

Impediments to Adherence to Post Myocardial Infarction Medications

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Abstract Non-adherence to evidence-based medications is a major public health problem. Less than 50 % of patients with coronary artery disease adhere to their prescribed therapies and this has important implications for morbidity, mortality, and health care spending. Like most complex behaviors, medication non-adherence is not solely the result of poor patient choices. Rather, there are myriad potential contributors attributable to patients, health care providers, and, more broadly, the health care system. Interventions including patient education and behavioral modification, improving patient-physician communication, and eliminating copayments for preventive pharmacotherapy have all been studied. Clinicians play a critical role in helping improve adherence and assessment of adherence must become a standard component of each clinical encounter. Ultimately, given the various etiologies that contribute to non-adherence, achieving meaningful gains will undoubtedly require payors, providers, and policymakers to develop, rigorously evaluate, and systematically deploy strategies that address key patient, clinician, and health system factors.

Keywords Post myocardial infarction · Medication adherence · Review

Introduction

Non-adherence to evidence-based medications is a major public health problem. It is estimated that over the long-term up to 80 % of patients do not adhere to their prescribed

therapies [1] and that this leads to “substantial worsening of disease, death, and increased health care costs” [2]. In the US, suboptimal adherence accounts for between 33 % and 69 % of medication related hospital admissions and \$100 billion of potentially avoidable health spending each year [2]. While there is no field of medicine that is immune from the effects of non-adherence, the consequences of non-adherence to cardiovascular secondary prevention are especially profound.

Coronary artery disease (CAD) remains the leading cause of morbidity and mortality in the United States [3]. There were over 1.5 million acute myocardial infarctions (AMI) in 2009, accounting for over \$500 billion in direct and indirect health care costs [4•]. There is a substantial body of evidence supporting the use of beta-blockers, statins, angiotensin-converting enzyme (ACE) inhibitors, or angiotensin II receptor blockers (ARB), adenosine diphosphate (ADP) receptor blockers, and aspirin for the secondary prevention of adverse cardiovascular events, all of which are endorsed by the American Heart Association (AHA) and American College of Cardiology (ACC) as Class I recommendations [5]. Use of these guideline-recommended therapies is estimated to be responsible for about half of the 50 % reduction in CHD mortality over the past 2 decades [6]. The clear benefits of guideline-recommended post-myocardial infarction (MI) medications [5, 7], coupled with the prevalence of coronary artery disease and its economic burden, make the importance of non-adherence to secondary prevention difficult to overstate [8]. Finally, the AHA 2020 Impact Goals “to improve the cardiovascular health of all Americans by 20 % while reducing deaths from cardiovascular disease and stroke by 20 %” would be difficult to realize without meaningful improvements in adherence [9•].

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Definitions and Assessment

Adherence may be defined as the “extent to which an individual’s behavior regarding a medical treatment regimen

corresponds with the agreed-upon recommendations of a health care professional” [10]. The term “adherence,” which implies collaboration between patients and health care professionals, is generally preferred to “compliance,” which suggests that patients are obeying the orders of their providers. In common usage, non-adherence refers to the inadequate long-term use of a prescribed therapy either due to erratic use (“secondary non-adherence”) or complete discontinuation (“non-persistence”). This is distinct from primary non-adherence, where a provider writes a prescription but it is never filled by the patient or never taken after being filled.

Adherence may be assessed in a variety of ways—subjective and objective. Subjective measures include self-reported adherence or assessments by caregivers, family members, and clinicians. Validated tools to help providers gauge patient adherence can be used during routine clinical encounters. For example, the Morisky Adherence Scale [11] relies on 4 questions: (1) Do you ever forget to take your medicine? (2) Are you careless at times about taking your medicine? (3) When you feel better, do you sometimes stop taking your medications? (4) Sometimes if you feel worse when you take the medicine, do you stop taking it?

Indirect, objective measures of adherence include electronic monitoring, pill counts, refill records, directly observed therapy, monitoring of serum drug concentrations, or use of biological markers or tracers [12]. Among these, administrative claims are most commonly used and with them measures such as “medication possession ratio,” which evaluate the number of days a patient has a supply of medication available to them in a given time period, can be calculated [13]. Patients are often considered “fully adherent” when they have medication available to them on $\geq 80\%$ of days.

Epidemiology and Consequences of Non-Adherence

Although rates of prescribing of post-MI secondary prevention at the time of hospital discharge have improved substantially over time [14], many of these prescriptions go unfilled and long-term adherence to guideline recommended pharmacotherapy remains suboptimal. A recent analysis from Ontario, Canada suggests that 27 % of all prescriptions are not filled within 7 days of hospital discharge after MI. In the case of cardiac medications, 8 % of patients did not fill their prescription for beta blockers and only 44 % of patient filled their antiplatelet prescription [15]. Low income patients, those primarily cared for by a cardiologist during their inpatient stay, and those receiving medication counseling at discharge were more likely to fill their prescriptions [15]. Contemporary US data find similar rates of primary non-adherence [16•].

