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Pharmacist Interventions for Medication Adherence: Community Guide Economic Reviews for Cardiovascular Disease

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Abstract

Introduction: Adherence to medications for cardiovascular disease (CVD) and its risk factors is less than optimal though greater adherence to medication has been shown to reduce the risk factors for CVD. This paper examines the economics of tailored pharmacy interventions to improve medication adherence for CVD prevention and management.

Methods: Literature from inception of databases to May 2019 was searched, yielding 29 studies for CVD prevention and 9 studies for CVD management. Analyses were done from June 2019 through May 2020. All monetary values are in 2019 U.S. dollars.

Results: The median intervention cost per patient per year was $246 for CVD prevention and $292 for CVD management. The median change in healthcare cost per person per year because of the intervention was −$355 for CVD prevention and −$2,430 for CVD management. The median

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total cost per person per year was −$89 for CVD prevention, with a median return on investment of 0.01. The median total cost per person per year for CVD management was −$1,080, with a median return on investment of 7.52 and 6 of 7 estimates indicating reduced healthcare cost averted exceeded intervention cost. For CVD prevention, the median cost per quality-adjusted life year gained was $11,298. There were no cost-effectiveness studies for CVD management.

Discussion: The evidence shows tailored pharmacy-based interventions to improve medication adherence are cost effective for CVD prevention. For CVD management, healthcare cost averted exceeds the cost of implementation for a favorable return on investment from a healthcare systems perspective.

INTRODUCTION

Greater adherence to medication is associated with reduction in risk factors for cardiovascular disease (CVD).[1–3] However, adherence to medications for CVD and CVD risk factors is less than optimal because the medications are not taken as prescribed.[4–6] Adherence is often indirectly measured using pharmacy dispensing data. A patient is commonly considered “adherent” to a medication if they have a supply of that medication ≥80% of the measured time period.[7] Among 1.8 million adults in 2001–2004 undergoing their first year of medication therapy, the percentage achieving adherence of ≥80% was 72.3% for hypertension, 65.4% for type 2 diabetes, and 54.6% for hypercholesterolemia.[8] A meta-analysis of >376,000 patients from 20 studies who were taking CVD preventive medications over the long term reported adherence rates of 50% for those with no prior myocardial infarction and 66% for those who have had a myocardial infarction.[6]

Medication non-adherence is associated with higher healthcare costs. A recent review based on 12 studies (9 from U.S.) of medication adherence for hypertension, dyslipidemia, and heart failure found that the mean annual incremental healthcare cost due to non-adherence ranged from $3,610 to just higher than $21,000.[9] A study by a large retail pharmacy chain found that higher medication costs incurred by adherent patients were recouped through lower overall healthcare costs for the group. The ratio of averted healthcare costs to medication costs for adherent patients was 10.1:1 for hypertension, 3.1:1 for dyslipidemia, 8.4:1 for congestive heart failure, and 6.7:1 for diabetes.[10]

Interventions that improve medication adherence can reduce CVD risk and reduce healthcare and other costs. Interventions delivered by pharmacists such as Medication Management Services,[11] including Medication Therapy Management services, have been proposed because Medication Therapy Managment services can identify and address patient-level barriers to adherence.[12–14] These interventions are tailored when adherence barriers are identified for each patient and they are provided guidance and services to reduce those barriers. In 2019, the Community Preventive Services Task Force (CPSTF), an independent, non-federal panel of population health experts,[15] recommended tailored pharmacy-based adherence interventions based on evidence from a systematic review of effectiveness in increasing patient adherence to medications for CVD prevention. CPSTF also found the intervention to be cost effective for CVD prevention based on a systematic economic review.[16] There were no studies of cost–benefit or cost-effectiveness analysis for CPSTF

to consider an economic finding for CVD management. The present study describes the process, results, and conclusions of the systematic economic review for CVD prevention and management.

The following research questions were addressed by the review:

- What is the cost to implement the interventions?
- What are the economic benefits of the interventions?
- How do intervention costs compare to economic benefits?
- Is the intervention cost effective?

METHODS

This study was conducted using established methods for systematic economic reviews developed by scientists at the Centers for Disease Control and Prevention and approved by CPSTF.[17] The study team included subject matter experts on CVD from various agencies, organizations, and academic institutions; CPSTF members; and experts in systematic economic reviews from the Community Guide Office at the Centers for Disease Control and Prevention. Two reviewers independently screened the search yield, abstracted information from the included studies, computed economic estimates, and scored each estimate for quality. Disagreements were resolved through discussions with the larger team.

Tailored pharmacy-based interventions aim to help patients with CVD risk conditions take their medications as prescribed. In the interventions recommended by CPSTF, community or health system pharmacies use assessment tools or interviews to identify adherence barriers for each patient and provide tailored guidance and services to reduce those barriers. Tailored guidance includes either focused medication counseling or motivational interviews. Services include ≥1 of the following: patient tools such as pillboxes, medication cards, and calendars; medication refill synchronization; and enhanced follow-up. Interventions may include additional components that align with the Pharmacists' Patient Care Process[16] such as patient education or communication and collaboration between the pharmacist and the patient's primary care provider. The interventions may be used alone, or they may be part of a broader intervention to reduce patients' CVD risk.

Several outcomes reported in economic evaluations relate to present review's research questions. The definitions of these outcomes are provided next.

Intervention cost.

Labor and materials are required to implement and deliver pharmacy-based adherence interventions. The intervention may be combined with additional interventions or may occur within interventions such as team-based care. The drivers of intervention cost are pharmacist and other staff salaries, the cost of patient education materials and adherence aids, and the cost of any added intervention.

Change in healthcare cost.

Improved adherence to medications is associated with reduction in risk factors such as high blood pressure, blood glucose, and cholesterol and subsequent CVD and comorbidities such as diabetes, retinopathy, neuropathy, and kidney failure, and thereby associate with decreased utilization of healthcare resources related to these conditions. All components of healthcare utilization are expected to change because of the intervention and are, therefore, considered to be cost drivers. Though reductions in hospitalization and emergency department visits are expected in the longer term, the cost of medication, laboratory testing, and office visits may increase simply because of greater adherence and refills in the shorter term. The net effect on healthcare cost is thus an empirical question, at least in the short term.

Total cost and return on investment.

Total cost is the sum of intervention cost and change in healthcare cost. Return on investment (ROI) is the ratio of the difference in intervention cost and change in healthcare cost to intervention cost. The ROI is from a healthcare systems perspective as the intervention cost is assumed to be borne by a healthcare payer and the only benefit considered is averted healthcare cost. A favorable economic outcome is indicated by negative values of total cost or ROI >0.

Life years lived.

Improved adherence to medications will prevent CVD and events, and increase both quantity and quality of life years lived. Economic evaluations measure this outcome as quality-adjusted life years (QALY) gained or disability-adjusted life years (DALY) averted.

Productivity.

Reduced morbidity and mortality also lead to greater productivity of patients at their worksites due to both increased number of work hours and increased output per hour of work.

Cost effectiveness.

Cost effectiveness is the total cost per QALY gained or the total cost per DALY averted. The CPSTF considers an intervention to be cost effective when the cost per QALY gained ≤$50,000[18] or the cost per DALY averted ≤ per capita gross domestic product of the relevant country.[19]

Quality Assessment of Evidence

Quality assessment.—Quality assessment was conducted for each estimate that contributed to the economic outcomes of interest: intervention cost and healthcare cost. Estimates that were modeled such as QALY were assessed for quality based on separate set of criteria. A quality assessment tool developed for the scope and objective of the present review along with full process description is in the Appendix (available online). Quality of capture was assessed as good, fair, or limited for each estimate for how well it captured the components that are deemed to be drivers of magnitude. Quality of measurement was

assessed as good, fair, or limited for each estimate for the appropriateness of design and statistical and analytic methods used to derive the estimates. The overall quality of an estimate was the lower of the quality assigned for capture and the quality assigned for measurement. Limited quality estimates were removed from the review. Finally, the quality assigned to estimates that were a combination of other estimates such as total cost per QALY gained was the lower of the quality assigned to total cost and QALY components. Key elements are briefly described in the following paragraph.

Quality based on capture of drivers was assigned to each estimate as good, fair, or limited as it included most, some, or almost none of the components considered to be drivers, respectively. The drivers of intervention cost were pharmacist and other staff wages and the cost of any additional intervention added to the pharmacy intervention. The drivers of healthcare cost were outpatient visits, inpatient stays, emergency department visits, medications, and labs. QALY estimates have no components and hence they are not examined for drivers. Next, quality of measurement was assessed for each estimate of intervention cost and healthcare cost based on limitation points for failing to follow appropriate measurement and statistical methods. Quality based on measurement was assigned to each estimate as good, fair, or limited as the number of limitations points were few, some, or many, respectively. The criteria for assessing limitation points were broadly classified into the domains of appropriate: population, analytic horizon, study or experiment design, data sources, and valuation. Briefly, limitation points for measurement were assigned for small sample size, populations that were predominantly young adults or seniors, time horizons that were too short to plausibly capture intervention effects, study designs that did not have an appropriate comparison group, economic outcomes that were not CVD-related, and others. For modeled estimates, additional criteria were considered for quality of measurement. Briefly, limitation points were assigned for model inputs not drawn from trials, short time horizons, model parameters without cited research, lack of sensitivity analysis, and others.

