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Recent Approaches to Improve Medication Adherence in Patients with Coronary Heart Disease: Progress Towards a Learning Healthcare System

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Abstract

Purpose of Review—Non-adherence to medications for the secondary prevention of myocardial infarction (MI) is a major contributor to morbidity and mortality in these patients. This review describes recent advances in promoting adherence to therapies for coronary artery disease (CAD).

Recent Findings—Two large randomized controlled trials to “incentivize” adherence were somewhat disappointing; neither financial incentives nor “peer pressure” successfully increased rates of adherence in the post-MI population. Patient education and provider engagement appear to be critical aspects of improving adherence to CAD therapies, where the provider is a physician, pharmacist, or nurse and follow-up is performed in person or by telephone. Fixed-dose combinations of CAD medications, formulated as a so-called “polypill,” have shown some early efficacy in increasing adherence. Technological advances that automate monitoring and/or encouragement of adherence are promising but seem universally dependent on patient engagement. For example, medication reminders via text message perform better if patients are required to respond. Multifaceted interventions, in which these and other interventions are combined together, appear to be most effective.

Summary—There are several available types of proven interventions through which providers, and the health system at large, can advance patient adherence to CAD therapies. No single intervention to promote adherence will be successful in all patients. Further study of multifaceted interventions and the interactions between different interventions will be important to advancing the field. The goal is a learning healthcare system in which a network of interventions responds and adapts to patients’ needs over time.

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Compliance with Ethical Standards

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Keywords

Coronary heart disease; Secondary prevention; Medication adherence; Patient education; Learning health care system

Introduction

Therapy for secondary prevention among patients with known coronary artery disease (CAD) is one of the great successes of modern medicine. Medications including anti-platelet agents, statins, beta-blockers, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), and aldosterone receptor antagonists (ARA) have all demonstrated significant morbidity and mortality benefits [1]. A new generation of medications such as direct oral anti-coagulants, glucose and cholesterol lowering agents, and anti-inflammatory therapies are also showing great promise to further reduce the risk of recurrent events [2–5]. Yet, among patients prescribed medication for CAD, suboptimal adherence continues to undermine their efficacy, leading to worse outcomes and higher costs for patients and the healthcare system as a whole [6, 7•]. This article will review recent literature focused on the epidemiology and outcomes of medication non-adherence in CAD patients as well as evaluate recent interventions aimed at improving adherence to secondary prevention therapies.

Classifying and Describing the Prevalence of Medication Non-adherence

Colloquially, the terms adherence and compliance have been used interchangeably. In the last 10 years, however, the term adherence has gained favor over compliance for being less pejorative [8]. As adherence research has matured, the term adherence has taken on two related meanings: (1) a specific research measure for the regularity with which patients take their medicines, typically expressed as a proportion or percentage of prescribed days and (2) a more general definition perhaps best exemplified by a World Health Organization (WHO) report, “the extent to which a person’s behavior—taking medication, following a diet, and/or executing lifestyle changes—corresponds with agreed recommendations from a health care provider” [9••]. This review will examine literature describing adherence using the WHO’s general definition, taking into consideration the following related concepts: (1) initiation, which refers to a patient starting a new therapy; (2) persistence, which refers to the duration of time that patients remain adherent to medicine(s); (3) discontinuation, refers to permanent or temporary abstinence from therapy; (4) reinitiation, whereby patients resume medication after a period of abstinence [10].

The WHO report on medication adherence goes on to describe five categories of factors that affect medication adherence: patient-related factors, socioeconomic factors, health team and system factors, therapy-related factors, and condition-related factors. The data and interventions reviewed herein will be categorized according to these five domains.

Patient-Related Factors

Patients' knowledge, beliefs, expectations, and attitudes related to a given medication can have a strong effect on their adherence. Fear of side effects and poor understanding of a medication's importance are common patient-related factors in non-adherence. The extent to which these factors are modifiable is the subject of debate. On the one hand, one interesting study showed a negative correlation between statin adherence and media coverage of statin side effects, suggesting that patient attitudes about statins are easily modified. This seemed to be especially true at the time of statin initiation [11]. On the other hand, some patient-related factors are clearly not within a patient's control. A recent and somewhat controversial study of Swedish registry patients determined that lower cognitive ability, measured years earlier with standardized testing, was associated with lower 1- and 2-year rates of statin adherence after a first myocardial infarction (MI) [12].