Over the longer term, less than half of CAD patients are adhering to their post-MI secondary prevention medications within 1 year of an acute MI [17–20], with the largest decrement occurring in the first 6 months after treatment initiation [21, 22]. Although rates of post-MI adherence have improved somewhat over time, they still remain suboptimal [23]. Using the Duke Databank for Cardiovascular Disease, Newby et al. found that self-reported use of aspirin, beta-blockers, lipid-lowering agents, and combination of all 3 agents among patients with CAD were 83 %, 61 %, 63 %, and 39 %, respectively [24]. Less than 20 % are adherent to all of the guideline-recommended classes of medications [17–20]. In the developing world, which faces a greater burden of cardiovascular disease than that seen in North America and Europe, rates of non-adherence to cardiovascular medications appear equally poor [25•].

There is an important association between adherence and clinical outcomes. Among 2175 patients in the Beta Blocker Heart Attack Trial, those with poor adherence, defined as taking $<75\%$ of prescribed therapy had a 2.5- to 3.1-fold increased risk of death within 1-year compared with patients with higher adherence. In a study of drug adherence and mortality in 31,455 patients who survived an acute MI and filled prescriptions for statins and beta blockers there was a step-wise increase in the risk of death in patients with high, intermediate, and low adherence [26]. Among patients with diabetes, non-adherent patients had higher systolic and diastolic blood pressure and HbA_{1c} and low-density lipoprotein cholesterol levels [27]. They also had higher rates of all-cause hospitalization and mortality. In a retrospective study of 15,767 patients with established CAD, non-adherence to beta-blockers, ACE inhibitors, and statins was associated with a 50 % to 85 % relative increase in the risk of all-cause mortality [28].

The consequences of non-adherence include suboptimal clinical outcomes but also extend to avoidable health care expenditures. When accounting for both direct and indirect costs, \$300 billion each year are attributable to non-adherence [29]. Still further, investments made toward improving adherence are a cost-saving proposition—it is estimated that each dollar spent on adherence to prescribed therapies would reduce overall medical costs by \$7 for diabetic patients, \$5 for hypercholesterolemic patients, and \$4 for hypertensive patients [30]. As a result, it has been argued 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” [10].

Beyond worse clinical outcomes and unnecessary health care expenditures, non-adherence has other implications that are important but difficult to enumerate. Physician frustration, intensification of therapy, misdiagnosis, and lost productivity for caregivers among others are additional downstream consequences of non-adherence.

Causes and Predictors of Non-Adherence

Like most complex behaviors, such as smoking, diet, and exercise, medication non-adherence is not solely the result of poor patient choices. Rather, there are myriad potential contributors attributable to patients, health care providers, and the health care system more broadly (Fig. 1).

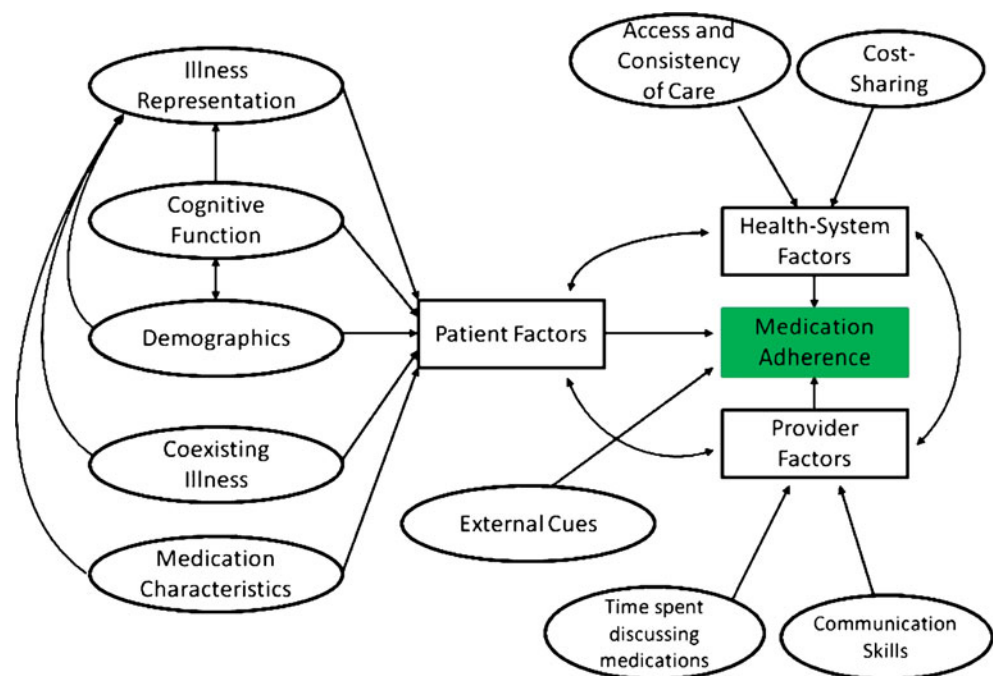
Patient Factors

Patients' sociodemographic characteristics as well as their insight into their medical problems, medications, and treatment plans have important implications for adherence. Among these, patient gender, race, and ethnicity are the most consistently observed predictors of non-adherence. For example, Medicare beneficiaries of the Black race have a 67 % higher odds of discontinuing statin therapy than patients of the White race [22], and women concomitantly using antihypertensive and lipid lowering therapy have 10 % lower odds of adherence than men [31]. As suggested in Fig. 1, these associations are likely multifactorial. One recently proposed contributor is caregiving status—women are more likely to provide informal care to loved ones and caregivers have substantially higher rates of non-adherence [32]. Income differences may also be important. In a retrospective analysis of 14,257 patients newly prescribed statins, 36 % were found to be fully adherent, with higher median income being a significant patient predictor [33]. Lower socioeconomic status has also been identified as a key predictor of primary medication non-adherence [34].

