Adherence to secondary prevention therapies in acute coronary syndrome

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"Drugs don't work in patients who don't take them."
— C Everett Koop

Despite the overwhelming evidence of the effectiveness of secondary prevention therapies,[1,2] surveys locally and overseas indicate poor uptake of medical treatments and lifestyle recommendations after an acute coronary syndrome (ACS),[3,4] and a concerning lack of recognition of this problem by clinicians.[3-5] In one cross-sectional survey of Australian general practices, only about a half of patients with known coronary heart disease were taking recommended treatments.[5] This is similar to findings from other high-income countries, and the situation is much worse in low- and middle-income countries.[6] Adherence to lifestyle recommendations is also poor, with only about a third of patients adherent to lifestyle recommendations on diet, exercise and smoking 6 months after their ACS.[7]

The World Health Organization defines adherence as "the extent to which a person's behaviour — taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider".[8] The terms *compliance* and *adherence* are conceptually similar. However, an important difference is that *adherence* better reflects active involvement of the patient and a therapeutic alliance with the physician, whereas *compliance* implies passive patient obedience.[9,10] Poor adherence may be conscious or unconscious, and includes patients missing doses, missing days, taking drug "holidays", and forgetting to renew their prescriptions. Adherence also encompasses *persistence* — the continued taking of medications for the intended course of therapy.

Poor adherence results from complex interplay of multiple factors (Box 1). At the individual level, this ranges from physical disability and mental health to patients' perceptions of their illness, health literacy and social context.[11] Physicians contribute to the problem by prescribing complex therapies, failing to identify non-adherence and failing to identify side effects. There is growing evidence that many trials underestimate the severity of side effects.[12,13] Also, clinicians may fail to recognise non-adherence in as many as half of their patients identified as non-adherent based on pharmacy claims data.[14]

While an ACS event would be expected to motivate a person to change behaviour, patients stop taking their medications as early as a few weeks after discharge, and non-adherence rates increase with time.[15,16] According to one study of 1521 patients with acute myocardial infarction (AMI), at 1 month after AMI, 18% reported discontinuing at least one of the three major drug classes (aspirin, β-blocker or statin).[15]

Not surprisingly, poor adherence is associated with worse outcomes. In one population-based longitudinal observational study of more than 30 000 AMI survivors, poor adherence to statins in the first year after AMI was associated with a 25% higher risk of mortality.[17] Premature discontinuation of thienopyridines (eg, clopidogrel) within a month after an AMI treated with drug-eluting stents was associated with increased mortality during the next 11 months (7.5% v 0.7%; $P < 0.001$) and increased hospitalisation (23% v 14%; hazard ratio, 1.5).[18] Similarly, among patients with stable coronary disease, non-adherence to angiotensin-converting enzyme (ACE) inhibitors, β-blockers and/or statins, identified in 25% of patients, were each associated with an increased relative risk of cardiovascular re-admissions (range, 10%–40%), coronary interventions (range, 10%–30%) and cardiovascular mortality (range, 50%–80%).[19] Good adherence is associated with improved outcomes. In analyses of the CRUSADE ACS registry, every 10% increase in the overall composite guideline adherence was associated with a 10% decrease in the likelihood of inhospital mortality.[20] Better outcomes with adherence may be due to a "healthy adherer" effect. In clinical trials, even patients more adherent to placebo have better outcomes.[7,21]

Summary

- Despite overwhelming evidence of the effectiveness of secondary prevention therapies, surveys indicate poor adherence to medical treatments and lifestyle recommendations after an acute coronary syndrome.
- The term *adherence* is preferred over *compliance*, as the former suggests a therapeutic alliance, whereas the latter reflects passive patient obedience.
- Poor adherence results from a complex interplay of multiple factors at patient, practitioner and system levels.
- Poor adherence among patients with stable coronary artery disease is associated with increased risk of cardiovascular admissions (10%–40%), coronary interventions (10%–30%) and cardiovascular mortality (50%–80%).
- Improving adherence is a complex process. A range of interventions that target modifiable factors influencing adherence have been explored, but there are no guidelines to guide the choice, and multidisciplinary efforts may be needed.
- Future research in the area should focus on comparative efficacy of interventions to enhance adherence.

