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The Modeled Lifetime Cost-Effectiveness of Published Adherence-Improving Interventions for Antihypertensive and Lipid-Lowering Medications

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ABSTRACT

Objective: We sought to compare the cost-effectiveness of different interventions that have been shown to improve adherence with antihypertensive and lipid-lowering therapy, by combining a burden of nonadherence model framework with literature-based data on adherence-improving interventions.

Methods: MEDLINE was reviewed for studies that evaluated ≥1 adherence intervention compared with a control, used an adherence measure other than self-report, and followed patients for ≥6 months. Effectiveness was assessed as Relative Improvement, ratio of adherence with an intervention versus control. Costs, standardized to 12 months and adjusted to 2007 US$, and effectiveness estimates for each intervention were entered into a previously published model designed to measure the burden of nonadherence with antihypertensive and lipid-lowering medications, in a hypertensive population. Outputs included direct medical costs and incremental costs per quality-adjusted life-year (QALY) gained.

Results: After screening, 23 eligible adherence-improving interventions were identified from 18 studies. Relative Improvement ranged from 1.13 to 3.60. After eliminating more costly/less effective interventions, two remained. Self-monitoring, reminders, and a educational materials incurred total health-care costs of $17,520, and compared with no adherence intervention, had an incremental cost-effectiveness ratio (ICER) of $4984 per QALY gained. Pharmacist/nurse management incurred total health-care costs of $17,896, and versus self-monitoring, reminders, and education had an ICER of $6358 per QALY gained.

Conclusions: Of published interventions shown to improve adherence, reminders and educational materials, and a pharmacist/nurse management program, appear to be cost-effective and should be considered before other interventions. Understanding relative cost-effectiveness of adherence interventions may guide design and implementation of efficient adherence-improving programs

Keywords: improving adherence, cost-effectiveness, literature review, adherence intervention, antihypertensive, lipid-lowering, cardiovascular disease.

Introduction

The efficacy of recommended treatment regimens depends on how well patients adhere to them. Accordingly, improving adherence with medications that manage risk factors of cardiovascular disease (CVD) has been shown to reduce cardiovascular events, including the risk of recurrent myocardial infarction (MI) and stroke, rehospitalizations, and all-cause mortality [1–4]. Improving adherence with medications is a key initiative of the World Health Organization [5], and similar organizations worldwide.

Various strategies for improving adherence with medication regimens, including medications for CVD, are available. These include intensive case management by a pharmacist and/or nurses [6–10]; patient education or counseling [11–13]; modifications to dosing regimens or modifications to medication packaging [14]; reminders for medications [14,15]; other interventions, including home blood pressure (BP) monitoring to improve adherence to hypertension medications [16]; and combinations of these approaches [15,17–19]. Nevertheless, different types of intervention are seldom compared in one study and overall costs of interventions are rarely captured.

A previous study using a comparative measure of "Relative Improvement" demonstrated that the most successful adherence interventions were personalized and intensive, typically including management and counseling by health-care professionals, such as a pharmacist or nurse [20]. Relative Improvement was calculated as the ratio of effectiveness with the intervention versus the control group, and enabled comparison across a diverse range of studies [20]. To further facilitate comparison among studies, costs were also estimated for each intervention. The authors found that personalized and intensive interventions that were most successful for improving adherence also tended to incur higher costs than other, less successful interventions such as reminders or changes to packaging [20].

To the best of our knowledge, a formal comparative cost-effectiveness analysis across interventions designed to improve adherence with CVD medications has not been undertaken. We therefore decided to utilize a previously developed model that analyzes the burden of nonadherence with antihypertensive and lipid-lowering therapy under different levels of adherence, to compare and contrast the cost-effectiveness of published adherence interventions [21]. This model, used to predict relative cost-effectiveness, permits modeling of real-world patient-care settings, where adherence and persistence often fall short of the "ideal" adherence seen in clinical trials [22,23]. A cost-effective adherence intervention would be a method that is effective for reducing the burden of illness associated with nonadherence, at an optimal level of resource use. Accordingly, it is important to consider the relative cost-effectiveness of adherence interventions, particularly for determining applicability within health-care environments in which resources are scarce.

We therefore sought to combine studies reporting a clear improvement in adherence through application of each

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adherence intervention into a burden of nonadherence framework [21], providing a comparative analysis of cost-effectiveness across different intervention types from a payer's perspective.

Methods

Study Identification and Data Extraction

A prior review of MEDLINE publications by Petrilla et al. [24], was extended to cover published articles (1972–2007) designed to improve adherence with antihypertensive and/or lipid-lowering medications. In short, eligible studies evaluated ≥1 adherence intervention compared with a control; used an adherence measure other than self-report; and followed patients for ≥6 months. Interventions were excluded if they did *not* demonstrate significant improvement in adherence, as interventions that reported negative or neutral outcomes would not have provided a positive measure of Relative Improvement suitable for comparison.

After screening 755 studies, five studies that described five interventions were identified. In addition to the 18 interventions previously identified [24]; this gave a total of 23 interventions identified from 18 studies (Fig. 1). This information is detailed in full in a separate publication [20].

Classification and Effectiveness of Adherence Interventions

From the studies identified, adherence-improving interventions were broadly classified into those that involved an active input from a health-care professional—physician, pharmacist, nurse—to improve adherence for the patient (*case management* [*M*]), those which involved education of the patient on the prescribed product (*reminders* being sent [*R*] or *education* [*E*]), *other* methods of intervention (*O*), or a *combination* of these approaches (*C*) [20]. Combined approaches were classified according to the primary method of intervention (e.g., *C*+*R*). Effectiveness was assessed using Relative Improvement, defined as adherence outcome reported in the intervention group divided by the adherence outcome reported in the control group.

