

Healthcare Information Technology Interventions to Improve Cardiovascular and Diabetes Medication Adherence

Alexander S. Misono, BA; Sarah L. Cutrona, MD, MPH; Niteesh K. Choudhry, MD, PhD;
 Michael A. Fischer, MD, MS; Margaret R. Stedman, PhD; Joshua N. Liberman, PhD;
 Troyen A. Brennan, MD, JD; Sachin H. Jain, MD, MBA; and William H. Shrank, MD, MSHS

Objective: To determine the efficacy of healthcare information technology (HIT) interventions in improving adherence.

Study Design: Systematic search of randomized controlled trials of HIT interventions to improve medication adherence in cardiovascular disease or diabetes.

Methods: Interventions were classified as 1-way patient reminder systems, 2-way interactive systems, and systems to enhance patient-provider interaction. Studies were subclassified into those with and without real-time provider feedback. Cohen's *d* effect sizes were calculated to assess each intervention's magnitude of effectiveness.

Results: We identified 7190 articles, only 13 of which met inclusion criteria. The majority of included studies (54%, 7 studies) showed a very small ES. The effect size was small in 15%, large in 8%, and was not amenable to calculation in the remainder. Reminder systems were consistently effective, showing the largest effect sizes in this review. Education/counseling HIT systems were less successful, as was the addition of real-time adherence feedback to healthcare providers. Interactive systems were rudimentary and not integrated into electronic health records; they exhibited very small effect sizes. Studies aiming to improve patient-provider communication also had very small effect sizes.

Conclusions: There is a paucity of data about HIT's efficacy in improving adherence to medications for cardiovascular disease and diabetes, although simple patient reminder systems appear effective. Future studies should focus on more sophisticated interactive interventions that expand the functionality and capabilities of HIT and better engage patients in care.

(Am J Manag Care. 2010;16(12 Spec No.):SP82-SP92)

For author information and disclosures, see end of text.

Nonadherence to essential medications is an important public health problem.^{1,2} Patients commonly do not adhere to chronic medication therapy, leading to substantial morbidity, mortality, and excess healthcare costs.³⁻⁶ Despite the significant impact of nonadherence on health, solutions are elusive. Meta-analyses evaluating interventions to improve adherence have consistently supported the use of resource-intensive, multifactorial approaches with multiple elements delivered over time, such as self-management plans, reinforcement, or rewards.^{7,8} In an effort to identify more cost-effective solutions, researchers and clinicians have begun exploring the role of healthcare information technology (HIT) in medication adherence interventions.

There are numerous potential applications for HIT in a medication adherence intervention. Electronic pharmacy data may allow for identification of nonadherence and facilitate data delivery to prescribers and pharmacists.⁹ Electronic systems might inexpensively remind patients and providers about refills. Interactive electronic systems may be used to educate patients about appropriate medication use, and widespread online connectivity should accommodate more sophisticated monitoring, interaction, and communication.

Although rigorous evaluation of the effectiveness of HIT adherence interventions is essential, little systematic assessment has been done to date. We conducted a systematic review of HIT interventions designed to improve medication adherence in cardiovascular disease and diabetes. Our goal was to assess the state of evidence in this field, identify interventions that were successful, and ascertain specific features of interventions that seem to be most associated with success.

METHODS

We performed a systematic search of peer-reviewed journals between 1966 and 2010 using MEDLINE and EMBASE. We limited our search to randomized controlled trials.

Our search terms related to the type of study (ie, randomized controlled trial); adherence (ie, adherence OR compliance OR medication adherence OR treatment adherence); prescription drugs (ie, drug OR medication OR antihypertensive OR antihyperlipidemic OR hypoglycemic); and cardiovascular disease and diabetes (ie, myocardial infarction, coronary heart disease,

In this issue
 Take-Away Points / SP83
www.ajmc.com
 Full text and PDF

heart failure, hypertension, hyperlipidemia, OR diabetes). Articles with at least 1 search term in 3 of the main categories (study type AND adherence AND either drug OR disease) met criteria for review.

Search terms and parameters were adjusted for both databases (MEDLINE and EMBASE) while maintaining a common overall architecture. Search results were then screened for duplicate entries, which were removed.

Study Selection

Studies were included if they reported results of randomized controlled trials studying interventions to improve adherence to medications used for prevention or treatment of diabetes or cardiovascular disease, the greatest source of mortality in the United States.¹⁰ We included only randomized trials in order to promote interventions based on the highest quality of evidence. Studies were limited to adult subjects (aged ≥ 18 years). Of these interventions, we included only interventions with any electronic component. Examples included the identification of patients with electronic tracking of adherence, electronic reminders to take medication, or electronically enhanced communication with patients or providers. Non-English studies were excluded.

Study Classification

After exclusions, 13 articles (Figure) were classified into 2 groups. The first group described the type of interaction with the patient: 1-way patient reminder systems, 2-way interactive systems, or systems to enhance patient–provider interaction. We selected these categories to assess how to best deliver interventions to patients, whether by simple patient reminders, engagement of patients with an electronic system, or enhancement of communication with the provider. Studies of reminder systems featured interventions providing audio and/or visual reminders of medication dosing. Interactive systems included computer-based tools aimed at patient education, counseling, and/or promoting favorable patient behaviors. Systems interacted with patients either immediately or via delayed feedback (eg, customized reading material).

The second group described the type of physician engagement. These types of interventions included those in which no real-time adherence information was passed on to providers and those that incorporated real-time feedback to providers. We included this categorization in an attempt to assess the incremental value of delivering additional feedback to the provider. In a third type of intervention, providers (or in 1 case, research assistants) directly interacted with patients as part of the intervention.

Take-Away Points

We performed a systematic review to assess the efficacy of healthcare information technology (HIT) interventions for improving patients' medication adherence.

- There is a striking paucity of clinical data despite increasing availability of HIT.
- Existing HIT adherence interventions are promising, with simple patient reminder systems providing the best evidence for use.
- The tested interactive systems (eg, education and counseling via interactive computer interface) were rudimentary and showed limited benefit.