To the extent that these factors are modifiable, educational and behavioral interventions, in various forms, have been the mainstay of strategies to address patient-related non-adherence to secondary prevention medications like statins [13]. A recent study by Zhao et al. found that while CAD patients on average had a poor understanding of their drug regimen, roughly 95% of them expressed interest in learning more about their medications via educational activities [14]. While the willingness is there, the success of such activities has been variable. For example, a study of 400 patients enrolled in cardiac rehab in Germany found that adding a comprehensive patient-centered education program did not significantly increase medication adherence rates. On the other hand, this intervention significantly increased patients' knowledge about their medications and resulted in beneficial behavioral changes such as increased physical activity and following a healthy diet [15]. How the education is administered may have some effect: live web-based educational interventions appear to perform as well as in-person education [16]; however, educational mailings and pamphlets appear to offer minimal benefit in isolation [17, 18]. Similarly, behavioral interventions, such as group therapy, have enjoyed variable success in part because of their heterogeneous design—among them, sessions in which patients share strategies to maintain medication adherence and another in which patient learned mindfulness through meditation [19].

It is worth noting that patient teaching, through education and behavioral strategies, may perform better when offered in tandem with other interventions that reinforce the skills learned, such as reminders [20••]. This is likely in part because more than a third of all cases of non-adherence can be attributed to forgetfulness [21]. Since forgetting to take one's medicines, sometimes referred to as “unintentional non-adherence,” seems to be reinforced by social and economic factors; the next two sections will examine how alignment of social and health system forces could help to overcome these lapses in memory [22].

Socioeconomic Factors

The field of health disparities research is growing rapidly and socioeconomic status (SES) is being increasingly recognized as a potent predictor of health-related outcomes [23]. While there are recent data to suggest that non-adherence alone does not explain the disparity in

outcomes among patients of disadvantaged SES [24•], prior data have shown that adherence to secondary prevention is highly dependent on social and economic determinants of health such as income, literacy, employment status, living and family conditions, proximity to health centers, cultural beliefs, and, of course, the high cost of medications.

Recent data have demonstrated that low SES patients continue to be associated with more high-risk health behaviors, such as poor diet and low medication adherence [25]. Parsing the root cause of these behaviors is difficult since they interdigitate with cultural, social, and societal norms. Interestingly, a recent systematic review found that not only are low SES patients more prone to behaviors that increase their risk of CAD, they are less likely to change behaviors related to diet and medication adherence following a first myocardial infarction [26]. This finding is likely tightly related to self-efficacy, or the belief in one's ability to affect his or her disease process, which also tends to be lower in patients with low SES [27]. Recent efforts to augment adherence in patients with low self-efficacy have been met with some success. In a randomized controlled trial (RCT) of approximately 500 CAD patients in an inner city primary care clinic, illustrated medication schedules combined with mailings doubled the odds of adherence among patients with polypharmacy, low self-efficacy scores and those who reported non-adherence at baseline [28].

Another approach to address socioeconomic factors of non-adherence is to leverage social relationships and behaviors. A recent RCT by Reese et al. examined two interventions that used “social forces”—more colloquially known as “peer pressure”—to try to improve statin adherence among high-risk patients with diabetes. The first arm attempted to motivate participants by providing them with data about their adherence in comparison to their peers. In the second arm, summary adherence data in varying intervals were given to a “medication adherence partner” identified by the participant, in hopes that this partner would encourage greater adherence by the participant. Unfortunately, participants in neither arm significantly improved their adherence during the trial. This negative finding may be in part due to selection bias given the low percentage of invited individuals who actually enrolled [29••]. Future trials need to clarify our ability to “motivate” greater medication adherence.

The high cost of medications is frequently cited by CAD patients as a major driver of non-adherence [30, 31]. This likely explains why prescription drug coverage has previously and, in recent literature, continues to be positively associated with medication adherence. In contrast, a lack of medication coverage is negatively associated with adherence [32–34]. Consistent with these observations, Choudhry et al. demonstrated that eliminating copayments for medications resulted in a 4–6% absolute increase in rates of medication adherence ($P < 0.001$) [35]. Interestingly, a recent large trial of lottery payments, in which daily lottery tickets were earned in the intervention arm due to medication adherence, did not significantly improve adherence to secondary prevention therapies in post-MI patients [36••]. The latter two studies highlight the difference in efficacy of two approaches that payers and insurers might use to incentivize adherence among post-MI patients. More specifically, they illustrate that differences in how a financial incentive is framed can have differential effects on the outcome. For example, a recent study of financial incentives for physical activity among obese patients found that an incentive framed as a loss had a greater impact on physical activity than the same incentive offered as a gain [37•].