All monetary values are in 2019 U.S. dollars, adjusted for inflation using the Consumer Price Index from the Bureau of Labor Statistics,[20] and converted from foreign currency denominations using purchasing power parities from the World Bank.[21] Estimates are reported in per patient per year (PPPY) terms, wherever possible. Summaries of estimates are reported as medians along with interquartile intervals (IQIs) where there are ≥4 estimates. All analyses were conducted during June 2019 through May 2020.

Results are presented separately for studies of patients with existing CVD and studies with patients who are at risk for CVD. The rationale for the separation was the expectation that both the cost to implement the intervention and the effects on healthcare utilization, productivity, and life years lived would be different for CVD management and CVD prevention.

Search Strategy

A search of the peer-reviewed literature for economic evaluations was conducted with the following inclusion criteria: met the definition of the intervention, conducted in a high-income country,[22] written in English, and included ≥1 economic outcomes described in

the research questions. Searches were conducted in PubMed, Embase, MEDLINE, Scopus, Cochrane, ERIC, CINAHL, Sociological Abstracts, and EconLit for papers published from inception of databases to May 2019. Reference lists in included studies were screened and subject matter experts were consulted for additional studies. The detailed search strategy is available on The Community Guide website.[23]

RESULTS

Figure 1 shows the search yield for the economic review that resulted in 38 included studies, 29 studies[24–52] for CVD prevention and 9 studies[50,53–60] for CVD management. Of 15 studies of patients with diabetes, 6 studies[30,31,44,46,48,52] were for patients with a type 2 diagnosis and 9[27,33,36,38,40,41,49–51] had both type 1 and type 2 patients; the term "diabetes" will be used in this review to cover both types. Table 1 provides intervention and population characteristics. The median sample sizes were 169 patients for CVD prevention and 174 patients for CVD management. There were more female participants in the studies for CVD prevention compared with those for CVD management (median=56% vs 45%) and the patients were younger (median age=57 vs 65 years). The CVD prevention studies included patients with high blood pressure (10 studies),[25,26,28,29,35,37,39,42,44,47] dyslipidemia (4 studies),[28,33,44,48] diabetes (14 studies),[27,30,31,33,36,38,40,41,44,46,48,49,51,52] and a combination of CVD risk factors (9 studies).[24,32,34,43–45,49–51] The CVD management studies included patients with heart failure (3 studies),[56,57,60] CVD (5 studies),[53–55,58,59] and multiple cardiovascular conditions and diabetes (1 study).[50]

Studies were based in the U.S. (27 studies),[24,25,27–29,32,34,36–48,51–55,57,58] the Netherlands (2 studies),[26,50] the United Kingdom (2 studies),[49,59] Canada (2 studies),[35,60] China (Hong Kong; 2 studies),[30,33] Taiwan (1 study),[31] and Spain (1 study).[56] Studies were set in pharmacies (20 studies),[26,28,29,32,34–36,41,44,46–51,54,56,57,59,60] primary care clinics (13 studies),[24,25,30,31,33,37–40,42,52,53,55] a mix of the two (1 study),[45] or the facilities of pharmaceuticals benefits managers (3 studies).[27,43,58] The majority were implemented in urban areas (19 studies)[24,25,28–31,33–38,40,41,45,51,53,54,57] and others in a mix of urban and rural (9 studies).[27,32,39,43,44,47,48,50,58]

Pharmacist activities related to medication adherence occurred in every study because it was an inclusion criterion. Other pharmacist activities that were reported in each study are identified in the tables of results. The description of these activities are provided in greater detail in Appendix Table 1.The non-adherence-related actions taken by the pharmacist were: patient education in 52% of CVD prevention studies[24,27–31,33,34,36,46–48,50–52] and 56% of CVD management studies[50,56–58,60]; lifestyle counseling in 34% of CVD prevention[24,25,28,30,33,37–39,42,46] and 56% of CVD management studies[53,54,56,59,60]; and the resolution of drug-related problems in 69% of CVD prevention[24,25,27–34,37–40,42,43,45,46,49,52] and 78% of CVD management studies.[53–55,57–60] Goal-setting activities were in 38% of CVD prevention studies[25,26,28,34,36,39,40,43,45,49,51] and in 22% of CVD management studies.[55,58]

Quality of estimates.

Table 2 shows that the majority of intervention cost estimates were of good quality (17 estimates) with the remainder of fair quality (9 estimates). The most frequently limitations were failure to include cost of patient education materials or adherence aids. Healthcare cost estimates were mixed in quality with 15 good, 20 fair, and 5 of limited quality (Table 2). The most frequently assessed limitations were failure to include inpatient or emergency department costs, inclusion of medication cost only, and estimates based on all causes rather than only CVD and risk factors. Limited quality estimates were excluded from consideration.

Intervention cost.

Table 2 shows that the median cost PPPY for interventions to prevent CVD was $246 (IQI=$95, $499), based on 20 estimates from 19 studies.[26,30–33,35,37–39,41–43,45–51] The median cost PPPY for interventions to manage CVD was $292 (IQI=$96, $422), based on 6 estimates from 6 studies.[50,53,56–59] Separating out the U.S. studies but not shown in the table, the median intervention cost PPPY was $467 (IQI=$254, $577)[32,37–39,41–43,45–48,51,52] and mean intervention cost PPPY was $514 (range=$372–$731)[53,57,58] for CVD prevention and CVD management, respectively. Intervention cost was substantially higher in the U.S. compared with other high-income countries.

The dispersion of intervention cost was partly explained by the size of the intervention group, with smaller intervention cost associated with larger groups for both studies of CVD prevention and those of CVD management. For the CVD prevention studies, the median intervention cost for estimates of good quality was $256 (IQI=$146, $504),[31–33,35,37–39,41,42,46–51] not shown in the table. This median for higher-quality estimates was only marginally higher than the median of $246 reported for all estimates. There were too few estimates of intervention cost from the CVD management studies to compare between good- and fair-quality estimates.

The median intervention cost PPPY was higher for CVD management at $292 than for CVD prevention at $246 (Table 2). The difference was not due to sample size because the median sample size of 169 for CVD prevention is close to the174 for CVD management. The table also shows there was little difference between studies of CVD prevention and CVD management in terms of intervention setting or pharmacist activities to explain the difference in median cost.

Healthcare cost.

Table 2 shows that the median change in healthcare cost PPPY for interventions to prevent CVD was −$355 (IQI= −$977, −$33), based on 21 estimates from 19 studies.[24,26,27,29–31,33,35,37,39,41,43–46,48–51] The median change in healthcare cost PPPY for interventions to manage CVD was −$2,430 (IQI= −$5,062, −$700), based on 7 estimates from 7 studies.[50,53,56–60] Separating out the U.S. studies but not shown in the table, the median healthcare cost averted PPPY was −$376 (IQI= −$898, −$112)[24,27,29,37,39,41,43–46,48,51] and mean healthcare cost averted PPPY was −$10,983 (range= −$26,216 to −$2,430)[53,57,58] for CVD prevention and CVD management,

respectively. Healthcare cost averted in CVD management was substantially larger in the U.S. compared with other high-income countries.

The median of the good quality estimates of change in healthcare cost for CVD prevention was −$376 (IQI=$741, −$249),[27,39,41,43,44,51] slightly higher than the median of −$355 reported for all estimates in absolute value. The median of the good-quality estimates in CVD management was −$2,283 (IQI= −$4,683, −$258),[50,57,59,60] lower than the median of −$2,430 reported for all estimates in absolute value. Somewhat counterinuitively, better capture of drivers of healthcare cost such as emergency department visits and inpatient stays produced estimates of healthcare cost avoidance that were higher for prevention and lower for management.

By contrast, the averted healthcare cost for CVD management was higher, with a median of $2,430 compared with $355 for CVD prevention. The difference in effect on healthcare cost is not likely due to either setting or pharmacist activities because they did not differ between the 2 sets of studies (Table 2). Among the 9 studies[50,53–60] of CVD management, 1 study[53] reported blood pressure and low-density lipoprotein cholesterol control improved, 1 study[55] reported reduction in low-density lipoprotein cholesterol, 1 study[59] found no change in guideline-concordant treatment, and 2 studies[50,57] did not report any clinical outcomes. Two studies were implemented among patients selected from hospital discharges. The study[56] for post-heart failure discharge found the intervention group had 54% less all-cause readmissions at 2 months and 32% less at 6 months. The other study[58] for post-cardiovascular condition discharges found a risk ratio of 0.55 for 30-day readmission. The poor reporting of intermediate clinical outcomes related to the medications makes it difficult to draw a causal argument from the adherence improving intervention to healthcare cost averted.

Total cost and return on investment.

