CLINICAL RESEARCH STUDY

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The Impact of Medication Adherence on Coronary Artery Disease Costs and Outcomes: A Systematic Review

Asaf Bitton, MD, MPH,[a,b] Niteesh K. Choudhry, MD, PhD,[c] Olga S. Matlin, PhD,[d] Kellie Swanton, BA,[c] William H. Shrank, MD, MS[c]

[a]Division of General Medicine, Brigham and Women's Hospital, Boston, Mass; [b]Department of Health Care Policy and Center for Primary Care, Harvard Medical School, Boston, Mass; [c]Division of Pharmacoepidemiology, Brigham and Women's Hospital, Boston, Mass; [d]CVS Caremark, Northbrook, Ill.

ABSTRACT

BACKGROUND: Given the huge burden of coronary artery disease and the effectiveness of medication therapy, understanding and quantifying known impacts of poor medication adherence for primary and secondary prevention is crucial. We sought to systematically review the literature on this topic area with a focus on quantified cost and clinical outcomes related to adherence.

METHODS: We conducted a systematic review of the literature between 1966 and November 2011 using a fixed search strategy, multiple reviewers, and a quality rating scale. We found 2636 articles using this strategy, eventually weaning them down to 25 studies that met our inclusion criteria. Three reviewers independently reviewed the studies and scored them for quality using the Newcastle Ottawa Scoring Scale.

RESULTS: We found 5 studies (4 of which focused on statins) that measured the impact of medication adherence on primary prevention of coronary artery disease and 20 articles that focused on the relationship between medication adherence to costs and outcomes related to secondary prevention of coronary artery disease. Most of these latter studies focused on antihypertensive medications and aspirin. All controlled for confounding comorbidities and sociodemographic characteristics, but few controlled for likelihood of adherent patients to have healthier behaviors ("healthy adherer effect"). Three studies found that high adherence significantly improves health outcomes and reduces annual costs for secondary prevention of coronary artery disease (between $294 and $868 per patient, equating to 10.1%-17.8% cost reductions between high- and low-adherence groups). The studies were all of generally of high quality on the Newcastle Ottawa Scale (median score 8 of 9).

CONCLUSIONS: Increased medication adherence is associated with improved outcomes and reduced costs, but most studies do not control for a "healthy adherer" effect.

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KEYWORDS: Coronary artery disease; Costs; Medication adherence; Outcomes; Pharmacoeconomics; Systematic review

Cardiovascular disease, of which coronary artery disease is the predominant form, is the most common cause of death in the US and has an annual health care cost of approximately $475 billion.[1] Adherence to medications has been associated with improved outcomes in primary and secondary coronary artery disease in some early studies.[2] Further literature suggests that, as is the case with diabetes,[3] improved adherence to a number of chronic disease medica-

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Requests for reprints should be addressed to Asaf Bitton, MD, MPH, Division of General Medicine, Brigham and Women's Hospital, Department of Health Care Policy, Harvard Medical School, 1620 Tremont St., 3rd Floor, Rm 3-002P, Boston, MA 02120.

E-mail address: abitton@partners.org

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tions also may reduce overall health care costs.[4] Support for new models of patient care, such as the patient-centered medical home and accountable care organizations, is in part premised upon the potential for these models to encourage improved patient self-management and medication adherence.[5]

However, a previous systematic review[2] on the association between adherence and coronary artery disease outcomes suggested that the existing literature was problematic due to heterogeneous methods and few available studies that directly measured outcomes. There is a large amount of literature on factors associated with adherence or nonadherence, but much less on what outcomes are improved through better adherence, and what the return on investment in improved adherence could be.

A further issue exists around whether the association between adherence and better outcomes is confounded by endogenous characteristics of the patients who are predisposed to take medication in a more consistent way. Termed the "healthy adherer" effect, this association could significantly amplify the measured relationship between medication adherence and health outcomes.

CLINICAL SIGNIFICANCE

- All 25 studies included in this systematic review found that higher medication adherence significantly improved primary and secondary prevention of coronary artery disease outcomes.
- Studies of secondary coronary artery disease prevention show 10.1%-17.8% cost reductions ($294 and $868 per patient) between high- and low-adherence patients.
- Significant methodological heterogeneity exists across these studies; most do not control for the likelihood of more adherent patients to have healthier behaviors ("healthy adherer effect").

The aim of this study was to review systematically the literature on the relationship between medication adherence and primary and secondary prevention of coronary artery disease, with a focus on key coronary artery disease-related mortality, service utilization, and cost outcomes. We also carefully appraised whether these studies controlled for the healthy adherer effect, and evaluated the strength of the evidence published in the prior decade since the last systematic review of the literature. Finally, we link the results of these studies to current discussion of health care delivery system reform in the US.

METHODS

Data Sources

We conducted a systematic search to identify studies addressing the effect of medication adherence on patient outcomes and costs. Initial searches were limited to articles published in MEDLINE and EMBASE between 1966 and November 30, 2011. We performed our search with the assistance of a professional librarian. The search focused on any term relating to adherence and coronary artery disease (eg, medication adherence AND cardiac ischemia OR myocardial infarction OR coronary heart disease). Our full search strategy can be found in the Appendix. Articles containing at least one search term were included in the review. Initial articles selected were mined for additional references.

Study Selection

Articles were included if they reported original cost or quality outcome results. Studies that only examined predictors of medication adherence without outcome measures comparing adherent and nonadherent populations of patients were not included. Case reports, case series, and simulation and modeling studies were excluded. Articles that did not directly pertain to coronary artery disease, or those not published in English, also were excluded. Two reviewers (AB, WS) evaluated the titles and abstracts of search results to identify potentially relevant articles, and 3 reviewers (AB, WS, KS) assessed complete articles for inclusion.