Data Extraction

Data were extracted by 3 investigators (ASM, SLC, WHS), with disagreements resolved by consensus. We assessed a number of variables related to the organization and outcome of studies including study design, setting, characteristics of population studied, number of participants, mean age (or age range) of participants, characteristics of the intervention, methods used to measure medication adherence, and medication adherence outcomes. Confidence intervals (CIs) were reported where they were available and *P* values where no CIs were available.

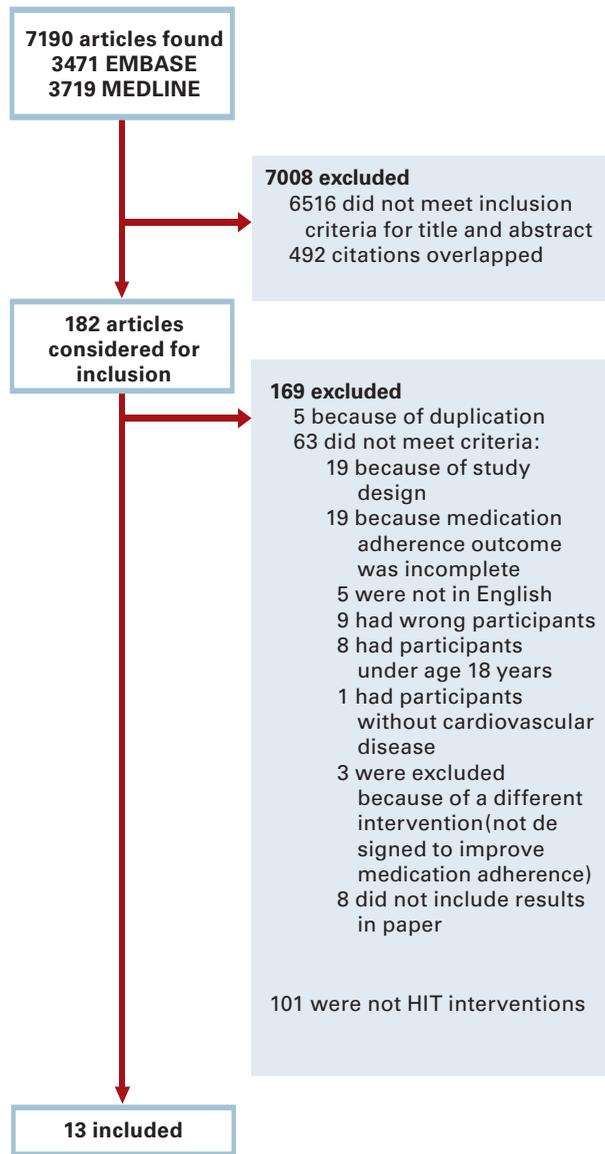
We identified those randomized controlled trials where means and standard deviations for medication adherence outcomes were presented. For these studies, we computed Cohen's *d* effect size (ES) statistics, which can be calculated for outcomes that are either binary (eg, survey responses or predefined adherence cutoffs) or continuous (eg, proportion of days covered).^{11,12} The ESs compare the difference in effect between the study groups divided by the standard deviation of this difference. When standard deviations were not reported, we derived them from the *P* value or *t* test statistic.

Using standard methods, we considered an ES of less than 0.2 to be very small, an ES of 0.2 to less than 0.5 to be small, an ES of 0.5 to less than 0.8 to be medium, and an ES of 0.8 or greater to be large. We assumed that the estimated Cohen's *d* statistics were independent of scale, sample size, and the standard deviation of the outcome studied.

RESULTS

Thirteen studies met criteria for our literature review (Table). Five studies used 1-way patient reminder systems, of which only 1 incorporated provider feedback. Six studies examined 2-way interactive systems, of which 3 included provider feedback. The remaining 2 studies were designed to test systems to enhance patient–provider interaction. Five studies used patient's self-reported adherence as an end point, whereas 8 studies used pill count, pill cap monitoring, or some other quantitative measure to determine adherence. A total of 11

■ **Figure.** Algorithm for Selection of HIT Articles



HIT indicates health information technology.

studies included patients with cardiovascular disease, and 2 studies were conducted with diabetic patients. Seven studies had a very small ES, 2 studies had a small ES, no studies had a medium ES, and 1 study had a large ES. There were 3 studies where the ES could not be determined from the published data.

One-Way Patient Reminder Systems Without Real-Time Provider Feedback

Four studies featuring reminder systems without provider feedback were identified in our search. Studies varied in

length from 12 weeks to 1 year. Only 1 study used a self-reported adherence measure. The ES could be calculated for 2 of the 4 studies, resulting in a very small effect and a large effect.

Christensen et al studied the impact of an electronic reminder device on adherence in hypertensive patients taking telmisartan.¹³ Patients with “untreated or ineffectively treated hypertension” were recruited from private practice or hospital ambulatory centers in Poland; 1577 patients were given the monitoring device, and 784 patients began using it. A total of 135 patients did not return the device, and 251 patients were excluded from analysis because they did not answer survey questions appropriately or investigators had “doubts about the authenticity of electronic monitoring data.” The intervention was an electronic blister card device, which recorded dispensing and provided audiovisual medication reminders. The study was a crossover design with 6 months per arm. At 6 months, before crossover, patients’ self-reported compliance was 90.6% in the intervention group and 85.1% in the control group ($P = .072$). The ES for this intervention was very small ($ES = 0.06$; 95% CI, 0.01-0.12).

McKenney et al followed 70 adult patients on antihypertensive medication in an ambulatory patient population from a retirement community or a primary care center.¹⁴ The intervention was a pill cap displaying the last time and day when the container was opened, as well as an audiovisual alarm reminder. The alarm sounded when a dose was due, and the digital face flashed if the alarm was ignored. The study was conducted in two 12-week phases. In each phase, the electronic cap was compared with standard vials. After phase 1, the intervention arm had adherence of 95.1% versus 78% in the control arm ($P = .0002$). After phase 2, the electronic cap arm had adherence of 94.6% versus 79% in the control arm ($P = .003$). The ES for the cap intervention was large ($ES = 0.85$; 95% CI, 0.14-1.56).