Total cost was measured as the sum of the change in healthcare cost due to intervention and the cost of intervention; a negative value indicates averted healthcare cost exceeds intervention cost. Estimates are shown in Table 3. The median total cost PPPY for interventions to prevent CVD was −$89 (IQI= −$656, $209), based on 21 estimates from 20 studies.[25,26,28,30,31,33,35–37,39–41,43,45,46,48–52] The total cost estimates for CVD prevention were mixed, with 9 estimates[25,26,31,37,39,41,49–51] reporting positive total cost and 12 estimates[28,30,33,35,36,40,43,45,46,48,51,52] reporting negative total cost. The median total cost PPPY for interventions to manage CVD was −$1,080 (IQI= −$2,816, −$163), based on 7 estimates from 7 studies.[50,53,55–59] For all but one[55] of the estimates, the reduced healthcare cost exceeded the cost of intervention. Separating out the U.S. studies but not shown in the table, the median total cost PPPY was −$187 (IQI= −$636, $176)[25,28,36,37,39–41,43,45,46,48,51,52] and −$2,816 (IQI= −$9,394, −$1,132)[53,55,57,58] for CVD prevention and CVD management, respectively. Total cost for CVD prevention was not much larger in the U.S compared to other high-income countries, with the IQI crossing 0 in both cases. However, total cost took substantially larger negative values, indicating cost savings, for CVD management in U.S studies compared with other high-income countries.

Of the 4 studies[53,55,57,59] of interventions to manage CVD that provided estimates for components of healthcare cost, 1 study[59] had inpatient cost accounting for >90% of the averted cost, 2 studies[53,57] had 70%, and 1 study[55] showed 10% of healthcare cost savings was attributable to inpatient stays. The median ROI for CVD prevention was 0.01 (IQI= –0.83, 3.25), based on 16 estimates from 15 studies.[26,30,31,33,35,37,39,41,43,45,46,48–51] The median ROI for CVD management was 7.52 (IQI=2.86, 16.62), based on 6 estimates from 6 studies.[50,53,56–59] A value of ROI >0 indicates a favorable economic outcome from a healthcare systems perspective.

Cost effectiveness.

The median cost per QALY gained for interventions to prevent CVD was $11,298 (IQI=$5,660, $28,416), based on 5 estimates from 5 studies[26,39,42,49,50] (Table 3). The median and third quartile were below a conservative $50,000 threshold.[18] Only 1 estimate[26] was above the threshold and that study computed cost per QALY based on health outcomes within a 9-month trial period. There were no studies that reported cost-effectiveness outcomes for interventions to manage CVD; however, total cost estimates showed that 6 of 7 estimates for averted healthcare cost exceeded the intervention cost, substantially from averted inpatient stays as noted earlier.

DISCUSSION

The study reviewed the cost, benefit, cost–benefit, and cost-effectiveness evidence for tailored pharmacy-based interventions to improve adherence to CVD medications. A Separate assessment of the evidence was conducted for the interventions implemented to prevent CVD and the interventions to manage CVD. The evidence indicates the interventions for the prevention of CVD were cost effective. There were no studies that reported cost-effectiveness outcomes for CVD management; however, 6 of 7 studies found that the healthcare costs averted exceeded the intervention costs.

Tailored pharmacy-based medication adherence interventions are cost effective in improving medication adherence for CVD prevention, and it is inferred that improved health outcomes result from adherence.[61–68] From the perspective of a healthcare system, the healthcare cost averted exceeds the cost to implement the interventions for CVD management. These findings may be used to inform local consideration of tailored pharmacy-based interventions for patients at risk for CVD (i.e., hypertension, diabetes, dyslipidemia, and chronic kidney disease). For patients with new or existing CVD, pharmacy-based adherence support can complement other health system interventions, such as structured cardiac rehabilitation and mobile health programs[69,70] to reinforce provider messages and encourage patients in their treatment adherence efforts.

It was noted that the averted healthcare cost for CVD management was much larger than for prevention, with a median of $2,430 and $355, respectively. This is likely a consequence of the much higher probability of CVD events even in the near term among patients who were older (median age=65 vs 58 years) and with existing CVD conditions[71] such as heart failure in the studies for CVD management compared with those for CVD prevention (Table 1). The interventions for CVD management where averted healthcare cost exceed the intervention

cost may also be cost effective from the societal perspective, if the changes in QALY/DALY are in the favorable direction. The review therefore also examined the clinical indicators for blood pressure, cholesterol, and blood glucose in the studies that reported estimates of total cost, which is the sum of intervention cost and healthcare cost averted (Table 3). Although it could not be concluded from the relatively small number of studies that observed reductions in healthcare cost were directly a consequence of improved health, 2 studies did report favorable impacts on blood pressure and cholesterol. Numerous other studies have demonstrated the benefit of reducing blood pressure, glucose, lipids, albuminuria, and serum creatinine on healthcare resource consumption, progression of disease, incidence of comorbidities, and cardiovascular and renal events.[61–68] This suggests that adherence to medication therapy in accordance with evidence-based treatment guidelines is important to reducing cardiovascular and renal events.[72–78] However, additional research is needed to validate a causal relationship between tailored pharmacy-based interventions aimed at improving medication adherence and improved health and economic outcomes.

The availability of these interventions in the U.S. varies. Availability may be particularly limited for those without health insurance coverage. For individuals with health insurance coverage, there is significant variation in reimbursement and patient eligibility for pharmacist-provided services outside of dispensing.[79,80] Despite variations in reimbursement, some pharmacies may attempt to provide these services to enhance patient care. However, the lack of available reimbursement opportunities limits availability.[81]

Limitations

There were no cost-effectiveness studies for CVD management. Most studies were implemented in urban areas and it is unclear what the economic outcomes might be when implemented in rural settings. Most studies of the intervention for CVD management did not report clinical outcomes that may be associated with the observed reductions in healthcare cost. These economic evaluations would be more helpful to the field if they included patient health outcomes (e.g., blood pressure, cholesterol) in their reports. The estimates for components of healthcare cost were often not reported in addition to the totals, thus precluding determination of which components of healthcare use led to the greatest changes in healthcare cost.

CONCLUSIONS

The systematic economic review finds tailored pharmacy-based interventions to improve medication adherence to prevent CVD are cost effective based on a median estimate of $11,298 per QALY gained, which is below a conservative $50,000 threshold. For CVD management, economic evidence indicates that the healthcare cost averted exceeds the cost of implementation with a median ROI of 7.52 from a healthcare systems perspective.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCES

1. Glader E-L, lander M, Eriksson M, Lundberg M. Persistent use of secondary preventive drugs declines rapidly during the first 2 years after stroke. Stroke. 2010;41(2):397–401. 10.1161/strokeaha.109.566950. [PubMed: 20075360]
2. Herttua K, Tabak AG, Martikainen P, Vahtera J, Kivimaki M. Adherence to antihypertensive therapy prior to the first presentation of stroke in hypertensive adults: population-based study. Eur Heart J. 2013;34(38):2933–2939. 10.1093/eurheartj/eht219. [PubMed: 23861328]
3. Ho PM, Magid DJ, Masoudi FA, McClure DL, Rumsfeld J. Adherence to cardioprotective medications and mortality among patients with diabetes and ischemic heart disease. BMC Cardiovasc Disord. 2006;6:48. 10.1186/1471-2261-6-48. [PubMed: 17173679]
4. Centers for Disease Control and Prevention. CDC Public Health Grand Rounds: Overcoming Barriers to Medication Adherence for Chronic Diseases. https://www.cdc.gov/grand-rounds/pp/2017/20170221-presentation-medication-adherence-H.pdf. Published 2017. Accessed October 1, 2021.
5. Viswanathan M, Golin CE, Jones CD, et al. Closing the quality gap: revisiting the state of the science (vol. 4: medication adherence interventions: comparative effectiveness). Evid Rep Technol Assess (Full Rep). 2012;(208.4):1–685.
6. Naderi SH, Bestwick JP, Wald DS. Adherence to drugs that prevent cardiovascular disease: meta-analysis on 376,162 patients. Am J Med. 2012;125(9):882–887.e1. 10.1016/j.amjmed.2011.12.013. [PubMed: 22748400]
7. Crowe M Do you know the difference between these adherence measures. Pharm Times. July 6, 2015. https://www.pharmacytimes.com/view/do-you-know-the-difference-between-these-adherence-measures. Accessed September 27, 2021.
8. Briesacher BA, Andrade SE, Fouayzi H, Chan KA. Comparison of drug adherence rates among patients with seven different medical conditions. Pharmacotherapy. 2008;28(4):437–443. 10.1592/phco.28.4.437. [PubMed: 18363527]
9. Cutler RL, Fernandez-Llimos F, Frommer M, Benrimoj C, Garcia-Cardenas V. Economic impact of medication non-adherence by disease groups: a systematic review. BMJ Open. 2018;8(1):e016982. 10.1136/bmjopen-2017-016982.
10. Roebuck MC, Liberman JN, Gemmill-Toyama M, Brennan TA. Medication adherence leads to lower health care use and costs despite increased drug spending. Health Aff (Millwood). 2011;30(1):91–99. 10.1377/hlthaff.2009.1087. [PubMed: 21209444]
11. Joint Commission of Pharmacy Practitioners. Medication Management Services (MMS) Definition and Key Points. https://jcpp.net/wp-content/uploads/2018/05/Medication-Management-Services-Definition-and-Key-Points-Version-1.pdf. Published March 14, 2018. Accessed September 27, 2021.
12. Martinez-Mardones F, Fernandez-Llimos F, Benrimoj SI, et al. Systematic review and meta-analysis of medication reviews conducted by pharmacists on cardiovascular diseases risk factors in ambulatory care. J Am Heart Assoc. 2019;8(22):e013627. 10.1161/jaha.119.013627. [PubMed: 31711390]
13. Mc Namara K, Alzubaidi H, Jackson JK. Cardiovascular disease as a leading cause of death: how are pharmacists getting involved? Integr Pharm Res Pract. 2019;8:1–11. 10.2147/iprp.s133088. [PubMed: 30788283]
14. Pina IL, Di Palo KE, Brown MT, et al. Medication adherence: importance, issues and policy: a policy statement from the American Heart Association. Prog Cardiovasc Dis. 2021;64:111–120. 10.1016/j.pcad.2020.08.003. [PubMed: 32800791]