Cost-Effectiveness Assessment

A "league table" listing all standardized interventions was used to identify interventions that were eligible for cost-effectiveness analysis. Steps in the league table comparison were: first, all interventions were ranked in ascending order of annualized cost; second, identical interventions applied to more than one setting or population were amalgamated into one intervention (average of costs and average of effects); and third, interventions that were more costly than interventions with higher efficacy were considered dominated (less effective and more costly). One study by McKenney et al. [7], used a 90% adherence threshold, rather than the commonly used and accepted threshold of ≥80% [2,4,22]. Furthermore, as McKenney et al. [7], did not provide enough information on adherence outside of this threshold to permit any inferences or calculations to standardize this study for inclusion, the study was excluded from further analysis. All nondominated interventions were entered into the cost-effectiveness model for calculation of relative cost-effectiveness.

An informal panel process was used to estimate resource use and costs for each intervention [20]. Studies were compared to identify a set of common inputs from which comparable costs could be inferred. Fixed costs at the site level, such as the cost of training staff for the intervention, were not included, because the average cost per patient would vary depending on scale. Drug costs were included when we looked at the entire analysis but the costs of the interventions themselves were initially determined without any drug costs [21]. "No intervention" represents adherence to calcium channel blocker (CCB) and lipid-lowering therapies without any adherence-improving intervention.

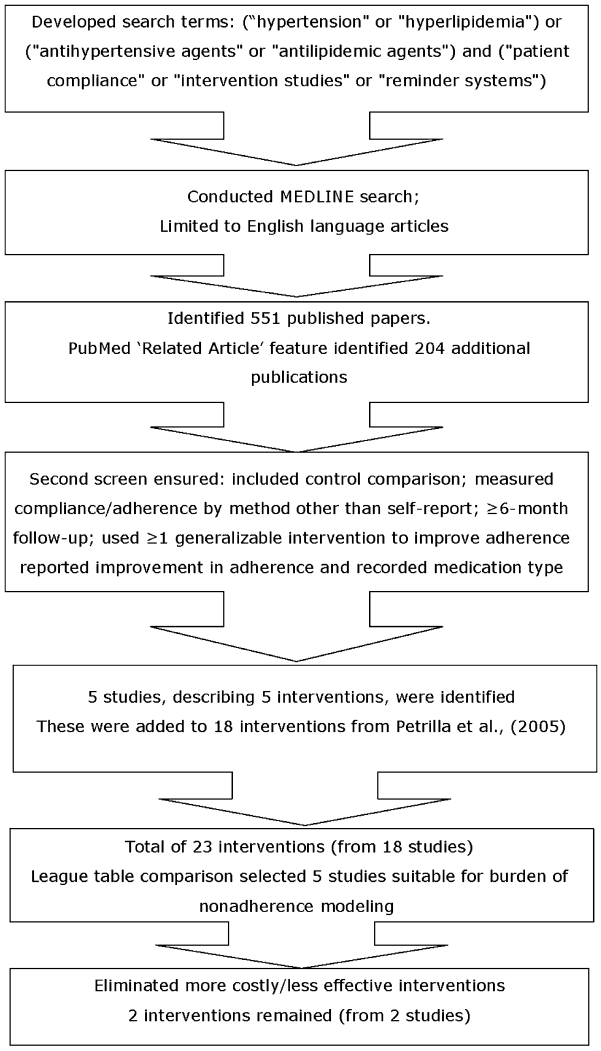

Figure 1 Search strategy for identifying interventions designed to improve adherence to antihypertensive and/or lipid-lowering therapy.

Costs and effectiveness, from a payer's perspective, for each nondominated intervention were entered into the burden of nonadherence model framework [21]. Costs were standardized to 12 months and adjusted to 2007 US$ using the medical care services component of the Consumer Price Index [25].

Burden of Nonadherence Modeling

Patient characteristics were modeled based on the population from the Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm (ASCOT-LLA) [26], namely hypertensive patients aged 40 to 79 years with total cholesterol ≤6.5 mmol/L (241 mg/dl) and ≥3 cardiovascular risk factors in addition to hypertension, including male sex, aged ≥55 years, stroke or transient ischemic attack, type 2 diabetes mellitus, left ventricular hypertrophy, abnormal electrocardiogram, peripheral vascular disease,

microalbuminuria, or proteinuria [26]. The studies describing adherence-improving interventions enrolled a variety of differing patient groups (e.g., some enrolled new starters; some enrolled previously nonadherent patients). Adjustments were not made for differences between the patient populations included in each of the adherence-improving intervention studies identified and the ASCOT-LLA population. The assumption was made that the patient population would not affect the outcome of the intervention.

Lifetime costs, morbidity, and mortality associated with adherence improvements from each intervention were estimated over a lifetime horizon using a Monte Carlo microsimulation model [21]. This model was constructed to compare costs and outcomes of primary and secondary prevention with antihypertensive and lipid-lowering medications under three adherence scenarios: no treatment, ideal adherence, and real-world adherence [21].

Briefly, the *no treatment* model projected the natural history of coronary heart disease and stroke in the absence of treatment and formed the foundation for the other scenarios. Patients in this model were taking neither antihypertensives nor lipid-lowering therapy. Event frequencies and costs were assumed to follow those found with nonadherent patients. The *ideal adherence* scenario extended the *no treatment* scenario by adding antihypertensive and lipid-lowering therapy and the associated relative event risk reductions and costs. The *real-world* adherence scenario was similar to the *ideal* adherence scenario but added *real-world* adherence data and costs and benefits associated with different level of adherence [21].

Adherence was assessed using proportion of days covered (PDC), calculated as number of days with drug on-hand divided by the number of days in the given time interval. PDC has the advantage of simultaneously reflecting both compliance and persistence [27,28] and provides a measure of overall medication exposure compatible with the 1-year health states in the model. PDC is also a commonly used parameter in adherence studies [2,4,29–32], and its use therefore facilitates meaningful comparisons across studies. For each therapy (antihypertensive and lipid-lowering), three possible levels of adherence were defined, patients were allowed to transition among them over time: fully adherent (PDC $\geq$ 80%); partially adherent (PDC 21%–79%); and nonadherent (PDC 0–20%) [21].