Data Extraction

Three reviewers (AB, WS, KS) extracted data from selected articles and resolved differences by consensus. Variables assessed included the main research questions, patient population, inclusion criteria, measure of adherence, study design (with a focus on how authors accounted for sources of unmeasured confounding), and results regarding outcomes and costs (**Table 1**,[6-8,10,30] and **Table 2**[9,11-29]). Two reviewers (AB, KS) used the Newcastle-Ottawa Scale to assess the quality of each cohort study on a scale of 1 to 9. Disagreements were adjudicated by a third reviewer (WS). Studies were grouped into 2 main evidence tables: articles pertaining to the effects of medication adherence on primary prevention of coronary artery disease (**Table 1**), and those pertaining to secondary prevention of coronary artery disease (**Table 2**).

RESULTS

Our search strategy yielded a total of 2636 articles, of which we selected 25 for inclusion in the analysis based on a priori criteria above (**Table 1** and **Table 2**). A total of 80% (20/25 studies pertained to secondary prevention of coronary artery disease, with 20% regarding primary prevention. Among the 5 studies of primary prevention of coronary artery disease, 80% focused exclusively on statins. Quality scoring of all these studies found that generally the studies were of high quality (median and mode score 8/9 on the Newcastle Ottawa Scale). Of the 20 studies on secondary prevention, 14 (70%) included antihypertensive medications.

Table 1 Adherence Effects on Primary Prevention of Coronary Artery Disease

Study: First Author, Country	Patient Population & Inclusion Criteria	Coronary Artery Disease Medications	Adherence Measure	Design Features	Outcomes	Newcastle Ottawa Rating
Bouchard (2007), Canada[6]	Cohort of patients collected (n = 20,543) using Québec provincial public health insurance databases. Eligible patients were 50-64 years old (mean = 58) without cardiovascular disease; newly treated with statins from 1998-2000.	Statins	Adherence level was percentage of prescribed medication doses used over specified period and classified as ≥90% or <90%. Measure based on the quantity dispensed and number of days supplied for each filled prescription.	Used a nested case-control design to study nonfatal coronary artery disease. Every case was matched with 20 randomly selected controls. Rate ratios of nonfatal coronary artery disease were calculated through conditional logistic regression adjusted for age, sex, socioeconomic status, diabetes and hypertension. Also conducted sensitivity analyses around different adherence cut-off levels and estimated the size necessary for an unmeasured confounding variable to alter the results.	Adherence >90% was associated with fewer nonfatal coronary artery disease events (rate ratio .81; .67, .97) compared with adherence <90% adherence.	8/9
Breekveldt-Postma (2008), Netherlands[7]	Used a pharmacy record linkage system to examine drug dispensing and hospitalizations for over 2 million patients in the Netherlands. Included new users of antihypertensive drugs ≥ 18 years of age between 1993 and 2002. Excluded patient using antihypertensive drugs for secondary prevention of coronary artery disease. 77,193 met the inclusion criteria of this study	All antihypertensive drugs except loop diuretics (to exclude heart failure only)	Permissible gaps of antihypertensive drugs therapy were determined. Persistence of antihypertensive drugs use was defined as the number of days of continuous use of any antihypertensive drugs from the index date meeting those criteria. Patients were defined as 2-year persistent or nonpersistent antihypertensive drugs users.	Patients initially followed for 2 years to determine persistence with antihypertensive drugs; then for a further 2 years or until first hospital admission for acute myocardial infarction or stroke, death, or end of study period. Effect of nonpersistence with antihypertensive drugs during first 2 years of treatment on risk of hospitalization for acute myocardial infarction or stroke thereafter was estimated in Cox regression model. Adjusted for age, sex, initial prescriber, number of different antihypertensive drug classes in first 2 years of treatment, initial antihypertensive drug class, year of start of antihypertensive drug use, and use of other drugs before start of outcome follow-up.	Overall percentage of nonpersistent patients was 55%. The lowest nonpersistence rates were for ARBs and ACE inhibitors (40%), with the highest rates for CCBs, BBs, and diuretics (range 54%-61%). Nonpersistent antihypertensive drug use associated with an increased risk of acute myocardial infarction (RR 1.15; 95% CI, 1.00-1.33) and increased risk of stroke (RR 1.28; 95% CI, 1.15-1.45).	8/9

