Hypertension

AHA SCIENTIFIC STATEMENT

Medication Adherence and Blood Pressure Control: A Scientific Statement From the American Heart Association

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ABSTRACT: The widespread treatment of hypertension and resultant improvement in blood pressure have been major contributors to the dramatic age-specific decline in heart disease and stroke. Despite this progress, a persistent gap remains between stated public health targets and achieved blood pressure control rates. Many factors may be important contributors to the gap between population hypertension control goals and currently observed control levels. Among them is the extent to which patients adhere to prescribed treatment. The goal of this scientific statement is to summarize the current state of knowledge of the contribution of medication nonadherence to the national prevalence of poor blood pressure control, methods for measuring medication adherence and their associated challenges, risk factors for antihypertensive medication nonadherence, and strategies for improving adherence to antihypertensive medications at both the individual and health system levels.

Key Words: AHA Scientific Statements ■ hypertension ■ medication adherence

Hypertension is a major risk factor for heart disease, stroke, and kidney disease and is the number 1 diagnosis for office visits to primary care clinicians. More than 55 million Americans are currently treated with antihypertensive drugs.[1] The widespread treatment of hypertension and resultant improvement in blood pressure (BP) have been major contributors to the dramatic age-specific decline in heart disease and stroke that has occurred in the United States over the past decades.[2]

Despite this progress, a persistent gap remains between stated public health targets and achieved BP control rates. Results from NHANES (National Health and Nutrition Examination Survey) conducted between 1999 and 2018 indicate that the prevalence of BP control, using the threshold of 140/90 mm Hg, increased from 31.8% to a high of 53.8% in 2014 but appears to have declined since, with only 43.7% of US adults with hypertension having controlled hypertension in 2018,[3] well short of the US Department of Health and Human Services goal of 61.2% by 2020.[4]

Many factors may be important contributors to the gap between population hypertension control goals and currently observed control levels. Among them is the extent to which patients adhere to prescribed treatment. The World Health Organization defines adherence as the extent to which a person's behavior—taking medication, following a diet, or executing lifestyle changes—corresponds with agreed-on recommendations from a health care professional.[5] Although all these health behaviors are important, medication adherence plays a specific and critical role in hypertension control and is the focus of this scientific statement.

The NHANES surveys provide a starting point for evaluating how nonadherence may rank among other factors affecting hypertension control. An analysis of the 2003–2010 NHANES sample that focused on the characteristics of people with uncontrolled hypertension showed that 39.4% of subjects were unaware of their hypertension, 15.8% were aware but not currently using medication, and only 44.8% were aware and being

The former chair of this scientific statement, David J. Hyman, MD, MPH, passed away in June 2020 before publication of the article occurred.

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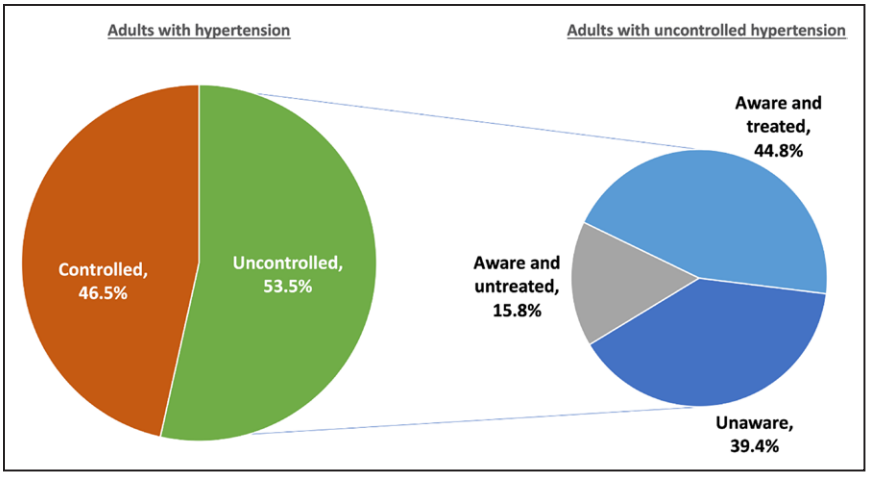

Figure. Classification of adults with uncontrolled hypertension: NHANES (National Health and Nutrition Examination Surveys) 2003 to 2010.[6]

treated (Figure).[6] Of the 60% of hypertensive patients who are aware of their diagnosis, several factors may contribute to poor control: (1) suboptimal dosing or treatment intensification by the treating clinician (commonly referred to as clinical inertia) or poor drug choice, (2) limited access to or use of health care attributable to either lack of insurance or infrequent contact with the health system, and (3) failure of individuals to adhere to prescribed antihypertensive treatment or other lifestyle recommendations. These factors are, of course, not mutually exclusive and highlight that there are many contributors to the failure to meet BP goals in general and to nonadherence in particular. For example, the unaffordability of medications and the inability of patients to pick up their prescribed medications because of long travel distances to their pharmacy or limited hours of operation are systemic factors that are not within patients' direct control.[7] Furthermore, evidence suggests that clinician failure to intensify medical regimens, often called clinical inertia, may be a greater contributor to uncontrolled BP than patient nonadherence to drug therapy.[8,9] For example, Daugherty et al[10] studied patients with resistant hypertension or uncontrolled BP in 2 US health systems and found that treatment was intensified in fewer than a quarter of visits with elevated BP and that treatment intensification, but not medication adherence, was associated with substantially better BP control. Thus, it is a mistake for clinicians to attribute poor BP control solely to patient nonadherence without first examining whether the treatment regimen is adequate. Nevertheless, medication nonadherence, including its broader systemic contributors, remains an important target for efforts to improve hypertension control.

The goal of this scientific statement is to summarize the current state of knowledge of (1) the contribution of medication nonadherence to the national prevalence of poor BP control, (2) methods for measuring medication adherence and their associated challenges, (3) risk factors for antihypertensive medication nonadherence, and (4) strategies for improving adherence to antihypertensive medications at the patient, clinician, and health system levels. This scientific statement was proposed by the Professional/Public Education and Publications Committee of the American Heart Association Council on Hypertension and approved by the Manuscript Oversight Committee, which is made up of the American Heart Association scientific council chairs. The American Heart Association Science Advisory Coordinating Committee had final approval of this document.

DEFINITIONS AND EPIDEMIOLOGY

Patient adherence to drug treatment has been classified into 3 major phases by systematic review and expert consensus surveys: (1) initiation, or failure to begin treatment; (2) implementation, or incomplete dosing (ie, not regularly taking prescribed doses of prescriptions); and (3) persistence, or continuation of treatment.[11,12]

It has been reported that 12% of patients with hypertension never fill initial prescriptions.[13] Estimates of the proportion of people with uncontrolled hypertension who are not persistent with treatment vary greatly. In studies that rely on insurance claims and managed care databases, the reported nonpersistence rates in the first year after starting treatment range from 30% to 80%.[14–21] This variability may be a function of patient demographics (eg, age is generally positively correlated with persistence), health plan characteristics (eg, persistence is typically higher in settings with more generous health benefits), or methods of calculating the persistence measure (eg, allowing longer grace periods before classifying a patient as nonpersistent results in higher levels of persistence).

In studies that include all treated people with hypertension, not only patients who have recently initiated treatment, pharmacy refill data indicate higher levels of adherence and persistence, ranging from 75% to 90%.[19,20,22–25] Both the initial filling of prescriptions and long-term adherence and persistence with treatment are likely to take on increased importance as the threshold and goals of treatment evolve to increasingly lower BP targets.[26]

Table 1. Methods to Assess Adherence

Method	Advantages	Disadvantages	Clinical applicability
Unstructured self-report or report by a proxy	Easy to obtain	Inaccurate; may overestimate compared with electronic pillbox	Yes
Multidomain detailed questionnaire	Inexpensive; validated against pharmacy data	May overestimate adherence compared with objective measurement tools but is superior to unstructured self-report	Yes
Electronic drug monitors	Accurate in capturing both timing and frequency of cap opening; can be linked to automated, context-specific adherence reminders	Cost not covered by insurance; may not truly reflect adherence if patients do not swallow the pills after cap opening; individual pill bottles may be challenging to use for patients on multiple medications	No
Digital sensor	Accurate in capturing timing and frequency of pill swallowing	Requires patients to wear and replace external patch daily; smartphone with software app of the system is also required	No
Direct observation	Easy to obtain for patients in clinical settings	Electronic observation methods are not universally available	Yes, in some facilities
Pharmacy fill	Easy to obtain and inexpensive; if linked to prescribing data, can be used to identify noninitiation	Inaccurate if prescription data are not captured from all potential sources or patients do not take the dispensed medications	Yes
Biochemical detection of drug levels	Relatively easy to obtain; highly sensitive	White coat adherence (taking the pills only when tested) may occur if patients are aware of the tests	Yes

App indicates application.

METHOD OF ADHERENCE MEASUREMENT

Adherence can be monitored by several methods such as unstructured self-report (or report by a proxy), detailed questionnaires, pill counts, prescription fill rate, electronic pillboxes, digital sensors, direct observation, and drug levels. We summarize these approaches, along with their advantages and disadvantages, in Table 1. A recent expert survey suggested that different adherence measures may be more or less appropriate, depending on the particular adherence behavior being measured.[11]

Patient's self-reported adherence is generally considered inaccurate because patients tend to overestimate their adherence to antihypertensive medications.[27] Numerous detailed adherence questionnaires such as the Adherence to Refills and Medications Scale have been developed and have been shown to be more reliable than unstructured self-reported adherence when validated against pharmacy refill data but not with all other methods of adherence assessment.[28,29]

Direct observation is the most accurate method of determining adherence but is generally not feasible in typical practice. Digital sensors are a promising emerging technology in monitoring and promoting adherence by using pills equipped with biodegradable sensors. Although these sensors are approved by the US Food and Drug Administration for drug treatment of psychiatric disorders (eg, Abilify), they are not yet approved or available for antihypertensive drug treatment or monitoring.