Detection of non-adherence

Measuring non-adherence is challenging. Even in the research setting, there is no gold standard tool. For some types of drugs, a direct technique can be applied; for example, measuring levels of the drug or its metabolite in blood or urine, or the effect of the drug on a known biochemical measure (eg, cholesterol levels). Other methods used in trials include pharmacy refill records and pill counts, but these do not account for "pill dumping" and pattern of intake (erratic timing). Several clinical trials use the MEMS (Medication Event Monitoring System), which is a microprocessor attached to a bottle to record

1 Examples of factors that may reduce adherence to therapy

Patient

- Physical impairment (impaired dexterity, poor vision)
- Cognitive impairment
- Psychological (depression)
- Language barriers (non-English speaking)
- Health literacy
- Comorbidities

Health system

- Poor patient–provider relationship
- Health professionals' lack of time and lack of incentives
- Poor continuity of care (hospital–community care transition)
- Geographic location and access to services, pharmacies and transport

Therapy

- Complex regimen (multiple dosing during the day)
- Complex dose (frequent titrations or substitution)
- Polypharmacy
- Side effects

Socioeconomic

- Income
- Low levels of patient education and/or literacy
- Poor social support (single status)
- Unstable living conditions (homeless, frequent travel, shift workers) ◆

2 Self-report questionnaires to assess medication non-adherence

Questionnaire	Components	Features
BMQ[22]	Three sets of questions: • Five-item "regimen screen" • Two-item "recall screen" • Two-item "belief screen"	Validated against MEMS
MARS-5[23]	Modified from MARS-10 Five-point Likert scale First question: unintentional non-adherence Other four statements: intentional non-adherence	Variable sensitivity reported in studies (when matched with pharmacy refill data)
MMAS[24]	Two versions: • MMAS-4 (original) • MMAS-8 (2008 modification)	Brief; ease of dichotomous response

BMQ = Brief Medication Questionnaire. MARS = Medication Adherence Rating Scale. MMAS = Morisky Medication Adherence Scale. MEMS = Medication Event Monitoring System. ◆

3 Modifiable factors influencing adherence and persistence and examples of interventions

Modifiable factor	Intervention
Regimen complexity	Simpler, less frequent dosing regimen
Cost of therapy	Prescription of generic medications
Pill burden	Combination polypill
Improved tolerability	Selection of medication with low side-effect profile
Patient acceptance of disease	Health literacy and counselling
Patient trust in therapy	Patient–prescriber–pharmacist relationship
Forgetfulness	Reminders

the occurrence and timing of bottle opening. However, even this cannot assess whether the patient actually takes the drug once the bottle is opened. While there is potential bias associated with misreporting and self-report, standardised questionnaires remain important tools to quantify non-adherence (Box 2).[25,26]

Interventions to improve medical adherence

Several interventions that target the modifiable factors that influence adherence have been explored (Box 3). Systematic reviews have examined improving medical adherence among chronic disease patients and identified a diverse range of interventions, including many that are complex. However, they have struggled with classifying interventions and thus pooling them to enable a comparison of their efficacy.[27]

There is very little research that directly trials interventions that improve medical adherence to secondary prevention drugs among patients with coronary heart disease. Secondary prevention programs, including cardiac rehabilitation programs, often include modules that focus on supporting lifestyle modification, risk factor management and medical adherence.[28,29] The intensity of these programs ranges from face-to-face involvement in inhospital programs and telephone counselling[30] to — more recently — text message reminder systems.[31] With regards to specific drugs, there has been examination of interventions to improve adherence to lipid-lowering drugs and hypertension medications in broader populations.[32] The more recent of these, with respect to lipid-lowering drugs, identified 11 studies and concluded that patient re-enforcement and reminding was the most promising category of interventions — it was investigated in six trials, of which four showed improved adherence, with an absolute increase in adherence ranging from 6% to 24%.[32]