While some interventions discussed herein have demonstrated a modest improvement in adherence by addressing socioeconomic barriers, no such interventions to date have demonstrated a reduction in major adverse cardiovascular events (MACE) or other hard outcomes. The ongoing ARTEMIS (Affordability and Real-world Antiplatelet Treatment Effectiveness After Myocardial Infarction Study) trial, a large multicenter RCT of copayment vouchers for P2Y₁₂ inhibitors after myocardial infarction, may offer some promise in this regard [38].

Health Team and System-Related Factors

Patients' adherence to medication is in many ways dependent on the health system's ability to adequately support and engage patients. Scarce access to providers and siloes of information about medication use, for example, between providers and pharmacies [39], result in systemic deficiencies in the understanding and follow-up of patient adherence behaviors. A recent Cochrane review of more than 35 studies demonstrates that addressing these system issues, mainly by increasing patient access to providers, improves short- and long-term adherence to cholesterol-lowering medications [40]. This section will review several of these studies as well as other recent efforts to improve adherence to secondary prevention therapies via better systems of care.

Increasing the frequency and availability of patient visits with providers is one simple domain through which adherence can be improved. In a recent study by Jia et al., post-PCI patients randomly assigned to more frequent follow-up visits with a physician had higher rates of medication adherence (56 vs. 46%, $p < 0.001$), as well as lower rates of MACE, than those assigned to the "usual care" group [41]. Supporting this finding, visiting with a cardiologist after MI discharge has been associated with 10–20% higher adherence to high-dose statin therapy at 6 months as well as similarly increased rates of persistence at 2 years [34]. Timing may be important in light of the observation of an association between patients who visit a provider within 6 weeks of MI discharge and a 5–10% higher (in absolute terms) adherence to post-MI therapies both short and long term [42•]. It merits mentioning that there are data that provider visits need not solely be with physicians. A recent review of pharmacist care in the management of CAD analyzed five studies in which pharmacist counseling not only resulted in greater adherence to secondary prevention therapies but, in some studies, lower cholesterol levels, lower blood pressure measurements, and lower rates of cardiovascular events [43]. Similarly, more intensive and frequent cardiac rehabilitation visits after MI has been associated with approximately 40% increase in medication adherence, as well as lower LDL-C and greater rates of smoking cessation [44].

While there is data regarding the positive impact of provider visits on adherence to CAD therapies, the value of lay community health workers to reinforce secondary prevention strategies has been unrecognized until recently. The foundation for this strategy was built on multiple studies of similar programs among infectious disease and post-partum patients, both in the USA and abroad [45]. Following these advances, a novel study of Indian patients published in 2016 demonstrated that post-ACS patients randomly assigned to receive educational visits from a community health worker were significantly more likely to adhere to their cardiac medication regimen (97 vs. 92%, $p = 0.006$) and were also more likely to

quit smoking (85 vs. 52%, $p < 0.001$) and exercise (89 vs. 60%, $p < 0.001$) [46•]. Future studies might seek to validate this finding in other healthcare settings.

In place of traditional provider or health worker visits, the use of telehealth is becoming increasingly common. For example, several recent studies have examined the effect of telephone encounters on medication adherence. In one RCT, Swedish ACS and stroke patients randomized to receive nurse-led telephone follow-up 1 and 12 months after hospital discharge had greater reductions in LDL-C levels than those in the usual care arm [47]. In Canada, a similar program of telephone calls from nurses 7 days, 1 month, 6 months, and 9 months improved adherence during the study period among patients randomized to the telephone calls compared to usual care. Furthermore, the percentage of participant's persistent with medication adherence at 12 months was nearly twice as high (87 vs. 43%) in the group of patients who received the phone calls [48]. Considering these findings, in tandem with the finding that visits from community health workers increase adherence, it may be worth testing whether peer or other lay person phone calls increase medication adherence.

A growing number of patients may prefer text messaging (TM) to traditional phone calls [49]. Accordingly, seven trials related to TM methods for promoting adherence in CAD patients have been published since 2013. A recent Cochrane analysis of these trials reports that the trials were underpowered and insufficient to make a reasonable conclusion about the effect of TM on adherence in the setting of secondary prevention [50]. Interestingly, a study by Park et al. showed that regular reminders and education sent to patients via TM resulted in a significant improvement in adherence to antiplatelet therapies but not statins [51] suggesting that the effect of TM on adherence may depend on the type of therapy. Adding another nuance to TM, a meta-analysis by Wald et al. found that requiring participants to respond with whether or not they had taken their medication (2-way TM) seemed to promote a more potent response to TM reminders [52•]. While there is significant promise in using TM for adherence reminders and patient education, larger studies are needed to determine the efficacy and pitfalls of this technique.

