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REVIEW

Clinical update

Non-adherence to cardiovascular medications

Kumaran Kolandaivelu[1,2], Benjamin B. Leiden[1], Patrick T. O'Gara[2], and Deepak L. Bhatt[2]*

[1]Institute for Medical Engineering and Sciences, Massachusetts Institute of Technology, 77 Massachusetts Ave. Bldg. E25-201, Cambridge, MA 02139, USA; and
[2]Cardiovascular Division, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, 75 Francis St., Boston, MA 02115, USA

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Despite evidence-based interventions, coronary heart disease (CHD) remains a leading cause of global mortality. As therapies advance, patient non-adherence to established treatments is well recognized. Non-adherence is a powerful confounder of evidence-based practice and can affect daily patient management, resulting in inappropriate therapeutic escalation with greater costs and potential for harm. Moreover, it increases risk for adverse cardiac events, including mortality. Yet, non-adherence is complex, remains difficult to define, and provider ability to identify its presence accurately remains limited. Improved screening tools are needed to detect at-risk patients, enabling appropriate targeting of interventions. Given the rapidly expanding global population with CHD and emerging clinical and cost–benefits of adherence, addressing non-adherence to prescribed therapies is a top priority.

Keywords Non-adherence • Coronary heart disease

Introduction

Coronary heart disease (CHD) remains a leading cause of global mortality despite established evidence-based therapies (*Table 1*).[1] While significant resources are allotted to develop newer treatments,[2–5] 'simple' non-adherence to existing medications has become well-recognized, yet is undermanaged.[6–8] In acute, primary, and secondary care settings, non-adherence undermines evidence-based therapy, contributing to hundreds of thousands of deaths annually and unnecessary healthcare expenditures exceeding hundreds of billions of dollars in the USA and Europe alone.[9,10]

Non-adherence remains complex, ill-characterized, and unpredictable. No longer considered non-compliance, which historically reflected the paternalistic view of patients refusing to comply with 'doctor's orders', the term adherence now acknowledges the consensual collaboration that must exist between patient and provider. Implicit in this expanded notion are the many societal and system-level factors that govern non-adherence. Increased awareness of its presence and effects has spurred efforts to begin to address it, already yielding improvements in outcomes and cost savings. Still, there remains great potential for improvement, and strategies to more accurately identify the presence of non-adherence and overcome its effects are needed.[4,10,11]

The non-adherence pandemic

Non-adherence to cardiovascular medications is a global threat (*Figure 1*) and can be broadly characterized by two related concepts: adherence, denoting the level of drug use, and persistence, relating to the duration.[6,12,13] Even following acute myocardial infarction (AMI), only 66% of patients in the PREMIER Registry reported taking key medications.[14] In the Ontario-based EFFECT Registry, only 78% of patients filled prescriptions within 120 days of an AMI.[15] Similarly, within 3 months of AMI discharge, only 72% reported taking prescribed medications in the CRUSADE and ACTION registries.[16]

Such statistics highlight the rapid decline in adherence following hospitalization. Overtime and in prevention settings, persistent use is even more dismal.[17] In the Ontario Database, only 40, 36, and 25% of nearly 150 000 patients remained adherent with prescription filling over 2 years in acute, secondary prevention, and primary prevention registry settings, respectively.[18–20] In a separate secondary prevention study of over 30 000 patients only 21% of patients consistently took aspirin, beta-blockers, and statins.[21] These dynamics may be hidden in randomized controlled trials (RCTs) obscuring the very notion of evidence-based efficacy (*Figure 2*). Further, non-adherence is not CHD-exclusive, but pervasive across cardiovascular diseases. In some reports, only 10% of patients were compliant with heart

* Corresponding author. Tel: +1 0118573071992, Fax: +1 0118573071955, Email: dlbhattmd@post.harvard.edu

Key review points

- Non-adherence to cardiovascular medications is pandemic and a leading risk factor for treatment failures and poor outcomes.
- The impact of non-adherence is medication-dependent; it must be defined and measured in the context of a particular therapy.
- Drivers for non-adherence are multifactorial and patient-specific; application of screening tools remains fragmented and ineffective.
- Treatment of non-adherence is multimodal and resource-intensive; linking accurate screens to tailored, collaborative interventions involving patients, providers, and payers are needed to maximize cost-effectiveness.

failure therapies, with up to 64% of readmissions resulting from poor adherence.[22,23]