A recent systematic review of more than 50 qualitative studies exploring patients' perspectives of hypertension found that non-adherence often results from a lack of understanding (ie, the belief that their blood pressure could not be elevated in the absence of clinical symptoms) and that this misunderstanding was similar across ethnic and geographical groups [35]. Focused interviews with 806 patients with diabetes and hypertension using the validated Beliefs About Medication questionnaire demonstrates that notions about long-term adverse effects of medications and low health literacy were associated with non-adherence after controlling for costs and demographic variables [36]. Interestingly, in a recent study examining adherence to statin therapy in elderly patients after hospitalization for CAD, those who underwent coronary revascularization, either surgical or percutaneous, had significantly lower adherence compared with those managed medically (70 % vs 79 %) postulated to derive in part from patients' feeling that they were "cured" if they underwent an invasive procedure [37].

Approximately one-third of patients with a recent MI or acute coronary syndrome (ACS) will meet the criteria for major or minor depression, which also has an important impact on their adherence to medications [38]. A cross sectional analysis of the Heart and Soul Study demonstrated that subjects with major depression were more than twice as likely to be non-adherent compared to subjects who were not depressed, even after adjusting for age, ethnicity, education, social support, and disease severity [39]. An observational study of patients with a recent hospitalization for ACS demonstrated a direct and stepwise correlation between depression and non-adherence—15 % of non-

Fig. 1 Contributors to, and inter-relationships among, the complex factors leading to medication non-adherence. Patient factors, provider factors, and health-care system factors represent 3 important categories of contributors to medication non-adherence. (Adapted from: Gellad WF, Grenard J, McGlynn EA. A review of barriers to medication adherence: a framework for driving policy options. RAND Corporation, 2009. Available at: http://www.rand.org/pubs/technical_reports/TR765.html. Accessed August 19, 2012) [76]



depressed patients, 29 % of mildly depressed patients, and 37 % of moderately-to-severely depressive symptoms took aspirin less than 80 % of the time [40].

Clinician Factors

Increasingly complex medication regimens have emerged as a major issue in the chronic management of cardiovascular disease as new additive or synergistic therapies are evaluated and shown to offer benefits to patients. While these drugs may provide better health, they also add “therapeutic complexity” that may undermine adherence. In a systematic review of studies comparing once-daily with twice-daily medication dosing for equivalent treatments, the former was associated with 44 % higher adherence [41]. In a similar analysis of 61 articles, Ingersoll and Cohen concluded that dosing frequency and regimen complexity are inversely correlated with medication adherence [42]. Another study of 4052 Medicare patients prescribed anti-hypertensive and lipid-lowering therapy found that adherence fell by 28 % when 2 additional prescription medications were added to the regimens of fully adherence patients [43]. The corollary is that combinations of pills are more widely available for cardiovascular disease and have been shown to improve adherence by 20 % compared with regimens where component drugs are taken separately [44]. The combination pill concept has evolved even further into the “polypill” containing aspirin, beta blocker, ACE inhibitor, and statin [45]. Given the established efficacy of these medication classes in patients with (or at risk) for cardiovascular disease as well as the improvements in adherence, the “polypill” has been estimated to reduce the worldwide burden of cardiovascular disease by more than 80 % [46].

Poor therapeutic relationships between patients and providers are another factor that contributes to medication non-adherence [2]. In a recent analysis of 239,911 new statin users, a follow-up visit with the physician who wrote the initial prescription was a powerful predictor of reinitiation of therapy suggesting that continuity of care and increased follow-up could promote long-term adherence [47]. Strategies to improve patient-provider interactions with consistent, patient-centered communication, and confirmation of mutual understanding of shared goals and treatment plans form the foundation for any efforts to address non-adherence [48•].

Health System Factors

Health care system factors in general, and medication cost in particular, are increasingly recognized as important contributors to non-adherence. In national surveys, almost 1 in 3 Americans report that they or a family member have had

difficulty paying for medications with a similar proportion acknowledging that they have not filled a prescription or have modified a prescribed drug as a result of cost [49, 50]. This is related to having insurance coverage and its generosity [51]. For example, Medicare beneficiaries with hypertension covered by plans with higher cost sharing were less likely to use medications than patients with more generous coverage [52]. Even with the introduction of the Medicare prescription drug benefit (Part D), Medicare beneficiaries with cardiovascular disease who reached the “doughnut hole” where their drug coverage lapsed were 57 % more likely to discontinue their medications as compared with propensity score matched beneficiaries whose coverage remained in place [53•]. In the Veterans Affairs hospital system, an increase in copayments from \$2 to \$7 for statin users was associated with a 7 % absolute decline in adherence and a 12 % absolute increase in prescription gaps of ≥ 90 days [54]. Among patients with more typical commercial or employer-sponsored insurance, doubling patient copayments resulted in a 34 % reduction in the use of lipid-lowering agents and a 26 % reduction in use of anti-hypertensives [55]. A systematic review of the association of prescription drug cost sharing with medication utilization across several drug classes and medical conditions concluded that each 10 % increase in cost sharing decreases prescription drug spending by 2 %–6 % while increasing utilization of medical services [56].