15. The Guide to Community Preventive Services (the Community Guide). About the Community Preventive Services Task Force. https://www.thecommunityguide.org/task-force/community-preventive-services-task-force-members. Accessed September 27, 2021.
16. The Guide to Community Preventive Services (the Community Guide). Cardiovascular Disease: Tailored Pharmacy-based Interventions to Improve Medication Adherence. Snapshot. https://www.thecommunityguide.org/findings/cardiovascular-disease-tailored-pharmacy-based-interventions-improve-medication-adherence. Accessed September 27, 2021.
17. The Guide to Community Preventive Services (the Community Guide). Methods Manual - Part 2: Economic Review Process. https://www.thecommunityguide.org/methods-manual/economic-review-methods. Accessed September 30, 2021.
18. Eichler HG, Kong SX, Gerth WC, Mavros P, Jönsson B. Use of cost-effectiveness analysis in health-care resource allocation decision-making: how are cost-effectiveness thresholds expected to emerge? Value Health. 2004;7(5):518–528. 10.1111/j.1524-4733.2004.75003.x. [PubMed: 15367247]
19. WHO Commission on Macroeconomics and Health, WHO. Macroeconomics and health: investing in health for economic development: executive summary/report of the Commission on Macroeconomics and Health. WHO; 2001. https://apps.who.int/iris/handle/10665/42463.
20. Bureau of Labor Statistics. Databases, Tables & Calculators by Subject: CPI for All Urban Consumers (CPI-U). https://data.bls.gov/timeseries/CUUR0000SA0?output_view=pct_1mth. Accessed September 27, 2021.
21. The World Bank. Purchasing Power Parities. PPP conversion factor, private consumption. https://data.worldbank.org/indicator/PA.NUS.PRVT.PP. Accessed September 27, 2021.
22. The World Bank. World Bank Country and Lending Groups. https://data.worldbank.org/about/country-and-lending-groups. Accessed September 27, 2021.
23. The Guide to Community Preventive Services (the Community Guide). Cardiovascular Disease: Tailored Pharmacy-based Interventions to Improve Medication Adherence. Supporting materials: Search Strategies – Economic Review. https://www.thecommunityguide.org/findings/cardiovascular-disease-tailored-pharmacy-based-interventions-improve-medication-adherence. Accessed September 27, 2021.
24. Altavela JL, Jones MK, Ritter M. A prospective trial of a clinical pharmacy intervention in a primary care practice in a capitated payment system. J Manag Care Pharm. 2008;14(9):831–843. 10.18553/jmcp.2008.14.9.831. [PubMed: 19006440]
25. Borenstein JE, Graber G, Saltiel E, et al. Physician-pharmacist comanagement of hypertension: a randomized, comparative trial. Pharmacotherapy. 2003;23(2):209–216. 10.1592/phco.23.2.209.32096. [PubMed: 12587810]
26. Bosmans JE, van der Laan DM, Yang Y, et al. The cost-effectiveness of an intervention program to enhance adherence to antihypertensive medication in comparison with usual care in community pharmacies. Front Pharmacol. 2019;10:210. 10.3389/fphar.2019.00210. [PubMed: 30899223]
27. Brophy L, Williams A, Berman EJ, et al. Collaborative DTM reduces hospitalization and healthcare costs in patients with diabetes treated with polypharmacy. Am J Manag Care. 2014;20(3):e72–e81. [PubMed: 24773329]
28. Bunting BA, Smith BH, Sutherland SE. The Asheville Project: clinical and economic outcomes of a community-based long-term medication therapy management program for hypertension and dyslipidemia. J Am Pharm Assoc (2003). 2008;48(1):23–31. 10.1331/japha.2008.07140. [PubMed: 18192127]
29. Carter BL, Barnette DJ, Chrischilles E, Mazzotti GJ, Asali ZJ. Evaluation of hypertensive patients after care provided by community pharmacists in a rural setting. Pharmacotherapy. 1997;17(6):1274–1285. [PubMed: 9399611]
30. Chan CW, Siu SC, Wong CK, Lee VW. A pharmacist care program: positive impact on cardiac risk in patients with type 2 diabetes. J Cardiovasc Pharmacol Ther. 2012;17(1):57–64. 10.1177/1074248410396216. [PubMed: 21335480]
31. Chen JH, Ou HT, Lin TC, Lai EC, Kao YH. Pharmaceutical care of elderly patients with poorly controlled type 2 diabetes mellitus: a randomized controlled trial. Int J Clin Pharm. 2016;38(1):88–95. 10.1007/s11096-015-0210-4. [PubMed: 26499503]

32. Christensen DB, Roth M, Trygstad T, Byrd J. Evaluation of a pilot medication therapy management project within the North Carolina State Health Plan. J Am Pharm Assoc. 2007;47(4):471–483. 10.1331/japha.2007.06111.
33. Chung JS, Lee KK, Tomlinson B, Lee VW. Clinical and economic impact of clinical pharmacy service on hyperlipidemic management in Hong Kong. J Cardiovasc Pharmacol Ther. 2011;16(1):43–52. 10.1177/1074248410380207. [PubMed: 20924095]
34. Connor SE, Snyder ME, Snyder ZJ, Pater Steinmetz K. Provision of clinical pharmacy services in two safety net provider settings. Pharm Pract (Granada). 2009;7(2):94–99. 10.4321/s1886-36552009000200005. [PubMed: 25152784]
35. Cote I, Gregoire JP, Moisan J, Chabot I, Lacroix G. A pharmacy-based health promotion programme in hypertension: cost-benefit analysis. Pharmacoeconomics. 2003;21(6):415–428. 10.2165/00019053-200321060-00005. [PubMed: 12678568]
36. Cranor CW, Bunting BA, Christensen DB. The Asheville Project: long-term clinical and economic outcomes of a community pharmacy diabetes care program. J Am Pharm Assoc. 2003;43(2):173–184. 10.1331/108658003321480713.
37. Dehmer SP, Maciosek MV, Trower NK, et al. Economic evaluation of the home blood pressure telemonitoring and pharmacist case management to control hypertension (Hyperlink) trial. J Am Coll Clin Pharm. 2018;1(1):21–30. 10.1002/jac5.1001. [PubMed: 30320302]
38. Fabel PH, Wagner T, Ziegler B, Fleming PA, Davis RE. A sustainable business model for comprehensive medication management in a patient-centered medical home. J Am Pharm Assoc (2003). 2019;59(2):285–290. 10.1016/j.japh.2018.11.001. [PubMed: 30611660]
39. Fishman PA, Cook AJ, Anderson ML, et al. Improving BP control through electronic communications: an economic evaluation. Am J Manag Care. 2013;19(9):709–716. [PubMed: 24304254]
40. Isetts BJ, Brummel AR, de Oliveira DR, Moen DW. Managing drug-related morbidity and mortality in the patient-centered medical home. Med Care. 2012;50(11):997–1001. 10.1097/mlr.0b013e31826ecf9a. [PubMed: 23047790]
41. Kraemer DF, Kradjan WA, Bianco TM, Low JA. A randomized study to assess the impact of pharmacist counseling of employer-based health plan beneficiaries with diabetes: the EMPOWER study. J Pharm Pract. 2012;25(2):169–179. 10.1177/0897190011418513. [PubMed: 21987530]
42. Kulchaitanaroaj P, Brooks JM, Chaiyakunapruk N, Goedken AM, Chrischilles EA, Carter BL. Cost-utility analysis of physician-pharmacist collaborative intervention for treating hypertension compared with usual care. J Hypertens. 2017;35(1):178–187. 10.1097/hjh.0000000000001126. [PubMed: 27684354]
43. Moore JM, Shartle D, Faudskar L, Matlin OS, Brennan TA. Impact of a patient-centered pharmacy program and intervention in a high-risk group. J Manag Care Pharm. 2013;19(3):228–236. 10.18553/jmcp.2013.19.3.228. [PubMed: 23537457]
44. Pringle JL, Boyer A, Conklin MH, McCullough JW, Aldridge A. The Pennsylvania Project: pharmacist intervention improved medication adherence and reduced health care costs. Health Aff (Millwood). 2014;33(8):1444–1452. 10.1377/hlthaff.2013.1398. [PubMed: 25092847]
45. Ramalho de Oliveira D, Brummel AR, Miller DB. Medication therapy management: 10 years of experience in a large integrated health care system. J Manag Care Pharm. 2010;16(3):185–195. 10.18553/jmcp.2010.16.3.185. [PubMed: 20331323]
46. Rashed SM, Goldstein S, Tolley E, Wilson-Relyea BJ. Cost outcomes of diabetes education in a specialized community pharmacy. Am J Pharm Benefits. 2010;2(7):421–428.
47. Shireman TI, Svarstad BL. Cost-effectiveness of Wisconsin TEAM model for improving adherence and hypertension control in black patients. J Am Pharm Assoc (2003). 2016;56(4):389–396. 10.1016/j.japh.2016.03.002. [PubMed: 27184784]
48. Spence MM, Makarem AF, Reyes SL, et al. Evaluation of an outpatient pharmacy clinical services program on adherence and clinical outcomes among patients with diabetes and/or coronary artery disease. J Manag Care Pharm. 2014;20(10):1036–1045. 10.18553/jmcp.2014.20.10.1036.
49. Twigg MJ, Wright D, Barton G, Kirkdale CL, Thornley T. The pharmacy care plan service: evaluation and estimate of cost-effectiveness. Res Social Adm Pharm. 2019;15(1):84–92. 10.1016/j.sapharm.2018.03.062. [PubMed: 29610052]