Electronic drug monitoring devices such as the Medical Event Monitoring System or electronic pillboxes are considered to be highly accurate in assessing adherence to the prescribed dosing schedule by capturing both timing and frequency of medication use by tracking bottle cap openings.[30] These devices have notable limitations as well: They may serve as reminders themselves (either because of embedded technology or because of their mere presence) and thus may overestimate true adherence in their absence; in addition, the technology is still largely limited to research settings because of the high costs.[31,32] Individual electronic pill bottles may be challenging to implement for patients on multiple medications and for medications that require special packaging such as blister packaging or transdermal delivery.[33] Electronic malfunction can occur in 5% to 20% of the devices.[33,34] Furthermore, patients may not actually take the medications after opening the bottles.[32,35] Patients may also remove multiple doses at once for later administration or to fill a pillbox (eg, pocket dosing).[36–38]

Despite its time-consuming nature, pill counting is often used in research settings. However, it has been shown to be only 50% to 70% as accurate as electronic pill bottles and only 68% as accurate as measurement of drug levels.[39] This technique also does not provide an accurate assessment of day-to-day medication adherence.

Pharmacy refill data, either from insurance claims or directly from pharmacies, are another popular indicator of medication adherence. The retail filling data of many pharmacies in the United States are now available to clinicians through their electronic health record by several networks such as Surescripts that capture the fills that are paid for by both cash and insurance. However, not all health systems have access to these data. Nevertheless, pharmacy refill databases may be the most

practical way of studying the behavior of large groups of patients over time. Prescribing data from electronic health records, which indicate prescriptions written but not necessarily filled, also have been used to measure medication adherence.[40] What defines a patient as fully adherent with prescribing- and filling-based adherence measures is a matter of some debate, although a threshold of 80% is widely used because it corresponds to the minimum level of adherence associated with reductions in clinically meaningful outcomes for post–myocardial infarction patients[41] and is the level used by health plans for quality improvement purposes.[42]

More recently, an increasing number of studies have indicated that biochemical measurement of drug levels in serum or urine samples with highly sensitive high-performance liquid chromatography–tandem mass spectrometry technique is highly reliable in detecting medication nonadherence in hypertension.[28,36–38,43,44] Although the biochemical assessment of adherence was previously thought to be impractical, testing for both urine and serum antihypertensive drug levels is widely available for clinical use and is covered by most health insurance plans.[28,44] Nondetectable drug levels are a strong marker of nonadherence, but drug levels could be inconclusive in cases of partial adherence. Unfortunately, current methods of biochemical assessment do not provide assessment of adherence to the therapeutic level of antihypertensive medications.[45]

RISK FACTORS AND PREDICTORS OF MEDICATION ADHERENCE

Decades of evidence indicates that adherence is multifactorial. The 2003 World Health Organization report "Adherence to Long-Term Therapy: Evidence for Action" identified 5 dimensions or categories of barriers to medication adherence.[5] Although additional information on risk factors has accumulated since that report, the framework remains useful clinically. An adapted version of the framework is presented to inform systematic efforts to identify and address barriers to adherence at the patient and population levels (Table 2).[47]

Several socioeconomic status, demographic, and environmental factors are associated with suboptimal adherence, although not all of these factors such as age, income, race and ethnicity, and health literacy, including digital literacy, have consistently been linked to adherence.[48–53] In the quest for a more reliable prediction of nonadherence, various combinations of clinical, socioeconomic, and demographic predictors have been considered. Nevertheless, composite scoring generated from multiple predictive factors, although statistically significant, does not necessarily lead to accurate prediction for individual patients, even in the studies from which the predictive model was developed.[36]

The therapeutic alliance between the patient and clinician, the communication style of the clinician, and the degree of patient-centeredness in treatment decisions have all been shown to affect adherence.[48–51,54,55] Trust is a key factor in interpersonal communication. Patients who participated in decisions on what medications are prescribed have been shown to be more adherent than patients who are not engaged in the decision process.[56] Team-based care, including effective patient-centered medical homes, is associated with better adherence and risk factor control compared with treatment settings without team-based approaches.[17,57]

Access to and cost of medications are clearly important for adherence.[48–51,58] Uninsured adults did not share the large improvement in hypertension control that occurred among privately and publicly insured adults between 1988 and 2010.[4] The increase in BP control among publicly insured adults was larger than the increase in treatment alone, which may suggest better adherence.[4] A similar pattern was observed with treatment and control of cholesterol levels and supports the notion that health insurance access may mitigate several social barriers to better health outcomes and has a greater role in heath disparities than previously estimated.[59]

Complex medication regimens, including polypharmacy and multiple doses daily, are well documented to reduce adherence.[48,50,51] A shorter time to control, which is documented to reduce cardiovascular events, and fewer therapeutic adjustments and prescribing medications with fewer adverse effects all foster higher adherence.[48,50,51]

Adults with hypertension often have multiple chronic conditions, including depression, posttraumatic stress disorder, and other behavioral health disorders such as drug and alcohol misuse, all of which can adversely affect adherence to medications and healthy lifestyles.[25,60] In addition, alterations of memory in elderly patients can result in missed doses and overdosing, in which drug ingestion is greater than prescribed, which may induce drug toxicity.[61] Major disabilities and low quality of life can also impair medication adherence, especially when the medications do not immediately attenuate the disability or enhance quality of life.[62] Comorbid chronic ailments such as those of the urinary or gastrointestinal tract can also make it difficult for patients to adhere to their prescribed therapies.[63] It is also noteworthy to note that severe chronic symptomatology can adversely affect adherence, as can chronic asymptomatic disease.[64]

Among patient-controlled factors, failure to accept the diagnosis is a major barrier to adherence. If patients perceive that prescription medications are ineffective in controlling hypertension or are likely to have major adverse effects, then adherence has been shown to be negatively affected.[65] The term hypertension itself

Table 2. Factors Associated With Nonadherence

Socioeconomic and demographic dimension	Limited English proficiency
	Low health literacy
	Lack of family or social support network (no spouse or partner)
	Unstable living conditions or homelessness
	Limited access to health care facilities
	Lack of health care insurance
	Inability to access or difficulty in accessing pharmacy
	Financial insecurity
Therapy-related dimension	Complexity of medication regimen (number of doses and concurrent medications)
	Duration of therapy
	Frequent changes in medication regimen
	Lack of immediate therapeutic benefit
	Medications with associated social stigma
	Actual or perceived unpleasant side effects
	Treatment interferes with lifestyle or requires significant behavioral change
Health care system/team dimension	Clinician-patient relationship
	Clinician communication skills
	Disparity between health beliefs of patient and clinician
	Lack of positive reinforcement from clinician
	Limited health system capacity for patient education and follow-up
	Lack of clinician knowledge about adherence and interventions for improving it
	Patient information materials written at too high a literacy level
	Changes or restrictions affecting formulary
	High drug costs or copayments
	Long wait times
	Lack of continuity of care
Patient-related dimension	Visual impairment
	Hearing impairment
	Cognitive impairment
	Impaired mobility and dexterity
	Swallowing problems
	Psychological and behavioral factors
	Perceived risk of susceptibility to disease
	Understanding the reason why medication is needed
	Expectations and attitudes toward treatment
	Beliefs about illness
	Perceived benefit of treatment
	Confidence in ability to follow treatment regimen
	Motivation
	Fear of possible adverse effects
	Fear of dependence
	Feeling stigmatized by disease
	Frustration with health care professionals
	Psychosocial stress, anxiety, or anger
	Alcohol or substance abuse
Condition-related dimension	Chronic conditions
	Lack of symptoms
	Severity of symptoms

(*Continued*)

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has been correlated with increased stress and can negatively affect adherence to proven BP-lowering medications.[66] Low self-efficacy, or lack of confidence in one's ability to self-manage a condition or disease effectively, is also a common barrier to adherence.[48–51,67] A lack of understanding of the benefits of treatment, how medications lower BP, and how they need to be taken is also related to nonadherence. Historical mistrust of the medical system may also reduce medication adherence.[68] In addition, patients who use alternatives to traditional or Western medicine are less likely to adhere to prescription medications.[69,70] An important consideration is that Black adults appear to have a greater use of alternative therapies than White adults, which may be a factor underlying racial differences in adherence.[71]

INTERVENTIONS TO IMPROVE ADHERENCE

A large number of trials designed to reduce nonadherence to antihypertensive medications have been conducted, with multiple systematic reviews published on this topic.[72,73] In a 2014 Cochrane database review of interventions to enhance medication adherence in general that included 182 randomized trials, Nieuwlaat and colleagues[72] concluded that "current methods of improving medication adherence for chronic health problems are mostly complex and not very effective."