Mengden et al studied 44 patients with uncontrolled hypertension from a hospital outpatient department in Germany.¹⁵ After a 4-week run-in period to identify patients with uncontrolled hypertension, patients had 1 antihypertensive substituted by candesartan/hydrochlorothiazide (16/12.5 mg). Adherence was tracked using a Medication Event Monitoring System (MEMS) cap, which was placed on each participant’s medication bottles. Patients were randomized to receive hypertension teaching and an interactive MEMS with visual reminders or usual care with noninteractive MEMS for monitoring. Adherence was calculated from MEMS data as the percentage of prescribed doses taken. Although adherence in patients with uncontrolled hypertension dropped significantly during the run-in ($P < .001$), it rebounded to excellent levels after drug substitution. At

HIT Adherence Interventions

■ **Table.** HIT Intervention Studies That Met Inclusion Criteria (N = 13)^a

Author, Year, and Site	Participants and Duration ^b	Intervention ^c	Adherence Measure(s)	Outcomes, Cohen's d Effect Sizes
One-Way Patient Reminder Systems Without Real-Time Provider Feedback				
Christensen et al 2010 ¹³ Poland	784 "ineffectively treated" HTN patients on telmisartan from ambulatory care/private practice offices 1 year (6 months per crossover arm)	I: Electronic compliance monitoring with audiovisual reminder device	Self-report: number of days in past week taking medication as prescribed; mean for population given as percentage Taking compliance (device activations/tablets); dosing compliance (days with correct number of device activations/days); timing compliance (number of correct dosing intervals/dosing intervals); drug holidays (number of calculated days missed/days)	Self-report at 6 months (before crossover): I: 90.6% C: 85.1% P = .072 ES = 0.06 (95% CI, 0.01-0.12)
McKenney et al 1992 ¹⁴ Richmond, VA	70 HTN patients aged ≥50 years from primary care center or retirement community 24 weeks (in two 12-week phases)	I: Phase I: 1. Timepiece cap (displays time opened and has audiovisual alarm) Phase II: 1. Timepiece cap 2. Cap and pocket cards 3. Cap, pocket cards, home BP cuffs	MPR calculated by pill count	After phase I: I: 95.1% C: 78% P = .0002 After phase II: C: 79% (SD = 22.61%) Timepiece cap: 94.6% (SD = 8.67%) P = .003 Timepiece cap + card: 98.7% (SD = 11.28%) P < .0001 Timepiece cap + card + BP cuff: 100.2% (SD = 7.02%) P < .0001 ES (for timepiece cap alone vs C after phase II) = 0.85 (95% CI, 0.14-1.56)
Mengden et al 2006 ¹⁵ Germany	44 uncontrolled HTN patients from outpatient cardiology department 12 weeks	I: Patients initiated on candesartan/HCTZ structured teaching program; interactive MEMS monitor including audiovisual reminder C: Noninteractive MEMS	MPR calculated using MEMS for monitoring	Mean: I: 99.7% C: 97.7% Between-group difference = NS Could not calculate ES
Santschi et al 2007 ¹⁶ Lausanne, Switzerland	25 HTN patients on irbesartan from outpatient clinic 4 months	Crossover study I: IDAS (electronic adherence monitor with visual and audio reminders) C: Interactive MEMS	Percentage of doses taken: calculated as number of times the MEMS/IDAS had been opened divided by number of times device should have been opened	Median I: 100.0 (range, 40.3-100.0) C: 100.0 (range, 50.0-101.8) P = NS Could not calculate ES
<i>(Continued)</i>				

■ **Table.** HIT Intervention Studies That Met Inclusion Criteria (N = 13)^a (Continued)

Author, Year, and Site	Participants and Duration ^b	Intervention ^c	Adherence Measure(s)	Outcomes, Cohen's d Effect Sizes
One-Way Patient Reminder Systems With Real-Time Provider Feedback				
Rosen et al 2004 ¹⁷ Connecticut	33 DM patients on metformin with <80% adherence after 4-week baseline from primary care clinic at VA Connecticut 28 weeks	I: Cue-dose training: given interactive MEMS, instruction on other cues Adherence data collected every 4 weeks and given to providers; providers urged to discuss data	MPR calculated using MEMS for monitoring; adherence defined as number of doses taken within 2 hours of an agreed-upon time divided by number of doses	Adherence at 16 weeks: I: 80% C: 60% <i>P</i> = .017 No numbers given for 28 weeks (graph only) ES = 0.43 (95% CI, -0.27-1.14)
Two-Way Interactive Systems Without Real-Time Provider Feedback				
Stacy et al 2009 ¹⁸ United States (unspecified)	497 new statin users from large health benefits company 6 months	I: IVR telephone technology providing tailored medication counseling and reinforcement on 3 separate occasions, followed by written, customized guide mailed to patient C: generic baseline telephone call; generic written guide	MPR calculated by claims data	MPR >80%: I: 47.0% C: 38.9% <i>P</i> < .10 ES = 0.08 (95% CI, 0.01-0.17)
Johnson et al 2006 ¹⁹ Massachusetts and Rhode Island	404 adults with hyperlipidemia recruited via multiple mechanisms including random dial 18 months	I: Population-based, computer-generated individualized assessment of stage of change (precontemplation, contemplation, preparation, action, maintenance) via questionnaire on 3 separate occasions, followed by written, customized report mailed to patient	Self-report: responses to 5 questions (on Likert scale) summed to create a continuous measure Calculated ORs of appropriate adherence	Adherence as continuous measure: 6-month OR = 2.03 (<i>P</i> > .05) 18-month OR = 2.86 (<i>P</i> < .05) ES = 0.18 (95% CI, -0.08-0.45)
Emmett et al 2005 ²⁰ Bristol, England	217 newly diagnosed HTN patients from primary care offices 3 years	I: 1. In-person administration of decision aid on HTN, CV risk; printed feedback sheet 2. Video and leaflet 3. Decision aid and video, leaflet	Self-report: proportion of patients who reported taking all their medications on questionnaire	Percentage reporting 100% adherence: Decision aid: 90% Adjusted OR = 1.56 (95% CI, 0.49 to 4.96) <i>P</i> = .45 ES = 0.15 (95% CI, -0.12-0.42)
Two-Way Interactive Systems With Real-Time Provider Feedback				
Friedman et al 1996 ²¹ Boston, MA	299 HTN patients recruited from community sites across greater Boston 6 months	I: Interactive computer-based home monitoring; patient self-checks of BP, weekly calls to automated phone counseling system; data collected weekly and transmitted to PCP	MPR calculated by pill count Adherers = MPR ≥80%	Mean change adherence, adjusted for baseline adherence: I: 17.7% C: 11.7%, <i>P</i> = .03 ES = 0.13 (95% CI, -0.12-0.37)

