed was assessed. They found that adherence to cardiovascular medications was not associated with hospitalization for lung, prostate, or breast cancer and concluded that the benefit of adherence was directly related to the cardiovascular medication rather than an epiphenomenon of a healthy adherer effect. Although the debate will continue, the medications under study have often been demonstrated in randomized, controlled clinical trials to be efficacious, and therefore, the importance of taking these medications as prescribed should be reinforced.

**Association Between Medication Adherence and Costs**

Surprisingly little is known about the association between medication adherence and healthcare costs in cardiovascular populations. Sokol et al.\textsuperscript{39} reported that greater adherence to medications for chronic conditions such as hypertension, diabetes mellitus, hypercholesterolemia, and heart failure was
associated with higher medication costs but lower nonmedication medical costs, yielding a net overall reduction in healthcare costs. A recent evaluation of statin medication adherence and healthcare costs among patients with coronary artery disease in a managed care organization demonstrated that higher medication adherence was associated with higher pharmacy costs and lower medical costs; however, overall healthcare costs were similar between nonadherent and adherent patients over several years of follow-up.60 On the basis of available studies to date, it thus remains unclear whether medication adherence is associated with lower overall healthcare costs or is “cost neutral” to the healthcare system. Either way, medication nonadherence is associated with worse patient outcomes, which supports the need for interventions to improve medication adherence. Yet, there is a clear need for more research to better understand the association between adherence and healthcare costs and for formal cost-effectiveness evaluations to be embedded in studies of interventions to improve medication adherence.

A larger number of studies have evaluated the impact of changing costs of medications on individual patient adherence. Among Medicare+Choice beneficiaries, patients who had drug benefit caps were more likely to be nonadherent to medications for hypertension, hyperlipidemia, and diabetes.41 In addition, patients with caps on drug benefits had worse intermediate outcomes (eg, LDL levels and blood pressure) and higher rates of emergency department visits and nonelective hospitalizations. In separate studies, changes to out-of-pocket spending doubled the risk of stopping statin therapy, and higher copayments were associated with lower adherence to statins.42,43 Taira et al44 also showed a graded relationship between the level of copayment and medication adherence, with patients more likely to refill medications for antihypertensive medications that had a lower copayment. Finally, Cole et al45 demonstrated that higher drug copayments for angiotensin-converting enzyme inhibitors and β-blockers were associated with a small decrease in the medication possession ratio among patients with heart failure. These studies suggest that medication costs can have a significant impact on nonadherence, and future studies are needed to assess whether lowering medication costs can improve medication adherence and clinical outcomes.

Patterns and Reasons for Medication Nonadherence

The reasons for poor medication adherence are often multifactorial. Nonadherence to medications can be intentional or nonintentional. Intentional nonadherence is an active process whereby the patient chooses to deviate from the treatment regimen.46 This may be a rational decision process in which the individual weighs the risk and benefits of treatment against any adverse effects. Unintentional nonadherence is a passive process in which the patient may be careless or forgetful about adhering to the treatment regimen. This is also referred to by Vrijens et al23 as the execution of the prescribed regimen, or how well patients adhere to the dosing regimen. On the basis of electronic monitoring data, there are 6 general patterns of execution: (1) Close to perfect adherence; (2) take nearly all doses with some timing irregularity; (3) miss an occasional single day’s dose, and some timing inconsistencies; (4) take drug holidays 3 to 4 times per year; (5) take drug holidays monthly or more often and have frequent omissions; and (6) take few or no doses.5,47 Most deviations in medication taking are due to omissions of doses or delays in taking doses. In addition, it is common for patients to improve their medication-taking behavior shortly before and after an appointment with a healthcare provider, which has been termed “white-coat adherence.”7