For this scientific statement, our goal was to identify those medication adherence interventions with the greatest strength of evidence. To identify interventions, we conducted a PubMed search from January 1, 2000, to November 1, 2020, to identify systematic reviews of medication adherence interventions.[47,65,72–83] We complemented our search by including important studies that had been published after the search date of the most recent systematic reviews.[84–96] We incorporated data from robust observational studies when no randomized controlled trial data were available on promising intervention approaches.[97–103] We included interventions that addressed adherence to medications for chronic diseases

because such approaches were viewed as being likely to apply to antihypertensive medications.[104–107]

We summarize effective medication adherence interventions in Table 3. We categorized interventions into 4 broad categories that represent the key active ingredient of the interventions. We provide descriptions of types of interventions within these categories, highlight the strength of evidence for these interventions, and provide examples of studies that demonstrate the benefit of the interventions, particularly if conducted in patients with hypertension. It is important to recall that medication adherence comprises multiple distinct health behaviors (eg, initiating a medication, implementing the medication regimen on a day-to-day basis) amenable to different types of adherence measurement.[11,111] Accordingly, we specify the adherence measurement approach used in our description of these studies.

Given the multitude of reasons for nonadherence and the heterogeneity of reasons underlying nonadherence in individual patients, it is not surprising that the most potent interventions have been intensive, multicomponent interventions that address multiple barriers concurrently.[72] For example, one of the more robust interventions combined clinical pharmacist management with the provision of medications in blister packs for older adults with cardiovascular disease risk factors.[108] This intervention improved not only antihypertensive medication adherence but also BP control. Similarly, Xavier and colleagues[112] randomized patients being discharged from hospital after acute coronary syndrome in India to usual care or a community health worker–based intervention that used unstructured discussions, visual methods, and patient diaries to educate patients on healthy lifestyle and drugs, as well as measures to enhance adherence. They found adherence to evidence-based drugs and healthy lifestyles, as well as improvements in BP, weight, and cholesterol. However, concerns have been raised about the cost-effectiveness and scalability of these more intensive, complex interventions.

There are also examples of simple interventions that patients and clinicians can incorporate into the management of hypertension. Patients can integrate reminder systems into their manner of taking medications. Although a trial of simple reminder pill bottles did not show an improvement in adherence,[87] using electronic pill devices that trigger text message reminders in conjunction with missed doses shows promise for improving adherence.[89] Several studies have evaluated polypills containing antihypertensives and other drugs. For example, Thom et al[110] randomized patients with or at risk of coronary disease to usual care or to 1 of 2 different polypills containing 2 antihypertensives. They found that polypill-treated patients were significantly more likely to report taking their BP medications and had small but significant improvements in BP and low-density lipoprotein cholesterol.[110] However, these studies have generally compared this strategy with usual care in which patients may not have received the component drugs, and thus the benefit of polypills for specifically improving adherence, in contrast with their being used as a population risk reduction strategy, remains to be determined.

Financial incentives, which have modest effects on medication adherence, are well suited to broad implementation. For example, several studies have shown that reducing or eliminating copays for antihypertensive medications has modest benefit in terms of improved medication refill adherence.[93,96] Although the effect of such an intervention may be small for an individual patient, when multiplied across a health system, the potential for population-level impact is substantial. Providing incentives for clinicians to improve medication adherence and disease control has been subject to only limited study. Asch et al[113] randomized patients with elevated cholesterol to a patient incentive, a physician incentive, or a shared incentive and found that only the shared incentive improved low-density lipoprotein cholesterol and adherence to a greater extent than control.

Some adherence interventions may not be particularly effective at reducing nonadherence but may be recommended because they have collateral benefits that lead to improved BP control. Notably, a systematic review demonstrated that encouraging self-monitoring of BP, a method that provides patients with direct feedback on the outcome of their medication-taking behavior, may have a modest impact on improved medication adherence.[80] Self-monitoring of BP, if done with support, also has the potential to reduce clinical inertia and has been shown to improve BP.[114] Similarly, giving clinicians objective feedback on their patient's level of adherence, although having indeterminate effects on medication adherence, may be useful for reducing clinical inertia with respect to uptitrating medications and hence might be an important strategy that clinicians and health systems can recommend.[115] In particular, therapeutic drug monitoring, in which levels of antihypertensive medication are assessed in urine or blood in advance of clinical visits, is a promising approach for improving medication adherence in patients with resistant hypertension.[28,44]

In Table 4, we highlight evidence-based interventions that key stakeholders (ie, patients and their partners, clinicians, pharmacies, health systems, and policymakers) can implement to optimize antihypertensive medication adherence. We organize these interventions according to the perspective of the stakeholder who would be responsible for implementing the intervention. For example, patients or their family members can address nonadherence by using special medication packaging that organizes pills (blister packaging) and reminds patients (smart pill bottles) to take their antihypertensive pills daily. Clinicians can incorporate motivational interviewing or other evidence-based counseling strategies into their practice when discussing medication adherence

Table 3. Interventions That Have Been Evaluated for Improving Medication Adherence

Intervention strategy	Description	Evidence synthesis	Example study
Patient education and counseling	Providing patients with information about their medical conditions and treatments or delivering counseling to increase motivation or self-management skills.	Patient education: Many studies have evaluated educational interventions alone or combined with other approaches, including among patients with hypertension. The most effective educational interventions appear to be those that are individualized, repeated, and delivered at the time of new diagnoses.[74] In a systematic review of hypertension adherence interventions, Gwadry-Sridhar and colleagues[65] found that 12 of 25 (40.8%) education-based strategies improved adherence to BP medications.	Nieuwkerk et al[104] evaluated in-person nurse practitioner–led cardiovascular risk factor counseling sessions delivered at months 3, 9, and 18 after statin initiation. They found that the educational intervention led to significantly increased self-reported adherence to statins and larger reductions in LDL cholesterol (between-group difference in change from baseline, −13 mg/dL) than usual care.
		Pharmacist consultation: Numerous studies have tested pharmacist-led counseling interventions either alone or in combination with other adherence interventions such as home BP monitoring or blister packaging. The specific interventions provided by the pharmacists have been quite variable (eg, medication adjustment based on home measurements, education on BP goals) and in some cases have also included behavioral counseling methods such as motivational interviewing. Several but not all of these studies have demonstrated improvements in clinical outcomes.	Lee et al[108] randomized elderly patients prescribed ≥4 medications to resumption of usual care or continuation of pharmacist-delivered individualized patient education (initial session 1 h, subsequent sessions 30 min every 2 mo) and blister packaging. The proportion of pills taken as determined by pill count was significantly greater in the intervention vs control group patients (96% vs 69% across 2 mo; $P<0.001$). There was also a significantly greater reduction in systolic BP among patients receiving the intervention (between-group difference, −6.9 mm Hg; $P=0.04$). Of note, it was not possible to disentangle whether pharmacist counseling or special packaging contributed to the success of this intervention.
		Behavioral counseling: Numerous studies have evaluated techniques such as motivational interviewing alone or in combination with other interventions. The most effective interventions have been delivered by trained counselors and involved multiple sessions.[72,74] Motivational interviewing, as a specific technique, has been associated with a small increase in medication adherence.[75]	Choudhry et al[84] randomized patients with poorly controlled hyperlipidemia, diabetes, and hypertension to usual care or a pharmacist-delivered brief negotiated interviewing intervention (a behavioral interviewing technique related to motivational interviewing) on the basis of which patients may also have been provided with other supportive measures such as text messaging and pillboxes. In intention-to-treat analyses, the intervention significantly increased adherence as assessed by pharmacy claims (between-group difference, 4.7%). The intervention also significantly reduced LDL cholesterol and emergency room visits, although it did not affect overall disease control or BP. Treatment effects were larger in as-treated analyses evaluating only those patients who received behavioral counseling.
Medication regimen management	Simplifying treatment regimens by consolidating doses, using fixed-dose combinations or extended-release formulations, or synchronizing pharmacy pickups	Dose consolidation, fixed-dose combinations, and polypills: Numerous studies measuring adherence with electronic monitors have shown a consistent inverse relationship between the number of daily doses of a single type and drug and adherence.[76] Nine cohort studies have compared fixed-dose combinations with the individual component drugs for patients with hypertension and found consistent improvements in adherence with fixed-dose combinations.[97] Nonstatistically significant drops in BP have been reported.[44] No large-scale high-quality randomized trials have compared the effect of fixed-dose combinations of antihypertensive medications and free-equivalent combinations on medication adherence. Several randomized studies have compared polypill medications made up of combinations of antihypertensive and other cardiovascular medications (eg, aspirin, statins) with the same medications individually and found improvements in adherence.[109] Several studies have also compared the provision of polypills with usual care and found improvements in cardiovascular risk.[85,86,110] These studies, however, cannot distinguish whether benefits were the result of greater adherence to or increased prescribing of recommended cardiovascular medications (ie, reduced clinical inertia).	Hsu et al[98] conducted a large retrospective cohort analysis and found that patients starting fixed-dose combinations of angiotensin receptor blockers and thiazides were significantly more adherent after starting therapy compared with patients using the individual components of these medications as assessed with insurance claims data (between-group difference, 6% at 1 y and 10% at 2 y after treatment initiation). Gerbino and Shoheiber[99] conducted a retrospective analysis (N=6206) comparing refill adherence in patients initiated on amlodipine+benazepril fixed-dose combination vs dihydropyridine CCB+ACE inhibitor as separate medications. The 1-y medication possession ratio for the fixed-dose combination was 88% vs 69% for free separate medications ($P<0.001$). Data were not adjusted for demographics or comorbidities.
		Medication refill synchronization: Several observational studies have evaluated medication synchronization programs in which patients pick up all of their medications at a single visit.[100] Compared with usual practice in which patients may make multiple separate visits to fill these medications, medication synchronization significantly improves refill adherence.[101,102] The programs appear most effective in those with lower baseline rates of adherence with an improvement of ≈10% over the improvement noted in control subjects.	Krumme et al[103] conducted a retrospective cohort study of patients filling cardiovascular medication at retail pharmacies offering medication synchronization and found that this intervention significantly improved refill adherence (proportion of days covered) as assessed with insurance claims data (between-group difference, 3%), and significantly reduced rates of hospitalization/emergency department visits and outpatient visits by 9% and 3%, respectively.