(Continued)

HIT Adherence Interventions

■ **Table.** HIT Intervention Studies That Met Inclusion Criteria (N = 13)^a (Continued)

Author, Year, and Site	Participants and Duration ^b	Intervention ^c	Adherence Measure(s)	Outcomes, Cohen's d Effect Sizes
Piette et al 2000 ²² California	280 DM patients on hypoglycemic medications from general medicine clinics; included Spanish-speaking patients 12 months	I: Biweekly automated assessment/education calls: hierarchically structured messages with adherence counseling; nurse given data and performed targeted follow-up calls per his/her clinical judgment	Self-report: patients considered nonadherent if they sometimes forgot or stopped medication	Adjusted for baseline intervention decreased proportion of patients with adherence problems by 21% (69% to 48%, <i>P</i> = .003) ES = 0.38 (95% CI, 0.12- 0.63)
Ramaekers et al 2009 ²³ Netherlands	101 patients with CHF 3 months	Used automated tele-monitoring "Health Buddy device" to gather patient information daily; provided interactive education/counseling and transmitted information to caregivers	Self-report: exact metric not specified	Self-reported medication adherence at baseline: I: 99.6% C: 99.4% Self-reported medication adherence at 3 months: I: 100% C: 100% Neither had SD/variance ES = -0.057 (95% CI, -0.46-0.34)

Systems to Enhance Patient–Provider Interaction

Tamblyn et al 2010 ²⁴ Montreal and Quebec, Canada	2293 patients on lipid lowering or HTN medications from primary care practices 6 months	I: Computerized complete drug profile with graphic displays, refill compliance calculation, and adherence alerts as part of computerized medical record used by PCPs C: Computerized medication list alone (usual care)	Mean refill adherence: proportion of days covered, accessed via daily retrieval of computerized dispensing information; real-time updates of records	Mean refill adherence: I: 73.5% C: 72.9% change mean adherence I: -6.2 (SD = 24.1) C: -6.4 (SD = 24.1) <i>P</i> = .90 ES = 0.01 (95% CI, -0.08-0.09)
Fulmer et al 1999 ²⁵ New York, NY	60 elderly CHF patients from urban home care agency or ambulatory clinic 10 weeks	I: Noninteractive MEMS 1. Daily phone reminders 2. Daily videophone reminders C: Noninteractive MEMS	MPR calculated by daily events adherence method using MEMS for monitoring	Adherence: Phone: 74% Videophone: 84% C: 57% <i>P</i> < .04 for change C (drop in adherence) <i>P</i> = NS for change phone, videophone interventions Cannot calculate ES

BP indicates blood pressure; C, control group; CHF, congestive heart failure; CI, confidence interval; CV, cardiovascular; DM, diabetes mellitus; ES, effect size; HCTZ,

hydrochlorothiazide; HIT, health information technology; HTN, hypertension; I, intervention group; IDAS, Intelligent Drug Administration System; IVR, interactive voice response; MEMS, Medication Event Monitoring System; MPR, medication possession ratio (medication doses taken divided by doses prescribed); NS, not significant; OR, odds ratio; PCP, primary care physician; SD, standard deviation.

^a For all studies where means and SDs for adherence outcomes were available, Cohen's d statistics were calculated. The effect sizes compare the difference in effect between the study groups divided by the SD of this difference. We considered an effect size of less than 0.2 to be very small, an effect size of 0.2 to less than 0.5 to be small, an effect size of 0.5 to less than 0.8 to be medium, and an effect size of 0.8 or greater to be large.

^b Duration indicates time until last follow-up when adherence was measured.

^c Controls received usual care unless otherwise specified.

12 weeks, patient adherence was remarkably high in all study arms: the intervention arm had adherence of 99.7% compared with 97.7% in the control arm and 97.8% in patients whose hypertension was considered to be controlled after the run-in period (no statistically significant differences). The ES could not be calculated. However, the high levels of adherence in control patients in this larger study are not representative of most patients.

Santschi et al compared 2 different electronic reminder systems in 25 patients with hypertension taking irbesartan being followed at 1 of 2 outpatient clinics in Switzerland.¹⁶ This crossover study compared the MEMS system with the Intelligent Drug Administration System, a blister pack–based medication tracking and reminder system. Each crossover period lasted 2 months. Adherence was calculated as the percentage of doses taken. At the end of the study, median adherence was 100% for each device, with no statistically significant difference. The ES could not be calculated.