Other complexities of the health care system also contribute to non-adherence. For example, a comprehensive analysis of more than 3 million individuals newly initiated on a statin or ACEI/ARB found that patients whose treatment regimen was more “consolidated,” meaning that they made fewer trips to the pharmacy to fill their medications, were more likely to be adherent even when taking into account the number of medications, prescribers, pharmacies, pharmacy visits, and patient comorbidity [57•].

Interventions to Improve Adherence among Post MI Patients

Numerous studies have evaluated interventions to improve adherence to cardiovascular medications, although relatively few have specifically targeted post-MI patients. Among post MI patients specifically, a randomized trial of direct to patient communication (2 mailings 2 months apart describing the importance of beta blocker use) led to a 4 % absolute increase in days covered per month and a 17 % relative increase in full adherence (≥ 80 % days covered) compared with patients in the control arm [58]. A forthcoming economic evaluation of post-MI adherence improvement strategies suggests that this approach is not only quality-improving, but also, cost-saving [59•].

Decreasing or eliminating copayments for post-MI medications also appears to hold much promise [60–62]. This has catalyzed a “value-based” design where copayments are reduced for the most effective medications. The recently completed Post Myocardial Infarction Free Rx Event and Economic Evaluation (MI FREEE) trial, randomized 5855 post MI patients with private health insurance to full vs usual prescription drug coverage for secondary preventive medications and found that patients with no cost sharing had 4 %–6 % absolute and 28 %–36 % relative increases in adherence to beta blockers, statins, ACE inhibitors, or ARBs, as well as significant reductions in the rate of major vascular events or revascularization [63••]. These clinical effects were associated with lower patient out-of-pocket spending for drugs and other health services without an increase in insurer costs. Still further, others have advocated for not only reducing or eliminating copayments, but providing financial remuneration for patients who are adherent to their medical regimens. Monetary incentives have been shown to significantly improve smoking cessation rates as well as promote weight loss and may represent an extension of the “pay-for-performance” movement.

Participation in a cardiac rehabilitation program is associated with improved medication adherence. A longitudinal observational study of patients after acute MI from Olmsted County demonstrated that enrollment in a cardiac rehabilitation program was associated with a significant 34 % and 30 % relative decrease in the rate of discontinuation of statins and beta blockers, respectively [64]. However, participation rates in structured cardiac rehabilitation programs remain disappointingly low with only 14 %–35 % of patients with acute MI successfully enrolling [65•].

The broader literature of adherence improvement interventions should add guidance for post-MI adherence improvement interventions. Several conclusions can be reached from these existing studies. First, behavioral interventions that reduce dosing demands and those involving monitoring and feedback have had the most consistent benefits with more limited efficacy for interventions that only provide information [66]. Second, interventions targeting all medication takers appear less effective than focused and dynamic interventions which specifically target patients who are non-adherers [67•]. Third, among person-independent adherence inventions, electronic interfaces have shown promise, and for person-dependent interventions, those occurring at hospital discharge and in the pharmacy during medication dispensing appear most effective [68•]. To this end, studies of other strategies to improve post-MI adherence are underway. For example, the Multifaceted Intervention to Improve Cardiac Medication Adherence and Secondary Prevention Measures (Medication) Study (NCT00903032) is recruiting patients with a recent

ACS to a patient-centered adherence intervention, which includes (1) pharmacy led medication reconciliation and tailoring; (2) patient education; (3) collaborative care between pharmacist and primary care provider/cardiologist; and (4) educational and medication refills voice messages [69•].

Novel approaches should involve practitioners and encourage the tailoring of clinician-focused adherence encouragement to the varying needs, constraints, and barriers that patients experience [70•]. As part of routine practice, it is likely that having clinicians ask patients about adherence and the difficulties they may have had taking their medications as prescribed may be an effective strategy. As with other efforts to change patient behavior, such as smoking cessation, physician engagement and close follow-up appear to substantially reduce gaps in therapy [47]. In this process patients should be counseled about expected and often transient side-effects, like the diuretic action of thiazides, which may lead them to unnecessarily stop therapy. Just as with efforts to improve outcomes, increase quality, and decrease costs for post MI patients, physicians must offer steadfast leadership while continuing to work with payors, advocating with policymakers, and engaging patients to improve medication adherence. Patients comprehend more and their decision-making is more concordant with provider recommendations when the most critical information is presented first, is easy to comprehend, and requires less cognitive effort [71]. Shrank et al. note that when providing information, patients desire to hear about more than just the medication’s name, dose, duration, and frequency but also want details regarding the indication, expected benefits, and potential side effects [72•].