(*Continued*)

Table 3. Continued

Intervention strategy	Description	Evidence synthesis	Example study
Reminders, monitoring, and feedback	Techniques intended to remind patients to take or fill their medications or to provide feedback about their patterns of adherence or BP control	Telephone or mail refill reminders: Numerous studies have evaluated reminders, sometimes combined with education and other forms of support. These studies have had mixed effects when reminders were used as standalone interventions. Refill reminders appear most effective when targeted at nonadherent patients.	Derose et al[105] randomized patients newly prescribed a statin to usual care or automated phone calls with a follow-up letter if needed and found that patients receiving pickup reminders were significantly more likely to initiate their prescribed medication (42% vs 26%; $P<0.001$) as assessed from pharmacy dispensation records. The differences in statin dispensing persisted up to 1 y after treatment initiation.
		Text messaging reminders: A recently published meta-analysis of 16 randomized trials of patients with a broad range of clinical conditions, including 1 study in patients with uncontrolled hypertension, found that text messages resulted in a moderately large improvement in medication adherence. Adherence was generally assessed by self-report.[77] The text message content was primarily medication reminders, but some studies also included educational informational or nonmedical content to improve engagement.	Bobrow et al[88] randomized patients on treatment for hypertension to 1 of 2 texting strategies or usual care and found that BP at 12 mo was significantly lower in patients receiving informational text messages (between-group difference, 2 mm Hg) but not in those receiving interactive text messages. Medication adherence was significantly higher than usual care for both texting arms (between-group difference, 5%).
		Electronic monitoring and feedback: Numerous randomized studies have evaluated the impact of electronic drug monitors and have demonstrated mixed effects. According to a recent systematic review, "Devices that are integrated into the care delivery system and that are designed to record dosing events are most frequently associated with improved adherence."[78] In addition, electronic drug monitors appear effective when combined with reminder messages for patients who have missed doses. In contrast, lower-cost, nonelectronic reminder devices (eg, bottle caps with digital times, toggle strips to indicate when medications have been taken, and standard pillboxes) appear not to be effective as standalone interventions.[87]	Reese et al[89] randomized kidney transplant recipients to wireless pill bottle adherence monitoring with customized reminders (including alarms, texts, telephone calls, or emails) plus clinician notification, wireless pill bottle monitoring with customized reminders, or wireless pill bottle use alone (control arm). Patients in both intervention arms had significantly higher adherence than control subjects (88% for customized reminders plus clinician notifications vs 78% for customized reminders vs 55% for control) as assessed by the electronic drug monitors over a 90-d period beginning 90 d after transplantation.
		Smartphone apps: More than a dozen randomized trials have evaluated various smartphone applications that can provide reminders, education, linkage to peer support, and motivational messages for improving adherence. Although many of these studies have found statistically significant improvements in adherence and some have demonstrated improvements in clinical outcomes, the quality of the underlying data is highly variable; thus, it is not possible to draw robust conclusions about the effectiveness of these interventions.[79]	Morawski et al[94] randomized patients with poorly controlled hypertension to usual care or a smartphone app that provided reminder alerts, adherence reports, and optional peer support and found that patients receiving the intervention had improved self-reported adherence 12 wk after randomization (between-group difference, 0.4 on the Morisky Medication Adherence Scale), but the intervention did not affect BP control
		SMBP: Numerous trials have evaluated the impact of SMBP on medication adherence and found small but significant improvements in medication adherence and improved BP control, primarily in studies that incorporated electronic adherence measurement.[80] In a systematic review, SMBP interventions that resulted in improved medication adherence were not associated with better BP control.	Márquez-Contreras and colleagues[95] randomized patients to receipt of home BP devices plus electronic pill bottles that tracked adherence vs electronic pill bottles alone. Patients in the SMBP group had higher electronic adherence than control (89% vs 84% d monitored; $P<0.001$). Hosseininasab and colleagues[96] randomized patients with hypertension to usual care or a wrist self-monitoring device and found that patients randomized to SMBP had significantly higher medication adherence assessed by pill counts (between-group difference, 1%–2%, depending on time point assessed), although adherence rates in both treatment groups were extremely high (>95%) and there was no between-group difference in BP.
Incentives	Reducing or eliminating out-of-pocket costs for patients or providing financial incentives for patients or clinicians for achieving chronic disease management goals. Incentives can be delivered through lotteries.	Patient out-of-pocket costs and financial incentives: Eliminating or reducing copays has consistently been shown to result in small improvements in adherence to medications.[73] Notably, such interventions have the potential to reduce disparities in adherence and clinical outcomes among patients with lower incomes and patients from underrepresented populations.[107] These improvements in adherence, however, have not been clearly associated with improved clinical outcomes. In contrast, providing financial incentives for adherence through lotteries or other approaches has not consistently been shown to improve medication adherence when used alone or when combined with other adherence interventions.[90,91]	Choudhry et al[106] randomized patients discharged from hospital after acute coronary syndrome to usual insurance coverage or no out-of-pocket costs for secondary prevention medications and found improvements in adherence as assessed by pharmacy claims data a mean of ≈1 y after initial hospital discharge (between-group difference, 4%–6%) and significant reductions in rates of first major vascular events (between-group difference, 1.8%), although the intervention did not significantly reduce the primary clinical outcome (a composite outcome of first major adverse coronary events or revascularization).

ACE indicates angiotensin-converting enzyme; app, application; BP, blood pressure; CCB, calcium channel blocker; LDL, low-density lipoprotein; and SMBP, self-monitoring of blood pressure.

*If no high-quality hypertension studies could be identified, example studies were drawn from interventions of other medication classes

Table 4. Strategies for Improving Antihypertensive Medication Adherence Categorized by Key Stakeholder

	Stakeholder			
Intervention strategy	Patient	Clinician network	Pharmacy	Health insurer
Patient education		X	X	X
Pharmacist consultation		X	X	X
Motivational interviewing		X	X	X
Dose consolidation		X		
Refill reminders			X	X
Text message reminders	X	X	X	X
Electronic monitoring and feedback	X	X	X	
Medication refill synchronization			X	X
SMBP	X	X		X
Patient financial incentives		X		X

SMBP indicates self-monitoring of blood pressure.

with their patients. They can also incorporate electronic monitoring and self-monitoring of BP into their practice. Pharmacies can partner with clinicians to assist with regimen simplification or provide educational and behavioral counseling. Pharmacists can also encourage initiation of and persistence with medication fills by providing patients with reminders and synchronizing medication refill dates. Policymakers can eliminate or reduce copays for antihypertensive medications or can promote reimbursement models that make it financially sustainable to deliver complex adherence interventions. These approaches may be cost-effective from a health system perspective.

CONCLUSIONS

To achieve maximum impact on population health, antihypertensive pharmacotherapy must be initiated in large numbers of people who then need to keep taking their medications, often for the rest of their lives. It is encouraging that so many patients treated for hypertension do so and have controlled their hypertension. However, improvement is needed if we are to achieve the full population health benefits of BP control. Clinicians, especially those who focus their practice on hypertension, often encounter patients who seemingly have uncontrolled resistant hypertension despite being prescribed multiple antihypertensives. Many such patients have significant issues with adherence that are not identified until drug level testing or other thorough evaluations of adherence. This review outlines interventions at the patient, clinician, pharmacy, and health system levels that have been shown to have at least some benefit in improving adherence in these patients. In addition to a wider dissemination of current evidence-based strategies, a broader set of effective interventions is clearly still needed.

To further improve adherence and adherence research, we must fully appreciate some of the often-noted limits on the very construct of adherence. A concept that focuses primarily on whether the patient does what they are advised to do by a health professional is incomplete.[116] Clinician and patient behaviors relevant to adherence must be viewed within the broader context of society and the health care system. Contributors such as the nature and structure of our health insurance system, cost, access, and literacy, among many others, are all relevant to medication taking. Furthermore, the contribution of these factors may differ according to where individuals are in the course in treatment. For example, issues with initiation, implementation, and persistence with treatment over the first year may differ from those associated with long-term maintenance.

We must also recognize the limits of targeting all BP control efforts at patient nonadherence. For example, we cannot assume that if one health care professional prescribes an antihypertensive, another will be enthusiastic about continuing it. As a result, what we measure as nonpersistence may in some cases reflect the decision by a new health care professional to discontinue medications or to not restart them after a lapse. Differences in clinician behavior may be an important factor in hypertension control. In the past, clinician perceptions of the BP level required for treatment were highly variable and often different from published guidelines.[117] These differences in clinician treatment thresholds may be even more important in the future. Organizations such as American College of Physicians, American Academy of Family Physicians, and European guidelines have higher thresholds for drug treatment than the American Heart Association.[118] Both patients and clinicians may decide against drug treatment, in some cases out of confusion, because some guidelines classify more people as hypertensive yet have categories of people with hypertension who do not require drug treatment.