Another type of intervention that has been explored more recently involves simplifying the regimen by using fixed-dose combination medication. The UMPIRE study examined the impact of a fixed-dose combination (a four-drug combination of aspirin, ACE inhibitor, statin, and either a β-blocker or a thiazide) in 2000 patients. The self-reported adherence in the intervention arm (polypill) at median 15-month follow-up was significantly higher (86% v 65%; relative risk of being adherent, 1.33; 95% CI, 1.26–1.41; $P < 0.001$). The effect size was most marked among patients with poor baseline adherence.[33]

What can a physician do?

While there is increasing research interest in drug adherence, comprehensive data are not yet available. There is little literature on the comparative efficacy of interventions and, as such, there is no clear best way of achieving improved medical adherence. Also, it is unlikely that there will be a "one-size-fits-all" solution for all patients.[34]

From a practical viewpoint, some suggested approaches are described here. Screening for medical adherence can be done simply and should be done at every patient consultation. The most practical approach is to have a high index of suspicion, and to interview patients in a non-judgemental manner. The discussion can be initiated with a neutral question, for example:

4 Questions to ask patients to assess their adherence to medicines[35]

To assess medicine-taking behaviour

- How are you going with those tablets?
- How have you been taking these medicines?

To assess beliefs and attitudes

- How do you feel about taking these medicines?
- Have you ever thought about changing your medicines?
- How well does this medicine work for you?

To assess both

- It must be hard trying to remember to take the tablets every time. Do you ever forget? How do you feel about that?
- People often have difficulty taking their pills, and I am interested in finding out any problems that occur so that I can understand them better. Do you ever miss taking your medicines? How often?
- When you feel better, do you sometimes stop taking your medicine? ◆

5 SIMPLE approach to enhance adherence[36]

S	Simplify the regimen	• Adjust timing, frequency and number of tablets to suit patient • Attempt to change the situation, not the patient • Encourage use of adherence aids (eg, mobile app reminders)
I	Impart knowledge	• Focus on patient–provider shared decision making • Provide written and verbal instructions • Simple language and 3–4 major points • Encourage involvement of nurse and pharmacist
M	Modify patient beliefs and human behaviour	• Empower patient to self-manage the condition • Ensure patient understands the risk of not taking the medication • Address fears and concerns of patient
P	Provide communication and trust	• Clear communication from provider • Build safe environment where patient feels comfortable • Informed and shared decision making
L	Leave bias	• Self-learning exercise in area and incorporating into practice • Use of culturally and linguistically appropriate interventions • Tailor education to patient's level of understanding
E	Evaluate adherence	• Periodic review • Self-report and medication adherence scales • Biochemical tests — definitive confirmation ◆

- "What do you think about taking these medications daily?"
- "How often do you miss taking them?"

Patients should also be asked about the cost of therapy and its affordability. It may also be important to ask about missed doses over longer periods (eg, the past month), to avoid the potential for "white-coat adherence" — a transient improvement in adherence for a few days before and after health personnel contact. A potential approach to questioning patients on adherence from the National Heart Foundation is summarised in Box 4. The American College of Preventive Medicine has also identified an approach that can be categorised under the mnemonic *SIMPLE* (Box 5).[36]

Conclusion

Non-adherence is a serious problem and a particularly important issue for patients with chronic disease requiring multiple medications. Low adherence is associated with increasing morbidity, mortality and increased costs of health care. Already, several innovative and effective strategies exist to improve adherence. Our standard of care needs to include identifying whether non-adherence exists, what individual factors are influencing it and what interventions may minimise non-adherence.

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