The Relative Improvement from each intervention study identified was applied to patients' baseline adherence in the model, and the improved adherence was used to assign adherence states based on their estimated adherence with antihypertensive and lipid-lowering therapies (e.g., Full [antihypertensive]–Full [lipid-lowering]; Full–Partial; Full–Non; Partial–Full; Partial–Partial; Partial–Non; Non–Full; Non–Partial; Non–Non).

Adherence distributions were modeled for each study. Ideal adherence was based on adherence and effectiveness observed in ASCOT-LLA [26]. Real-world adherence status was assigned at the start of each model cycle according to real-world transitions. Initial adherence status and transitions were drawn from prescription claims data from California Medicaid (Medi-Cal) data [33]. Nonadherent patients experienced the same cardiovascular event rates as untreated patients, although fully adherent patients receiving either treatment had a relative risk reduction applied based on the ASCOT-LLA [26] data for patients treated with the CCB, amlodipine besylate, and lipid-lowering agent, atorvastatin calcium. The cardiovascular event rates for partially adherent patients were estimated based on an arbitrary assumption of 50% efficacy.

Annual Adherence Transitions

Adherence status transition probability matrices were made for each year's transition. Adherence transitions for year 1 were based on the Relative Improvement from each adherence intervention as applied to the ASCOT-LLA population's baseline adherence. Transitions beyond the first year were based on existing annual adherence status transition probabilities in the model, which were derived from filled prescription records from Medi-Cal data [33]. Therefore, the benefits of the adherence interventions were captured in the first year of treatment, although adherence levels for patients beyond year 1 were based on long-term adherence patterns seen in a representative population.

Statistical Analyses

Simulations of 200 trials of 5000 patients were conducted; means of the 200 trials for each intervention were reported. Outputs were calculated on a per-person basis: costs (discounted) (angina, MI, stroke, pharmacy, total); events (discounted) (angina, MI, stroke, total); life-years (discounted); and quality-adjusted life-years (QALYs) (discounted). The model employed a payer perspective, including direct pharmacy and medical costs in 2007 $US with future costs and benefits discounted by 3% annually [34]. The models were constructed and analyzed using TreeAge Pro 2006 (TreeAge Software Inc., Williamstown, MA). One-way sensitivity analyses were conducted by varying our assumptions around the percentage of therapeutic effectiveness patients receive when they are partially adherent (PDC between 20% and 80%), and the proportion of patients who are assumed to start out fully adherent (PDC $\geq$ 80%) for both antihypertensive and lipid-lowering medications. Values for many of the modeled intervention variables were not reported in the reviewed literature, making it difficult to specify plausible ranges; therefore, multiway and probabilistic sensitivity analyses were not performed.

Results

Eligible Studies

After the league table comparison of 23 interventions from 18 studies identified from the literature analysis [20], five interventions were eligible for analysis (Fig. 1): 1) mailed reminders (Skaer et al. [14]); 2) combination intervention with self-monitoring, reminders, and educational materials (Saunders et al. [19]); 3) telephone counseling (Faulkner et al. [11]); 4) pharmacy and nurse management (Bond and Monson [6]); and 5) pharmacist management in an ambulatory setting (Monson et al. [10]).

Adherence distributions were modeled for the base-case (no adherence) and each of the five studies (Table 1). For the base-case of no adherence intervention, only 25% of patients were estimated to be fully adherent with both CCB and lipid-lowering therapies (Table 1). In contrast, 48% (Saunders et al. [19]) to 89% (Monson et al. [10]) of patients in the intervention groups were estimated to be fully adherent with both therapies.

Effectiveness of Adherence-Improving Intervention

The Relative Improvement in adherence ranged from 1.13 for mailed reminders [14] to 3.60 for a pharmacist management program in an ambulatory setting [10] (Fig. 2). Annualized intervention costs ranged from $19.18 per patient for mailed prescription reminders [14] to $ 259.56 per patient for a pharmacists management program in an ambulatory setting [10]. A combination program involving self-monitoring, reminders, and educational materials [19] was $25.46 more costly per patient than reminders alone [14]. Pharmacist management in an ambulatory

Table 1 Initial adherence distributions for selected adherence-improving interventions

Adherence state (antihypertensive–statin)	Adherence distribution					
	No adherence intervention*	Skaer [14] (*R*)	Saunders [19] (*C+R*)	Faulkner [11] (*E*)	Bond [6] (*M*)	Monson [10] (*M*)
Full–Full	0.246	0.447	0.482	0.525	0.779	0.887
Full–Partial	0.165	0.121	0.114	0.104	0.049	0.025
Full–Non	0.030	0.022	0.020	0.019	0.009	0.004
Partial–Full	0.095	0.070	0.065	0.060	0.028	0.014
Partial–Partial	0.228	0.167	0.157	0.144	0.067	0.034
Partial–Non	0.047	0.034	0.032	0.030	0.014	0.007
Non–Full	0.078	0.057	0.054	0.049	0.023	0.012
Non–Partial	0.072	0.053	0.049	0.045	0.021	0.011
Non–Non	0.039	0.029	0.027	0.025	0.011	0.006

*No adherence intervention = calcium channel blocker + statin only.
C+R, Combination + reminders; *E*, Education; *M*, Case management; *R*, Reminders.

setting, where the pharmacist had sole responsibility for managing and educating patients [10], was $79.76 more expensive per patient than a combined pharmacist and nurse management program of compliance [6].

Cost-Effectiveness of Adherence-Improving Interventions

Modeled total cardiovascular events were highest for the group receiving no adherence intervention (0.575), as would be expected, and lowest for a pharmacist management program in the ambulatory setting [10] (0.557) (Table 2). MI contributed the highest event rate (0.222 to 0.230), followed by stroke (0.206 to 0.210), and angina (0.130 to 0.135). Predicted age of death was highest (80.8 years) for the management programs [6,10] in comparison with the other interventions for improving adherence [11,14,19].