In addition to improving communication and patient insight, interventions aimed at facilitating medication-taking into daily life may have shown promise to help post MI patients with medication adherence. Self-monitoring, interactive reinforcement, and patient accountability interfaces are not only being developed but will arguably become more prevalent as technology is increasingly brought to this arena. In particular, reminder systems integrated into developing health information technology infrastructure may enable significant improvements in adherence for patients with CV disease [73•]. Finally, reminder systems using short message services (ie, the ACC’s CardioSmart TXT program) and/or other social media interfaces which have been successfully developed for smoking cessation and cardiovascular disease prevention may also prove effective at increasing medication adherence.

Conclusions

Over the past 20 years, there has been tremendous progress in the development and testing of novel pharmacotherapeutic

agents in cardiovascular medicine in general and, in particular, for acute coronary syndromes. Numerous randomized clinical trials have convincingly demonstrated the efficacy of various cardiovascular drugs and drug classes. As such, the AHA/ACC practice guidelines recommend that all patients with acute MI and without a contraindication are prescribed aspirin, beta blockers, statins, and ACE inhibitors or ARBs for secondary prevention of CHD [5, 7, 74••]. Rates of prescribing guideline recommended medications to post-MI patients have improved steadily over time (though important opportunities for improvement remain) [75•]. However, as former surgeon general C. Everett Koop famously noted, “Drugs don’t work in patients who don’t take them” [2]. Medication non-adherence has emerged as a significant public health problem and threatens to squander the gains that basic, translational, and clinical research have brought to cardiovascular medicine. Given the various etiologies that contribute to non-adherence, achieving meaningful gains will undoubtedly require payors, providers, and policymakers to develop, rigorously evaluate, and systematically deploy strategies that address key patient, clinician, and health system factors.

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References

Papers of particular interest, published recently, have been highlighted as:

- Of importance
 - Of major importance
1. DiMatteo MR. Variations in patients' adherence to medical recommendations: a quantitative review of 50 years of research. *Medical Care*. 2004;42:200–9.
 2. Osterberg L, Blaschke T. Adherence to medication. *N Engl J Med*. 2005;353:487–97.
 3. Yusuf S, Reddy S, Ounpuu S, Anand S. Global burden of cardiovascular diseases: Part I: general considerations, the epidemiologic transition, risk factors, and impact of urbanization. *Circulation*. 2001;104:2746–53.
 4. •• Lloyd-Jones D, Adams RJ, Brown TM, Carnethon M, Dai S, De Simone G, et al. Heart disease and stroke statistics—2010 update: a report from the American Heart Association. *Circulation*. 2010;121:e46–e215. *This report from the American Heart Association offers important statistics about the burden of CAD and acute myocardial infarction in the United States.*
 5. Antman EM, Hand M, Armstrong PW, Bates ER, Green LA, Halasyamani LK, et al. 2007 focused update of the acc/aha 2004 guidelines for the management of patients with st-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association task force on practice guidelines: Developed in collaboration with the Canadian Cardiovascular Society endorsed by the American Academy of Family Physicians: 2007 writing group to review new evidence and update the ACC/AHA 2004 guidelines for the management of patients with st-elevation myocardial infarction, writing on behalf of the 2004 writing committee. *Circulation*. 2008;117:296–329.
 6. Ford ES, Ajani UA, Croft JB, Critchley JA, Labarthe DR, Kottke TE, et al. Explaining the decrease in U.S. Deaths from coronary disease, 1980–2000. *N Engl J Med*. 2007;356:2388–98.
 7. Anderson JL, Adams CD, Antman EM, Bridges CR, Califf RM, Casey Jr DE, et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-st-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association task force on practice guidelines (writing committee to revise the 2002 guidelines for the management of patients with unstable angina/non-st-elevation myocardial infarction) developed in collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine. *J Am Coll Cardiol*. 2007;50:e1–e157.
 8. Choudhry NK, Winkelmayer WC. Medication adherence after myocardial infarction: A long way left to go. *J Gen Intern Med*. 2008;23:216–8.
 9. • Lloyd-Jones DM, Hong Y, Labarthe D, Mozaffarian D, Appel LJ, Van Horn L, et al. Defining and setting national goals for cardiovascular health promotion and disease reduction: The American Heart Association's strategic impact goal through 2020 and beyond. *Circulation*. 2010;121:586–613. *This report outlines the American Heart Association's 2020 Goal.*
 10. Haynes RB, McDonald H, Garg AX, Montague P. Interventions for helping patients to follow prescriptions for medications. *Cochrane Database Syst Rev*. 2002;2:CD000011.
 11. Morisky DE, Green LW, Levine DM. Concurrent and predictive validity of a self-reported measure of medication adherence. *Medical Care*. 1986;24:67–74.
 12. Chisholm-Burns MA, Spivey CA, Garrett C, McGinty H, Mulloy LL. Impact of clinical pharmacy services on renal transplant recipients' adherence and outcomes. *Patient Preference Adherence*. 2008;2:287–92.
 13. Choudhry NK, Shrank WH, Levin RL, Lee JL, Jan SA, Brookhart MA, et al. Measuring concurrent adherence to multiple related medications. *Am J Manag Care*. 2009;15:457–64.
 14. Peterson ED, Shah BR, Parsons L, Pollack Jr CV, French WJ, Canto JG, et al. Trends in quality of care for patients with acute myocardial infarction in the national registry of myocardial infarction from 1990 to 2006. *Am Heart J*. 2008;156:1045–55.
 15. Jackevicius CA, Li P, Tu JV. Prevalence, predictors, and outcomes of primary nonadherence after acute myocardial infarction. *Circulation*. 2008;117:1028–36.
 16. • Fischer MA, Choudhry NK, Brill G, Avorn J, Schneeweiss S, Hutchins D, et al. Trouble getting started: Predictors of primary medication nonadherence. *Am J Med*. 2011;124:1081–e1089–22. *This study examines the prevalence, predictors, and outcomes of primary nonadherence.*
 17. Tricoci P, Roe MT, Mulgund J, Newby LK, Smith Jr SC, Pollack Jr CV, et al. Clopidogrel to treat patients with non-st-segment elevation acute coronary syndromes after hospital discharge. *Archives of Internal Medicine*. 2006;166:806–11.
 18. Ganz DA, Kuntz KM, Benner JS, Avorn J. Correction: cost-effectiveness of statins in older patients with myocardial infarction. *Ann Intern Med*. 2002;136:635.
 19. Akincigil A, Bowblis JR, Levin C, Jan S, Patel M, Crystal S. Long-term adherence to evidence based secondary prevention