Although past efforts aimed at improving adherence may have been disappointing, there is reason for

optimism.[20] Recent interventions that target individuals who are documented to be nonadherent seem to be effective.[119] It is likely that evidence on effective adherence interventions has been obscured by study designs that enrolled patients exclusively on the basis of elevated BP, including those on a suboptimal regimen. Accurately determining baseline adherence with established and evolving measurement techniques will likely be valuable in research and practice. Tailoring the intervention to the barrier is also likely to be critical to successful adherence interventions. Other recent studies that appreciate the broad social factors underlying nonadherence and the dynamic nature of adherence in their interventions also bode well for the discovery of successful antihypertensive adherence interventions.

ARTICLE INFORMATION

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

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*Modest.

†Significant.

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*Significant.

REFERENCES

1. Centers for Disease Control and Prevention. Facts about hypertension. Accessed November 9, 2020. https://www.cdc.gov/bloodpressure/facts.htm
2. Mensah GA, Wei GS, Sorlie PD, Fine LJ, Rosenberg Y, Kaufmann PG, Mussolino ME, Hsu LL, Addou E, Engelgau MM, et al. Decline in cardiovascular mortality: possible causes and implications. *Circ Res*. 2017;120:366–380. doi: 10.1161/CIRCRESAHA.116.309115
3. Muntner P, Hardy ST, Fine LJ, Jaeger BC, Wozniak G, Levitan EB, Colantonio LD. Trends in blood pressure control among US adults with hypertension, 1999–2000 to 2017–2018. *JAMA*. 2020;324:1–12. doi: 10.1001/jama.2020.14545
4. Egan BM, Li J, Hutchison FN, Ferdinand KC. Hypertension in the United States, 1999 to 2012: progress toward Healthy People 2020 goals. *Circulation*. 2014;130:1692–1699. doi: 10.1161/CIRCULATIONAHA.114.010676
5. World Health Organization. Adherence to long-term therapies: evidence for action, section 1: setting the scene. Accessed January 17, 2020. https://www.who.int/chp/knowledge/publications/adherence_full_report.pdf
6. Centers for Disease Control and Prevention. Vital signs: awareness and treatment of uncontrolled hypertension among adults–United States, 2003–2010. *MMWR Morb Mortal Wkly Rep*. 2012;61:703–709.
7. Lauffenburger JC, Choudhry NK. A call for a systems-thinking approach to medication adherence: stop blaming the patient. *JAMA Intern Med*. 2018;178:950–951. doi: 10.1001/jamainternmed.2018.0790
8. Rose AJ, Berlowitz DR, Orner MB, Kressin NR. Understanding uncontrolled hypertension: is it the patient or the provider? *J Clin Hypertens (Greenwich)*. 2007;9:937–943. doi: 10.1111/j.1524-6175.2007.07332.x
9. Bellows BK, Ruiz-Negrón N, Bibbins-Domingo K, King JB, Pletcher MJ, Moran AE, Fontil V. Clinic-based strategies to reach United States Million Hearts 2022 blood pressure control goals. *Circ Cardiovasc Qual Outcomes*. 2019;12:e005624. doi: 10.1161/CIRCOUTCOMES.118.005624
10. Daugherty SL, Powers JD, Magid DJ, Masoudi FA, Margolis KL, O'Connor PJ, Schmittdiel JA, Ho PM. The association between medication adherence and treatment intensification with blood pressure control in resistant hypertension. *Hypertension*. 2012;60:303–309. doi: 10.1161/HYPERTENSIONAHA.112.192096
11. Kronish IM, Thorpe CT, Voils CI. Measuring the multiple domains of medication nonadherence: findings from a Delphi survey of adherence experts. *Transl Behav Med*. 2021;11:104–113. doi: 10.1093/tbm/ibz133
12. Vrijens B, De Geest S, Hughes DA, Przemyslaw K, Demonceau J, Ruppar T, Dobbels F, Fargher E, Morrison V, Lewek P, et al; ABC Project Team. A new taxonomy for describing and defining adherence to medications. *Br J Clin Pharmacol*. 2012;73:691–705. doi: 10.1111/j.1365-2125.2012.04167.x
13. Lemstra M, Nwankwo C, Bird Y, Moraros J. Primary nonadherence to chronic disease medications: a meta-analysis. *Patient Prefer Adherence*. 2018;12:721–731. doi: 10.2147/PPA.S161151
14. Adams AS, Uratsu C, Dyer W, Magid D, O'Connor P, Beck A, Butler M, Ho PM, Schmittdiel JA. Health system factors and antihypertensive adherence in a racially and ethnically diverse cohort of new users. *JAMA Intern Med*. 2013;173:54–61. doi: 10.1001/2013.jamainternmed.955
15. Bloom BS. Continuation of initial antihypertensive medication after 1 year of therapy. *Clin Ther*. 1998;20:671–681. doi: 10.1016/s0149-2918(98)80130-6
16. Elliott WJ, Plauschinat CA, Skrepnek GH, Gause D. Persistence, adherence, and risk of discontinuation associated with commonly prescribed antihypertensive drug monotherapies. *J Am Board Fam Med*. 2007;20:72–80. doi: 10.3122/jabfm.2007.01.060094
17. Lauffenburger JC, Landon JE, Fischer MA. Effect of combination therapy on adherence among US patients initiating therapy for hypertension: a cohort study. *J Gen Intern Med*. 2017;32:619–625. doi: 10.1007/s11606-016-3972-z
18. Monane M, Bohn RL, Gurwitz JH, Glynn RJ, Levin R, Avorn J. The effects of initial drug choice and comorbidity on antihypertensive therapy compliance: results from a population-based study in the elderly. *Am J Hypertens*. 1997;10(pt 1):697–704. doi: 10.1016/s0895-7061(97)00056-3
19. Tajeu GS, Kent ST, Huang L, Bress AP, Cuffee Y, Halpern MT, Kronish IM, Krousel-Wood M, Mefford MT, Shimbo D, et al. Antihypertensive medication nonpersistence and low adherence for adults <65 years initiating treatment in 2007-2014. *Hypertension*. 2019;74:35–46. doi: 10.1161/HYPERTENSIONAHA.118.12495
20. Tajeu GS, Kent ST, Kronish IM, Huang L, Krousel-Wood M, Bress AP, Shimbo D, Muntner P. Trends in antihypertensive medication discontinuation and low adherence among Medicare beneficiaries initiating treatment from 2007 to 2012. *Hypertension*. 2016;68:565–575. doi: 10.1161/HYPERTENSIONAHA.116.07720
21. van Wijk BL, Shrank WH, Klungel OH, Schneeweiss S, Brookhart MA, Avorn J. A cross-national study of the persistence of antihypertensive medication use in the elderly. *J Hypertens*. 2008;26:145–153. doi: 10.1097/HJH.0b013e32826308b4
22. Bramley TJ, Gerbino PP, Nightengale BS, Frech-Tamas F. Relationship of blood pressure control to adherence with antihypertensive monotherapy in 13 managed care organizations. *J Manag Care Pharm*. 2006;12:239–245. doi: 10.18553/jmcp.2006.12.3.239
23. Briesacher BA, Andrade SE, Fouayzi H, Chan KA. Comparison of drug adherence rates among patients with seven different medical conditions. *Pharmacotherapy*. 2008;28:437–443. doi: 10.1592/phco.28.4.437
24. Meddings J, Kerr EA, Heisler M, Hofer TP. Physician assessments of medication adherence and decisions to intensify medications for patients with uncontrolled blood pressure: still no better than a coin toss. *BMC Health Serv Res*. 2012;12:270. doi: 10.1186/1472-6963-12-270
25. Siegel D, Lopez J, Meier J. Antihypertensive medication adherence in the Department of Veterans Affairs. *Am J Med*. 2007;120:26–32. doi: 10.1016/j.amjmed.2006.06.028
26. Bundy JD, Li C, Stuchlik P, Bu X, Kelly TN, Mills KT, He H, Chen J, Whelton PK, He J. Systolic blood pressure reduction and risk of cardiovascular disease and mortality: a systematic review and network meta-analysis. *JAMA Cardiol*. 2017;2:775–781. doi: 10.1001/jamacardio.2017.1421
27. Zeller A, Ramseier E, Teagtmeyer A, Battegay E. Patients' self-reported adherence to cardiovascular medication using electronic monitors as comparators. *Hypertens Res*. 2008;31:2037–2043. doi: 10.1291/hypres.31.2037