Alternative modes of telehealth, such as websites and phone-based applications, have also been tested as a means of improving secondary prevention strategies. A limitation of the studies to date in this regard is that most have focused on improving physical activity [53]. Further, a Cochrane review of this literature found the studies to be too heterogeneous in approach to draw definitive conclusions regarding their efficacy [54]. In some ways, the large variation in telephone applications for medication adherence suggests that there is significant room for innovation in this space. For example, one such application used games and quizzes to remind participants to take their medications [55]. Several ongoing clinical trials leveraging web-based applications and support may help shed light on the utility of these tools.

In addition to the diverse menu of telehealth options for promoting medication adherence, the rapidly expanding universe of digital health offers tremendous promise in terms of monitoring and encouraging patient adherence. It is well known and has recently been affirmed that providers can use routine vital signs like heart rate and blood pressure to

estimate patients' adherence to certain therapies, like beta blockers [56]. There are efforts underway to leverage data from wearable activity and heart rate monitors to predict numerous health-related behaviors and outcomes, including non-adherence [57, 58]. One study even used ingestible sensors detected by a small wearable patch in combination with a mobile device application and a provider portal [59•]. As has been previously noted, however, the benefit of digital health monitors will likely depend more on how these devices promote engagement and adherence than on the individual features of each monitor's technology [60]. So while one could imagine a wearable monitor sensing a rise in heart rate, which then triggers an automated reminder for patients to take their beta-blocker, it remains to be seen whether this approach is the best engagement strategy for promoting adherence.

Therapy-Related Factors

In some cases, characteristics of the therapy itself can deter patient adherence. This includes but is not limited to patients' experience with adverse effects. Some patients choose not to take medicines simply because of a perceived decrement in their quality of life with having to do so [61]. Other aspects of therapeutic regimens that can deter adherence include complexity of the regimen, previous treatment failures, and lack of experience of the therapy's beneficial effects. For example, as it pertains to complexity, both multi-compartment dose administration aids (pill boxes) and giving patients longer prescriptions for cardiac secondary prevention medications at hospital discharge seems to increase the likelihood of persistence among elderly patients [62, 63•]. Recent advances in strategies for alleviating adverse effects and simplifying drug regimens are reviewed in this section.

Regarding the adverse effects of secondary prevention therapies, the study of statins has been most illustrative. Whereas it is well known that statin non-adherence is associated with worse outcomes, a recent retrospective analysis also suggests that statin intolerance is similarly associated with increased risk of recurrent MI [64]. Fortunately, not only are therapeutic alternatives now available, but among patients who discontinue therapy, there is recent evidence that lowering the dose or changing to a different agent is associated with reinitiation of therapy [65].

The aspect of therapy-related factors that has received the most attention, however, is the complexity of the regimen. Polypharmacy is common among CAD patients and continues to be associated with significantly lower rates of adherence [33, 34]. While pill boxes discussed above are the current mainstays for addressing polypharmacy, the so-called "polypill," consisting of multiple pharmacologic therapies formulated together in one pill, has been heralded as a panacea for polypharmacy. The data for the polypill's efficacy in promoting adherence are mostly related to primary prevention of CAD. A recent Cochrane analysis concluded that while there is clear improvement in self-reported adherence with the polypill, evidence of benefit in terms of hard outcomes has thus far been elusive [66]. For example, a 2015 study of the polypill in primary prevention found a greater percentage of patients in the polypill arm of the study reported adherence with combination primary prevention therapy; however, no differences in blood pressure or cholesterol were observed between the groups [67]. In the FOCUS trial, similar improvements in self-reported adherence among patients

with a recent MI were observed [68•]. Several major trials are underway to further examine the effects of the polypill on hard clinical outcomes in patients status post-MI [69].

Condition-Related Factors

Recent data suggests that the highest risk MI patients are, unfortunately, the least likely to be persistent with secondary prevention medical therapy [70]. These observations represent important condition-related predictors of non-adherence and modifying them presents one of the major challenges to combatting non-adherence.