- therapies after acute myocardial infarction. *J Gen Intern Med.* 2008;23:115–21.
20. Jackevicius CA, Mamdani M, Tu JV. Adherence with statin therapy in elderly patients with and without acute coronary syndromes. *JAMA.* 2002;288:462–7.
 21. Kramer JM, Hammill B, Anstrom KJ, Fetterolf D, Snyder R, Charde JP, et al. National evaluation of adherence to beta-blocker therapy for 1 year after acute myocardial infarction in patients with commercial health insurance. *Am Heart J.* 2006;152:454–e451–8.
 22. Benner JS, Glynn RJ, Mogun H, Neumann PJ, Weinstein MC, Avorn J. Long-term persistence in use of statin therapy in elderly patients. *JAMA.* 2002;288:455–61.
 23. Choudhry NK, Setoguchi S, Levin R, Winkelmayr WC, Shrank WH. Trends in adherence to secondary prevention medications in elderly post-myocardial infarction patients. *Pharmacoepidemiol Drug Saf.* 2008;17:1189–96.
 24. Newby LK, LaPointe NM, Chen AY, Kramer JM, Hammill BG, DeLong ER, et al. Long-term adherence to evidence-based secondary prevention therapies in coronary artery disease. *Circulation.* 2006;113:203–12.
 25. • Bowry AD, Shrank WH, Lee JL, Stedman M, Choudhry NK. A systematic review of adherence to cardiovascular medications in resource-limited settings. *J Gen Intern Med.* 2011;26:1479–91. *This review discusses adherence to cardiovascular medications in resource-limited settings.*
 26. Rasmussen JN, Chong A, Alter DA. Relationship between adherence to evidence-based pharmacotherapy and long-term mortality after acute myocardial infarction. *JAMA.* 2007;297:177–86.
 27. Ho PM, Magid DJ, Masoudi FA, McClure DL, Rumsfeld JS. Adherence to cardioprotective medications and mortality among patients with diabetes and ischemic heart disease. *BMC Cardiovasc Disord.* 2006;6:48.
 28. Ho PM, Magid DJ, Shetterly SM, Olson KL, Maddox TM, Peterson PN, et al. Medication nonadherence is associated with a broad range of adverse outcomes in patients with coronary artery disease. *Am Heart J.* 2008;155:772–9.
 29. Enhancing prescription medicine adherence: a national action plan. National Council on Patient Information and Education. August 2007. Available at http://www.talkaboutrx.org/documents/enhancing_prescription_medicine_adherence.pdf. Accessed August 19, 2012.
 30. Sabate E. Adherence to long term therapies: evidence for action. Geneva, Switzerland: World Health Organization; 2003. Accessed August 19, 2012.
 31. Chapman RH, Benner JS, Petrilla AA, Tierce JC, Collins SR, Battleman DS, et al. Predictors of adherence with antihypertensive and lipid-lowering therapy. *Arch Intern Med.* 2005;165:1147–52.
 32. • Shrank WH, Liberman JN, Fischer MA, Kilabuk E, Girdish C, Cutrona S, et al. Are caregivers adherent to their own medications? *J Am Pharm Assoc (2003).* 2011;51:492–8. *This study examines adherence patterns among caregivers.*
 33. • Chan DC, Shrank WH, Cutler D, Jan S, Fischer MA, Liu J, et al. Patient, physician, and payment predictors of statin adherence. *Med Care.* 2010;48:196–202. *This study examines patient, physician, and payment predictors of statin adherence.*
 34. • Fischer MA, Choudhry NK, Brill G, Avorn J, Schneeweiss S, Hutchins D, et al. Trouble getting started: predictors of primary medication nonadherence. *Am J Med.* 2011;124:1081.e1089–1081.e1022. *This study examines the prevalence, predictors, and outcomes of primary nonadherence.*
 35. • Marshall IJ, Wolfe CD, McKevitt C. Lay perspectives on hypertension and drug adherence: Systematic review of qualitative research. *BMJ.* 2012;345:e3953.
 36. Aikens JE, Piette JD. Diabetic patients' medication underuse, illness outcomes, and beliefs about antihyperglycemic and antihypertensive treatments. *Diabetes Care.* 2009;32:19–24.