The World Health Organization has categorized potential reasons for medication nonadherence into 5 broad groupings that include patient, condition, therapy, socioeconomic, and health system–related factors.48–62 Examples for each of these categories are detailed in the Table. Patient factors associated with medication nonadherence include younger age, nonwhite race, and depression. Conditions that are asymptomatic and chronic in nature that require long-term therapy have also been associated with nonadherence. For therapy-related factors, the complexity of the regimen and the perceived or experienced side effects can impact adherence. Socioeconomic factors such as lower education level and low health literacy have been correlated with nonadherence. Although the cost of medications is another important socioeconomic factor, medication nonadherence remains common even when cost is less of a factor, such as in the Canadian healthcare system or the US Veterans Health Administration. Finally, it remains unclear whether these individual factors can adequately discriminate between patients who are adherent or are not adherent, and this suggests that evaluations of nonadherence cannot be targeted to specific patient populations/characteristics.

Next, although patients are often implicated as the cause for medication nonadherence, healthcare system factors can also have a significant impact on a patient’s nonadherence to medications. Makaryus et al63 found that <50% of patients were able to list all of their medications, and even fewer could recount the purpose of their medications at hospital discharge, which suggests that system factors like the educational process at hospital discharge can impact medication adherence after discharge. Supporting this idea is a prior study that found that discharge counseling was associated with improved adherence after hospital discharge for myocardial
infarction. Next, Coleman et al. found that medication discrepancies, defined as lack of agreement between the prehospital, discharge, and posthospital medication regimens, were common after hospital discharge, occurring ≈15% of the time. The causes for these discrepancies were just as likely to be related to system factors (e.g., conflicting information, incomplete discharge instructions) as to patient factors. Furthermore, system-level factors such as the bureaucratic processes associated with insurance claims can also influence adherence. In a qualitative study, Bokhour et al. found that in approximately one third of hypertension-related visits in which blood pressure was not controlled, the care provider did not even ask about medication taking, and closed-ended questions during the visit inhibited discussions on medications or medication-taking behaviors. Finally, Svensson et al. found that adherence to antihypertensive medication was related to faith in the physician, which suggests that the quality of the provider-patient relationship was also an important determinant. Although patients are central to taking medications as prescribed, there are many non-patient-related factors that can also affect adherence to medications.

**Interventions to Improve Medication Adherence**

To date, interventions targeting medication adherence have produced only modest success. In general, unimodal interventions have been less successful than multimodal interventions, because the reasons for nonadherence are often multifactorial. Unimodal interventions that have demonstrated some success include those that reduced the number of daily doses of medications, used motivational strategies, packaged medications into special containers (e.g., pill boxes or blister packs), provided more convenient care, educated patients, or involved monitoring and feedback. For example, Smith et al. recently published findings of a cluster randomized trial in 4 geographically dispersed health maintenance organizations that sent informational mailings on β-blocker therapy to patients recently discharged for acute myocardial infarction and prescribed β-blockers. The intervention resulted in an absolute increase of 4.3% of days covered per month for β-blocker medications compared with usual-care patients and a 17% relative increase in the likelihood of being adherent to β-blockers. Although the study findings are positive, it is unclear whether the modest improvement in adherence will translate into differences in clinical outcomes.

Multimodal interventions have shown the most promise and have improved both adherence and outcomes. For example, Piette et al. randomized veterans with diabetes mellitus to an intervention that consisted of telemonitoring with interactive voice response technology and weekly nurse feedback and demonstrated improvements in medication adherence and diabetes-related symptoms, as well as a trend for improvement in hemoglobin A1C. For heart failure, Murray et al. randomized clinically stable outpatients with a diagnosis of heart failure to an intensive pharmacist-led intervention versus usual care and found a 10.9% improvement in adherence to cardiovascular medications. The intervention patients also had fewer emergency department visits and hospital admissions, as well as lower healthcare costs. In contrast, Lee et al. randomized patients to an intervention composed of patient education, medication reminder packaging, and frequent clinic visits (every 2 months) versus usual care and showed improvements in medication adherence (~30%) and systolic blood pressure but not LDL cholesterol. Across these studies, one of the consistent features of successful interventions has been regular follow-up with the healthcare system. Although multimodal interventions are more likely to be successful than unimodal interventions, some of the study findings remain mixed with regard to outcomes, and the complexity of the interventions makes it difficult to implement them in routine clinical care.