While non-adherence is unquestionably common, its prevalence remains difficult to gauge due to lack of robust definitions and gold-standard screens.[24] In settings with constrained data access as is common in observational registries, patients may appear 'non-adherent' when reduced use is confounded by factors such as variable-prescribing practices, subjective reporting, or inability to track over-the-counter dispensation (*Figure 1*).[13,24,25] Even when lapses are ascribed to true non-adherence, some individuals may not take obtained medications, i.e. secondary non-adherence, while others may fail to fill prescriptions, i.e. primary non-adherence—patterns that require unique considerations.[26] Moreover, coarse-classifications often originate in clinical trials and may be used to bin patients as 'adherent' or 'non-adherent', yet such definitions may not possess the granularity needed to capture clinically relevant real-world variations (*Figure 3A*).[27,28] Confounding is that the relevance of variations is itself contextual. While antihypertensives such as hydrochlorothiazide and diltiazem (short-acting) lose effect within 24 h of holding a dose, others such as chlorthalidone and amlodipine can maintain some degree of blood pressure control for 2 to 3 days (*Figure 3B*).[29–32] In addition to drug-specific pharmacokinetics, the implications of treatment lapses must also be considered as strict adherence in some cases, as with dual antiplatelet therapy post-stenting, may be critical (*Figure. 3C* and *D*).[33–36]

Non-adherence and clinical outcomes

Non-adherence to cardiovascular therapy is associated with increased mortality.[37] Importantly, *absolute* mortality differences associated with non-adherence can exceed incremental benefits observed with new therapies, often expressed in *relative* terms (*Figure 4*).[14,38–40]

In PREMIER, mortality hazard ratios for patients discontinuing treatment when compared with those continuing ranged from 1.82 (95% CI: 1.09–3.03) for aspirin to 2.86 (9 5% CI: 1.47–5.55) for statins.[14] Absolute mortality for those stopping all medications was five-fold higher, rising from 2.3 to 11.5% ($P < 0.001$).[14] In a subset receiving drug-eluting stents (DES) and a thienopyridine, one in seven discontinued thienopyridines within 1 month, correlating with a nine-fold excess mortality rate.[41] Another study showed one in six patients receiving DES failed to fill clopidogrel prescriptions on discharge day, correlating with a 1.8-fold increased risk of death or myocardial infarction (14.2 vs. 7.9%; $P < 0.001$).[42] In EFFECT, composed of an older population, 1-year absolute mortality of patients failing to fill prescriptions was 30.4% as compared with 20.5 or 12.8% in patients who filled some or all prescriptions.[15] These are global trends. In the REACH registry spanning 44 countries, risk of cardiovascular death, myocardial infarction, or stroke increased from 13.4 to 17.4% (HR: 1.18, 95% CI, 1.11–1.25) for patients non-adherent at baseline, being even worse in patients who went from taking to not taking medications at 1-year (HR: 1.36; 95% CI, 1.17–1.57).[43,44]

Non-adherence is not only associated with worse outcomes, but can dominate risk. In an observational study of DES thrombosis,

Table 1 Hazard ratios (mortality, symptomatic coronary heart disease, and stroke) for common evidence-based therapies used in the primary and secondary prevention of coronary heart disease

	Death	Coronary heart disease (95% CI)	Stroke
Primary prevention			
Aspirin	–	0.68 (0.60–0.77)	0.84 (0.75–0.93)
ACEI and Calcium-channel blocker	–	0.66 (0.60–0.71)	0.51 (0.45–0.58)
Statin	–	0.64 (0.55–0.74)	0.94 (0.78–1.14)
Secondary prevention			
Aspirin	0.85 (0.81–0.89)	0.66 (0.6–0.72)	0.78 (0.72–0.84)
β-Blocker	0.77 (0.69–0.85)	0.73 (0.75–0.87)	0.71 (0.68–0.74)
ACEI	0.84 (0.75–0.95)	0.80 (0.70–0.90)	0.68 (0.56–0.84)
Statin	0.78 (0.69–0.87)	0.71 (0.62–0.82)	0.81 (0.66–1.00)

Non-adherence negates these benefits. Adapted from Gaziano *et al.*[1] with permission of Elsevier, Inc.