Depression after MI provides the best and most studied example for how a disease process can modify adherence. It has long been known that there is a strong association between recent MI and the development of depression, and that depressed MI patients have worse long-term outcomes [71]. Recent data suggest that one etiologic factor in this association is that depression is a significant driver of non-adherence and diminished persistence among these patients [68•, 72]. Based on this, one could reasonably posit that the treatment of depression might improve medication adherence and thereby improve outcomes. And indeed, the treatment of depression, via counseling or medication, has recently been associated with a lower risk of MACE [73]. And while this study did not connect depression treatment with improved adherence, smaller studies have identified that a key component of depression treatment in these patients is engagement with their disease process and emphasis on the importance of medication adherence [74].

Multi-faceted Interventions

While this review has treated each factor of non-adherence independently, the example of depression after MI demonstrates their interconnectedness. While interventions are often studied in isolation, in practice, they are often best deployed as a cohesive program targeting multiple aspects of non-adherence. A few such examples are discussed in this section.

A recent RCT within the Veteran's Affairs health system demonstrated that a multifaceted intervention targeting system, patient- and therapy-related factors in non-adherence significantly increased adherence to secondary prevention medications in the year after ACS hospital discharge. The intervention was comprised of pharmacist-led education during the patient's MI admission, a pharmacist visit for medication counseling after discharge, collaborative care between the pharmacist and the patients' outpatient clinicians, a pill box as well as attempts by the pharmacist to synchronize medication refills, and, finally, automated voice messages that provided medication reminders and education. The intervention did not result in more patients achieving their goal cholesterol or BP targets, and it was not powered or designed to detect a difference in hard clinical outcomes [20••].

In contrast to the success of the latter trial, a recent RCT found no benefit in terms of adherence or outcomes with a multifaceted intervention mainly targeting socioeconomic and patient-related factors in non-adherence. The intervention not only offered daily lottery financial incentives based on adherence, but also the option of enlisting a family member or friend as an adherence partner, access to social workers, and, lastly, a staff engagement advisor to monitor adherence via data transmitted from electronic pill bottles [36••]. So why

was there benefit in one multifaceted trial but not this one? A key difference between the trials is how they engaged patients. The study by Ho et al. used providers, mainly pharmacists to engage patients. The study by Volpp et al. in contrast was designed to mimic services a health plan could offer following an MI without the direct involvement of providers. This seems to support results discussed earlier that provider engagement is critical to encouraging optimal medication adherence in the post-MI population. Another possibility is that the electronic pill bottles used to trigger engagement were more of an impediment to adherence than a useful tool.

These trials emphasize how critical it is that future studies determine the relative efficacy of different adherence interventions. The forthcoming ISLAND trial offers some promise in this regard as it will attempt to study the additional benefit achieved by adding automated interactive telephone calls to a regular system of educational mailings. Interestingly, the automated telephone system will also trigger a personalized phone call from a trained lay health worker if non-adherence is a concern [63•]. This example of a trial with multiple intervention arms is one technique for evaluating the relative contribution of each component to optimal adherence, but there are multiple prospective and retrospective techniques for making similar comparisons.

Conclusions

This review outlines recent interventions aimed at increasing adherence to secondary prevention medicines in the post-MI population. A few observations stand out. Novel approaches to promoting adherence, such as financial incentives, social partnerships, and the polypill, have shown mixed and, in some cases, disappointing results in terms of improving adherence to secondary prevention therapies. New technologies for monitoring and prompting adherence have had some success, but appear to be highly dependent on the user engagement strategy. Somewhat surprisingly, counseling from front-line providers, whether it comes from physicians, pharmacists, or nurses, continues to be the most potent and consistently successful method for encouraging adherence to CAD therapies.

The next iteration of studies needs to better discern how these different interventions interact and better define them according to subpopulations in which they might be successful. These steps will then allow the medical community and healthcare systems to adopt more comprehensive and targeted strategies for promoting medication adherence. In tandem with this, healthcare institutions should feel a mandate to create better feedback loops through which they can learn about their patients' behaviors. Is our strategy to promote adherence in this patient working? Being able to answer this question, especially, will be critical to designing a healthcare delivery system that learns and improves.

A learning healthcare system continuously refines and customizes care; best practices are embedded into delivery processes and updated as new knowledge becomes available; patient interactions with the system (e.g., not filling a medication prescription) are monitored and abnormalities are identified early; interventions then target abnormalities based on proven success in similar patients; and care continues to adapt and improve based on feedback from the system [75•]. Such a system is ideally suited to combatting non-adherence, in which an

isolated intervention cannot possibly meet the evolving needs, preferences and behaviors of even a single patient. Only by continuously learning from patients and their interactions with the healthcare system can we optimally promote adherence.

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