One-Way Patient Reminder Systems With Real-Time Provider Feedback

One study fit the criteria for a reminder system with provider feedback. Rosen et al used interactive MEMS as part of a cue dose training regimen.¹⁷ A total of 33 type 2 diabetes patients receiving metformin were recruited from a primary care clinic at the Veterans Administration Connecticut Healthcare System. The intervention included interactive MEMS with audiovisual reminders to take medication. Data from the interactive MEMS were collected every 4 weeks and shared with healthcare providers. Study coordinators contacted providers and urged them to discuss the MEMS findings with their patients. Control patients were monitored with noninteractive MEMS. The intervention lasted 16 weeks with a 12-week follow-up period. Adherence was defined as a percentage of prescribed doses taken. At baseline, adherence was approximately 60% in both groups. At 16 weeks, adherence in the intervention arm was 80% versus 60% in the control ($P = .017$). The ES was small (ES = 0.43; 95% CI, -0.27-1.14). Adherence was noted to fall after the intervention period concluded. Investigators also surveyed patients and doctors about the experience of discussing MEMS data. Both parties generally found the discussions to be moderately helpful and comfortable.

Two-Way Interactive Systems Without Real-Time Provider Feedback

We found 3 articles describing interactive systems without provider feedback. All 3 systems sought to educate/counsel patients and influence adherence behavior either via real-time interaction or customized feedback reports. Of the 3

studies, 2 used self-reported adherence measures. The ESs for all 3 studies were very small.

Stacy et al recruited 497 of 1219 commercially insured subjects from a large health plan who had been newly prescribed a statin.¹⁸ Case and control patients received at least 1 interactive voice recognition (IVR) call providing behavioral advice. Patients randomized to the intervention received tailored behavioral support and print material and 2 additional tailored IVR calls. Tailored print material provided personalized advice based on patients' responses during the IVR call. More than 25% of patients participated in all 3 calls; 42% of patients participated in 2 of 3 calls. Patients in the control arm received 1 nontailored IVR call and generic print materials. The adherence end point was calculated as percentage of pills taken by using insurance claims data, with an 80% adherence threshold. At 6 months, 47.0% of the intervention and 38.9% of the control patients, respectively, were adherent to at least 80% of their medications. The ES was very small (ES = 0.08; 95% CI, 0.01-0.17).

Johnson et al studied the impact of an individualized transtheoretical model expert system intervention on 404 adults with hyperlipidemia prescribed a cholesterol-lowering medication.¹⁹ The transtheoretical model explains and predicts how and when individuals change behaviors with stages classified as precontemplation, contemplation, preparation, action, and maintenance. The expert system was built on normative databases to mimic reasoning and problem solving of human experts, and generated individualized reports for patients relevant to their current stage of change. Adherence in both the intervention and control arms was assessed by the system at 6-month intervals over 18 months on a 5-point Likert scale. The odds ratios of improved adherence in the intervention group compared with the control group were 2.03 ($P > .05$) at 6 months, 3.67 ($P < .05$) at 12 months, and 2.86 ($P < .05$) at 18 months. The ES at the conclusion of the study was very small (ES = 0.18; 95% CI, -0.08-0.45).

Emmett et al studied 217 newly diagnosed adult patients with hypertension considering antihypertensive therapy initiation from 21 primary care practices around Bristol, United Kingdom.²⁰ These newly diagnosed patients received either (1) a computerized utility assessment interview with individualized risk assessment and decision analysis followed by a printed feedback sheet, (2) an informational video and leaflet about hypertension, (3) both interventions, or (4) usual care. At 3-year follow-up, adherence was determined via patient survey results. The study authors did not elaborate on how responses were quantified for analysis. Patients receiving the computerized decision analysis reported adherence of 90% (adjusted odds ratio = 1.56, $P = .45$). The ES for this intervention was very small (ES = 0.15; 95% CI, -0.12-0.42).

Two-Way Interactive Systems With Real-Time Provider Feedback

Three studies met criteria for interactive systems with provider feedback. These studies provided interactive media for patients to report and receive feedback and counseling about their adherence, as well as a system to provide caregivers with adherence data. Of the 3 studies, 2 measured adherence by self-report. The ES was very small in 2 studies and small in 1 study.

Friedman et al studied 299 patients with hypertension at 29 community sites in Boston taking antihypertensive medications.²¹ The intervention was an interactive telephone-linked computer system. Patients dialed into the telephone-linked computer system on a weekly basis and interacted via touch-tone keypad, receiving personalized education and counseling in return. Printed results were sent to the patients' physicians, with clinically significant information highlighted, although no effort was made to prompt physicians to discuss the data with patients. Patients were randomized to the telephone-linked computer system arm or to usual care. Adherence was determined by home pill count audit, which calculates the number of prescribed pills taken, using 80% as the adherence threshold. Baseline adherence was very high at 93% to 94%. At 6 months, the mean change in dichotomized adherence was 17.7% for the intervention and 11.7% for the control ($P = .03$). The ES was very small (ES = 0.13; 95% CI, -0.12-0.37). Patients who were nonadherent at entry had statistically significant improvements in adherence with the intervention ($P = .03$), whereas adherent patients had no change. Attrition rate was higher in the intervention arm (15%) than in the control arm (8%).

Piette et al studied 280 adult patients with type 2 diabetes treated with hypoglycemic medications.²² This study was unique in that it included both Spanish-speaking and English-speaking patients. Patients were recruited from 2 general medicine clinics in a county healthcare system. There were 588 patients initially targeted for recruitment. The intervention included biweekly automated assessment, education, and counseling phone calls using hierarchically structured messages and interaction via touch-tone keypad. The system generated patient-specific reports to be provided to a diabetes nurse educator. The nurse used the reports to perform targeted follow-up phone calls. At baseline and 12 months, surveys were conducted with patients in their native language, and adherence failures were identified. At study conclusion, after adjustment for baseline, 48% of intervention patients had adherence problems as opposed to 69% in the control arm ($P = .003$). The ES was small (ES = 0.38; 95% CI, 0.12-0.63).

Ramaekers et al studied the role of an automated telemonitoring device in 101 patients with congestive heart failure from 3 Dutch hospitals.²³ The intervention was an interactive

system that educated and counseled, gathered information, and transmitted information to caregivers on the cardiology team. Adherence was assessed as part of a postal survey at baseline and at 3 months; the exact measure of adherence was not specified. Self-reported adherence at baseline was 99.6% for the intervention group and 99.4% for the control group. At 3 months, self-reported adherence was 100% without variance in both arms. The ES was very small (ES = -0.057; 95% CI, -0.46-0.34).