50. Vegter S, Oosterhof P, van Boven JF, Stuurman-Bieze AG, Hiddink EG, Postma MJ. Improving adherence to lipid-lowering therapy in a community pharmacy intervention program: a cost-effectiveness analysis. J Manag Care Spec Pharm. 2014;20(7):722–732. 10.18553/jmcp.2014.20.7.722. [PubMed: 24967525]
51. Wertz D, Hou L, DeVries A, et al. Clinical and economic outcomes of the Cincinnati Pharmacy Coaching Program for diabetes and hypertension. Manag Care. 2012;21(3):44–54.
52. Yu J, Shah BM, Ip EJ, Chan J. A Markov model of the cost-effectiveness of pharmacist care for diabetes in prevention of cardiovascular diseases: evidence from Kaiser Permanente Northern California. J Manag Care Pharm. 2013;19(2):102–114. 10.18553/jmcp.2013.19.2.102. [PubMed: 23461426]
53. Delate T, Olson KL, Rasmussen J, et al. Reduced health care expenditures after enrollment in a collaborative cardiac care service. Pharmacotherapy. 2010;30(11):1127–1135. 10.1592/phco.30.11.1127. [PubMed: 20973686]
54. Ditusa L, Luzier AB, Brady PG, Reinhardt RM, Snyder BD. A pharmacy-based approach to cholesterol management. Am J Manag Care. 2001;7(10):973–979. [PubMed: 11669361]
55. Ellis SL, Carter BL, Malone DC, Billups SJ, Okano GJ, Valuck RJ, et al. Clinical and economic impact of ambulatory care clinical pharmacists in management of dyslipidemia in older adults: the IMPROVE study. Pharmacotherapy. 2000;20(12):1508–1516. 10.1592/phco.20.19.1508.34852. [PubMed: 11130223]
56. Lopez Cabezas C, Falces Salvador C, Cubi Quadrada D, et al. Randomized clinical trial of a postdischarge pharmaceutical care program vs regular follow-up in patients with heart failure. Farm Hosp. 2006;30(6):328–342. 10.1016/s1130-6343(06)74004-1. [PubMed: 17298190]
57. Murray MD, Young J, Hoke S, al. Pharmacist intervention to improve medication adherence in heart failure: a randomized trial. Ann Intern Med. 2007;146(10):714–725. 10.7326/0003-4819-146-10-200705150-00005. [PubMed: 17502632]
58. Polinski JM, Moore JM, Kyrychenko P, et al. An insurer's care transition program emphasizes medication reconciliation, reduces readmissions and costs. Health Aff (Millwood). 2016;35(7):1222–1229. 10.1377/hlthaff.2015.0648. [PubMed: 27385237]
59. Scott A, Tinelli M, Bond C, Community Pharmacy Medicines Management Evaluation Team. Costs of a community pharmacist-led medicines management service for patients with coronary heart disease in England: healthcare system and patient perspectives. Pharmacoeconomics. 2007;25(5):397–411. 10.2165/00019053-200725050-00004. [PubMed: 17488138]
60. Tsuyuki RT, Fradette M, Johnson JA, et al. A multicenter disease management program for hospitalized patients with heart failure. J Card Fail. 2004;10(6):473–480. 10.1016/j.cardfail.2004.02.005. [PubMed: 15599837]
61. Afkarian M, Sachs MC, Kestenbaum B, et al. Kidney disease and increased mortality risk in type 2 diabetes. J Am Soc Nephrol. 2013;24(2):302–308. 10.1681/asn.2012070718. [PubMed: 23362314]
62. Bakris GL, Williams M, Dworkin L, et al. Preserving renal function in adults with hypertension and diabetes: a consensus approach. National Kidney Foundation Hypertension and Diabetes Executive Committees Working Group. Am J Kidney Dis. 2000;36(3):646–661. 10.1053/ajkd.2000.16225. [PubMed: 10977801]
63. Brenner BM, Cooper ME, de Zeeuw D, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med. 2001;345(12):861–869. 10.1056/nejmoa011161. [PubMed: 11565518]
64. Drury PL, Ting R, Zannino D, et al. Estimated glomerular filtration rate and albuminuria are independent predictors of cardiovascular events and death in type 2 diabetes mellitus: the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study. Diabetologia. 2011;54(1):32–43. 10.1007/s00125-010-1854-1. [PubMed: 20668832]
65. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med. 2004;351(13):1296–1305. 10.1056/nejmoa041031. [PubMed: 15385656]
66. UK Prospective Diabetes Study Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with

type 2 diabetes (UKPDS 33). Lancet. 1998;352(9131):837–853. 10.1016/s0140-6736(98)07019-6. [PubMed: 9742976]

67. Lewis EJ, Hunsicker LG, Clarke WR, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med. 2001;345(12):851–860. 10.1056/nejmoa011303. [PubMed: 11565517]
68. Zannad F, Rossignol P. Cardiorenal syndrome revisited. Circulation. 2018;138(9):929–944. 10.1161/circulationaha.117.028814. [PubMed: 30354446]
69. Gandhi S, Chen S, Hong L, et al. Effect of mobile health interventions on the secondary prevention of cardiovascular disease: systematic review and meta-analysis. Can J Cardiol. 2017;33(2):219–231. 10.1016/j.cjca.2016.08.017. [PubMed: 27956043]
70. The Guide to Community Preventive Services (the Community Guide). Cardiovascular Disease: Mobile Health (mHealth) Interventions for Treatment Adherence among Newly Diagnosed Patients. https://www.thecommunityguide.org/findings/cardiovascular-disease-mobile-health-interventions-treatment-adherence-among-newly-diagnosed-patients. Accessed August 24, 2021.
71. D'agostino RB, Vasan RS, Pencina MJ, et al. General cardiovascular risk profile for use in primary care. Circulation. 2008;117(6):743–753. 10.1161/circulationaha.107.699579. [PubMed: 18212285]
72. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2019;74(10):e177–e232. 10.1016/j.jacc.2019.03.010. [PubMed: 30894318]
73. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2019;74(10):1376–1414. 10.1016/j.jacc.2019.03.009. [PubMed: 30894319]
74. American Diabetes Association. Microvascular complications and foot care: Standards of Medical Care in Diabetes−2020. Diabetes Care. 2020;43(suppl 1):S135–S151. 10.2337/dc20-s011. [PubMed: 31862754]
75. Flack JM, Adekola B. Blood pressure and the new ACC/AHA hypertension guidelines. Trends Cardiovasc Med. 2020;30(3):160–164. 10.1016/j.tcm.2019.05.003. [PubMed: 31521481]
76. National Kidney Foundation. KDOQI clinical practice guideline for diabetes and CKD: 2012 update. Am J Kidney Dis. 2012;60(5):850–886. 10.1053/j.ajkd.2012.07.005. [PubMed: 23067652]
77. Unger T, Borghi C, Charchar F, Khan NA, Poulter NR, Prabhakaran D, et al. 2020 International Society of Hypertension global hypertension practice guidelines. Hypertension. 2020;75(6):1334–1357. 10.1161/hypertensionaha.120.15026. [PubMed: 32370572]
78. Hoover LE. Cholesterol management: ACC/AHA Updates Guideline. Am Fam Physician. 2019;99(9):589–591. [PubMed: 31038893]
79. Houle SK, Grindrod KA, Chatterley T, Tsuyuki RT. Paying pharmacists for patient care: a systematic review of remunerated pharmacy clinical care services. Can Pharm J (Ott). 2014;147(4):209–232. 10.1177/1715163514536678. [PubMed: 25360148]
80. Pharmacist-Provided Medication Therapy Management in Medicaid. Atlanta, GA: Centers for Disease Control and Prevention, HHS; 2021.
81. Rodis JL, Capesius TR, Rainey JT, Awad MH, Fox CH. Pharmacists in federally qualified health centers: models of care to improve chronic disease. Prev Chronic Dis. 2019;16:190163. 10.5888/pcd16.190163.