28. Brinker S, Pandey A, Ayers C, Price A, Raheja P, Arbique D, Das SR, Halm EA, Kaplan NM, Vongpatanasin W. Therapeutic drug monitoring facilitates blood pressure control in resistant hypertension. *J Am Coll Cardiol*. 2014;63:834–835. doi: 10.1016/j.jacc.2013.10.067
29. McNaughton CD, Brown NJ, Rothman RL, Liu D, Kabagambe EK, Levy PD, Self WH, Storrow AB, Collins SP, Roumie CL. Systolic blood pressure and biochemical assessment of adherence: a cross-sectional analysis in the emergency department. *Hypertension*. 2017;70:307–314. doi: 10.1161/HYPERTENSIONAHA.117.09659
30. Christensen A, Osterberg LG, Hansen EH. Electronic monitoring of patient adherence to oral antihypertensive medical treatment: a systematic review. *J Hypertens*. 2009;27:1540–1551. doi: 10.1097/HJH.0b013e32832d50ef
31. Diaz E, Levine HB, Sullivan MC, Sernyak MJ, Hawkins KA, Cramer JA, Woods SW. Use of the Medication Event Monitoring System to estimate medication compliance in patients with schizophrenia. *J Psychiatry Neurosci*. 2001;26:325–329.
32. Levin JB, Sams J, Tatsuoka C, Cassidy KA, Sajatovic M. Use of automated medication adherence monitoring in bipolar disorder research: pitfalls, pragmatics, and possibilities. *Ther Adv Psychopharmacol*. 2015;5:76–87. doi: 10.1177/2045125314566807
33. De Bleser L, De Geest S, Vandenbroeck S, Vanhaecke J, Dobbels F. How accurate are electronic monitoring devices? A laboratory study testing two devices to measure medication adherence. *Sensors (Basel)*. 2010;10:1652–1660. doi: 10.3390/s100301652
34. Pladevall M, Brotons C, Gabriel R, Arnau A, Suarez C, de la Figuera M, Marquez E, Coca A, Sobrino J, Divine G, et al; Writing Committee on behalf of the COM99 Study Group. Multicenter cluster-randomized trial of a multifactorial intervention to improve antihypertensive medication adherence and blood pressure control among patients at high cardiovascular risk (the COM99 study). *Circulation*. 2010;122:1183–1191. doi: 10.1161/CIRCULATIONAHA.109.892778
35. Farmer KC. Methods for measuring and monitoring medication regimen adherence in clinical trials and clinical practice. *Clin Ther*. 1999;21:1074–1090. doi: 10.1016/S0149-2918(99)80026-5
36. Jung O, Gechter JL, Wunder C, Paulke A, Bartel C, Geiger H, Toennes SW. Resistant hypertension? Assessment of adherence by toxicological urine analysis. *J Hypertens*. 2013;31:766–774. doi: 10.1097/HJH.0b013e32835e2286
37. Pandey A, Raza F, Velasco A, Brinker S, Ayers C, Das SR, Morisky DE, Halm EA, Vongpatanasin W. Comparison of Morisky Medication Adherence Scale with therapeutic drug monitoring in apparent treatment-resistant hypertension. *J Am Soc Hypertens*. 2015;9:420–426.e2. doi: 10.1016/j.jash.2015.04.004
38. Tomaszewski M, White C, Patel P, Masca N, Damani R, Hepworth J, Samani NJ, Gupta P, Madira W, Stanley A, et al. High rates of non-adherence to antihypertensive treatment revealed by high-performance liquid chromatography-tandem mass spectrometry (HP LC-MS/MS) urine analysis. *Heart*. 2014;100:855–861. doi: 10.1136/heartjnl-2013-305063
39. Pullar T, Kumar S, Tindall H, Feely M. Time to stop counting the tablets? *Clin Pharmacol Ther*. 1989;46:163–168. doi: 10.1038/clpt.1989.121
40. Fischer MA, Choudhry NK, Brill G, Avorn J, Schneeweiss S, Hutchins D, Liberman JN, Brennan TA, Shrank WH. Trouble getting started: predictors of primary medication nonadherence. *Am J Med*. 2011;124:1081.e9–1081.22. doi: 10.1016/j.amjmed.2011.05.028
41. Choudhry NK, Glynn RJ, Avorn J, Lee JL, Brennan TA, Reisman L, Toscano M, Levin R, Matlin OS, Antman EM, et al. Untangling the relationship between medication adherence and post-myocardial infarction outcomes: medication adherence and clinical outcomes. *Am Heart J*. 2014;167:51–58.e5. doi: 10.1016/j.ahj.2013.09.014
42. Schmittdiel JA, Nichols GA, Dyer W, Steiner JF, Karter AJ, Raebel MA. Health care system-level factors associated with performance on Medicare STAR adherence metrics in a large, integrated delivery system. *Med Care*. 2015;53:332–337. doi: 10.1097/MLR.0000000000000328
43. Azizi M, Pereira H, Hamdidouche I, Gosse P, Monge M, Bobrie G, Delsart P, Mounier-Véhier C, Courand PY, Lantelme P, et al; DENERHTN Investigators. Adherence to antihypertensive treatment and the blood pressure-lowering effects of renal denervation in the Renal Denervation for Hypertension (DENERHTN) Trial. *Circulation*. 2016;134:847–857. doi: 10.1161/CIRCULATIONAHA.116.022922
44. Gupta P, Patel P, Štrauch B, Lai FY, Akbarov A, Gulsin GS, Beech A, Marešová V, Topham PS, Stanley A, et al. Biochemical screening for nonadherence is associated with blood pressure reduction and improvement in adherence. *Hypertension*. 2017;70:1042–1048. doi: 10.1161/HYPERTENSIONAHA.117.09631
45. Sutherland JJ, Morrison RD, McNaughton CD, Daly TM, Milne SB, Daniels JS, Ryan TP. Assessment of patient medication adherence, medical record accuracy, and medication blood concentrations for prescription and over-the-counter medications. *JAMA Netw Open*. 2018;1:e184196. doi: 10.1001/jamanetworkopen.2018.4196
46. American College of Preventive Medicine. Medical adherence— improving health outcomes: a resource from the American College of Preventive Medicine. Accessed March 1, 2021. https://ogg.osu.edu/media/documents/agingconnections/MedicationAdherenceTool_syndromes-screenings.pdf
47. Ferdinand KC, Senatore FF, Clayton-Jeter H, Cryer DR, Lewin JC, Nasser SA, Fiuzat M, Califf RM. Improving medication adherence in cardiometabolic disease: practical and regulatory implications. *J Am Coll Cardiol*. 2017;69:437–451. doi: 10.1016/j.jacc.2016.11.034
48. Burnier M. Drug adherence in hypertension. *Pharmacol Res*. 2017;125(pt B):142–149. doi: 10.1016/j.phrs.2017.08.015
49. Gellad WF, Grenard JL, Marcum ZA. A systematic review of barriers to medication adherence in the elderly: looking beyond cost and regimen complexity. *Am J Geriatr Pharmacother*. 2011;9:11–23. doi: 10.1016/j.amjopharm.2011.02.004
50. Hill MN, Miller NH, Degeest S, Materson BJ, Black HR, Izzo JL Jr, Oparil S, Weber MA; American Society of Hypertension Writing Group. Adherence and persistence with taking medication to control high blood pressure. *J Am Soc Hypertens*. 2011;5:56–63. doi: 10.1016/j.jash.2011.01.001
51. Osterberg L, Blaschke T. Adherence to medication. *N Engl J Med*. 2005;353:487–497. doi: 10.1056/NEJMra050100
52. Zhang NJ, Terry A, McHorney CA. Impact of health literacy on medication adherence: a systematic review and meta-analysis. *Ann Pharmacother*. 2014;48:741–751. doi: 10.1177/1060028014526562
53. Arbuckle C, Tomaszewski D, Brown L, Schommer J, Morisky D, Parlett-Pelleriti C, Linstead E. Exploring the relationship of digital information sources and medication adherence. *Comput Biol Med*. 2019;109:303–310. doi: 10.1016/j.compbiomed.2019.04.023
54. Ryan D, Carr A. A study of the differential effects of Tomm's questioning styles on therapeutic alliance. *Fam Process*. 2001;40:67–77. doi: 10.1111/j.1545-5300.2001.4010100067.x
55. Schoenthaler A, Chaplin WF, Allegrante JP, Fernandez S, Diaz-Gloster M, Tobin JN, Ogedegbe G. Provider communication effects medication adherence in hypertensive African Americans. *Patient Educ Couns*. 2009;75:185–191. doi: 10.1016/j.pec.2008.09.018
56. Roumie CL, Greevy R, Wallston KA, Elasy TA, Kaltenbach L, Kotter K, Dittus RS, Speroff T. Patient centered primary care is associated with patient hypertension medication adherence. *J Behav Med*. 2011;34:244–253. doi: 10.1007/s10865-010-9304-6
57. Proia KK, Thota AB, Njie GJ, Finnie RK, Hopkins DP, Mukhtar Q, Pronk NP, Zeigler D, Kottke TE, Rask KJ, et al; Community Preventive Services Task Force. Team-based care and improved blood pressure control: a community guide systematic review. *Am J Prev Med*. 2014;47:86–99. doi: 10.1016/j.amepre.2014.03.004
58. Steiner JF, Ho PM, Beaty BL, Dickinson LM, Hanratty R, Zeng C, Tavel HM, Havranek EP, Davidson AJ, Magid DJ, et al. Sociodemographic and clinical characteristics are not clinically useful predictors of refill adherence in patients with hypertension. *Circ Cardiovasc Qual Outcomes*. 2009;2:451–457. doi: 10.1161/CIRCOUTCOMES.108.841635
59. Egan BM, Li J, Sarasua SM, Davis RA, Fiscella KA, Tobin JN, Jones DW, Sinopoli A. Cholesterol control among uninsured adults did not improve from 2001–2004 to 2009–2012 as disparities with both publicly and privately insured adults doubled. *J Am Heart Assoc*. 2017;6:e006105. doi: 10.1161/JAHA.117.006105
60. Eze-Nliam CM, Thombs BD, Lima BB, Smith CG, Ziegelstein RC. The association of depression with adherence to antihypertensive medications: a systematic review. *J Hypertens*. 2010;28:1785–1795. doi: 10.1097/HJH.0b013e32833b4a6f
61. Mulhem E, Lick D, Varughese J, Barton E, Ripley T, Haveman J. Adherence to medications after hospital discharge in the elderly. *Int J Family Med*. 2013;2013:901845. doi: 10.1155/2013/901845
62. Holt EW, Muntner P, Joyce CJ, Webber L, Krousel-Wood MA. Health-related quality of life and antihypertensive medication adherence among older adults. *Age Ageing*. 2010;39:481–487. doi: 10.1093/ageing/afq040
63. Gupta P, Patel P, Štrauch B, Lai FY, Akbarov A, Marešová V, White CMJ, Petrák O, Gulsin GS, Patel V, et al. Risk factors for nonadherence to antihypertensive treatment. *Hypertension*. 2017;69:1113–1120. doi: 10.1161/HYPERTENSIONAHA.116.08729
64. Miller NH. Compliance with treatment regimens in chronic asymptomatic diseases. *Am J Med*. 1997;102:43–49. doi: 10.1016/s0002-9343(97)00467-1