Systems to Enhance Patient-Provider Interaction

Two studies met criteria for systems enhancing patient-provider interaction. Both studies used objective measures of adherence, and ES was very small in one and not calculable in the second.

Tamblyn et al studied 2293 primary care patients in Quebec taking lipid-lowering or antihypertensive medications.²⁴ Patients were randomized to either an enhanced or basic electronic medical record interface. The enhanced interface provided doctors with real-time adherence information and featured complete medication profiles with a graphic, chronological display of medication prescribing and dispensing, refill compliance calculation, and automated alerts for adherence less than 80%. Adherence was defined as the proportion of days in which an individual had a supply using pharmacy claims data. At 6 months, the intervention group had adherence of 73.5% versus the control at 72.9%, which was not a statistically significant difference. The ES was very small (ES = 0.01; 95% CI, -0.08-0.09). Of note, the study authors reported that physicians frequently asked for the enhanced interface for patients in the control arm, despite being aware of the ongoing study.

Fulmer et al examined the role of videophone and/or phone in encouraging patient compliance.²⁵ Sixty community-dwelling elderly patients with congestive heart failure were recruited from among 600 eligible patients at a large urban home health-care agency or ambulatory clinic. Participants were taking an angiotensin-converting enzyme inhibitor, calcium channel blocker, or beta blocker. The interventions included either a daily phone or videophone call every weekday. During the call, patients were asked whether they had taken their medications the previous day. Videophone images had a 2-second frame delay, but allowed patients and researchers to communicate on a screen. The control arm received usual care. Adherence was tracked using a MEMS cap, which was placed on each participant's medication bottles at baseline and used solely to track medication use. After the 10-week study period, patients in the control arm were found to have adherence of 57% versus 81% at baseline ($P < .04$). Patients with phone reminders had adherence of 74% versus 76% at baseline, and patients with video-

phone reminders had adherence of 84% versus 82% at baseline. There was no statistically significant difference between phone and videophone reminder arms. The ES could not be calculated from the data published.

DISCUSSION

Nonadherence is a significant public health problem, and better understanding of the role of HIT interventions is essential. This review highlights the paucity of prospective data on the effectiveness of HIT interventions to improve adherence in cardiovascular disease or diabetes, as well as the lack of evidence to guide development and implementation of future adherence interventions. Many of the studies identified had small sample sizes or tested rather rudimentary interventions, limiting the conclusions that could be drawn. However, electronic reminder systems appear to encourage improved medication-taking behavior and show promise. Stronger conclusions about the incremental value of interactive programs cannot be drawn from the evidence identified, and there are limited data evaluating HIT programs that promote patient engagement and motivation or doctor–patient communication.

Simple reminder systems were consistently successful and demonstrated the strongest ESs in this review. Reminder systems are unique relative to other HIT interventions because they have the potential for seamless integration into patients' daily routines. In contrast with weekly or less frequent contact with interactive systems and/or providers, reminder systems reinforce the regularity of medication regimens without requiring additional effort on the part of the patient. These findings suggest that further attention be directed to other “infiltrative” interventions, whether via personal computer, electronic agendas, or cell phones. Furthermore, studies examining electronically enhanced reminder systems in conjunction with other interventions may be valuable.

Studies examining interactive HIT for education and counseling were less successful. This is consistent with previous reviews of nonelectronic adherence interventions, which have found that education alone is a rather ineffective approach to change behavior and that multifactorial interventions including education as 1 of several elements tend to be more effective.^{7,8} Our findings indicate that electronic delivery of education does not substantially alter its effectiveness.

We expected to find that HIT enhanced the effectiveness of adherence interventions by generating real-time adherence feedback for healthcare providers. However, in this review, the addition of provider feedback to reminder systems and interactive systems did not result in demonstrable improvement in outcomes relative to the reminder interventions alone. It is worth noting that only the studies by Rosen et al¹⁷ and Piette et

al²² prodded or protocolized caregivers to actually discuss adherence data; these studies showed modestly improved intervention effects, although the ESs remained small. The effectiveness of providing real-time adherence information delivery to providers in conjunction with reminder systems is not yet clear.

Previous literature suggests that patient engagement in care is associated with improved treatment adherence.^{26,27} We expected our review to uncover HIT interventions that capitalize on the interactive capabilities of technology. Although several studies aimed to create an interactive system for patients, they generally did this by gathering data from patients through relatively crude mechanisms (ie, touch-tone keypad) and sending back automated, albeit customized, feedback designed to educate and counsel. These systems did not promote engagement by providing positive reinforcement via rewards or recognition, developing peer networks or social support, or creating an environment that is inviting to patients—interventions shown to be effective in the literature.²⁶⁻³¹

Furthermore, the interventions we identified required a substantial degree of patient motivation at the outset. Whether expecting patients to call IVRs themselves or read feedback materials, this degree of patient proactiveness may be unrealistic in the absence of additional motivators. Future studies must pursue new strategies to stimulate patient engagement and promote behavior change. Increasing sophistication of HIT also provides for a more interactive medium to deliver more personal, targeted messages to patients.

Our study has several limitations. Most importantly, we found only 13 studies using HIT to improve adherence to medications for cardiovascular disease and diabetes. These findings highlight the disappointing state of the evidence on a topic that is of substantial public health importance and underscore the need for further study. Similar reviews including other disease states may identify additional relevant evidence and should be conducted. Moreover, we did not include results from observational or other nonrandomized designs. Additional evidence can likely be captured from such studies, although we must aim to base policy decisions on a higher standard of evidence.

Our definition of HIT was liberal, and we included interventions with any electronic component. Many of the studies we included did not benefit from connectivity to electronic medical records, as we would expect in a more mature HIT environment. Cohen's *d* effect sizes can be difficult to interpret. As a result, we included the absolute, reported effect size of each intervention in the tables to provide readers with additional data for more nuanced interpretation.