Table 1 Continued

Study: First Author, Country	Patient Population & Inclusion Criteria	Coronary Artery Disease Medications	Adherence Measure	Design Features	Outcomes	Newcastle Ottawa Rating
Corrao (2010), Italy[8]	Identified 90,832 adults without ischemic heart disease, newly treated with statins in 2002 to 2003 from a health services database	Statins	PDC by therapy with statins, classified as very low (≤25%), low (26%-50%), intermediate (51%-75%), or high (>75%) coverage.	Proportional hazards model to estimate HR and 95% CIs for association between time-dependent categories of PDC and time of ischemic heart disease hospitalization. Controlled for age, sex, type of statin dispensed at start, Charlson comorbidity index, current use of other drugs (ie, antidiabetics, nitrates, antihypertensive drugs, or other cardiac medications), and whether or not a patient switched statins.	A total of 59.5% of patients had low or very low adherence to statins. In adjusted models, patients with low, intermediate, or high statin coverage had HR (95% CI) for ischemic heart disease hospitalization of .85 (.72-.98), .82 (.71-.95), and .81 (.71-.94), respectively, compared with patients with very low coverage.	8/9
Dragomir (2010), Canada[30]	A total of 55,134 who were newly treated with statins were followed from public health insurance databases in Quebec. The authors included patients aged 45-85 without cardiovascular disease who were initially treated with statins between 1999 and 2002, with at least 3 years of follow-up.	Statins	Adherence to statins measured using the MPR-, and categorized as >80% or <80%.	Adjusted OR of cardiovascular events between high and low adherence groups was estimated using polytomous logistic analysis. Covariates included age, sex, hypertension, overall health status (modified Van Korff chronic disease score), social assistance status, previous hospitalization in the year before entry of cohorts, and mean number of physician visits per year. They analyzed mean costs of direct health-care services categorized as medical services, hospitalization, or drug related.	Mean MPR in high adherence level was 96% vs 42% for low adherence. Patients with low statin adherence were more likely to have coronary artery disease (OR 1.07; 95% CI 1.01-1.13), cerebrovascular disease (OR 1.13; 95% CI, 1.03-1.25), and chronic heart failure within 3-year period of follow-up (OR 1.13; 95% CI, 1.01-1.26). Low adherence to statins associated with increased risk of hospitalization (OR 1.04; 95% CI, 1.01-1.09). Among hospitalized patients, low statin adherence associated with statistically significant increase of hospitalization costs by $1060/patient for the 3-year period.	8/9

Table 1 Continued

Study: First Author, Country	Patient Population & Inclusion Criteria	Coronary Artery Disease Medications	Adherence Measure	Design Features	Outcomes	Newcastle Ottawa Rating
Perreault (2009), Canada[10]	A cohort of 115,290 patients was constructed using public health insurance database in Québec. Patients were aged 45 to 85 years without cardiovascular disease, and newly treated with statins between 1999 and 2004 were included.	Statins	MPR as measure of adherence, categorized as >80% or <80%.	Used a nested case-control design to study CAD. Cases matched for age and duration of follow-up with randomly selected controls.	High adherence was associated with relative risk reduction of 18% (RR .82; 95% CI .77-.87) compared with lower adherence level.	8/9

ARBs = angiotensin receptor blocker; ACE = angiotensin-converting enzyme; CAD = coronary artery disease; CCBs = calcium channel blockers; BBs = beta-blockers; CI = confidence interval; HR = hazard ratio; MPR = medication possession ratio; OR = odds ratio; PDC = proportion of days covered; RR = relative risk.

Primary Prevention: Statins

Four studies evaluated adherence to statin medications for primary prevention. Of these studies, 3 came from the same research group in Canada using a similar retrospective approach to claims data.[6,10,30] In 2 studies,[6,10] using variations of the medication possession ratio (MPR), high adherence (>80% MPR) was associated with adjusted risk reduction of between 18% and 19%, compared with low-adherence patients. Dragomir et al (2010)[30] found an adjusted odds ratio for incident hospitalization for coronary artery disease of 1.07 (95% confidence interval [CI], 1.01-1.13) in patients with <80% adherence. They estimated that among patients who were hospitalized, low adherence to statins before hospitalization was associated with a statistically significant increase in hospitalization costs of Canadian $1060 ($1.00 Canadian = $0.974 USD, December 12, 2011) per patient hospitalized over 3 years.

Primary Prevention: Antihypertensive Medications

One study from the Netherlands evaluated claims data from a pharmaceutical claims database.[7] The investigators found that over a 2-year period after treatment initiation, those patients with medication nonpersistence had a 15% increased risk (95% CI, 1.00-1.33) of hospitalization for myocardial infarction.

Secondary Prevention: Statins

Three of the 7 studies about statin adherence in secondary prevention of coronary artery disease focused exclusively on that drug family. Notably, 2 of these 3 studies included cost end-point measures. Aubert et al[12] retrospectively analyzed adherence measured as MPR for 2 years, and found that patients with MPR <80% had 8 more hospitalizations per 100 patients than more adherent counterparts (3.8% absolute difference), leading to a statistically significant annual difference in costs of $868 per patient ($4908 vs $4040). Pittman[9] studied retrospective claims data in a similar fashion, finding a significant adjusted odds ratio of 1.26 for cardiovascular disease hospitalization in the lowest- (MPR <60%) compared with the highest-adherence group. This translated into an annual per-patient difference of $294 between these groups ($2395 vs $2689). A retrospective Scottish cohort study measuring proportion of days covered (PDC) with a statin found that, compared with patients with no adherence, those with high PDC (>80%) had adjusted hazard ratios (HR) of .19 (95% CI, .08-.47) for recurrent myocardial infarction, and HR .47 (95% CI, .22-.99) for all-cause mortality.[29] Shalev[26] found, in a similar Israeli cohort study, that the adjusted HR for each 10% increase was .94 (95% CI, .93-.95).