Simulated overall costs ranged from $18,082 for pharmacist management program in the ambulatory setting [10] to $17,325 (no adherence intervention) (Table 3). Prescription costs were the highest contributor to overall costs for each intervention and ranged from $7990 for pharmacist management program in the ambulatory setting [10] to $6982 (no adherence intervention). Cardiovascular event costs (angina, MI, stroke) were lower with any adherence-improving intervention than for no intervention.

After eliminating less effective/more costly interventions, two interventions remained: self-monitoring, reminders, and educational materials (Saunders et al. [19]); and a pharmacist/nurse

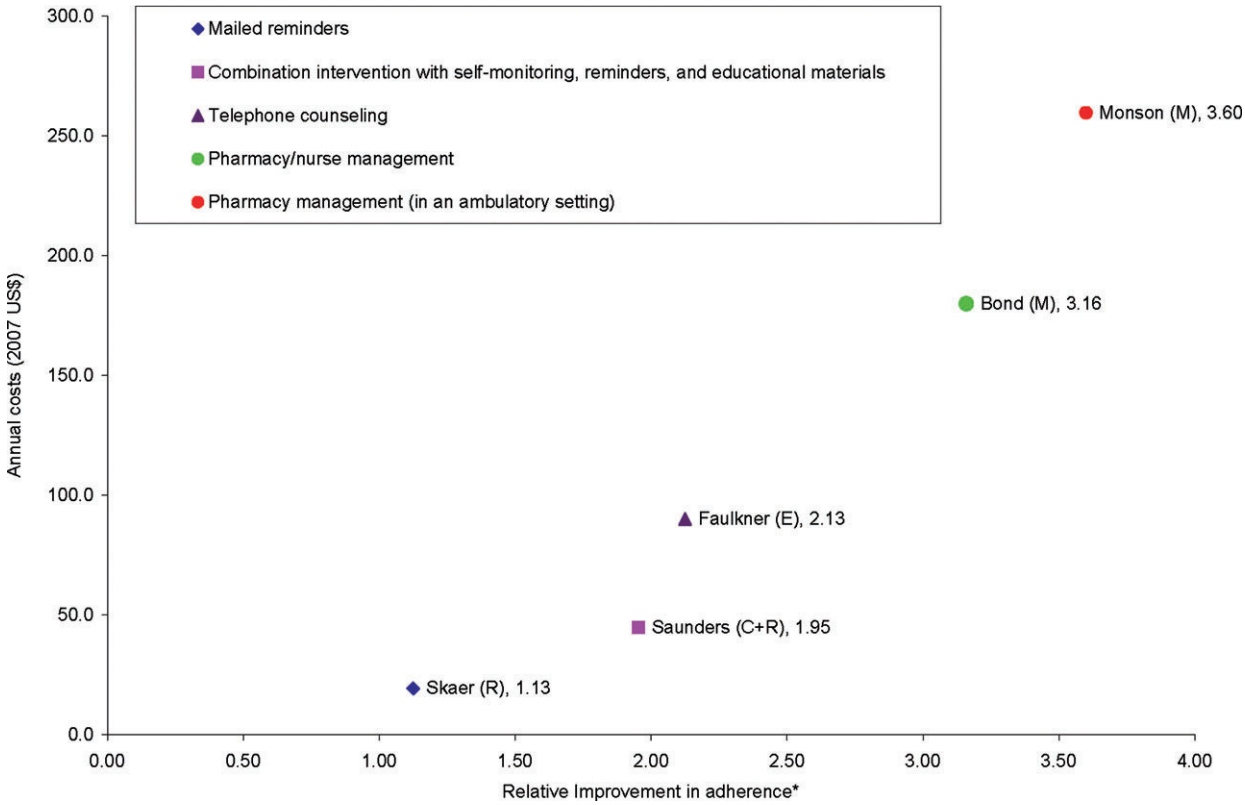

Figure 2 Costs versus Relative Improvement in adherence, by type of intervention. *Relative Improvement = adherence outcome reported in the intervention group divided by the adherence outcome reported in the control group. *C+R*, Combination + reminders; *E*, Education; *M*, Case management; *R*, Reminders.

Table 2 Mean (95% confidence interval [CI]) simulated cardiovascular events per person for selected adherence-improving interventions

Scenario	Mean age of death (years)	Cardiovascular event			Total
		Angina	Myocardial infarction	Stroke	
No adherence intervention*	80.7	0.135 (0.13–0.15)	0.230 (0.22–0.24)	0.210 (0.20–0.22)	0.575 (0.55–0.60)
Skaer [14] (*R*)	80.7	0.133 (0.13–0.14)	0.227 (0.22–0.24)	0.210 (0.20–0.22)	0.569 (0.55–0.59)
Saunders [19] (*C+R*)	80.7	0.133 (0.12–0.14)	0.226 (0.21–0.24)	0.208 (0.20–0.22)	0.567 (0.54–0.59)
Faulkner [11] (*E*)	80.7	0.133 (0.13–0.14)	0.226 (0.22–0.24)	0.208 (0.20–0.22)	0.567 (0.55–0.59)
Bond [6] (*M*)	80.8	0.132 (0.12–0.14)	0.222 (0.21–0.24)	0.206 (0.19–0.22)	0.560 (0.54–0.58)
Monson [10] (*M*)	80.8	0.130 (0.12–0.14)	0.222 (0.21–0.24)	0.206 (0.20–0.22)	0.557 (0.54–0.58)

*No adherence intervention = calcium channel blocker + statin only.
C+R, Combination + reminders; *E*, Education; *M*, Case management; *R*, Reminders.

management program (Bond and Monson [6]) (Table 4). (Monson [10] was an extension of the Bond and Monson [6] intervention, and was dominated for cost per life-year gained.) Compared with no adherence intervention, an intervention involving self-monitoring, reminders, and educational materials [19] had an ICER of $4984 per QALY gained, of $22,406 per cardiovascular event avoided, and of $3642 per life-year gained. The ICERs for a pharmacist/nurse management program [6] versus self-monitoring, reminders, and educational materials [19] were $6358 per QALY gained, $54,766 per cardiovascular event avoided, and $4973 per life-year gained.