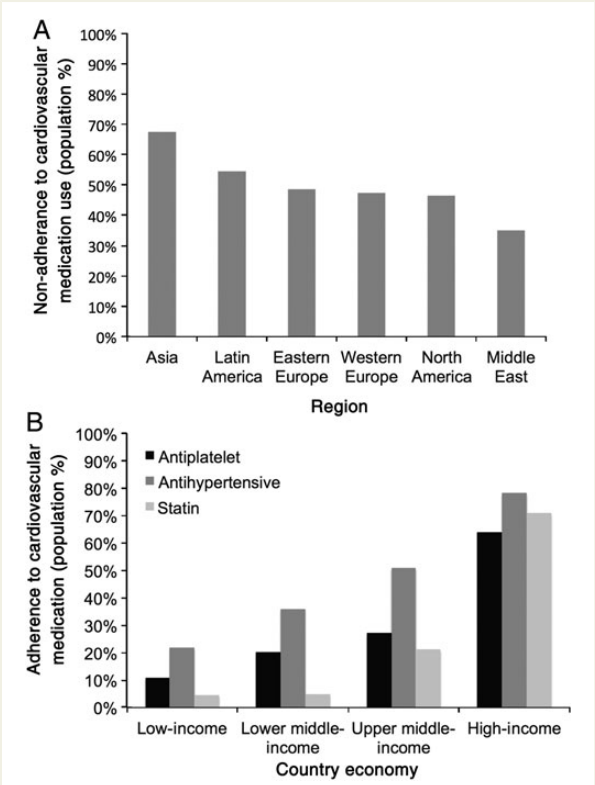

Figure 1 Non-adherence is pandemic. (*A*) Data from the REACH registry depicting regional differences in medication use. Perceived non-adherence is often confounded by measurement bias and factors such as regional variations in provider practices and cultural beliefs, resource limitations, and variable public awareness.[13] (*B*) Data from the PURE study, demonstrating strong association between medication use and regional economy across cardiovascular drug type; drug-dependent effects, such as relative increase in statin use with regional economy, are present.[25]

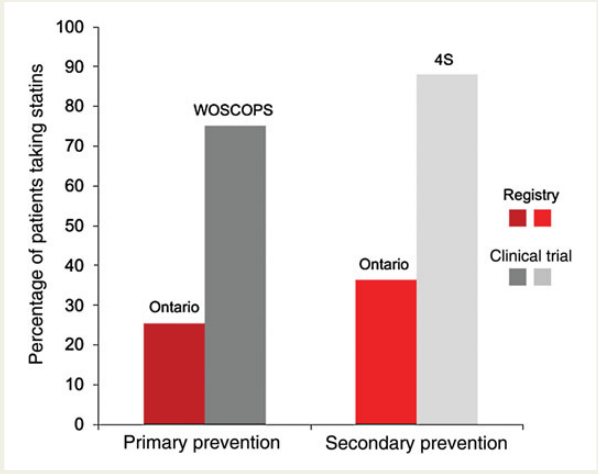

Figure 2 Two-year adherence to statin therapy as assessed by prescription dispensation in patients with primary or secondary indications.[20] Registry data (Ontario Database; displayed in red) can be compared with the much higher rates of adherence observed in RCTs [88% in the 4S[19] secondary prevention study (dark grey) and 75% in the WOSCOPS[18] primary prevention study (light grey)].

stopping antiplatelet therapy correlated with a 90-fold increase in stent thrombosis risk, an order of magnitude greater than other factors.[45] In CHARISMA, which considered addition of clopidogrel to aspirin in high-risk, stable populations, patients discontinuing clopidogrel therapy experienced a 4.3-fold increased hazard of death—eclipsing risk factors including uncontrolled blood pressure, tobacco use, or prior MI (hazard ratios 1.02, 1.55, and 1.83 respectively; $P \leq 0.0014$; *Figure 5*).[46]

Intriguingly, non-adherence to either active drug or placebo has been correlated with poor outcomes in several RCTs, including CHARISMA.[46–48] Such data implicate a potential 'healthy adherer' or 'sick stopper' effect where confounding factors may drive outcomes independently of drug.[4,6,49] Despite confounders, other studies have validated pharmacological bases for adherence-related outcomes, with, for example, the benefits of ticagrelor over clopidogrel observed in patients with AMI being even more pronounced in adherent subsets.[37,42,50,51] Further efforts to understand and treat this multi-faceted phenomenon are needed.

Understanding and predicting non-adherence

Treatment-, patient-, and healthcare system-related factors all influence adherence (*Table 2*).[6,24,52] While prediction remains challenging, new technologies and data repositories promise to yield approaches to better manage the highly individualized nature of non-adherence. As screening strategies improve, it is essential that risk factors be recognized.

Many cardiovascular medications produce adverse drug events (ADEs); patients may be reluctant to take therapies with minor side effects.[53,54] Such effects may be idiopathic, as with statin-induced myalgias, or mechanistic, as with bleeding and antithrombotic use.[55] While large bleeds are relatively uncommon, 'nuisance' bleeds occur in up to 60% of patients on dual antiplatelet therapies and correlate with non-adherence.[54] In CHARISMA, minor bleeding was reported in 42.5 and 25.1% of patients non-adherent or adherent to study drug (clopidogrel or placebo), respectively.[46]

Regimen complexity also contributes. In the CRUSADE/ACTION registries, non-adherence to multi-drug regimens increased by 1.06 (95% CI, 1.02–1.10) for each added medication.[16] In a large review, as dosing frequency increased from one to four times daily, adherence declined from 80 to 50%.[56] 'Poly-pills' composed of multiple medications may increase adherence. In the UMPIRE trial, patients prescribed a poly-pill of aspirin, simvastatin, and blood pressure medications reported higher 12-month adherence (86 vs. 65% $P < 0.001$) compared with patients taking medications individually.[57] However, while patients may be non-adherent to components of multi-drug regimens, those non-adherent to poly-pills would not receive any therapy. This is worrisome, since in both UMPIRE and The Indian Polycap Study (TIPS), nearly 15% of patients discontinued therapy[57,58]—numbers that may grow over time.