Included studies evaluated patients over a variety of study durations—some as short as 10 weeks. There was little consistency in outcomes reported, which made direct comparisons

challenging and suggested a need for standardized metrics in future studies. Patient populations also were highly variable. For instance, some unsuccessful studies were conducted in populations with surprisingly high baseline adherence, rendering significant adherence improvements difficult to demonstrate. Future studies might further utilize HIT to identify and recruit nonadherent patients from the outset. Also, further study in vulnerable patient populations, such as was done by Piette et al,²² or in populations with poor health literacy, may offer even greater benefit.^{31,32} For some of the studies evaluated, the HIT intervention and related end points were not the primary targets of intervention. Therefore, lack of conclusive results may simply be a reflection of trial design.

This systematic review suggests that HIT interventions are promising tools in the effort to improve medication adherence, but additional studies are needed. Simple HIT interventions such as reminder systems appear effective, and efforts to implement them broadly would seem to be an efficient and relatively low-cost approach to improve adherence. However, reminders alone will not solve the problem. Innovative systems are needed to further engage and motivate patients to adhere to their medications. Few published studies describe sophisticated interactive interventions that expand the functionality and capabilities of electronic health systems to provide patients and providers with more valuable and timely information, leaving us with limited evidence to guide the development and implementation of HIT adherence interventions.

As the United States invests substantially in the broad implementation of HIT, innovative adherence interventions that build on the capabilities of HIT are essential and must be rigorously tested to develop best practices. Medication adherence is a unique concern, as virtually all participants in the marketplace—pharmaceutical manufacturers, insurers, pharmacy benefits managers, pharmacies, and patients—benefit when patients adhere to therapy. However, the business case for any single party can be hard to make. Developers should consider how to find collaborative reimbursement approaches to support innovative adherence interventions and directly evaluate the return on investment expected from the intervention. The formation of accountable care organizations that result from health reform also may create new incentives for health systems to better manage chronic disease and to play a more central role in stimulating adherence to medications. As HIT-based interventions to improve adherence are developed and implemented, evaluations should focus on how such interventions reduce downstream healthcare costs and must highlight the business case for their existence for the payers or providers that must invest in them.

Acknowledgments

We would like to thank Amber Servi for her help identifying the relevant articles.

Author Affiliations: From the Division of Pharmacoepidemiology and Pharmacoeconomics (ASM, NKC, MAF, MRS, WHS), Brigham and Women's Hospital, Boston, MA; Center for American Political Studies (SLC, WHS), Harvard University, Boston, MA; CVS Caremark (JNL, TAB), Woonsocket, RI; and Office of the National Coordinator (SHJ), Department of Health and Human Services, Washington, DC.

Funding Source: This work was funded by a research grant from CVS Caremark, a large retail pharmacy and pharmacy benefits manager. CVS Caremark has a financial interest in improved medication adherence, and 2 of the authors (JNL, TAB) are employees at CVS Caremark. Dr Shrank is supported by a career development award from the National Heart, Lung, and Blood Institute. The authors from Brigham and Women's Hospital, Harvard Medical School, and Harvard University have received research funding from CVS Caremark, Express Scripts, and Aetna—all of whom have an interest in medication adherence.

Author Disclosures: Drs Liberman and Brennan report being employees of CVS Caremark. Dr Brennan also report holding options and stock in the company. Drs Cutrona and Shrank report receiving grant support from CVS Caremark. Dr Choudhry reports receiving multiple grants for research related to medication adherence. Dr Fischer report grants pending for a potential study of adherence with SureScripts. The authors (ASM, MRS, SHJ) report no relationship or financial interest with any entity that would pose a conflict of interest with the subject matter of this article.

Authorship Information: Concept and design (ASM, SLC, NKC, MAF, TAB, SHJ, WHS); acquisition of data (ASM, SLC, TAB, WHS); analysis and interpretation of data (ASM, SLC, NKC, MAF, MRS, JNL, WHS); drafting of the manuscript (ASM, SLC, SHJ, WHS); critical revision of the manuscript for important intellectual content (ASM, SLC, NKC, MAF, JNL, TAB, SHJ, WHS); statistical analysis (MRS, WHS); provision of study materials or patients (ASM); obtaining funding (JNL, WHS); administrative, technical, or logistic support (ASM, MRS, SHJ, WHS); and supervision (ASM, SHJ, WHS).

Address correspondence to: William H. Shrank, MD, MSHS, Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital, 1620 Tremont Suite, Ste 3030, Boston, MA 02120. E-mail: wshrank@partners.org.

REFERENCES

- Institute of Medicine.** *100 Initial Priority Topics for Comparative Effectiveness Research.* 2009. <http://www.iom.edu/-/media/Files/Report%20Files/2009/ComparativeEffectivenessResearchPriorities/Stand%20Alone%20List%20of%20100%20CER%20Priorities%20-%20for%20web.ashx>. Accessed June 8, 2010.
- World Health Organization.** *Adherence to Long-Term Therapies: Evidence for Action.* Geneva, Switzerland: WHO; 2003.
- Avorn J, Monette J, Lacour A, et al.** Persistence of use of lipid-lowering medications: a cross-national study. *JAMA.* 1998; 279(18):1458-1462.
- Rasmussen JN, Chong A, Alter DA.** Relationship between adherence to evidence-based pharmacotherapy and long-term mortality after acute myocardial infarction. *JAMA.* 2007;297(2):177-186.
- Stuart BC, Simoni-Wastila L, Zhao L, Lloyd JT, Doshi JA.** Increased persistency in medication use by U.S. Medicare beneficiaries with diabetes is associated with lower hospitalization rates and cost savings. *Diabetes Care.* 2009;32(4):647-649.
- New England Healthcare Institute.** *Thinking Outside the Pillbox: A System-wide Approach to Improving Patient Medication Adherence for Chronic Disease.* August 12, 2009. http://www.nehi.net/publications/44/thinking_outside_the_pillbox_a_systemwide_approach_to_improving_patient_medication_adherence_for_chronic_disease. Accessed May 27, 2010.
- Kripalani S, Yao X, Haynes R.** Interventions to enhance medication adherence in chronic medical conditions: a systematic review. *Arch Intern Med.* 2007;167(6):540-550.
- Haynes RB, Ackloo E, Sahota N, McDonald HP, Yao X.** Interventions for enhancing medication adherence. *Cochrane Database Syst Rev.* 2008(2):CD000011.
- Cutrona SL, Choudhry NK, Stedman M, et al.** Physician effectiveness in interventions to improve cardiovascular medication adherence: a systematic review. *Gen Intern Med.* 2010;25(10):1090-1096.