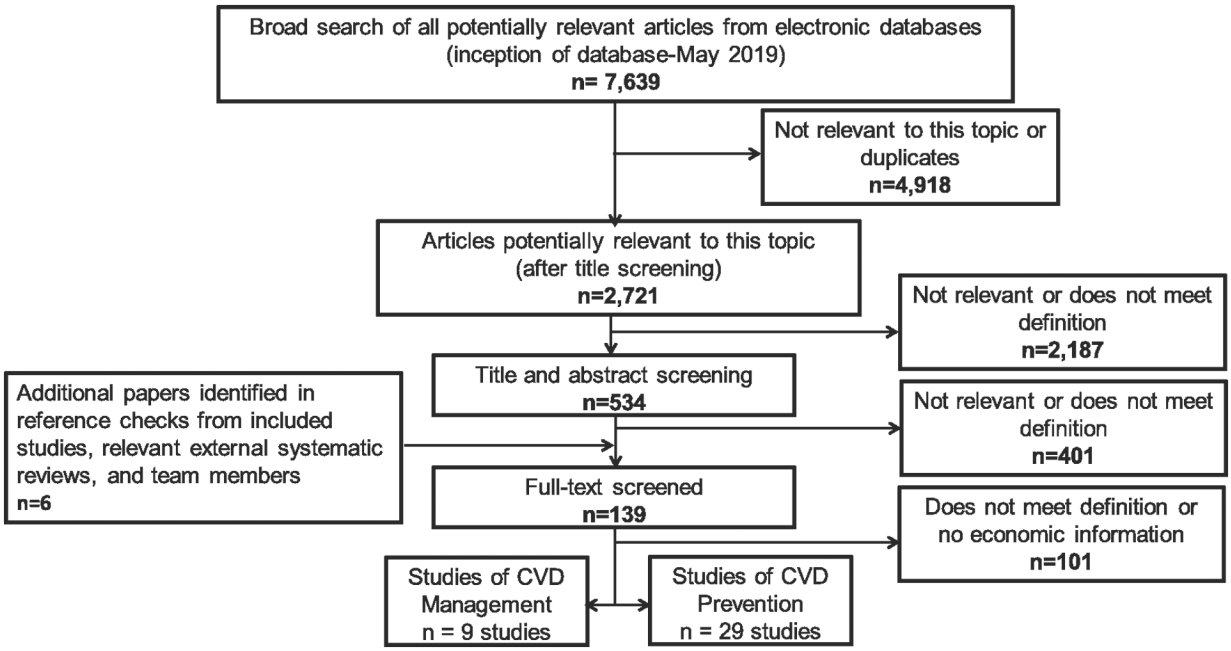

Figure 1.

Search yield.

CVD, cardiovascular disease

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Table 1.

Patient and Intervention Characteristics

Study **Country**	**Intervention sample size** **Setting** **Urbanicity**	**Pharmacist activities other than adherence related**	**Mean age** **Percent Female**	**Non-White minority percent**	**Baseline mean clinical indicators**	**Baseline disease and risk factors**
Altavela 2008[24] U.S.	127 CL Urban	PE, LC, DP	NR 65%	NR	NR	MCV
Borenstein 2003[25] U.S.	98 CL Urban	LC, DP, GS	61.5 y 61%	33.5%	SBP 159 DBP 91	BP
Bosmans 2019[26] Netherlands	85 RP NR	GS	60 y 52%	5%	SBP 145 DBP 88	BP
Brophy 2014[27] U.S.	954 PBM Mixed	PE, DP	NR 68.5%	56%	NR	DM
Bunting 2008[28] U.S.	620 RP Urban	PE, LC, PC, DP, GS	50 y 53%	18%	SBP 137.3 DBP 82.6	BP, LD
Carter 1997[29] U.S.	25 RP Urban	PE, PC, DP	67 y 76%	NR	SBP 146 DBP 83	BP
Chan 2012[30] China (Hong Kong)	51 CL Urban	PE, LC, DP	NR 41%	NR	SBP 141 DBP 75 A1c 9.7	DM
Chen 2016[31] Taiwan	50 CL Urban	PE, DP	72 y 50%	NR	SBP 135 DBP 75 A1c 9.22	DM
Christensen 2007[32] U.S.	85 RP Mixed	DP	68 y 63%	NR	NR	MCV
Chung 2011[33] China (Hong Kong)	150 CL Urban	PE, LC, DP	56 y 45%	NR	LDL 3.53	LD, DM
Connor 2009[34] U.S.	100 RP Urban	PE, PC, DP, GS	49 y 33%	61%	SBP 137 DBP 85 LDL 108 A1c 10.3	MCV
Cote 2003[35] Canada	41 RP Urban	PC	NR 65%	NR	NR	BP

Study Country	Intervention sample size Setting Urbanicity	Pharmacist activities other than adherence related	Mean age Percent Female	Non-White minority percent	Baseline mean clinical indicators	Baseline disease and risk factors
Cranor 2003[36] U.S.	187 RP Urban	PE, PC, GS	47.7 y 51%	17%	LDL 116 A1c 7.8	DM
Dehmer 2018[37] U.S.	148 CL Urban	LC, DP	63 y 46%	13.4%	SBP 148 DBP 83	BP
Fabel 2019[38] U.S.	602 CL Urban	LC, PC, DP	NR NR	NR	SBP 150 DBP 94 A1c 12.1	DM
Fishman 2013[39] U.S.	261 CL Mixed	LC, DP, GS	NR 50%	17%	SBP 151.3 DBP 88.9	BP
Isetts 2012[40] U.S.	823 CL Urban	DP, GS	NR 60%	NR	NR	DM
Kraemer 2012[41] U.S.	36 RP Urban	None	56 y 39%	10%	SBP 136.3 DBP 80.6 LDL 99.5 A1c 7.28	DM
Kulchaitanaroaj 2017[42] U.S.	399 CL NR	LC, DP	NR 57%	14%	SBP 151.4 DBP 86.9	BP
Moore 2013[43] U.S.	2,250 PBM Mixed	DP, GS	NR 60%	NR	NR	MCV
Oliveira 2010[45] U.S.	9,068 CL and RP Urban	DP, GS	NR 76%	NR	NR	MCV
Pringle 2014a[44] U.S.	107 Mixed	None	NR 57%	NR	NR	MCV, DM
Pringle 2014a[44] U.S.	107 RP Mixed	None	NR 57%	NR	NR	MCV, DM
Rashed 2010[46] U.S.	22 RP NR	PE, LC, DP	57 y 59%	32%	LDL 140.4 A1c 8.99	DM
Shireman 2016[47] U.S.	276 RP Mixed	PE, PC	54 y 62%	100%	SBP 151 DBP 92	BP

Study Country	Intervention sample size Setting Urbanicity	Pharmacist activities other than adherence related	Mean age Percent Female	Non-White minority percent	Baseline mean clinical indicators	Baseline disease and risk factors
Spence 2014[48] U.S.	1,480 RP Mixed	PE	56.5 y 51%	NR	LDL 134.5 A1c 9.28	LD, DM
Twigg 2019[49] UK	378 RP NR	PC, DP, GS	NR 56%	NR	SBP 139.5 DBP 78.4	MCV, DM
Vegter 2014[50] Netherlands	Modeled RP Mixed	PE	61 y 45%	NR	NR	MCV
Wertz 2012a[51] U.S.	307 RP Urban	PE, PC, GS	59 y 51%	50%	SBP 136.1 DBP 79.3 LDL 104.1	MCV, DM
Wertz 2012b[51] U.S.	307 RP Urban	PE, PC, GS	59 y 51%	50%	SBP 136.1 DBP 81 LDL 91.6 A1c 7.9	MCV, DM
Yu 2013[52] U.S.	204 CL NR	PE, DP	55.5 y NR	NR	SBP 128.9: DBP 73.9 A1c 9.5	DM
Summary for CVD prevention studies Median (IQI)	Intervention sample size 169 (85 to 450)	Frequency: PE 16; LC 10; PC 10; DP 20; GS 12	Age 57 y (56 y to 62 y) Percent female 56% (50% to 62%)	18% (14% to 50%)	SBP 141 (136 to 150) DBP 83 (79 to 88) LDL 108 (102 to 125) A1c 9.3 (8.2 to 9.7)	Frequency: BP 9; LD 3; DM 16; MCV 11.
Delate 2010[53] U.S.	628 CL Urban	LC, PC, DP	61.7 y 33%	NR	NR	CVD
DiTusa 2001[54] U.S.	300 RP Urban	LC, DP	67 y 30%	NR	SBP 145 DBP 82 A1c 7.3	CVD
Ellis 2000[55] U.S.	208 CL NR	PC, DP, GS	65 y 4%	NR	LDL 129.4	CVD
Lopez-Cabezas 2006[56] Spain	70 HP NR	PE, LC	76 y 53%	NR	NR	HF
Murray 2007[57] U.S.	122 RP Urban	PE, DP	61.4 y 68%	46	SBP 132.9 DBP 68.9	HF
Polinski 2016[58] U.S.	131 PBM Mixed	PE, DP, GS	61.8 y 58%	30	NR	CVD

Study Country	Intervention sample size Setting Urbanicity	Pharmacist activities other than adherence related	Mean age Percent Female	Non-White minority percent	Baseline mean clinical indicators	Baseline disease and risk factors
Scott 2007[59] UK	980 RP NR	LC, DP	68.7 y 52.6%	NR	SBP 138.8 DBP 77.2	CVD
Tsuyuki 2004[60] Canada	140 HP NR	PE, LC, DP	71 y 42%	NR	NR	HF
Vegter 2014[50] Netherlands	Modeled RP Mixed	PE	61 y 45%	NR	NR	CVD, DM
Summary for CVD management studies Median (IQI)	Intervention sample size 174 (129 to 382)	Frequency: PE 5; LC 5; PC 2; DP 7; GS 2	Age 65 y (62 y to 69 y) Percent female 45% (33% to 53%)	38%[a]	SBP 139[a] DBP 76[a] LDL 129[a] A1c 7.3[a]	Frequency: HF 3; CVD 6; DM 1

[a]Mean.