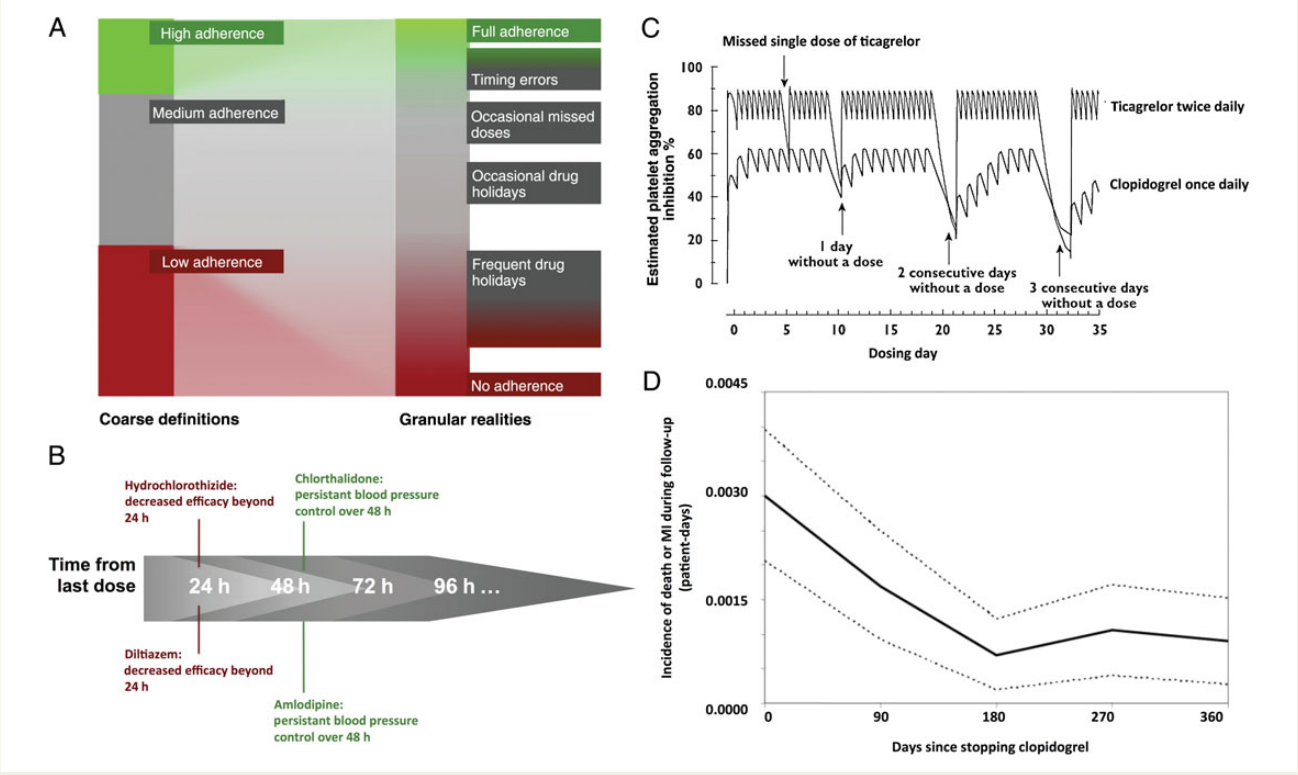

Figure 3 (*A*) Patients are often coarsely classified, i.e. 'high adherence' (≥80%, green), 'intermediate adherence' (40–80%, grey), and 'poor adherence' (≤40%, red).[6,37] In reality, patients exist in a continuum.[28] Definitions of adherence must be made in the context of specific drugs. (*B*) For example, while some antihypertensives (hydrochlorothiazide, short-acting diltiazem; red) rapidly lose effect, others (chlorthalidone, amlodipine; green) exhibit more lasting response (green donates protection from occasional missed doses; red susceptibility).[30,31,96] (*C*) Drugs are characterized by unique pharmacokinetics governing responsiveness to non-adherence, as illustrated by lapses in ticagrelor (twice daily) vs. clopidogrel (once daily) administration.[32] (*D*) The clinical impact of stopping a drug is also contextual; clopidogrel demonstrates an elevated early incidence of hard-outcomes such as death or myocardial infarction.[35] Panel (*C*) adapted from Vrijens *et al.*[32] with permission of Blackwell Publishing; Panel (*D*) adapted from Ho *et al.*[35] with permission of the American Heart Association.

