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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•].

Definitions and Assessment

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

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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-

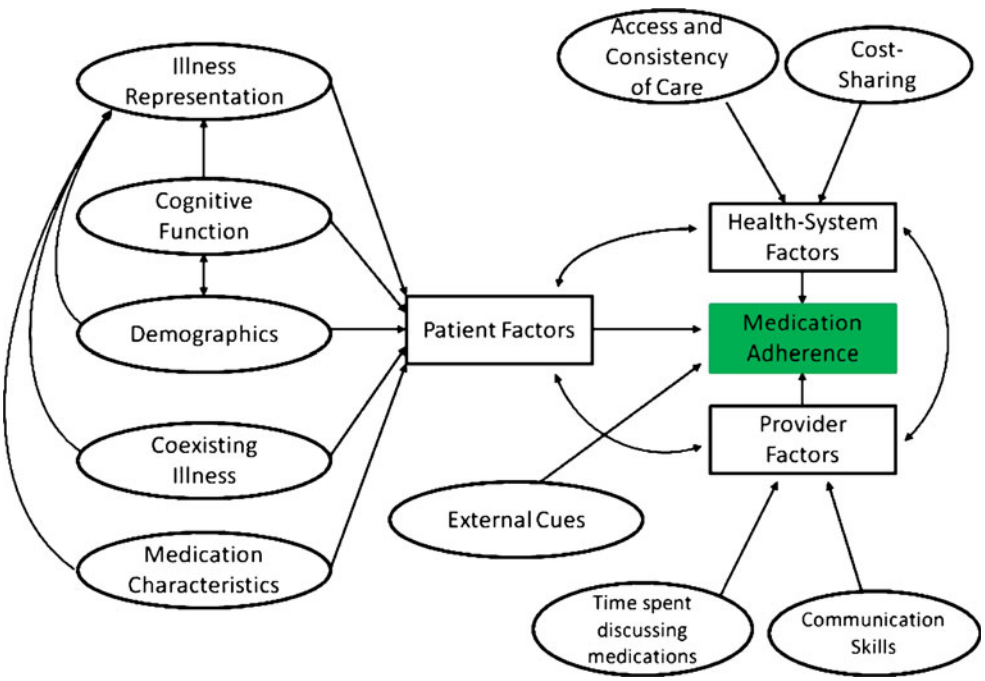

Fig. 1 Contributors to, and inter-relationships among, the complex factors leading to medication non-adherence. Patient factors, provider factors, and health-care system factors represent 3 important categories of contributors to medication non-adherence. (Adapted from: Gellad WF, Grenard J, McGlynn 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 antihypertensive 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 nonadherence [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 antihypertensives [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 renumeration 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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