65. Gwadry-Sridhar FH, Manias E, Lal L, Salas M, Hughes DA, Ratzki-Leewing A, Grubisic M. Impact of interventions on medication adherence and blood pressure control in patients with essential hypertension: a systematic review by the ISPOR Medication Adherence and Persistence Special Interest Group. *Value Health*. 2013;16:863–871. doi: 10.1016/j.jval.2013.03.1631
66. Bokhour BG, Kressin NR. What is in a name? How biomedical language may derail patient understanding of hypertension. *Circ Cardiovasc Qual Outcomes*. 2015;8:452–454. doi: 10.1161/CIRCOUTCOMES.114.001662
67. Morrison VL, Holmes EA, Parveen S, Plumpton CO, Clyne W, De Geest S, Dobbels F, Vrijens B, Kardas P, Hughes DA. Predictors of self-reported adherence to antihypertensive medicines: a multinational, cross-sectional survey. *Value Health*. 2015;18:206–216. doi: 10.1016/j.jval.2014.12.013
68. Cuffee YL, Hargraves JL, Rosal M, Briesacher BA, Schoenthaler A, Person S, Hullett S, Allison J. Reported racial discrimination, trust in physicians, and medication adherence among inner-city African Americans with hypertension. *Am J Public Health*. 2013;103:e55–e62. doi: 10.2105/AJPH.2013.301554
69. Brown CM, Segal R. The effects of health and treatment perceptions on the use of prescribed medication and home remedies among African American and White American hypertensives. *Soc Sci Med*. 1996;43:903–917. doi: 10.1016/0277-9536(95)00434-3
70. Krousel-Wood MA, Muntner P, Joyce CJ, Islam T, Stanley E, Holt EW, Morisky DE, He J, Webber LS. Adverse effects of complementary and alternative medicine on antihypertensive medication adherence: findings from the Cohort Study of Medication Adherence Among Older Adults. *J Am Geriatr Soc*. 2010;58:54–61. doi: 10.1111/j.1532-5415.2009.02639.x
71. Axon RN, Bradford WD, Egan BM. The role of individual time preferences in health behaviors among hypertensive adults: a pilot study. *J Am Soc Hypertens*. 2009;3:35–41. doi: 10.1016/j.jash.2008.08.005
72. Nieuwlaat R, Wilczynski N, Navarro T, Hobson N, Jeffery R, Keepanasseril A, Agoritsas T, Mistry N, Iorio A, Jack S, et al. Interventions for enhancing medication adherence. *Cochrane Database Syst Rev*. 2014:CD000011. doi: 10.1002/14651858.CD000011.pub4
73. Viswanathan M, Golin CE, Jones CD, Ashok M, Blalock SJ, Wines RC, Coker-Schwimmer EJ, Rosen DL, Sista P, Lohr KN. Interventions to improve adherence to self-administered medications for chronic diseases in the United States: a systematic review. *Ann Intern Med*. 2012;157:785–795. doi: 10.7326/0003-4819-157-11-201212040-00538
74. Kini V, Ho PM. Interventions to improve medication adherence: a review. *JAMA*. 2018;320:2461–2473. doi: 10.1001/jama.2018.19271
75. Palacio A, Garay D, Langer B, Taylor J, Wood BA, Tamariz L. Motivational interviewing improves medication adherence: a systematic review and meta-analysis. *J Gen Intern Med*. 2016;31:929–940. doi: 10.1007/s11606-016-3685-3
76. Claxton AJ, Cramer J, Pierce C. A systematic review of the associations between dose regimens and medication compliance. *Clin Ther*. 2001;23:1296–1310. doi: 10.1016/s0149-2918(01)80109-0
77. Thakkar J, Kurup R, Laba TL, Santo K, Thiagalingam A, Rodgers A, Woodward M, Redfern J, Chow CK. Mobile telephone text messaging for medication adherence in chronic disease: a meta-analysis. *JAMA Intern Med*. 2016;176:340–349. doi: 10.1001/jamainternmed.2015.7667
78. Checchi KD, Huybrechts KF, Avorn J, Kesselheim AS. Electronic medication packaging devices and medication adherence: a systematic review. *JAMA*. 2014;312:1237–1247. doi: 10.1001/jama.2014.10059
79. Ng R, Carter SR, El-Den S. The impact of mobile applications on medication adherence: a systematic review. *Transl Behav Med*. 2020;10:1419–1435. doi: 10.1093/tbm/ibz125
80. Fletcher BR, Hartmann-Boyce J, Hinton L, McManus RJ. The effect of self-monitoring of blood pressure on medication adherence and lifestyle factors: a systematic review and meta-analysis. *Am J Hypertens*. 2015;28:1209–1221. doi: 10.1093/ajh/hpv008
81. Burnier M, Egan BM. Adherence in hypertension. *Circ Res*. 2019;124:1124–1140. doi: 10.1161/CIRCRESAHA.118.313220
82. Conn VS, Ruppar TM, Chase JA, Enriquez M, Cooper PS. Interventions to improve medication adherence in hypertensive patients: systematic review and meta-analysis. *Curr Hypertens Rep*. 2015;17:94. doi: 10.1007/s11906-015-0606-5
83. Viswanathan M, Kahwati LC, Golin CE, Blalock SJ, Coker-Schwimmer E, Posey R, Lohr KN. Medication therapy management interventions in outpatient settings: a systematic review and meta-analysis. *JAMA Intern Med*. 2015;175:76–87. doi: 10.1001/jamainternmed.2014.5841
84. Choudhry NK, Isaac T, Lauffenburger JC, Gopalakrishnan C, Lee M, Vachon A, Iliadis TL, Hollands W, Elman S, Kraft JM, et al. Effect of a remotely delivered tailored multicomponent approach to enhance medication taking for patients with hyperlipidemia, hypertension, and diabetes: the STIC2IT cluster randomized clinical trial. *JAMA Intern Med*. 2018;178:1182–1189. doi: 10.1001/jamainternmed.2018.3189
85. Muñoz D, Uzoije P, Reynolds C, Miller R, Walkley D, Pappalardo S, Tousey P, Munro H, Gonzales H, Song W, et al. Polypill for cardiovascular disease prevention in an underserved population. *N Engl J Med*. 2019;381:1114–1123. doi: 10.1056/NEJMoa1815359
86. Roshandel G, Khoshnia M, Poustchi H, Hemming K, Kamangar F, Gharavi A, Ostovaneh MR, Nateghi A, Majed M, Navabakhsh B, et al. Effectiveness of polypill for primary and secondary prevention of cardiovascular diseases (PolyIran): a pragmatic, cluster-randomised trial. *Lancet*. 2019;394:672–683. doi: 10.1016/S0140-6736(19)31791-X
87. Choudhry NK, Krumme AA, Ercole PM, Girdish C, Tong AY, Khan NF, Brennan TA, Matlin OS, Shrank WH, Franklin JM. Effect of reminder devices on medication adherence: the REMIND randomized clinical trial. *JAMA Intern Med*. 2017;177:624–631. doi: 10.1001/jamainternmed.2016.9627
88. Bobrow K, Farmer AJ, Springer D, Shanyinde M, Yu LM, Brennan T, Rayner B, Namane M, Steyn K, Tarassenko L, et al. Mobile phone text messages to support treatment adherence in adults with high blood pressure (SMS-Text Adherence Support [StAR]): a single-blind, randomized trial. *Circulation*. 2016;133:592–600. doi: 10.1161/CIRCULATIONAHA.115.017530
89. Reese PP, Bloom RD, Trofe-Clark J, Mussell A, Leidy D, Levsky S, Zhu J, Yang L, Wang W, Troxel A, et al. Automated reminders and physician notification to promote immunosuppression adherence among kidney transplant recipients: a randomized trial. *Am J Kidney Dis*. 2017;69:400–409. doi: 10.1053/j.ajkd.2016.10.017
90. Volpp KG, Troxel AB, Long JA, Ibrahim SA, Appleby D, Smith JO, Jaskowiak J, Helweg-Larsen M, Doshi JA, Kimmel SE. A randomized controlled trial of negative co-payments: the CHORD trial. *Am J Manag Care*. 2015;21:e465–e473.
91. Volpp KG, Troxel AB, Mehta SJ, Norton L, Zhu J, Lim R, Wang W, Marcus N, Terwiesch C, Caldarella K, et al. Effect of electronic reminders, financial incentives, and social support on outcomes after myocardial infarction: the HeartStrong randomized clinical trial. *JAMA Intern Med*. 2017;177:1093–1101. doi: 10.1001/jamainternmed.2017.2449
92. Persaud N, Bedard M, Boozary AS, Glazier RH, Gomes T, Hwang SW, Juni P, Law MR, Mamdani MM, Manns BJ, et al; Carefully Selected and Easily Accessible at No Charge Medicines (CLEAN Meds) Study Team. Effect on treatment adherence of distributing essential medicines at no charge: the CLEAN Meds randomized clinical trial. *JAMA Intern Med*. 2019;180:27–34. doi: 10.1001/jamainternmed.2019.4472
93. Wang X, Chen H, Essien E, Wu J, Serna O, Paranjpe R, Abughosh S. Medication adherence to antihypertensive triple-combination therapy among patients enrolled in a Medicare Advantage plan. *J Manag Care Spec Pharm*. 2019;25:678–686. doi: 10.18553/jmcp.2019.25.6.678
94. Morawski K, Ghazinouri R, Krumme A, Lauffenburger JC, Lu Z, Durfee E, Oley L, Lee J, Mohta N, Haff N, et al. Association of a smartphone application with medication adherence and blood pressure control: the MedISAFE-BP randomized clinical trial. *JAMA Intern Med*. 2018;178:802–809. doi: 10.1001/jamainternmed.2018.0447
95. Márquez-Contreras E, Martell-Claros N, Gil-Guillén V, de la Figuera-Von Wichmann M, Casado-Martínez JJ, Martin-de Pablos JL, Figueras M, Galera J, Serra A; Compliance Group of the Spanish Society of Hypertension (SEE). Efficacy of a home blood pressure monitoring programme on therapeutic compliance in hypertension: the EAPACUM-HTA study. *J Hypertens*. 2006;24:169–175. doi: 10.1097/01.hjh.0000198023.53859.a2
96. Hosseininasab M, Jahangard-Rafsanjani Z, Mohagheghi A, Sarayani A, Rashidian A, Javadi M, Ahmadvand A, Hadjibabaie M, Gholami K. Self-monitoring of blood pressure for improving adherence to antihypertensive medicines and blood pressure control: a randomized controlled trial. *Am J Hypertens*. 2014;27:1339–1345. doi: 10.1093/ajh/hpu062
97. Leeds IL, Canner JK, Gani F, Meyers PM, Haut ER, Efron JE, Johnston FM. Increased healthcare utilization for medical comorbidities prior to surgery improves postoperative outcomes. *Ann Surg*. 2020;271:114–121. doi: 10.1097/SLA.0000000000002851
98. Hsu CI, Hsiao FY, Wu FL, Shen LJ. Adherence and medication utilisation patterns of fixed-dose and free combination of angiotensin receptor blocker/thiazide diuretics among newly diagnosed hypertensive patients: a population-based cohort study. *Int J Clin Pract*. 2015;69:729–737. doi: 10.1111/ijcp.12591
99. Gerbino PP, Shoheiber O. Adherence patterns among patients treated with fixed-dose combination versus separate antihypertensive agents. *Am J Health Syst Pharm*. 2007;64:1279–1283. doi: 10.2146/ajhp060434