Economic factors and payer policies also impact adherence. Globally, 1.7 billion people are unable to afford essential medications, 80% of whom are in developing countries.[59] Expensive, proprietary medications may be prescribed instead of generics—a practice that can worsen adherence and be augmented by poor payer coverage. In one study, increasing monthly co-payments from $2 to $7 resulted in a precipitous drop in statin use.[60] In other studies, co-payment correlated with non-adherence to antihypertensive therapies[61] while Medicare patients with capped benefits were less adherent to preventive therapies.[62]

Several patient factors have also been implicated, albeit inconsistently. Across groups, poor health literacy is associated with worse adherence.[63] While race was not a predictor of non-adherence in the Get with the Guidelines Coronary Artery Disease (GWTG-CAD) registry,[64] the global region was in the REACH registry.[13] Though economics and varied patient education may contribute, further confounding are factors such as region-dependent provider and cultural beliefs that may influence prescribing practices. Gender differences have also been observed. Women, similar to elderly individuals, had poorer adherence in six of six hospital discharge adherence metrics in the GWTG-CAD registry.[64] In the PARIS registry, women were more likely to stop dual antiplatelet therapy possibly due to increased bleeding.[65]

Poor mental health also correlates with poor adherence.[64] The SADHART trial demonstrated patients with major depression following ACS had lower adherence than patients whose depression improved (68.6 vs. 77.4%; $P = 0.002$).[66] Similarly, post traumatic stress disorder, common after cardiovascular events, correlates with poor adherence independent of depression.[67] Even subtle personality types, i.e. 'Type D', may play a role.[68]

Patient contributors to non-adherence are further confounded by provider and system factors. Often, inadequate time is spent reviewing medication habits. In a study of patients with uncontrolled hypertension, providers failed to investigate medication behaviour in 33% of cases.[69] In another study, 90% of patients reported not discussing medication-related ADEs, whereas 81% of respective physicians reported having a discussion.[70] Such errors compound during care transitions and can be responsible for significant medication discrepancies and inadvertent cessation.[71,72]

There is intense effort to develop predictive screens to better identify at-risk patients prospectively.[73] For example, machine-learning classifiers trained on just 78 patients predicted heart

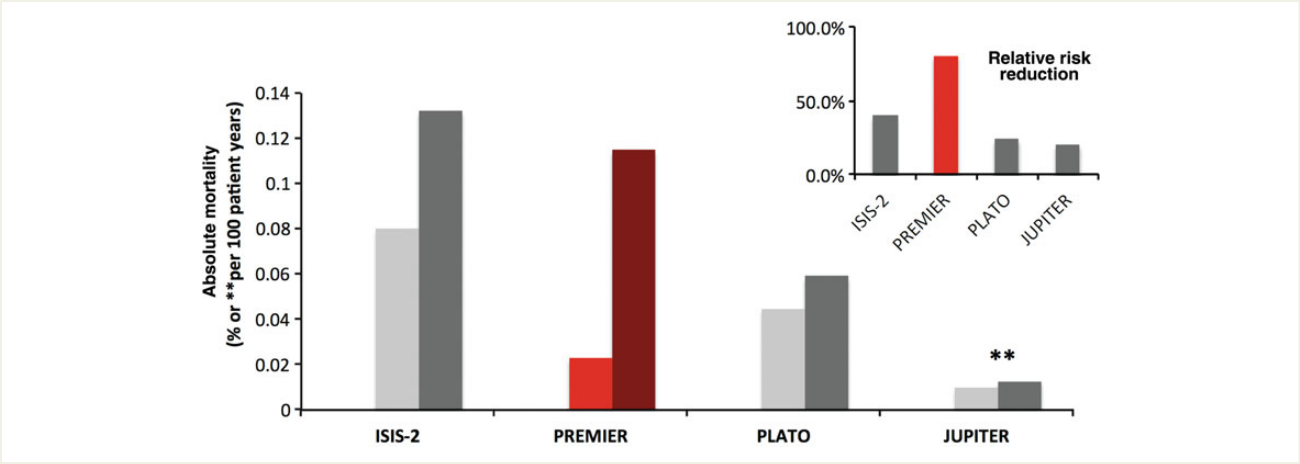

Figure 4 Large trials detect the incremental benefits of new treatments, often expressed as relative risk reductions (inlay), rather than absolute effects (shown as % mortality or mortality per 100 patient years**). Aspirin and streptokinase treatment in patients with acute infarction in the ISIS-2 Study (1988) yielded 5% absolute mortality reduction compared with placebo (relative risk reductions 39%).[38] In 2009, ticagrelor demonstrated 1.4% absolute mortality improvement compared with clopidogrel in patients undergoing coronary stenting (relative risk reductions 24%).[39] In 2008, use of rosuvastatin in low-risk primary prevention settings resulted in a 0.25% absolute reduction in mortality (per 100 patient years**; relative risk reductions 20%).[40] The potential impact of medication non-adherence can far exceed these effects as evidenced in the PREMIER registry (red).[14]