 37. • Kulik A, Shrank WH, Levin R, Choudhry NK. Adherence to statin therapy in elderly patients after hospitalization for coronary revascularization. *Am J Cardiol.* 2011;107:1409–14. *This study examines the impact of coronary revascularization on adherence to statin therapy.*
 38. Jiang W, Glassman A, Krishnan R, O'Connor CM, Califf RM. Depression and ischemic heart disease: what have we learned so far and what must we do in the future? *Am Heart J.* 2005;150:54–78.
 39. Gehi A, Haas D, Pipkin S, Whooley MA. Depression and medication adherence in outpatients with coronary heart disease: findings from the heart and soul study. *Arch Intern Med.* 2005;165:2508–13.
 40. Rieckmann N, Gerin W, Kronish IM, Burg MM, Chaplin WF, Kong G, et al. Course of depressive symptoms and medication adherence after acute coronary syndromes: An electronic medication monitoring study. *J Am Coll Cardiol.* 2006;48:2218–22.
 41. Saini SD, Schoenfeld P, Kaulback K, Dubinsky MC. Effect of medication dosing frequency on adherence in chronic diseases. *Am J Manag Care.* 2009;15:e22–33.
 42. Ingersoll KS, Cohen J. The impact of medication regimen factors on adherence to chronic treatment: a review of literature. *J Behav Med.* 2008;31:213–24.
 43. 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;25:885–92.
 44. Bangalore S, Kamalakkannan G, Parkar S, Messerli FH. Fixed-dose combinations improve medication compliance: a meta-analysis. *Am J Med.* 2007;120:713–9.
 45. Yusuf S. Two decades of progress in preventing vascular disease. *Lancet.* 2002;360:2–3.
 46. Wald NJ, Law MR. A strategy to reduce cardiovascular disease by more than 80 %. *BMJ.* 2003;326:1419.
 47. Brookhart MA, Patrick AR, Schneeweiss S, Avorn J, Dormuth C, Shrank W, et al. Physician follow-up and provider continuity are associated with long-term medication adherence: a study of the dynamics of statin use. *Arch Intern Med.* 2007;167:847–52.
 48. •• Bosworth HB, Granger BB, Mendys P, Brindis R, Burkholder R, Czajkowski SM, et al. Medication adherence: a call for action. *Am Heart J.* 2011;162:412–24. *This comprehensive review examines the prevalence, predictors, and interventions to address non-adherence.*
 49. Choudhry NK, Brennan T, Toscano M, Spettell C, Glynn RJ, Rubino M, et al. Rationale and design of the post-mi free trial: a randomized evaluation of first-dollar drug coverage for post-myocardial infarction secondary preventive therapies. *Am Heart J.* 2008;156:31–6.
 50. Rector TS, Venus PJ. Do drug benefits help medicare beneficiaries afford prescribed drugs? *Health Aff (Millwood).* 2004;23:213–22.
 51. Felland LE, Reschovsky JD. More nonelderly Americans face problems affording prescription drugs. *Tracking Rep/Center for Studying Health System Change.* 2009:1–4.
 52. Adams AS, Soumerai SB, Ross-Degnan D. Use of antihypertensive drugs by medicare enrollees: does type of drug coverage matter? *Health Aff (Millwood).* 2001;20:276–86.
 53. • Polinski JM, Shrank WH, Glynn RJ, Huskamp HA, Roebuck MC, Schneeweiss S. Beneficiaries with cardiovascular disease and the part d coverage gap. *Circ Cardiovasc Qual Outcomes.* 2012;5:387–95. *This study explores the relationship between medication cost and adherence among patients with cardiovascular disease.*
 54. Doshi JA, Zhu J, Lee BY, Kimmel SE, Volpp KG. Impact of a prescription copayment increase on lipid-lowering medication adherence in veterans. *Circulation.* 2009;119:390–7.
 55. Goldman DP, Joyce GF, Escarce JJ, Pace JE, Solomon MD, Laouri M, et al. Pharmacy benefits and the use of drugs by the chronically ill. *JAMA.* 2004;291:2344–50.