Table 2 Adherence Effects on Secondary Prevention of Coronary Artery Disease

Study: First Author, Country	Patient Population, & Inclusion Criteria	Coronary Artery Disease Medications	Adherence Measure	Design Features	Outcomes	Newcastle Ottawa Rating
Amin (2009), USA[11]	Consecutive patients admitted to a coronary care unit at a large urban hospital in Chicago with myocardial infarction during 2003 and 2004.	Aspirin, clopidogrel, angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, statin	Proportion of days covered (PDC). Poor compliance was defined as ≤80%. The authors constructed a noncompliance score (0,1) for each of 5 meds. Patients with score ≥4 were labeled as "noncompliant" in main analysis	Cox proportional hazard models adjusting for severity of coronary artery disease, left ventricular dysfunction ≥30%, acuity of myocardial infarction, diabetes, dyslipidemia, hypertension, race, insurance status, current/past smoking, cocaine or polysubstance abuse, homelessness, mean frequency of all 5 classes of meds, global registry of acute coronary events risk score for predicting death during 6 months post-discharge, and number of outpatient cardiology follow-up visits.	Main outcome was a composite of all-cause mortality and reinfarction. Patients non-compliant with ≥4 meds had HR 2.83 (95% CI, 1.60-5.01). Kaplan-Meier survival curves separated at 6 months (log rank $P < .001$). Noncompliance with 2 or 3 meds was statistically nonsignificant, whereas noncompliance with 0 or 1 meds had a HR of .44 (95% CI, .25-.78).	8/9
Aubert (2010), USA[12]	Retrospective analysis of statin adherence on hospitalization rates and direct medical costs in 10,227 total patients. Patients included in the study received first statin prescription in 2001 and 2002, had continuous health coverage for 6 months prior and 3 years after index prescription, and continued therapy after index date.	Statin	Medication adherence measured using the MPR over the first 2 years of therapy. Nonadherence was defined as MPR <80%. Patients also stratified into quartiles of MPR	Cost analyzed using linear regression. Logistic regression model used for hospitalization event controlling for age, sex, chronic disease score, cardiovascular diseases, cardiovascular medications, and other comorbidities	A total of 33 hospitalizations per 100 patients were found in the nonadherent group vs 25 hospitalizations/100 patients in the adherent group. Total of 23 cardiovascular - related conditions in nonadherent vs 16 in adherent group. 19.3% nonadherent patients hospitalized vs 15.5% adherent patients hospitalized during the study period. Cost analysis showed $4908 annual per-patient direct medical costs in nonadherent group vs $4040 in adherent group (all $P < .01$)	8/9

Table 2 Continued

Study: First Author, Country	Patient Population, & Inclusion Criteria	Coronary Artery Disease Medications	Adherence Measure	Design Features	Outcomes	Newcastle Ottawa Rating
Chapman (2010), USA[13]	Retrospective cohort study evaluating effect of single-pill amlodipine - atorvastatin vs 2-pill calcium channel-blocker adherence on cardiovascular events. 19,447 patients already taking one of the 2 medications, who initiated single combination pill or added other medication were followed.)	Single-pill amlodipine - atorvastatin, calcium channel blocker, statin	Proportion of days covered. Nonadherence PDC ≤80% for 6-month study period.	Cox proportional hazards models adjusting for age, sex, therapy type, geographic region, insurance status, related comorbidities, and number of prior antihypertensive medications.	Adherence to calcium channel blocker and statin medications was associated with lower risk of cardiovascular events, with an incidence rate of 1.79 vs 2.26 in the adherent vs nonadherent groups. Patients receiving combination pill were more likely to be adherent than the 2-pill group. (56.5% vs 21.4%)	8/9
Choudhry (2011), USA[14]	Patients discharged from after a myocardial infarction who received both medical and prescription drug coverage through one health insurer	Angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, beta-blocker Statin	Medication adherence measured using the MPR multiplied by 100 to generate absolute adherence percentages. Nonadherence considered MPR <80%	Randomized controlled trial that assigned patients to full prescription drug coverage or usual coverage. Authors analyzed effect of drug costs on medication adherence as a secondary outcome. Utilized an identity link function with normally distributed errors to compare MPRs between 2 randomized groups, and a logit link function with binary distributed errors to compare rates of full adherence	Rates of adherence increased by 5.6% (CI 3.4-7.7) for angiotensin-converting enzyme inhibitor or angiotensin receptor blockers, by 4.4% (CI 2.3-6.5) for beta-blockers; by 6.2% (CI 3.9-8.5) for statins; and by 5.4% (CI 3.6-7.2) for all medication classes. ($P < .001$ for all comparisons). Odds of full adherence to study meds increased by 31% to 41% ($P < .001$). Out-of-pocket spending was reduced for both prescription drugs (relative spending, .70; 95% CI .65-.75; $P < .001$) and for nondrug medical services (relative spending, .82; 95% CI .72-.94; $P = .005$). Mean total spending was $66,008 in full-coverage group and $71,778 in usual-coverage group (relative spending, .89; 95% CI, .50-1.56; $P = .68$).	N/A

Table 2 Continued

Study: First Author, Country	Patient Population, & Inclusion Criteria	Coronary Artery Disease Medications	Adherence Measure	Design Features	Outcomes	Newcastle Ottawa Rating
Corrao (2011), Italy[15]	Population-based prospective cohort study of 242,594 patients in a national Italian database newly treated for hypertension during 2000-2001, analyzed through 2007).	BP meds (all)	Proportion of days covered. Four levels of adherence: very low (≤25%), low (26-50%), intermediate (51-75%) and high (>75%)	Cox proportional hazard regression model adjusted for sex, age, Charlson index, antihypertensive drugs prescribed (both type and number), and use of nonhypertensive drugs Two types of sensitivity analyses: varying the definition of adherence to treatment. and evaluating confounders on the results (ie, depression)	Compared with patients with very low adherence, reduction in risk was 20% for intermediate adherence, and 25% for high adherence (P <.05). Significant reduction in HR with increasing adherence was still observed after accounting for confounders such as age or length of follow-up	8/9
Gallagher (1993), USA[16]	Post hoc analysis of randomized controlled trial of propranolol following myocardial infarction. 505 of original 3837 women included in this analysis aged 30-69 years who had adherence data available	Beta-blocker (propranolol)	At each 3-month follow-up interval during the RCT, patients asked to return all unused medications. Adherence defined as proportion of prescribed meds actually taken. Adherence in each patient was the mean of the quarterly adherence estimates, high adherence defined as >75%.	Cox proportional hazard models included age, smoking status, race, education, clinical severity composite score, high risk myocardial infarction, sociodemographic composite score, myocardial infarction severity (postevent complications, including heart failure), heart failure at baseline	Overall mortality was main outcome. Of 505 women with fully available data, adherence <75% was associated with 2.4 increased RR of mortality (95% CI, 1.1-5.6). Adjustment for any of the covariates led to RR of between 2.5 and 3.0 (P <.02)	N/A
Gehi (2007), USA[17]	Prospective evaluation of 1015 patients with stable coronary heart disease. Patients enrolled between 2000 and 2002, and followed by telephone annually for average of 3.9 yrs.	All meds (specific classes not specified)	Single survey question about overall medication adherence, using a Likert scale.	Cox proportional hazards computed and adjusted for age, sex, race, education, hypertension, diabetes, smoking status, depression, angina, number of cardiovascular meds, beta-blocker use, statin use, cholesterol levels, left ventricular ejection fraction.	Among 1007 with complete follow-up data, nonadherent patients had HR of cardiovascular events of 2.3 (95% CI, 1.3-4.3).	8/9