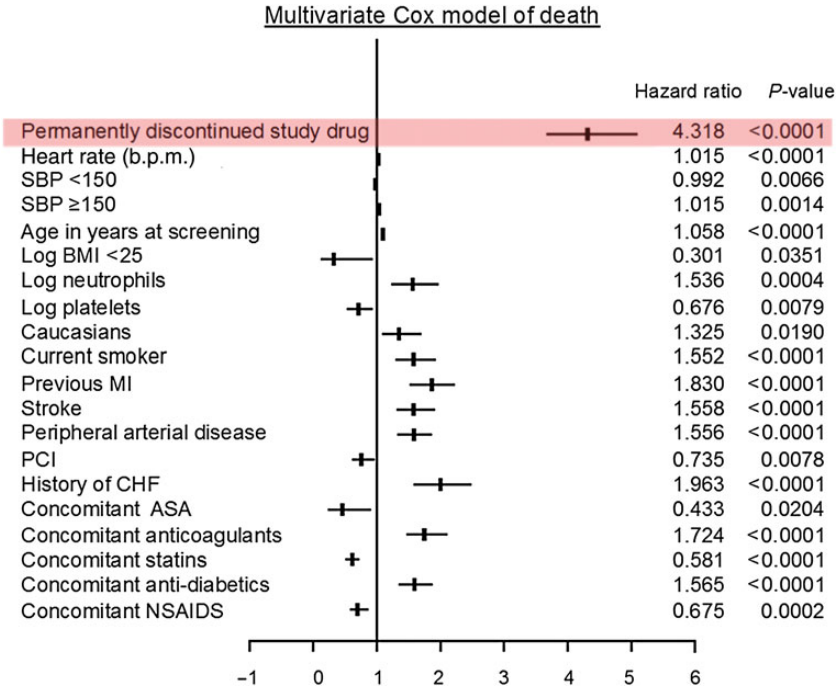

Figure 5 In many trials, as in CHARISMA, non-adherence dominates risk.[46] Adapted from Collet *et al.*[46] with permission of Elsevier, Inc.

failure medication non-adherence with an accuracy of 0.78.[74] In 4850 patients discharged following an acute coronary event, neural networks predicted persistent medication use more accurately than standard regression (area under curve 0.80 vs. 0.69).[75] The proprietary ScreenRX platform by Express Scripts employs over 400 variables, reporting accuracies as high as 98%.[76] While promising, these models are historical, and must be validated prospectively in populations of interest. As patterns of non-adherence may shift, predictive tools must not be static, but rather evolve with new data.

Table 2 Barriers to medication adherence span treatment and patient-related factors to healthcare system and policy-related ones

Category	Factors Associated with Nonadherence
Treatment	Medication Side Effects (On-target versus off-target)
	Treatment Complexity (Multiple doses; polypharmacy)
	Cost
Patient	Low health literacy; education
	Socioeconomic status
	Age; Gender
	Region, Race, Ethnicity
	Cultural and experiential beliefs
	Mental health
Healthcare System	Lack of evidence based solutions
Provider	Inadequate communication
	Judgmental
	Prescribing practices (polypharmacy; use of non-generics)
	Cultural and experiential beliefs
Hospital	Lack of robust screening tools
	Lack of supportive infrastructure
	Short visit times
	Frequent care transitions
Payer	Poor medication coverage / reimbursement

Actions to Overcome Nonadherence
SYSTEM-LEVEL
• Raise public health awareness and address regional differences
• Prioritize infrastructural support to promote adherence
• Support and adopt team based approaches
• Acknowledge and provide adequate time for teams to manage
• Leverage growing IT infrastructures
• Develop screening aides
• Develop and validate evidence based approaches
• Align meeting adherence goals with adequate incentives
PATIENT/PROVIDER-LEVEL
• Discuss benefits of medication
• Discuss side-effects of management approaches
• Discuss concerns and beliefs nonjudgmentally
• Individualize treatment plans, acknowledging patient preferences / lifestyle
• Avoid polypharmacy and multiple day dosing when possible
• Review and reconcile medications; Stop unneeded medications
• Use generics when possible

Overcoming non-adherence must be multimodal, with focus on raising awareness, creating supportive infrastructure, adopting team-based approaches, improving patient-provider communication, providing adequate incentives at each level, and developing effective screening tools linked with evidence-based actions. Intersecting lines indicate actions impacting particular barriers, demonstrating the multi-scale complexities in overcoming non-adherence.