100. Krumme AA, Isaman DL, Stolpe SF, Dougherty S, Choudhry NK. Prevalence, effectiveness, and characteristics of pharmacy-based medication synchronization programs. *Am J Manag Care*. 2016;22:179–186.
101. Doshi JA, Lim R, Li P, Young PP, Lawnicki VF, State JJ, Troxel AB, Volpp KG. A synchronized prescription refill program improved medication adherence. *Health Aff (Millwood)*. 2016;35:1504–1512. doi: 10.1377/hlthaff.2015.1456
102. Girdish C, Shrank W, Freytag S, Chen D, Gebhard D, Bunton A, Choudhry N, Polinski J. The impact of a retail prescription synchronization program on medication adherence. *J Am Pharm Assoc (2003)*. 2017;57:579–584.e1. doi: 10.1016/j.japh.2017.05.016
103. Krumme AA, Glynn RJ, Schneeweiss S, Gagne JJ, Dougherty JS, Brill G, Choudhry NK. Medication synchronization programs improve adherence to cardiovascular medications and health care use. *Health Aff (Millwood)*. 2018;37:125–133. doi: 10.1377/hlthaff.2017.0881
104. Nieuwkerk PT, Nierman MC, Vissers MN, Locadia M, Greggers-Peusch P, Knape LP, Kastelein JJ, Sprangers MA, de Haes HC, Stroes ES. Intervention to improve adherence to lipid-lowering medication and lipid-levels in patients with an increased cardiovascular risk. *Am J Cardiol*. 2012;110:666–672. doi: 10.1016/j.amjcard.2012.04.045
105. Derose SF, Green K, Marrett E, Tunceli K, Cheetham TC, Chiu VY, Harrison TN, Reynolds K, Vansomphone SS, Scott RD. Automated outreach to increase primary adherence to cholesterol-lowering medications. *JAMA Intern Med*. 2013;173:38–43. doi: 10.1001/2013.jamainternmed.717
106. Choudhry NK, Avorn J, Glynn RJ, Antman EM, Schneeweiss S, Toscano M, Reisman L, Fernandes J, Spettell C, Lee JL, et al; Post-Myocardial Infarction Free Rx Event and Economic Evaluation (MI FREEE) Trial. Full coverage for preventive medications after myocardial infarction. *N Engl J Med*. 2011;365:2088–2097. doi: 10.1056/NEJMsa1107913
107. Choudhry NK, Bykov K, Shrank WH, Toscano M, Rawlins WS, Reisman L, Brennan TA, Franklin JM. Eliminating medication copayments reduces disparities in cardiovascular care. *Health Aff (Millwood)*. 2014;33:863–870. doi: 10.1377/hlthaff.2013.0654
108. Lee JK, Grace KA, Taylor AJ. Effect of a pharmacy care program on medication adherence and persistence, blood pressure, and low-density lipoprotein cholesterol: a randomized controlled trial. *JAMA*. 2006;296:2563–2571. doi: 10.1001/jama.296.21.joc60162
109. Castellano JM, Sanz G, Peñalvo JL, Bansilal S, Fernández-Ortiz A, Alvarez L, Guzmán L, Linares JC, García F, D'Aniello F, et al. A polypill strategy to improve adherence: results from the FOCUS project. *J Am Coll Cardiol*. 2014;64:2071–2082. doi: 10.1016/j.jacc.2014.08.021
110. Thom S, Poulter N, Field J, Patel A, Prabhakaran D, Stanton A, Grobbee DE, Bots ML, Reddy KS, Cidambi R, et al; UMPIRE Collaborative Group. Effects of a fixed-dose combination strategy on adherence and risk factors in patients with or at high risk of CVD: the UMPIRE randomized clinical trial. *JAMA*. 2013;310:918–929. doi: 10.1001/jama.2013.277064
111. Steiner JF. Rethinking adherence. *Ann Intern Med*. 2012;157:580–585. doi: 10.7326/0003-4819-157-8-201210160-00013
112. Xavier D, Gupta R, Kamath D, Sigamani A, Devereaux PJ, George N, Joshi R, Pogue J, Pais P, Yusuf S. Community health worker-based intervention for adherence to drugs and lifestyle change after acute coronary syndrome: a multicentre, open, randomised controlled trial. *Lancet Diabetes Endocrinol*. 2016;4:244–253. doi: 10.1016/S2213-8587(15)00480-5
113. Asch DA, Troxel AB, Stewart WF, Sequist TD, Jones JB, Hirsch AG, Hoffer K, Zhu J, Wang W, Hodlofski A, et al. Effect of financial incentives to physicians, patients, or both on lipid levels: a randomized clinical trial. *JAMA*. 2015;314:1926–1935. doi: 10.1001/jama.2015.14850
114. Tucker KL, Sheppard JP, Stevens R, Bosworth HB, Bove A, Bray EP, Earle K, George J, Godwin M, Green BB, et al. Self-monitoring of blood pressure in hypertension: a systematic review and individual patient data meta-analysis. *PLoS Med*. 2017;14:e1002389. doi: 10.1371/journal.pmed.1002389
115. Zaugg V, Korb-Savoldelli V, Durieux P, Sabatier B. Providing physicians with feedback on medication adherence for people with chronic diseases taking long-term medication. *Cochrane Database Syst Rev*. 2018;1:CD012042. doi: 10.1002/14651858.CD012042.pub2
116. DiMatteo MR. Social support and patient adherence to medical treatment: a meta-analysis. *Health Psychol*. 2004;23:207–218. doi: 10.1037/0278-6133.23.2.207
117. Hyman DJ, Pavlik VN. Self-reported hypertension treatment practices among primary care physicians: blood pressure thresholds, drug choices, and the role of guidelines and evidence-based medicine. *Arch Intern Med*. 2000;160:2281–2286. doi: 10.1001/archinte.160.15.2281
118. Messerli FH, Bangalore S. The blood pressure landscape: schism among guidelines, confusion among physicians, and anxiety among patients. *J Am Coll Cardiol*. 2018;72:1313–1316. doi: 10.1016/j.jacc.2018.07.026
119. Allemann SS, Nieuwlaat R, Navarro T, Haynes B, Hersberger KE, Arnet I. Congruence between patient characteristics and interventions may partly explain medication adherence intervention effectiveness: an analysis of 190 randomized controlled trials from a Cochrane systematic review. *J Clin Epidemiol*. 2017;91:70–79. doi: 10.1016/j.jclinepi.2017.07.011