Table 2 Continued

Study: First Author, Country	Patient Population, & Inclusion Criteria	Coronary Artery Disease Medications	Adherence Measure	Design Features	Outcomes	Newcastle Ottawa Rating
Ho (2006), USA[18]	Registry, interview, and chart analysis of 2498 patients with acute myocardial infarction in 2003-2004 recruited from 19 US hospitals (academic centers, inner-city hospitals, several single-payer systems, and nonuniversity hospitals).	Aspirin, beta-blocker, statin	Main adherence measure was medication discontinuation at 1 month following myocardial infarction, abstracted from hospital records and telephone interviews after discharge.	Adjusted Cox proportional hazard models for age, sex, race, insurance, marital status, education status, diabetes, hypercholesterolemia, hypertension, heart failure, cerebrovascular disease, renal failure, chronic lung disease, smoking, depression, prior coronary disease, myocardial infarction type, coronary revascularization social support cost-related nonadherence, and site of enrollment	Patients who discontinued use of all medications were at increased adjusted risk of death during 1-year follow-up (HR 3.81; 95% CI, 1.88-7.72) Beta-blocker therapy discontinuation (HR 1.96; 95% CI, 1.10-3.45) was individually associated with higher mortality, as was statin therapy discontinuation (HR 2.86; 95% CI, 1.47-5.55)	8/9
Ho (2008), USA[19]	Retrospective cohort study of 10,447 patients in Kaiser Permanente Colorado with coronary artery disease evaluated the impact of medication nonadherence and therapy intensification on reaching target BP goals. Modeled 3 clinically relevant SBP groups: 1) patients with controlled blood pressure that remained stable over time based on systolic pressure $\leq$140 mm Hg (normal-normal); 2) patients who started with high blood pressure that decreased over time (hi-normal); and 3) those who started with high blood pressure that remained high (hi-hi).	Blood pressure meds (all)	Medication adherence calculated from pharmacy records as the PDC for filled prescriptions of antihypertensive medications.	Because statins were prescribed for most patients (85%), evaluated for healthy adherer effect using statin adherence (PDC $>$.80) as a surrogate. Controlled for age, sex, smoking status, previous revascularization procedure or myocardial infarction, hypertension, cerebrovascular accident, diabetes, atrial fibrillation, heart failure, obstructive lung disease, cancer, sleep apnea, hyperlipidemia, dementia, depression	Medication nonadherence was significantly associated with uncontrolled blood pressure (hi-hi group) compared with high blood pressure that became controlled over time (hi-normal group) (OR 1.73; 95% CI, 1.34-2.24). No association found between medication nonadherence and being in the hi-normal group compared with the normal-normal group. Statin adherence associated with BP control (OR .53; 95% CI, .44-.65), even after adjustment for blood pressure medication adherence and therapy intensification (OR .54; 95% CI, .43-.66).	8/9

Table 2 Continued

Study: First Author, Country	Patient Population, & Inclusion Criteria	Coronary Artery Disease Medications	Adherence Measure	Design Features	Outcomes	Newcastle Ottawa Rating
Ho (2008), USA[20]	Retrospective cohort study of 15,767 patients in Kaiser Permanente Colorado with coronary artery disease looking at the impact of medication nonadherence and therapy intensification on reaching target blood pressure goals.	Beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, statin	Medication adherence was calculated as PDC, for the following classes: Beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and statin medications. Patients were classified as "nonadherent" based on a PDC $<$.80, calculated at 180-day intervals	Controlled for age, sex, smoking status, previous revascularization procedure or myocardial infarction, hypertension, cerebrovascular accident, diabetes, atrial fibrillation, heart failure, obstructive lung disease, cancer, sleep apnea, hyperlipidemia, dementia, depression	Medication nonadherence was significantly associated in adjusted models with increased all-cause mortality risk for beta-blockers (HR 1.50, 95% CI, 1.33-1.71), angiotensin converting enzyme inhibitors (HR 1.74, 95% CI, 1.52-1.98), and statins (HR 1.85, 95% CI, 1.63-2.09). Nonadherence was significantly associated with higher risk of cardiovascular mortality for beta-blockers (HR 1.53, 95% CI, 1.16-2.01), angiotensin-converting enzyme inhibitors (HR 1.66, 95% CI, 1.26-2.20), and statins (HR 1.62, 95% CI, 1.124-2.13).	8/9
Irvine (1999), Canada[21]	1141 patients participated in multicenter double-blind, placebo-controlled trial of amiodarone treatment for the prevention of sudden cardiac death in patients with frequent or repetitive ventricular ectopy after an acute myocardial infarction.	Amiodarone	Adherence assessed by pill count at each clinic visit, calculated as the proportion of pills not returned, multiplied by 100, averaged over the 2 years of follow-up for the trial	Controlled for age, previous myocardial infarction, history of heart failure; heart failure at the time of hospitalization for the index acute myocardial infarction; ventricular ectopy on baseline 24-hour Holter monitoring record; high ventricular ectopy rate, diabetes	In multivariate models, low adherence associated with a significantly higher risk of total cardiac deaths (RR 2.04, 95% CI, 1.12-3.72, P $<$.02) and all-cause mortality (RR 2.25, 95% CI, 1.27-3.97, P $<$.001) in the placebo group and total cardiac deaths (RR 2.49, 95% CI, 1.32-4.72, P $<$.01) and all-cause mortality in the amiodarone treatment group (RR 2.34, 95% CI, 1.32-4.17, P $<$.004).	7/9