CL, clinic; RP, retail pharmacy; HP, hospital pharmacy; PBM, pharmacy benefits manager; PE, patient education; LC, lifestyle counseling; PC, limited patient care; DP, resolution of drug problems; GS, goal setting; BP, high blood pressure; LD, dyslipidemia; DM, diabetes mellitus; HF, heart failure; CVD, cardiovascular disease; MCV, multiple cardiovascular risk factors; SBP, mean systolic blood pressure in millimeters of mercury; DBP, mean diastolic blood pressure in millimeters of mercury; A1c, mean glycated hemoglobin in percent; LDL, mean low density lipoprotein in mmoL/dL; NR, not reported; UK, United Kingdom; y, years.

Table 2.

Intervention Cost and Change in Healthcare Cost: Estimates, Components, and Quality of Estimates

Study	Intervention sample size Intervention duration in months	Pharmacist activities other than adherence related	Intervention cost per patient per year	Quality of intervention cost estimate	Drivers included in intervention cost	Change in healthcare cost per patient per year	Quality of healthcare cost estimate	Drivers included in healthcare cost
Altavela 2008[24]	127 12	PE, LC, DP	NR	NA	NA	−$2,846	Fair	OP, IP, ED, Med, Lab
Borenstein 2003[25]	98 12	LC, DP, GS	NR	NA	NA	$75[a]	Fair	OP, Med
Bosmans 2019[26]	85 9	GS	$76	Fair	PL	$1,439	Fair	OP, IP, Med
Brophy 2014[27]	954 12	PE, DP	NR	NA	NA	−$662	Good	OP, IP, ED, Med
Bunting 2008[28]	620 12	PE, LC, PC, DP, GS	NR	NA	NA	−$89[a]	Fair	OP, IP, ED, Med, Lab
Carter 1997[29]	25 6	PE, PC, DP	NR	NA	NA	$224	Fair	OP, Med
Chan 2012[30]	51 60	PE, LC, DP	$100	Fair	PL	−$1,190	Fair	OP, IP, ED, Med, Lab
Chen 2016[31]	50 12	PE, DP	$81	Good	PL, PM	−$13	Fair	OP, IP, Med
Christensen 2007[32]	85 6	DP	$479	Good	PL	$105	Limited	Med
Chung 2011[33]	150 12	PE, LC, DP	$144	Good	PL	−$1,402	Fair	OP, IP, ED, Med, Lab
Connor 2009[34]	100 12	PE, PC, DP, GS	NR	NA	NA	−$3,528	Limited	Med
Cote 2003[35]	41 12	PC	$147	Good	PL, CDSS	−$355	Fair	OP, IP, Med
Cranor 2003[36]	187 60	PE, PC, GS	NR	NA	NA	−$6,207[a]	Fair	OP, IP, ED, Med, Lab
Dehmer 2018[37]	148 12	LC, DP	$1,552	Good	PL	−$413	Fair	IP, Med
Fabel 2019[38]	602 12	PE, PC, DP	$238	Good	PL	−$3,346	Limited	IP
Fishman 2013[39]	261 12	LC, DP, GS	$467	Good	PL, TBC	$0	Good	OP, IP, ED, Med

Study	Intervention sample size Intervention duration in months	Pharmacist activities other than adherence related	Intervention cost per patient per year	Quality of intervention cost estimate	Drivers included in intervention cost	Change in healthcare cost per patient per year	Quality of healthcare cost estimate	Drivers included in healthcare cost
Isetts 2012[40]	823 12	DP, GS	NR	NA	NA	−$576[a] Median	Fair	OP, Med
Kraemer 2012[41]	36 12	None	$259	Good	PL	−$49	Good	OP, IP, ED, Med, Lab
Kulchaitanaroaj 2017[42]	399 Lifetime	LC, DP	$698	Good	PL, TBC	$4,047 lifetime	Good	OP, IP, ED, Med, Lab
Moore 2013[43]	2,250 12	DP, GS	$559	Fair	NR	−$1,216	Good	OP, IP, ED, Med
Oliveira 2010[45]	9,068 120	DP, GS	$29	Fair	NR	−$38	Fair	OP, IP, ED, Med
Pringle 2014a[44]	107 12	None	NR	NA	NA	CVD-related −$370	Good	OP, IP, ED, Med
Pringle 2014a[44]	107 12	None	NR	NA	NA	DM- related −$382	Good	OP, IP, ED, Med
Rashed 2010[46]	22 36	PE, LC, DP	$435	Good	PL	−$6,247	Fair	OP, IP, Med
Shireman 2016[47]	276 6	PE, PC	$254	Good	PL	$208	Limited	Med
Spence 2014[48]	1,480 12	PE	$17	Good	PL	−$302	Fair	IP, ED, Med
Twigg 2019[49]	378 12	PC, DP, GS	$214	Good	PL	$53	Fair	OP, IP, ED
Vegter 2014[50]	Modeled	PE	$45	Good	PL	−$33	Fair	OP, IP, Med
Wertz 2012a[51]	307 12	PE, PC, GS	Heart Health $577	Good	PL, TBC	HTN related - $315	Good	OP, IP, ED, Med
Wertz 2012b[51]	307 12	PE, PC, GS	Diabetes Care $655	Good	PL, TBC	DM and CVD-related −$977	Good	OP, IP, ED, Med
Yu 2013[52]	204 12	PE, DP	NR	NA	NA	−$984[a]	Good	OP, IP, ED, Med, Lab
Summary for CVD prevention studies Median (IQI)	Intervention sample size 169 (85 to 450) Duration 12 (12 to 12)	Frequency: PE 17; LC 9; PC 10; DP 20; GS 12	$246 ($95 to $499)	Frequency: Good 16, Fair 4, Limited 0	Frequency: CDSS 1, PL 18, PM 1, TBC 4	−$355 (−$977 to −$33)	Frequency: Good 10, Fair 17, Limited 4	Frequency: OP 25, IP 25, ED 30, Med 29, Lab 8
Delate 2010[53]	628 12	LC, PC, DP	$439	Fair	PL	−$26,216	Fair	OP, IP, ED, Med, Lab

Study	Intervention sample size Intervention duration in months	Pharmacist activities other than adherence related	Intervention cost per patient per year	Quality of intervention cost estimate	Drivers included in intervention cost	Change in healthcare cost per patient per year	Quality of healthcare cost estimate	Drivers included in healthcare cost
DiTusa 2001[54]	300 6	LC, DP	NR	NA	NA	−$175	Limited	Med
Ellis 2000[55]	208 12	PC, DP, GS	NR	NA	PL	$570[a]	Good	OP, IP, Med, Lab
Lopez-Cabezas 2006[56]	70 12	PE, LC	$58	Fair	PL	−$1,138	Fair	IP
Murray 2007[57]	122 9	PE, DP	$372	Good	PL	−$4,304	Good	OP, IP, ED, Med, Lab
Polinski 2016[58]	131 1	PE, DP, GS	$731	Fair	PL	−$2,430	Fair	IP
Scott 2007[59]	980 12	LC, DP	$211	Fair	PL	−$261	Good	OP, IP, Med
Tsuyuki 2004[60]	140 6	PE, LC, DP	NR	NA	NA	−$5,819	Good	OP, IP, ED, Med
Vegter 2014[50]	Modeled	PE	$45	Fair	PL	−$248	Good	OP, IP, Med, Lab
Summary for CVD management studies Median (IQI)	Intervention sample size 174 (129 to 382) Duration 11 (6 to 12)	Frequency: PE 5; LC 5; PC 2; DP 7; GS 2	$292 ($96 to $422)	Frequency: Good 1, Fair 5, Limited 0	Frequency: CDSS 0, PL 7, PM 0, TBC 0	−$2,430 (−$5,062 to −$700)	Frequency: Good 5, Fair 3, Limited 1	Frequency: OP 6, IP 8, ED 7, Med 7, Lab 4

[a]Healthcare cost includes intervention cost.

PE, patient education; LC, lifestyle counseling; PC, limited patient care; DP, resolution of drug problems; GS, goal setting; CDSS, clinical decision support system; PL, pharmacist labor; PM, patient materials and adherence aids; TBC, team-based care; OP, outpatient; IP, inpatient; ED, emergency department; Med, medications; Lab, laboratory and imaging; IQI, interquartile interval; NR, not reported; NA, not applicable; HTN, hypertension; CVD, cardiovascular disease; DM, diabetes mellitus.