Sensitivity Analyses

Our base-case analysis assumed that patients who were partially adherent (PDC between 21% and 79%) received 50% of the therapeutic effectiveness that would be obtained by a fully adherent patient. (Nonadherent patients, with PDC from 0% to 20%, were assumed to get no therapeutic effect.) In a one-way sensitivity analysis, this assumption was varied to assume 0%, 25%, 75%, and 100% of therapeutic effectiveness for the partially adherent patients. The results of these analyses are shown in Figure 3. As expected, QALYs gained increase, and costs decrease, as partial effectiveness increases. These increases were not linear however, as small variations in cost and effectiveness changed the rank-ordering of the adherence interventions. In general, the combination intervention with self-monitoring, reminders, and educational materials (Saunders et al. [19]), pharmacy and nurse management (Bond and Monson [6]), and pharmacist management in an ambulatory setting (Monson et al. [10]) remained relatively cost-effective.

A second set of sensitivity analyses was performed on the initial percentage of patients that were considered fully adherent to both medication types (antihypertensive and lipid-lowering). That proportion depends on assumptions about the correlation between rates of adherence to each medication type. If that correlation is higher, more patients will be adherent to both; if lower, we would expect fewer patients adherent to both (i.e., more patients adherent to one but not the other). To test the sensitivity of our results, the proportion of patients who were initially fully adherent was varied by ±25%. Results were not sensitive to 25% greater full adherence, with the same cost-effectiveness rankings as in the base-case (Table 4). Nevertheless, when 25% fewer patients were assumed to be fully adherent, only the intervention involving reminders alone (Skaer et al. [14]) and pharmacist management in an ambulatory setting (Monson et al. [10]) were found to be cost-effective.

Discussion

Despite an increased interest in improving adherence to therapies for CVD [5], there are relatively few controlled studies evaluating intervention strategies designed to improve adherence, and fewer still include a cost-effectiveness assessment. Also, the overall costs associated with these strategies for improving adherence with medications for CVD may vary widely, raising the question of which adherence intervention will provide the greatest benefit for the resources expended, and make the most economic sense to recommend for a health care environment.

In this study, we were able to successfully combine data from published interventions that improve adherence with antihypertensive and lipid-lowering agents into a burden of nonadherence framework [21]. By incorporating differences in adherence levels within the model, we were able to assess how these different adherence interventions would theoretically perform under a real-world patient care setting.

Among the published adherence interventions evaluated, a combination program involving self-monitoring, reminders, and educational materials [19] and a pharmacist/nurse management program [6] were estimated to be the most cost-effective methods of improving adherence with antihypertensive and lipid-lowering therapy in a real-world patient care setting. An intervention involving reminders alone [14] incurred the lowest per-patient costs, but was dominated by a combination program (i.e., provided less benefit for the cost), which additionally involved educational materials and self-monitoring [19]. Combination interventions address more than one cause of poor adherence, which may explain their effectiveness compared with single-intervention programs. For example, a single-intervention approach of offering weekly phone calls alone by a pharmacist to reinforce the importance of adherence [11] was not shown to be cost-effective relative to the other interventions in this analysis.

Using a standardization procedure, the present study has enabled a novel comparison of the efficacy of disparate adherence-improving interventions. We observed that despite incurring higher costs, a pharmacist/nurse adherence intervention program is cost-effective for improving adherence with antihypertensive and lipid-lowering therapies, in comparison with other interventions designed to improve adherence with CVD therapies. Furthermore, the comparison showed that even within pharmacist management approaches to improving adherence, the design of the program can impact its overall cost-effectiveness. For example, the additional costs of pharmacist's time through management in the ambulatory setting [10], where the pharmacist had sole responsibility for seeing the patient in a clinical setting and following up regarding compliance, side effects and advising about potential drug effects, did not make the intervention any more cost-effective.

The pharmacist/nurse management study by Bond and Monson, derived overall health-care cost savings through improved medication adherence, which were reported to be more than sufficient to compensate for costs of the clinical pharmacist and nurse required to provide the intervention program.

Table 3 Mean simulated costs (2007 US$) per person for selected adherence-improving interventions

Scenario	Intervention		Mean cost (2007 US$) per person (95% CI)				Total
			Angina	Myocardial infarction	Stroke	Prescription	
No adherence Intervention*	0	(0–0)	1,146 (1,045–1,252)	3,548 (3,290–3,784)	5,647 (5,271–6,024)	6,982 (6,867–7,083)	17,325 (16,873–17,802)
Skaer [14] (*R*)	19	(19–19)	1,117 (1,024–1,217)	3,474 (3,232–3,700)	5,594 (5,170–5,974)	7,301 (7,185–7,395)	17,505 (16,978–17,977)
Saunders [19] (*C+R*)	45	(45–45)	1,115 (1,018–1,217)	3,455 (3,214–3,676)	5,548 (5,200–5,936)	7,357 (7,247–7,450)	17,520 (17,069–17,987)
Faulkner [11] (*E*)	90	(90–90)	1,113 (1,012–1,223)	3,460 (3,220–3,720)	5,546 (5,172–5,927)	7,420 (7,323–7,529)	17,628 (17,190–18,096)
Bond [6] (*M*)	180	(180–180)	1,094 (994–1,190)	3,355 (3,149–3,616)	5,438 (5,064–5,869)	7,829 (7,730–7,936)	17,896 (17,420–18,360)
Monson [10] (*M*)	260	(260–260)	1,066 (979–1,158)	3,344 (3,120–3,601)	5,422 (5,049–5,813)	7,990 (7,883–8,074)	18,082 (17,604–18,522)

*No adherence intervention = calcium channel blocker + statin only.
C+R, Combination + reminders; CI, confidence interval; *E*, Education; *M*, Case management; *R*, Reminders.