Table 2 Continued

Study: First Author, Country	Patient Population, & Inclusion Criteria	Coronary Artery Disease Medications	Adherence Measure	Design Features	Outcomes	Newcastle Ottawa Rating
Kleiner (2009), USA[22]	Retrospective study of beta-blocker adherence on mortality and repeat myocardial infarction using health insurance claims records of all patients who were discharged alive after AMI between 1/03 and 6/04, with prescription drug coverage, and prescribed BBs (n = 3923)	Beta-blocker	Calculated adherence using claims data algorithm, similar to PDC. Adherence split it into quartiles	Adjusted for age, sex, income, presence of smoker in household, and specialty of patient's primary care physician. Also adjusted comorbidity risk score (quartiles) measured before the initial event. Created overall model controlling for presence of atherosclerosis, aortic aneurysm, cerebrovascular disease, depression, dysrhythmias, ischemic heart disease, liver disease, neoplasm, renal disease, obesity, diabetes, lipid disorders, congestive heart failure, interventional testing, cardiac testing, carotid endarterectomy, peripheral vascular disease, and medications taken.	In the adjusted survival model the hazard ratio was .37 (95% CI, .25-.54) for the most adherent vs least adherent patients. Similar results were found for mortality or admission for repeat myocardial infarction, with an adjusted hazard ratio of .43 (95% CI, .33-.57)	8/9
Newby (2006), USA[23]	Registry study of 31,750 living patients with documented coronary artery disease who underwent cardiac procedure at large academic medical center since 1969 and had at least 2 consecutive follow-up surveys completed between 1995 and 2002. Stratified subgroups into those with and without heart failure	Aspirin, beta-blocker; statin	Defined 4 patterns of an individual's medication use in survey questions: 1) Always using; 2) never using; 3) no use to use (positive "converters"); 4) use to no use (negative "converters"). "Consistent use" was defined as reporting a medication use on ≥2 consecutive occasions and continuing until death, withdrawal from survey, or end of study period. Patients were considered inconsistent users if did not meet criteria for any patterns.	Controlled age, sex, and race, year of entry into database, smoking, diabetes, hyperlipidemia, hypertension, prior documented cardiovascular events or procedures cerebrovascular disease, peripheral vascular disease, chronic obstructive pulmonary disease, renal disease, heart failure, peptic ulcer disease, systolic and diastolic BP at entry, events during the study period, and medications at first follow-up.	Consistent medication use of the following medications was associated with lower adjusted mortality: aspirin HR .58 and 95% CI, .54-.62; beta-blocker, HR .63 and 95% CI, .59-.67; statin, HR .52 and 95% CI, .42-.65; all 3 medications, HR .67 and 95% CI, .59-.77; aspirin and beta-blocker, HR .61 and 95% CI, .57-.65	7/9

Table 2 Continued

Study: First Author, Country	Patient Population, & Inclusion Criteria	Coronary Artery Disease Medications	Adherence Measure	Design Features	Outcomes	Newcastle Ottawa Rating
Pittman (2010), USA[24]	Retrospective analysis of 625,620 in a national pharmacy benefits database of de-identified pharmacy and medical claims among patients with hypertension, with 2 or more claims for antihypertensive medications. Excluded patients >64 years; those with cancer or HIV; those without continuous eligibility for prescription drug coverage; those without data from 2006-2008	Antihypertensive medications (all)	MPR with antihypertensive medications 3 adherence categories: adherent (MPR ≥80%); moderate adherence (MPR 60-79%); low adherence (MPR <60%)	Binary outcome variable of high adherence vs low-to-moderate adherence. Logistic regression analysis used to assess possible predictors of adherence, which included demographics alone and together with comorbidities, chronic disease score, antihypertensive class, out-of-pocket cost for medication, and use of mail order. Logistic regression used to evaluate association of level of adherence with CV-related hospitalizations and emergency department visits. Adjusted general linear models used to determine mean cost for each level of adherence.	After adjustment, low and moderate adherence patients more likely to be hospitalized for a CV event (ORs 1.33 [low] and 1.28 [moderate]) or have 1 or more CV-related ED visit (ORs 1.45 [low] and 1.27 [moderate]). Patients in high adherence group had significantly lower total health care costs ($7182) compared with patients in moderate ($7560) and low ($7995) adherence groups (P <.001 for both)	8/9
Pittman (2011), USA[9]	Retrospective cohort study of 381,422 adults with using a statin medication during 2008-2009. Compiled cohort from integrated pharmacy and medical claims database. Assessed relation among statin adherence, subsequent hospitalizations, and health care costs.	Statin	MPR with statins. 3 adherence categories: adherent (MPR ≥80%); moderate adherence (MPR 60%-79%); low adherence (MPR <60%)	Logistic regression analysis to study predictors of adherence controlling for age, sex, comorbidities, out-of-pocket costs for medication chronic disease score, and use of mail-order pharmacy. Generalized linear models performed to determine average costs in follow-up period for each level of adherence, adjusted for age, sex, comorbidities, first-year total medication and health costs.	Adjusted OR of cardiovascular disease-related hospitalization (compared with fully adherent group): 1.26 (low adherence) and 1.12 (moderate adherence) (P <.05). Fully adherent patients had cardiovascular-related medical costs = $2395 ± 20.5 compared with moderate ($2583 ± $40.4) and low ($2689 ± $43.9) adherence ($P$ <.001).	8/9