Table 3.

Summary of Economic Outcomes: Total Cost, Return on Investment (ROI), and Cost-effectiveness

Study	Intervention effects on clinical indicators and adherence	Pharmacist activities other than adherence related	Total cost per patient per year (quality of estimate)	ROI health systems perspective (quality)	Cost-effectiveness Cost per QALY gained (Time horizon) (Quality of estimate)
Borenstein 2003[25]	SBP/DBP reduced 11.0/1.0 mmHg at 12 months Adherence not reported	LC, DP, GS	$75 (Fair)	NR (NA)	NR
Bosmans 2019[26]	SBP/DBP reduced 0.3/2.2 mmHg at 9 months MARS-5 increased 0.23	GS	$1,594 (Fair)	−20.06 (Fair)	$70,762 (9 months) (Fair)
Bunting 2008[28]	SBP/DBP reduced 8.0/3.5 mmHg at 12 months Adherence not reported	PE, LC, PC, DP, GS	−$89 (Fair)	NR (NA)	NR
Chan 2012[30]	SBP/DBP reduced 3.2/2.1 mmHg and LDL reduced 0.33 mmol/dl at 9 months Tablets taken/Tablets needed increased 20.5 pct pt	PE, LC, DP	−$1,090 (Fair)	10.92 (Fair)	NR
Chen 2016[31]	No clinical outcomes reported. Strict adherence claimed in study with no details.	PE, DP	$68 (Fair)	−0.84 (Fair)	NR
Chung 2011[33]	LDL reduced 0.49 mmol/dl at 24 months Percent adherent increased 13.7 pct pt	PE, LC, DP	−$1,258 (Fair)	8.76 (Fair)	NR
Cote 2003[35]	No clinical outcomes reported. Adherence not reported.	PC	−$208 (Fair)	1.41 (Fair)	NR
Cranor 2003[36]	Percentage at optimal LDL increased 15.8 pct pt at 60 months and at optimal A1c increased 18.2 pct pt at 36 months Adherence not reported.	PE, PC, GS	−$6,207 (Fair)	NR (NA)	NR
Dehmer 2018[37]	SBP/DBP reduced 9.7/5.1 mmHg at 12 months Adherence not reported	LC, DP	$1,140 (Fair)	−0.73 (Fair)	NR
Fishman 2013[39]	SBP/DBP reduced 8.9/3.6 mmHg at 12 months Adherence not reported	LC, DP, GS	$467 (Good)	−1.00 (Good)	$2,381[a] (Patient lifetime) (Good)
Isetts 2012[40]	Percentage at DM care 5-point benchmark 40% versus 17.5% statewide. 828 adherence-related problems resolved	DP, GS	−$576 (Fair)	NR (NA)	NR
Kraemer 2012[41]	SBP/DBP reduced 5.9/1.9 mmHg, LDL reduced 4.0 mmol/dl, A1c reduced 0.34 pct pt at 12 months ASK-20 total barrier score reduced 0.4	None	$209 (Good)	−0.81 (Good)	NR
Kulchaitanaroaj 2017[42]	SBP reduced 12 mmHg at 9 months Adherence not reported.	LC, DP	NR (NA)	NR (NA)	$28,416 (Patient lifetime) (Good)

Study	Intervention effects on clinical indicators and adherence	Pharmacist activities other than adherence related	Total cost per patient per year (quality of estimate)	ROI health systems perspective (quality)	Cost-effectiveness Cost per QALY gained (Time horizon) (Quality of estimate)
Moore 2013[43]	No clinical outcomes reported. Medication possession ratios at 12 months increased 4.6 pct pt for HTN, 4.71 pct pt for dyslipidemia, 2.37 pct pt for DM	DP, GS	−$656 (Fair)	1.17 (Fair)	NR
Oliveira 2010[45]	No clinical outcomes reported. 33,706 encounters with 16.5% of drug related problems identified as adherence	DP, GS	−$8 (Fair)	0.29 (Fair)	NR
Rashed 2010[46]	LDL reduced 34.6 mmol/dl at 36 months. Study reports adherence improvement with no details.	PE, LC, DP	−$5,812 (Fair)	13.36 (Fair)	NR
Spence 2014[48]	LDL reduced 7.4 mmol/dl and A1c reduced 0.34 pct pt at 12 months. Percent of DM patients adherent increased 16.1 pct pt and medication possession ratio of patients with dyslipidemia decreased 1 pct pt.	PE	−$285 (Fair)	17.14 (Fair)	NR
Twigg 2019[49]	SBP/DBP reduced 2.9/1.8 mmHg at 12 months. MMAS-8 increased 0.26	PC, DP, GS	$267 (Fair)	−1.25 (Fair)	$11,298 (12 months) (Fair)
Vegter 2014[50]	No clinical outcomes reported. Non-adherence hazard 0.47 for primary prevention of CVD	PE	$12 (Fair)	−0.27 (Fair)	$5,660 (Patient lifetime) (Fair)
Wertz 2012a[51]	SBP/DBP reduced 6.6/4.2 mmHg, LDL reduced 6.9 mmol/dl at 12 months HTN Meds 11 pct pt, Statins 11 pct pt, Antidiabetic 8 pct pt	PE, PC, GS	$262 (Good)	−0.45 (Good)	NR
Wertz 2012b[51]	SBP/DBP reduced 5.7/4.7 mmHg, LDL reduced 7.6 mmol/dl, A1c reduced 0.8 pct pt at 12 months HTN Meds 7.1 pct pt, Statins 11 pct pt, Antidiabetic 0 pct pt	PE, PC, GS	−$322 (Good)	0.49 (Good)	NR
Yu 2013[52]	OR of control for SBP/DBP and for LDL 2.0, OR of control for A1c 3.9 at 12 months. Percent adherent increased 15 pct pt	PE, DP	−$984 (Good)	NR (NA)	Cost-saving (NR) (Good)
Summary for CVD prevention studies Median (IQI)	–	Frequency: PE 11; LC 8; PC 6; DP 14; GS 11	−$89 (−$656 to $209) Quality: Good 5, Fair 16, Limited 0	0.01 (−0.83 to 3.25) Quality: Good 4, Fair 12, Limited 0	$11,298 ($5,660 to $28,416) Quality: Good 3, Fair 3, Limited 0
Delate 2010[53]	Percent with LDL<100 mg/dl 70%, and SBP/DBP <140/90 70% Use of statins, beta blockers, antiplatelets after MI 87%, 100%, and 97%, respectively.	LC, PC, DP	−$25,778 (Fair)	58.77 (Fair)	NR
Ellis 2000[55]	LDL reduced 10.6 mmol/dl compared to control. Resolved 55% of cases drugs not taken as prescribed	PC, DP, GS	$570 (Good)	NR (NA)	NR
Lopez-Cabezas 2006[56]	12-month inpatient HF readmissions reduced by mean of 3.7 days. Patients taking more than 85% of dose at 12-months increased 11 pct pt versus control	PE, LC	−$1,080 (Fair)	18.64 (Fair)	NR

Study	Intervention effects on clinical indicators and adherence	Pharmacist activities other than adherence related	Total cost per patient per year (quality of estimate)	ROI health systems perspective (quality)	Cost-effectiveness Cost per QALY gained (Time horizon) (Quality of estimate)
Murray 2007[57]	Overall CVD Medication Event Monitoring System (MEMS) increased 10.9 pct pt.	PE, DP	−$3,933 (Good)	10.58 (Good)	NR
Polinski 2016[58]	Risk ratio of 30-day readmission for CVD 0.55 and Respiratory 0.61. Annual supply of meds for intervention (control): 220.3 (207.4)	PE, DP, GS	−$1,699 30 days (Fair)	2.32 (Fair)	NR
Scott 2007[59]	No change in treatment meeting guidelines versus control. No change in adherence versus control.	LC, DP	−$50 (Fair)	0.24 (Fair)	NR
Vegter 2014[50]	No clinical outcomes reported. Non-adherence hazard ratio for secondary prevention of CVD 0.54	PE	−$275 (Fair)	4.46 (Fair)	NR
Summary for CVD management studies Median (IQI)	–	Frequency: PE 4; LC 3; PC 2; DP 5; GS 2	−$1,080 (−$2,816 to −$163) Quality: Good 2, Fair 5, Limited 0	7.52 (2.86 to 16.62) Quality: Good 1, Fair 5, Limited 0	NA

[a]Versus self-measured blood pressure (SMBP) (where SMBP dominated Usual care)

PE, patient education; LC, lifestyle counseling; PC, limited patient care; DP, resolution of drug problems; GS, goal setting; A1c, glycosylated hemoglobin; ASK-20, Adherence Starts with Knowledge questionnaire; CVD, cardiovascular disease; HTN, hypertension; IQI, interquartile interval; LDL, low density lipoprotein cholesterol; MARS, Medication Adherence Rating Scale; QALY, quality adjusted life year; SBP, systolic blood pressure; DBP, diastolic blood pressure; DM, diabetes mellitus; NR, not reported; NA, not applicable; pct pt, percentage points; MMAS, Morisky Medication Adherence Scale; MI, myocardial infarction; HF, heart failure.