Accordingly, they considered their adherence intervention program to be cost-effective. The data presented herein concur with their assessment that a pharmacist and nurse adherence reinforcement program could be cost-effective in the patient care setting. Indeed, their 6-month retrospective analysis demonstrated a significant improvement in drug documentation, compliance, and BP control compared with before the adherence intervention program. Most studies identified did not correlate health outcomes with improved adherence. Importantly, Bond and Monson reported a significant correlation between compliance (refill patterns) and adequate BP control [6], as reported by others [18,35]. Nevertheless, when interventions, such as this study by Bond and Monson, are assessed in isolation or versus a control group alone, comparative analyses of cost-effectiveness and economic viability are not feasible. Furthermore, studies are often carried out in a variety of patient populations, therefore complicating a direct comparison with another adherence intervention from a separate study. The present study extends the conclusion by Bond and Monson by suggesting that their pharmacist and nurse adherence reinforcement program is cost-effective versus other adherence-improving interventions for CVD therapies.

The present study also confirms an earlier analysis showing that, of eligible interventions, the most effective approaches for improving adherence, giving the highest Relative Improvement, were the personalized, intensive interventions, involving a pharmacist management programs [6,10] or weekly telephone counseling [11]. These intensive interventions, often providing individualized patient care, enable adherence with CVD therapies to be closely monitored. Indeed, the higher Relative Improvement was previously shown to be generally associated with studies [6,7,10] that required more than one visit or contact with a health-care professional during follow-up [20]. Adherence is a continuous process and may change over time. Therefore, regularly contacting patients and reinforcing the importance of medication and lifestyle compliance may allow health-care professionals to provide educational and psychological support at critical junctures. For example, adherence to antihypertensive and lipid-lowering therapy is known to decrease over time, particularly within the first 6 months of therapy [22,29,36]. In this manner, drug therapy and lifestyle modifications can be optimized during regular follow-up and any patient concerns appropriately managed. With optimized adherence with therapy on a patient-by-patient basis, each individual will be more likely to achieve their therapeutic goals [37–39]. But, as outlined, these interventions need to be balanced and assessed against their higher costs.

A number of factors need to be considered when evaluating the cost-effectiveness of any intervention or program designed to improve adherence with medications. For example, overall costs should be adjusted for a potential increase in the cost of medications because of the patient remaining more adherent with their therapy and potentially persisting with their treatment regimen for longer. Conversely, any reduction in overall cost of health-care services which may occur due to a patient remaining adherent with their medication should be accounted for. In the case of antihypertensive and lipid-lowering agents this will be driven by a reduction in cardiovascular events.

Using an analytic framework, we were able to adjust for the differing levels of adherence which are seen in real-world clinical practice [22,23]. A prior analysis demonstrated that, from a payer's perspective, increasing adherence to ideal levels with a program costing up to approximately US$8400 per patient would be as cost-effective as initiating this number of patients on dual antihypertensive and lipid-lowering therapies at real-world adherence, while also conferring absolute benefits in life expect-

Table 4 Incremental cost-effectiveness ratio (ICER) per quality-adjusted life-year (QALY) gained, per cardiovascular event avoided and per life-year gained

	Total		Incremental			
	Costs (2007 US$)	QALYs	Costs (2007 US$)	QALYs	ICER per QALY gained	ICER per QALY gained
ICER per QALY gained						
No adherence intervention*	17,325	14.97				
Skaer [14] (*R*)	17,505	15.00	179	0.031	5,712	dominated†
Saunders [19] (*C+R*)	**17,520**	**15.01**	**15**	**0.008**	**1,958**	**4,984**
Faulkner [11] (*E*)	17,628	15.01	109	0.006	17,229	dominated†
Bond [6] (*M*)	**17,896**	**15.07**	**267**	**0.053**	**5,059**	**6,358**
Monson [10] (*M*)	**18,082**	**15.07**	**186**	**0.004**	**45,110**	**45,110**
ICER per cardiovascular event avoided						
No adherence intervention*	17,325	0.58				
Skaer [14] (*R*)	17,505	0.57	179	–0.006	29,562	dominated†
Saunders [19] (*C+R*)	**17,520**	**0.57**	**15**	**–0.003**	**5,695**	**22,406**
Faulkner [11] (*E*)	17,628	0.57	109	0.001	dominated	dominated
Bond [6] (*M*)	**17,896**	**0.56**	**276**	**–0.007**	**54,766**	**54,766**
Monson [10] (*M*)	**18,082**	**0.56**	**186**	**–0.002**	**76,090**	**76,090**
ICER per life-year gained (undiscounted years)						
No adherence intervention*	17,325	21.94				
Skaer [14] (*R*)	17,505	21.98	179	0.041	4,391	dominated†
Saunders [19] (*C+R*)	**17,520**	**21.99**	**15**	**0.012**	**1,187**	**3,642**
Faulkner [11] (*E*)	17,628	22.00	109	0.012	8,904	dominated†
Bond [6] (*M*)	**17,896**	**22.07**	**267**	**0.063**	**4,216**	**4,973**
Monson [10] (*M*)	18,082	22.06	186	–0.001	dominated	dominated

*No adherence intervention = calcium channel blocker + statin only.
†Via extended dominance.
Bold type indicates interventions remaining after less effective/more costly interventions are eliminated.
C+R, Combination + reminders; *E*, Education; *M*, Case management; *R*, Reminders.

ancy and event reduction [21]. Accordingly, influencing factors such as changes in costs and adherence levels need to be taken into consideration when a complete cost-effectiveness assessment is undertaken.