Table 2 Continued

Study: First Author, Country	Patient Population, & Inclusion Criteria	Coronary Artery Disease Medications	Adherence Measure	Design Features	Outcomes	Newcastle Ottawa Rating
Rasmussen (2007), Canada[25]	Population-based, observational, longitudinal study of 31,455 elderly (66 and older) acute myocardial infarction survivors between 1999 and 2003 in Ontario. Patients had to have survived ≥1 year and 3 months after initial hospitalization All patients filled a prescription for statins, beta-blockers, or calcium channel blockers. The use of calcium channel blockers was considered a control given absence of clinical trial-proven survival benefits.	Statin; beta-blocker, calcium channel blocker	Claims data used to calculate the PDC. Adherence subdivided a priori into 3 categories: high (PDC >80%), intermediate (PDC 40%-79%), and low (PDC <40%).	The research team used Ontario acute myocardial infarction mortality prediction rule to control for severity of illness, including age, sex, severity of cardiac disease, and presence of coexisting illnesses (stroke, diabetes, cancer, and acute or chronic renal disease). They also adjusted for whether patients received revascularization procedures, admission for ischemic heart disease, metabolic diseases, mental disorders, stroke, diseases of the respiratory system, concomitant use of other cardiac meds, and the number of all-cause admissions during the study period. To disentangle biological drug effects from healthy adherer effects, they evaluated impact of cardiovascular drug adherence on sample of prespecified outcomes with neither clinical evidence nor biological plausibility (lung, breast, and prostate cancer).	Among statin users, compared with their high-adherence counterparts, low adherence patients had the highest significantly increased mortality risk (adjusted HR 1.25; 95% CI, 1.09-1.42; $P = .001$). This increased risk was somewhat attenuated for intermediate adherers (adjusted HR 1.12; 95% CI, 1.01-1.25; $P = .03$). Similar but less pronounced dose-response–type adherence-mortality association observed for beta-blockers, in which low adherence HR was 1.13 (95% CI, 1.03-1.25); intermediate was 1.01 (95% CI, .93-1.09). Mortality and cancer-related admissions were not associated with adherence to calcium channel blockers, outcomes for which biological plausibility do not exist.	9/9

Table 2 Continued

Study: First Author, Country	Patient Population, & Inclusion Criteria	Coronary Artery Disease Medications	Adherence Measure	Design Features	Outcomes	Newcastle Ottawa Rating
Shalev (2009), Israel[26]	Retrospective cohort study of adult enrollees in an Israeli health maintenance organization who initiated statin treatment from 1998 through 2006. Two cohorts were formed: primary (136,052) and secondary prevention statin users (93,866).	Statin	PDC with statins	Full multivariate model age, sex, marital status, nationality, SES, place of residency, immigration status, nationality, disability status, presence of chronic comorbidities, utilization of health services, lipid level, efficacy of the initial statin therapy, and chronic conditions (psychotic disease, chronic lung disease, morbid obesity, Alzheimer disease, asthma, diabetes, cancer)	Adjusted HR associated with each 10% increase in PDC was .94 (95% CI, .93-.95) and .93 (.93-.94) in the primary and secondary prevention cohorts, respectively. Compared with PDC of $<$10%, PDC of 90% or higher associated with an adjusted HR of .42 (95% CI, .37-.47) and .39 (95% CI, .36-.42) among the primary prevention and secondary prevention cohorts.	8/9
Spertus (2006), USA[27]	Retrospectively collected registry data study from 19-center study of myocardial infarction patients. 2003 and 2004, 2498 patients prospectively screened and enrolled into Prospective Registry Evaluating Myocardial Infarction: Events and Recovery (PREMIER) Study, of which 500 patients were studied in this cohort study	Thienopyridines	Patients contacted by telephone 1 month after initial procedure to determine current medical regimen. At 30-day interview, patients were surveyed about adherence to thienopyridines as a yes/no question.	Authors constructed multivariable logistic regression models to identify predictors of discontinuing thienopyridine therapy. Covariates included age, sex, race, marital status, education level, avoidance of health care because of cost, depression screen any prior condition (myocardial infarction, revascularization procedure, stroke, or documented peripheral arterial disease); anemia, warfarin use, receipt of instructions on discharge medications; and referral to cardiac rehabilitation.	Adjusting for the propensity to discontinue, patients who stopped thienopyridine therapy by 30 days were significantly more likely to die during the next 11 months (7.5% vs .7%, P $<$.0001; adjusted HR 9.0; 95% CI, 1.3-60.6) and to be rehospitalized (23% vs 14%, P = .08; adjusted HR 1.5; 95% CI, .78 to 3.0).	8/9