56. Goldman DP, Joyce GF, Zheng Y. Prescription drug cost sharing: associations with medication and medical utilization and spending and health. *JAMA*. 2007;298:61–9.
57. • Choudhry NK, Fischer MA, Avorn J, Liberman JN, Schneeweiss S, Pakes J, et al. The implications of therapeutic complexity on adherence to cardiovascular medications. *Arch Intern Med*. 2011;171:814–22. *This study highlights the impact of therapeutic complexity on adherence, demonstrating that beyond number of medications, refill consolidation and number of different prescribers have important effects on adherence.*
58. Smith DH, Kramer JM, Perrin N, Platt R, Roblin DW, Lane K, et al. A randomized trial of direct-to-patient communication to enhance adherence to beta-blocker therapy following myocardial infarction. *Arch Intern Med*. 2008;168:477–83.
59. • Ito K, Shrank WH, Avorn J, Patrick AR, Brennan TA, Antman EM, et al. Comparative cost-effectiveness of interventions to improve medication adherence after myocardial infarction. *Health Serv Res*. (in press). *This study demonstrates that interventions that improve adherence post myocardial infarction are cost-saving.*
60. Choudhry NK, Avorn J, Antman EM, Schneeweiss S, Shrank WH. Should patients receive secondary prevention medications for free after a myocardial infarction? An economic analysis. *Health Aff (Millwood)*. 2007;26:186–94.
61. Choudhry NK, Patrick AR, Antman EM, Avorn J, Shrank WH. Cost-effectiveness of providing full drug coverage to increase medication adherence in post-myocardial infarction medicare beneficiaries. *Circulation*. 2008;117:1261–8.
62. Chernew ME, Shah MR, Wegh A, Rosenberg SN, Juster IA, Rosen AB, et al. Impact of decreasing copayments on medication adherence within a disease management environment. *Health Aff (Millwood)*. 2008;27:103–12.
63. •• Choudhry NK, Avorn J, Glynn RJ, Antman EM, Schneeweiss S, Toscano M, et al. Full coverage for preventive medications after myocardial infarction. *N Engl J Med*. 2011;365:2088–97. *This randomized trial of full coverage vs standard coverage for preventive medications after myocardial infarction demonstrates that the former was associated with improvements in adherence and major vascular events without increasing costs.*
64. Shah ND, Dunlay SM, Ting HH, Montori VM, Thomas RJ, Wagie AE, et al. Long-term medication adherence after myocardial infarction: experience of a community. *Am J Med*. 2009;122:961 e967–913.
65. • Kwan G, Balady GJ. Cardiac rehabilitation 2012: advancing the field through emerging science. *Circulation*. 2012;125:e369–73. *This is a review of the benefits of cardiac rehabilitation.*
66. Kripalani S, Yao X, Haynes RB. Interventions to enhance medication adherence in chronic medical conditions: a systematic review. *Arch Intern Med*. 2007;167:540–50.
67. • Cutrona SL, Choudhry NK, Fischer MA, Servi AD, Stedman M, Liberman JN, et al. Targeting cardiovascular medication adherence interventions. *J Am Pharmts Assoc*. 2012;52:381–97. *This study examines various approaches to improving adherence, finding that targeted interventions are more effective than broad interventions.*
68. • Cutrona SL, Choudhry NK, Fischer MA, Servi A, Liberman JN, Brennan TA, et al. Modes of delivery for interventions to improve cardiovascular medication adherence. *Am J Manage Care*. 2010;16:929–42. *This study examines the impact of different modes and locations of adherence interventions.*
69. • Lambert-Kerzner A, Del Giacco EJ, Fahdi IE, Bryson CL, Melnyk SD, Bosworth HB, et al. Patient-centered adherence intervention after acute coronary syndrome hospitalization. *Circ Cardiovasc Qual Outcomes*. 2012;5:571–6. *This paper describes an ongoing trial of a multifaceted intervention to improve adherence after myocardial infarction.*
70. • Choudhry NK. Promoting persistence: improving adherence through choice of drug class. *Circulation*. 2011;123:1584–6. *This paper highlights the impact of provider prescribing choice on medication adherence.*
71. Peters E, Dieckmann N, Dixon A, Hibbard JH, Mertz CK. Less is more in presenting quality information to consumers. *Med Care ResRev MCCR*. 2007;64:169–90.
72. • Shrank WH, Parker R, Davis T, Pandit AU, Knox JP, Moraras P, et al. Rationale and design of a randomized trial to evaluate an evidence-based prescription drug label on actual medication use. *Contemp Clin Trials*. 2010;31:564–71. *This study examines patient beliefs about effective communications about their medical regimens.*
73. • Misono AS, Cutrona SL, Choudhry NK, Fischer MA, Stedman MR, et al. Healthcare information technology interventions to improve cardiovascular and diabetes medication adherence. *Am J Manag Care*. 2010;16:SP82–92. *This study explores the impact of health information technology based interventions on medication adherence.*
74. •• Anderson JL, Adams CD, Antman EM, Bridges CR, Califf RM, Casey Jr DE, et al. 2011 ACCF/AHA focused update incorporated into the ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2011;123:e426–579. *These are the 2011 guidelines for patients with non-ST segment elevation acute coronary syndromes.*
75. • Roe MT, Messenger JC, Weintraub WS, Cannon CP, Fonarow GC, Dai D, et al. Treatments, trends, and outcomes of acute myocardial infarction and percutaneous coronary intervention. *J Am Coll Cardio*. 2010;56:254–63. *This is a contemporary examination of patterns of care for patients with acute myocardial infarction.*
76. Gellad WF, Grenard J, McGlynn EA. A review of barriers to medication adherence: a framework for driving policy options. RAND Corporation. 2009. Available at http://www.rand.org/pubs/technical_reports/TR765.html. Accessed August 19, 2012.