Although observational studies have highlighted opportunities to improve medication adherence, the implementation of these interventions in routine clinical practice poses many hurdles. First, the successful interventions to date have included multiple components, and the components have often been heterogeneous, which makes implementation into routine practice difficult. These multiple components often require clinical personnel to manage and/or coordinate them, which increases the cost of implementing the intervention. Furthermore, because of the current fractured healthcare system, there are logistical challenges to the coordination of any intervention between various care providers and across different healthcare systems. Although integrated health systems like Kaiser or the Veterans Administration may be able to overcome these barriers, it remains a significant problem for the rest of the healthcare system. Finally, current financial incentives are not aligned with the promotion of the importance of medication adherence. Until some of these barriers are lowered, improving medication adherence broadly in routine clinical practice will remain challenging.

**Research and Clinical Implications**

There have been great strides made toward a better understanding of medication adherence and its impact in clinical practice; however, more research is needed to address critical issues in the field. One of these issues is coming to a consensus on how to uniformly report measures of medication adherence and persistence. Because of the variety of data sources and adherence measures, it is often difficult to compare adherence rates across studies and conditions. A consensus on the method(s) of measurement will provide more comparability across studies. Second, prospective studies focusing on adherence should measure adherence using different methods to help inform the specific type of nonadherence behavior, such as primary nonadherence or problems with execution of the regimen, because each of these behaviors may necessitate a different intervention. Third, new strategies to improve medication adherence need to be tested to add to the current knowledge base on how to improve medication adherence and persistence. These interventions should focus on improving medication adherence, in addition to intermediate and hard outcomes. Finally, more research is needed to better understand the association between adherence and healthcare costs, and there is a need for formal cost-effectiveness evaluations to be embedded in studies of interventions to improve medication adherence. Many new
cardiovascular therapies have been introduced in the past decade that reduce morbidity and mortality, and the next challenge will be to get patients to take these therapies as prescribed.

Although research is continuing to enable us to better understand medication adherence, there is an urgent need to improve current rates of nonadherence. One of the first steps is a broader recognition of the problem of medication nonadherence, given that it is frequently unrecognized. For example, akin to vital signs obtained for outpatient clinic visits, a screening question on medication nonadherence can be incorporated into each visit. Although insensitive, patient self-report of nonadherence is specific and predicts future adverse outcomes. For healthcare systems in which pharmacy records are readily available, a review of the refill frequency and the date of the last refill may also help identify nonadherence. Once medication nonadherence is recognized, care providers and patients can work collaboratively to develop patient-specific solutions to address adherence barriers. There are simple, evidence-based strategies that can be implemented, such as reducing the number of daily doses of medications, organizing medications in pill boxes, using motivational interviewing, and educating patients on the importance of medication adherence.59 In addition, if feasible, it may be helpful to have clinical personnel follow up with patients through telephone calls to ensure that patients are taking their medications as directed, particularly for those who have a history of nonadherence. This strategy may be especially important in the post–hospital discharge setting. While we await additional evidence from studies, these strategies can be easily implemented in routine clinical practice without much additional time or resources to help patients take their medications as prescribed.

Conclusions

Building on recent improvements in the prescription of indicated cardiovascular medication to patients, the next step is to improve adherence to prescribed medications.78 Nonadherence to medications is common and is associated with adverse outcomes.Nonadherence is not solely a patient problem but is impacted by both care providers and the healthcare system. As the first step toward improving adherence, there needs to be a broader recognition of the problem of nonadherence, and once identified, simple strategies should be implemented in daily practice to improve adherence. Certainly, there are still many challenges in further understanding the reasons for nonadherence and designing better interventions to improve adherence; however, getting patients to take their medication as prescribed is a worthy goal in order for patients to derive the maximal benefit of prescribed therapies and is also highly consistent with one of the Institute of Medicine’s goals of care of patient centeredness.79

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Disclosures

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