The present study indicates that educating the patient is a key component of a cost-effective approach to improving adherence, as both the pharmacist/nurse management program [6] and the combined intervention [40] involved a large educational component. Nevertheless, despite health-care professionals being acutely aware of the morbidity and mortality risks associated with CVD, especially in the presence of uncontrolled risk factors, effective treatments are often not prescribed, or are utilized suboptimally [5]. Thus, a different approach is needed to address CVD risk reduction, and adherence interventions may help toward this objective. It is important also to note that pharmacists, nurses, or other trained health-care professionals are ideally positioned to supervise an adherence intervention program, encouraging early initiation and long-term maintenance of effective therapy [38,41]. The cost-effectiveness of a physician's assistant (extender) for dyslipidemia management has, for example, been reported versus usual care [39]. Conversely, a nurse-led adherence intervention program for BP control was not cost-effective versus usual care [42]. As discussed, personalized interventions need to be offset by higher costs and the nurse-led intervention costs, estimated to be approximately £357.20 per patient (approx. 2007 US$712.27) [42], were substantially higher than costs incurred in any of the management studies identified in the present study.

This study should be interpreted in light of some limitations. As with any literature-based analyses, these findings may be subject to a publication bias whereby positive findings are more likely to be published than negative findings. Nevertheless, negative studies would have been omitted during study selection, as we were only interested in reviewing studies that documented an adherence improvement. Observational studies have demonstrated an association between adherence with CVD medications above the 80% level and better therapeutic outcomes [1,2,4], and correspondingly, an intervention would need to improve adherence to have application in a patient care setting. Therefore, there would be little need to assess cost-effectiveness for negative studies, as an objective of this analysis was to offer prescriptive recommendations on which adherence interventions would confer the greatest benefits in real-world use. By excluding any studies that did not improve adherence, it is possible that cost-effectiveness is overestimated. Studies with negative findings might lead us to revise downward the expected benefits from similar interventions that found positive effects. Nevertheless, it is difficult to determine whether such differences in findings are due to differences in the interventions being evaluated rather than to a true variation across the same intervention. Although these negative findings are valid and useful from the perspective of providing information on aspects of interventions that may not work, we do not think they should be included in the present quantitative analysis.

The adherence intervention studies identified were highly heterogeneous with regard to study design, patient type, and compliance measurement reported. Nevertheless, steps were taken to standardize studies such that only eligible studies were included in the cost-effectiveness model and using a standardized population helped to remove this variable from the cost-effectiveness analysis. The stringent inclusion criteria may have excluded other adherence-improving interventions that were efficacious but could not be included because of their study design not complying with the criteria for this analysis. Comparison between the relative costs and effectiveness of these interventions necessitated calculation of standardized costs. To accomplish this, we truncated all interventions to a 6-month follow-up period and, to the extent possible, applied a common method to estimate both costs and effects.

The assumption was made that the hypothetical ASCOT-LLA-like population would not affect the outcome of the intervention and accordingly, no adjustments were made for differences between the patient populations included in each of