Overcoming non-adherence

Detecting non-adherence does not equate with overcoming it; screens must be linked with management plans and existing/emerging technologies. The most widely used aids remain low-tech pill-boxes and calendars.[77] Blister packs and MEMS (Medication Event Monitoring Systems) developed for RCTs have since been adapted for general use. More recent innovations include reminder services, mobile applications, real-time provider feedback, networkable MEMS, and automated dispensers.[78] Even biomarkers are in development that can be administered with drugs and monitor adherence objectively.

Despite increased availability of high-tech systems, widespread implementation remains limited.[78] Many solutions are prohibitively expensive, and complex. Fragmented electronic infrastructures and limited interoperability pose additional barriers. Also, design of many consumer devices places the burden of adherence primarily on the patient, while effective approaches must involve partnerships between patients, providers, and payers (*Table 2*).[24]

Patient outreach and education are among the most effective, proven methods of improving patient adherence.[79,80] In FAME, elderly patients with coronary risk factors were randomized to usual care (UC) vs. a multi-component programme (PC). In the PC intervention, medications were distributed in blister packs and patients were provided ongoing education and follow-ups. In contrast, patients in the UC arm received no special care. Initially, both groups received UC, demonstrating 5% adherence.[81] Subsequently, all patients received PC yielding dramatic increases (98.7%; $P < 0.001$).[81] Finally, half were switched to UC while half continued PC. Within 6 months, the PC group remained highly adherent (97.4%) while adherence in the UC group plummeted (21.7%; $P < 0.001$; *Figure 6A*).[81] While the potential to improve adherence exists, it likely requires significant, ongoing effort.

Payer policies also motivate adherence. In the Post-MI FREEE study, medication was provided freely to a group of patients discharged after MI and at 'normal cost' to controls.[82] Those with full-coverage exhibited 4–6% greater adherence than controls ($P < 0.001$), yet even the active arm exhibited only 43% adherence. Worryingly, in a low-income cohort in France, access to free medical care was actually associated with worse adherence.[83] Though free medications alone may not suffice, positive incentive programmes, where patients are actively rewarded for adherence, could help.[84]

System- and provider-level efforts can also impact patient adherence. Organized efforts, such as the Delphi Expert Panel in Europe, have provided a consensus approach to prioritizing solutions, continuing to uphold a multipronged strategy stressing patient-education, provider-awareness, and patient-provider communication (*Table 2*).[85] Reducing care transition errors is critical, and can be aided through the use of integrated electronic health record systems (EHR) containing embedded medication reconciliation