10. Lloyd-Jones D, Adams RJ, Brown TM, et al; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2010 update: a report from the American Heart Association. *Circulation*. 2010;121(7):e46-e215.
11. Cohen J. *Statistical Power Analysis for the Behavioral Sciences*. New York: Lawrence Erlbaum Associates; 1988.
12. Dunlap W, Cortina J, Vaslow J, Burke M. Meta-analysis of experiments with matched groups or repeated measures designs. *Psychol Methods*. 1996;1:170-177.
13. Christensen A, Christrup LL, Fabricius PE, et al. The impact of an electronic monitoring and reminder device on patient compliance with antihypertensive therapy: a randomized controlled trial. *J Hypertens*. 2010;28(1):194-200.
14. McKenney JM, Munroe WP, Wright JT Jr. Impact of an electronic medication compliance aid on long-term blood pressure control. *J Clin Pharmacol*. 1992;32(3):277-283.
15. Mengden T, Vetter H, Toussef E, Uen S. Management of patients with uncontrolled arterial hypertension—the role of electronic compliance monitoring, 24-h ambulatory blood pressure monitoring and candesartan/HCTZ. *BMC Cardiovasc Disord*. 2006;6:36.
16. Santschi V, Wuerzner G, Schneider MP, Bugnon O, Burnier M. Clinical evaluation of IDAS II, a new electronic device enabling drug adherence monitoring. *Eur J Clin Pharmacol*. 2007;63(12):1179-1184.
17. Rosen MI, Rigsby MO, Salahi JT, Ryan CE, Cramer JA. Electronic monitoring and counseling to improve medication adherence. *Behav Res Ther*. 2004;42(4):409-422.
18. Stacy JN, Schwartz SM, Ershoff D, Shreve MS. Incorporating tailored interactive patient solutions using interactive voice response technology to improve statin adherence: results of a randomized clinical trial in a managed care setting. *Popul Health Manag*. 2009;12(5): 241-254.
19. Johnson SS, Driskell MM, Johnson JL, et al. Transtheoretical model intervention for adherence to lipid-lowering drugs. *Dis Manag*. 2006;9(2):102-114.
20. Emmett CL, Montgomery AA, Peters TJ, Fahey T. Three-year follow-up of a factorial randomised controlled trial of two decision aids for newly diagnosed hypertensive patients. *Br J Gen Pract*. 2005;55(516):551-553.
21. Friedman RH, Kazis LE, Jette A, et al. A telecommunications system for monitoring and counseling patients with hypertension. Impact on medication adherence and blood pressure control. *Am J Hypertens*. 1996;9(4 pt 1):285-292.
22. Piette JD, Weinberger M, McPhee SJ, Mah CA, Kraemer FB, Crapo LM. Do automated calls with nurse follow-up improve self-care and glycemic control among vulnerable patients with diabetes? *Am J Med*. 2000;108(1):20-27.
23. Ramaekers BL, Janssen-Boyne JJ, Gorgels AP, Vrijhoef HJ. Adherence among telemonitored patients with heart failure to pharmacological and nonpharmacological recommendations. *Telemed J E Health*. 2009;15(6):517-524.
24. Tamblyn R, Reidel K, Huang A, et al. Increasing the detection and response to adherence problems with cardiovascular medication in primary care through computerized drug management systems: a randomized controlled trial. *Med Decis Making*. 2010;30(2):176-188.
25. Fulmer TT, Feldman PH, Kim TS, et al. An intervention study to enhance medication compliance in community-dwelling elderly individuals. *J Gerontol Nurs*. 1999;25(8):6-14.
26. Sayers SL, Riegel B, Pawlowski S, Coyne JC, Samaha FF. Social support and self-care of patients with heart failure. *Ann Behav Med*. 2008;35(1):70-79.
27. Mosen DM, Schmittziel J, Hibbard J, Sobel D, Remmers C, Bellows J. Is patient activation associated with outcomes of care for adults with chronic conditions? *J Ambul Care Manage*. 2007;30(1):21-29.
28. Johnson MO, Chesney MA, Goldstein RB, et al; NIMH Healthy Living Project Team. Positive provider interactions, adherence self-efficacy, and adherence to antiretroviral medications among HIV-infected adults: a mediation model. *AIDS Patient Care STDS*. 2006;20(4):258-268.
29. Volpp KG, Loewenstein G, Troxel AB, et al. A test of financial incentives to improve warfarin adherence. *BMC Health Serv Res*. 2008;23(8):272.
30. Criswell TJ, Weber CA, Xu Y, Carter BL. Effect of self-efficacy and social support on adherence to antihypertensive drugs. *Pharmacotherapy*. 2010;30(5):432-441.
31. Johnson VR, Jacobson KL, Gazmararian JA, Blake SC. Does social support help limited-literacy patients with medication adherence? A mixed methods study of patients in the Pharmacy Intervention for Limited Literacy (PILL) study. *Patient Educ Couns*. 2010;79(1):14-24.
32. Kripalani S, Gatti ME, Jacobson TA. Association of age, health literacy, and medication management strategies with cardiovascular medication adherence. *Patient Educ Couns*. 2010;81(2):177-181. ■