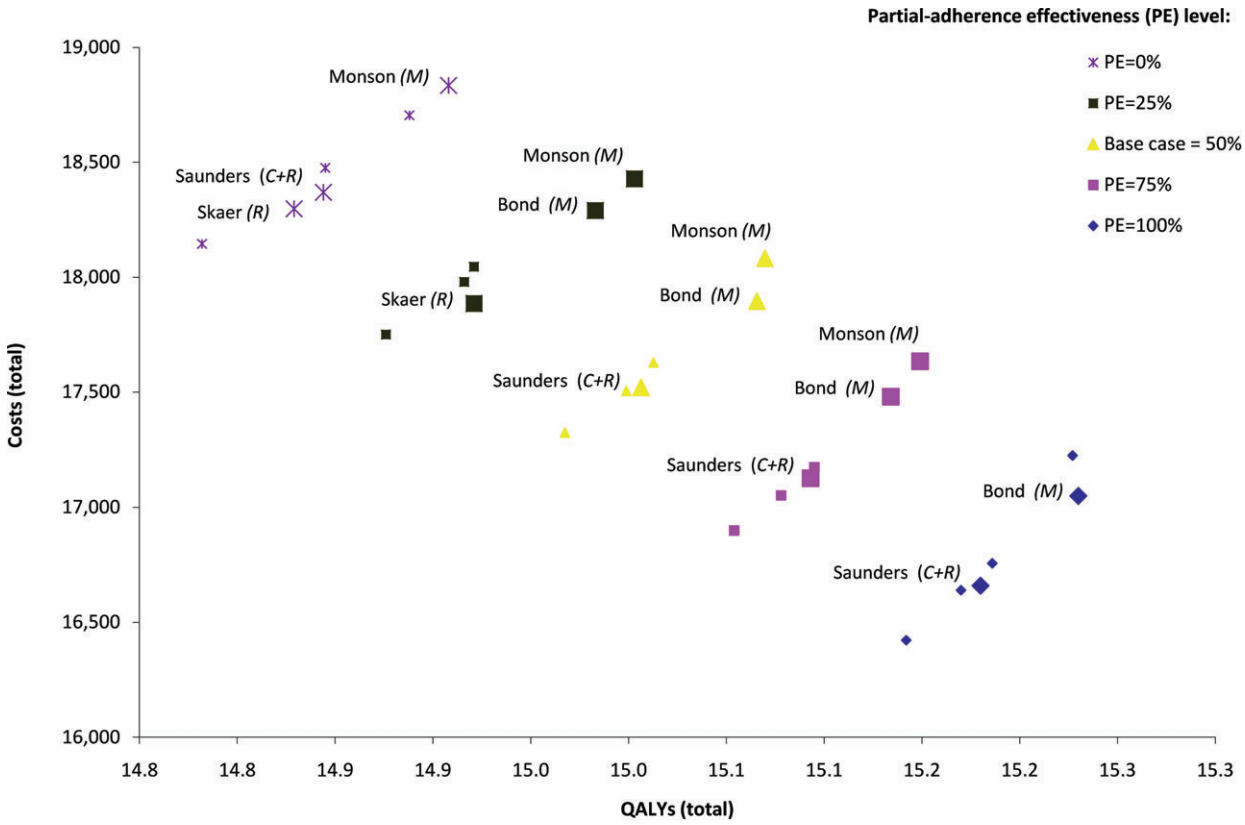

Figure 3 Total costs versus quality adjusted life-years (QALYs) for each intervention adjusted* by partial-adherence effectiveness (PE) level. *The base-case analysis assumed patients who were partially adherent (PDC 20–80%) received 50% of the therapeutic effectiveness that would be obtained by a fully adherent patient. In a one-way sensitivity analysis, this assumption was varied to assume 0%, 25%, 75%, and 100% of therapeutic effectiveness for the partially adherent patients. *C+R*, Combination + reminders; *E*, Education; *M*, Case management; *R*, Reminders.

the adherence-improving intervention studies identified. Using a single hypothetical population facilitated comparison of the adherence interventions within the model and prevented the need to adjust for any influence of different populations, such as age or existing comorbidities. Indeed, an independent study of the ASCOT population has shown that the two-pill amlodipine + atorvastatin combination is the cost-effective option over a lifetime horizon compared with amlodipine therapy alone [43], and thus supports the use of a CCB + statin combination in an ASCOT-LLA-like population as in the present cost-effectiveness analysis. We used any CCB + statin as the base-case comparator, and there is a possibility that different cardiovascular outcomes might result when using specific CCB and/or statin products. Nevertheless, using a general base-case comparison cohort enabled the same "no adherence intervention" group to be used for each intervention.

Limitations to the cost-effectiveness model have been published previously [21], and include assumptions on adherence rates after a cardiovascular event and the short-term interaction of adherence and effectiveness, and extrapolations of long-term effectiveness of antihypertensive and lipid-lowering therapy. Assessing adherence based on measures of PDC over time may overestimate actual drug-taking behavior because it assumes that patients take all of the medications for prescriptions that are filled. Additionally, in our analysis, a given day was assumed to be covered if any drug for the indication of interest was available. Such an approach is likely to be accurate for lipid-lowering therapy, which generally consists of statins alone. Nevertheless, for the treatment of hypertension, use of multiple drug regimens is common, and we may therefore have overestimated adherence with this method [21].

PDC has the advantage of simultaneously reflecting both compliance and persistence [27,28], and is an ideal measure for incorporation into Markov states of fixed duration. Future adherence studies should consider reporting PDC along with other measures of adherence and persistence, to facilitate comparisons across interventions. Ideally, adherence studies would include information on the distribution of medication possession ratio (MPR) or PDC as well as proportion of patients reaching an adherence threshold (e.g., MPR or PDC $\geq$ 80%). Improvements in study methodology and reporting standards will enable more robust comparisons of adherence interventions across studies, which may translate into more cost-effective uses of adherence-improving programs in clinical practice.

Past adherence research has identified a "healthy adherer" effect, whereby patients who are observed to be more adherent, even while taking placebo, tend to achieve better outcomes [44]. This effect has been attributed to the positive correlation between medication adherence behaviors and other healthy lifestyle choices. The burden of nonadherence model [21] did not adjust for baseline patient behavior or any differences in nonmedication adherent behaviors which could influence the likelihood of positive outcome. This is consistent with the choice of effectiveness estimates in the model, which were informed by the efficacy of treatments as observed in randomized clinical trials versus placebo, where adherence to active treatment and placebo was

similar. Therefore, modeled cost-effectiveness was based purely on the incremental efficacy expected by proper use of the active medication above no medication, and any difference in adherence behaviors for patients who have discontinued treatment compared with those who continued treatment would be a separate effect.

Our specification of adherence parameters may have some influence on cost-effectiveness estimates. Categorization of "*Nonadherent*" patients with PDC ≤20% included both patients with poor adherence and those that were totally nonadherent (e.g., PDC of 0). Therefore, these patients with low adherence behavior may receive some benefits from taking their antihypertensive and/or lipid-lowering medication and their event rate may be overestimated as a result. Additionally, the results of this analysis were found to be sensitive to changes in our assumptions around partial effectiveness and the percentage of patients fully adherent. Furthermore, the duration of therapeutic effects after discontinuation or reduction in adherence to medication is unknown, and patients may continue to see benefits after stopping therapy. The model assumed that a change in adherence resulted in a change in event risk within 1 year, as patients were assigned relative event risks based on current adherence status [21]. Nevertheless, through using transition probabilities in the model derived from filled prescription records from Medi-Cal data [33], adherence levels for patients beyond year 1 were based on long-term adherence patterns seen in a representative population. Despite these limitations, combining published data with a burden of nonadherence model has enabled a novel comparative analysis of the cost-effectiveness of different interventions that improve adherence.

Conclusion

The present study has successfully combined data describing different adherence-improving interventions for antihypertensive and lipid-lowering agents into a burden of nonadherence framework [21]. We were therefore able to use a standardized procedure to compare cost-effectiveness based on modeled costs across interventions from a variety of studies.

Of published adherence-improving interventions, reminders and educational materials and a pharmacist management program appear to be the most cost-effective, and should be considered before other types of intervention for improving adherence with antihypertensive and lipid-lowering therapy. Combining cost-effectiveness assessment and Relative Improvement, we feel that in particular a pharmacist/nurse management program should be considered before other types of published intervention for improving adherence with CVD therapies. This study provides a novel approach to assessing useful information on the relative cost-effectiveness of adherence interventions, which may help with both the design and successful implementation of efficient adherence-improving programs.

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