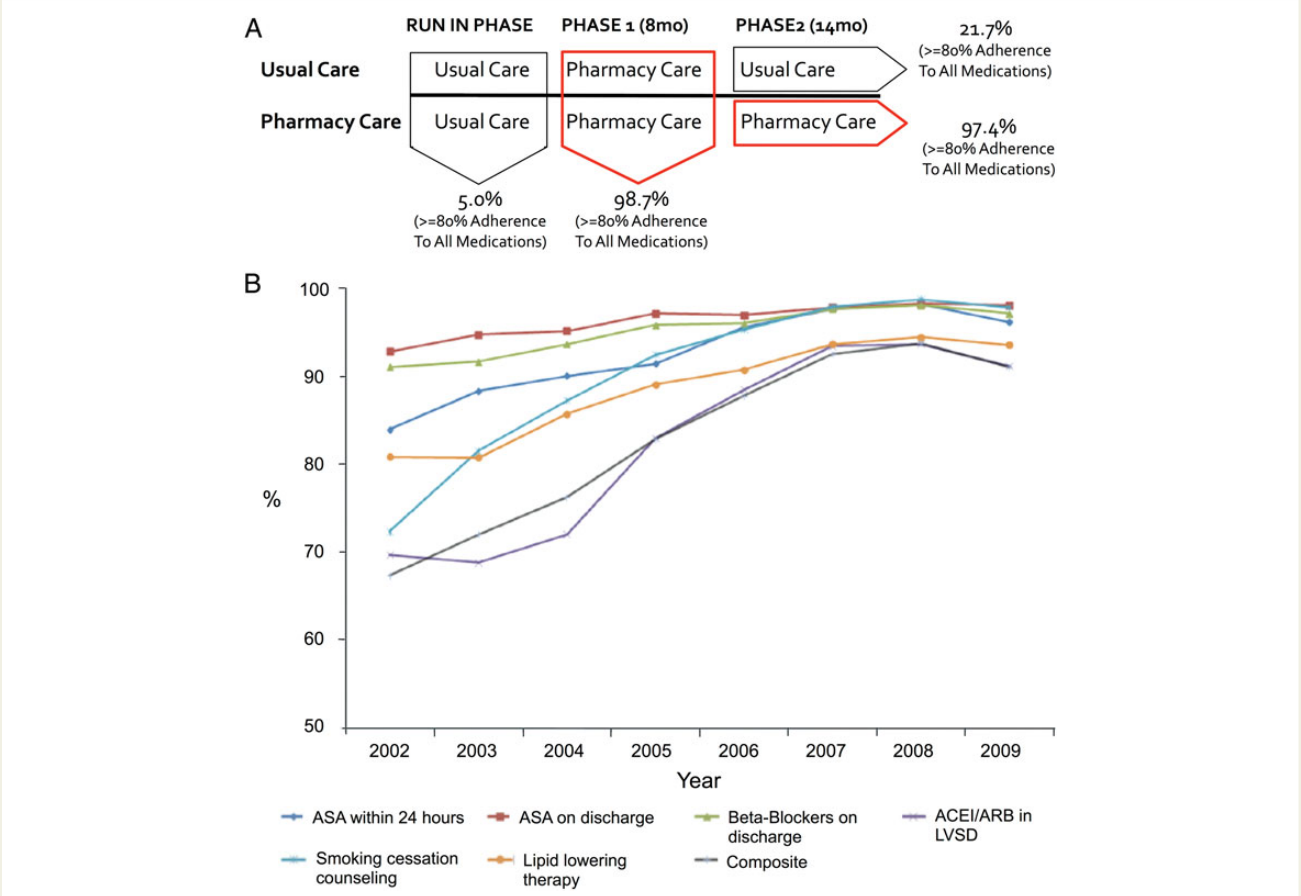

Figure 6 (*A*) In FAME, patients received usual care or a comprehensive pharmacy care intervention. Pharmacy care was associated with marked improvement in adherence, though when a subset of patients was switched back to usual care, they reverted quickly to poor adherence rates.[81] (*B*) Seven-year adherence trends with six performance measures following hospitalization for acute myocardial infarction in the Get with the Guidelines—Coronary Artery Disease registry showing systematic improvements over time.[64] Panel (*B*) adapted from Kumbhani *et al.*,[64] with permission of the American College of Physicians.

applications, particularly with appropriate user training.[71,86,87] Such efforts can be bolstered by patient discharge counselling.[88] At a provider-level, patients can be actively engaged regarding medication habits. Care can be taken to reduce medications complexities through avoiding polypharmacy, using regimens with fewer daily doses, and adopting therapies with less stringent dosing requirements and reduced side effects.[89,90]

While much remains to be done, the benefits of adherence-improving strategies are beginning to be realized. Already, widespread improvements in adherence have been demonstrated in programmes such as the Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines (CRUSADE) National Quality Improvement Initiative, Guidelines Applied in Practice (GAP) programme, Cardiac Hospitalization Atherosclerosis Management Programme (CHAMP), and the GWTG programme (*Figure 6B*).[64,91,92] In a review of team-based interventions, Carter *et al.*[80] reported adherence interventions effectively lowered blood pressure. Similarly, adherent patients in the FAME and UMPIRE trials showed reductions in blood pressure and LDL while other studies demonstrated reductions in non-adherence-related readmissions.[57,81,93] Though not universal, a review by Boswell *et al.*,[94] showed improved adherence improves healthcare utilization. Among the growing number of examples, two hospital networks found implementing medication adherence-programmes resulted in savings of 5–7% per patient and $476 per patient, respectively.[95] To maximize cost-effectiveness, accurate, tailored screening tools must be linked to tailored management strategies.

Conclusions and next steps

Non-adherence to evidence-based cardiovascular medications has become increasingly recognized. If undiagnosed, non-adherence can lead to inappropriate intensification of therapy and is often the dominant risk factor for poor outcomes. Yet provider ability to predict individuals prone towards non-adherence remains inadequate. Accurate, cost-effective screening tools with adequate drug-specific resolution are needed to target interventions to appropriate patients. Consensus documents may help align fragmented efforts in this space, while establishing research priorities and gold standards

for reporting and validation. The efficacy of interventions must be assessed in RCTs and confirmed in real-world registries where the dynamics of adherence differ. Lasting solutions will likely be multimodal and personalized, yet practical. They must incorporate easy to use, affordable therapies with favourable side-effect profiles in conjunction with ongoing communication among patient, provider, and an expanding health-care network of pharmacists, nurses, nurse practitioners, social workers, and insurance carriers empowered by emerging technologies. In the face of a rapidly expanding, global population at risk for CHD, effective means of ensuring patient adherence to evidence-based therapy are urgently needed.

Search strategy and selection criteria

This review was compiled from a search using PubMed and a personal collection of papers. Relevant, peer-reviewed, full-text articles, and reviews published in English within the past 10 years were selected, as were the reference lists of the identified papers. Database search terms included 'adherence', 'antiplatelet', 'aspirin', 'beta-blocker', 'clopidogrel', 'evidence-based', 'cardiovascular', 'compliance', 'hypertension', 'medication', 'mortality', 'platelet', 'poly-pill', 'prevention', 'resistance', 'responsiveness', and 'statin' alone or in combination.

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