Table 2 Continued

Study: First Author, Country	Patient Population, & Inclusion Criteria	Coronary Artery Disease Medications	Adherence Measure	Design Features	Outcomes	Newcastle Ottawa Rating
Sun (2008), USA[28]	National retrospective administrative data analysis of patients discharged from the hospital with a primary diagnosis of myocardial infarction or heart failure between 2003- and 2006. Included patients were >18 years at the time of diagnosis and followed for 1 year after index date via medical and prescription records.	Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers	Medication adherence measured using the MPR in the 1 year after their hospitalization. Adherence, partial adherence, and nonadherence defined as having a MPR <.8, .5-.79, or <.5, respectively. Nonpersistence was defined as any gap of >30 days in therapy.	The authors constructed logistic regression models controlling for age, sex, and comorbidities (measured through the Charlson comorbidity index)	Among patients in the myocardial infarction group, adherent patients compared with nonadherent, patients were no less likely to be rehospitalized after discharge (OR .66; 95% CI, .31-1.41; P = NS). Findings for the partially adherent group also were not statistically significant (OR 1.10; 95% CI, .50-2.43; P = NS). However, patients persistent with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers were significantly less likely to be rehospitalized (OR .50; 95% CI, .27-.95; P <.036).	7/9
Wei (2002), Scotland[29]	Scottish patients who experienced their first myocardial infarction between 1990 and 1995 identified from Tayside hospital discharge data. Maximum follow-up was 6 years.	Statin	Adherence to statin treatment calculated as PDC. Adherence divided into 4 categories: 0%, <39%, 40-79%, and >80%. For each prescription for a statin authors had electronic record access to tablet strength, number of tablets dispensed, and instructions on how these should be taken.	Multivariate analyses adjusted for age, sex, socioeconomic deprivation, statin daily dose, lipid lowering drug treatment before myocardial infarction, serum total cholesterol concentration, diabetes, other cardiovascular drug prescriptions, and other hospitalizations (excluding surgical events) during the follow-up.	In multivariate analyses, compared with those with 0% adherence, those with <39% adherence had an adjusted HR for myocardial infarction recurrence = .59 (95% CI, .22-1.59); those with 40%-79% adherence had an adjusted HR = .51 (95% CI, .19-1.35); and those with 80%-100% adherence had an adjusted HR = .19 (95% CI, .08-.47). Compared with 0% adherence, 80%-100% adherence adjusted HR = .47 for all-cause mortality (95% CI, .22-.99)	9/9

CI = confidence interval; HR = hazard ratio; NS = nonsignificant; MPR = medication possession ratio; BP = blood pressure; OR = odds ratio; PDC = proportion of days covered; CV = cardiovascular; RR = relative risk.

Secondary Prevention: Antihypertensive Medications

Two studies evaluated the impact of adherence to beta-blockers alone. Gallagher et al (1993)[16] performed a post hoc analysis of a randomized controlled trial of propranolol use after myocardial infarction. In a randomized controlled trial subset of 505 women studied for adherence, those whose direct pill counts of unused medications from the trial showed adherence of <75% had a relative risk for mortality of 2.4 (95% CI, 1.1-5.6) compared with those with higher adherence. Kleiner et al[22] retrospectively studied adherence to beta-blockers in a health insurance claims database using PDC, finding an adjusted HR for survival of .37 (95% CI, .25-.54) for most- versus least-adherent patients.

Secondary Prevention: Multiple Medication Regimens and Other Medications

A number of studies looked at the effect of adherence to various combinations of antihypertensive medications and statins on outcomes. While most evaluated specific combinations of medications examined, a number of studies did not specify regimens clearly. The Canadian study by Rasmussen et al[25] and the randomized controlled trial by Choudhry et al[14] are the most sound methodologically. Rasmussen et al[25] evaluated the relationship between mortality and adherence to essential cardiac medications (statin and beta-blocker) after a myocardial infarction. Notably, they controlled for adherence to another medication, a calcium channel blocker, which has not been shown to have meaningful effects on mortality in postmyocardial infarction patients. They found that patients who were least adherent to statins were 25% more likely to die than patients who were most adherent. Intermediate adherers were 12% more likely to die than the best adherers. There was no significant relationship between adherence to calcium channel blockers and mortality. Interestingly, the magnitude of the relationship between adherence and health outcomes in the Rasmussen et al article[25] was similar in magnitude to an earlier meta-analysis of medication adherence in coronary artery disease results from DiMatteo et al.[2]

Choudhry et al[14] randomly assigned 5855 patients who suffered a myocardial infarction to full prescription drug coverage post myocardial infarction for all coronary artery disease-related medications or usual coverage, and analyzed effects on medication adherence, cardiovascular events, and total, cardiovascular, pharmaceutical, and nonpharmaceutical spending. Adherence in the drug coverage group increased between 4% and 6% in each drug class. First major vascular event or revascularization rates did not differ, but total major vascular events or revascularization rates were significantly decreased in the drug coverage group compared with the usual coverage group. Pharmaceutical drug spending increased, but nondrug spending was reduced, leading to a nonsignificant overall decrease in total spending between the 2 groups.

Pittman et al[24] looked at a retrospective cohort of pharmacy beneficiaries in the US with multiple claims for a number of different antihypertensive medications. They found that those with MPR <60% had 30%-40% higher adjusted odds ratio for emergency department visit and hospitalization for a cardiovascular event, resulting in an annual cost difference of $813 ($7995 vs $7182), compared with those patients with MPR >80%.

Two studies examined adherence to medications not for lipid or blood pressure control, one of which was for thienopyridines (antiplatelet drugs) and one which examined antiarrhythmic effects (amiodarone). At 30 days post stenting for myocardial infarction, Spertus et al[27] found that those patients who stopped thienopyridines experienced a statistically significantly absolute increase in risk of death of 6.8% over the succeeding 11 months, even after adjusting for a patient's propensity to discontinue medications. Irvine et al[21] examined a post hoc analysis of pill counts for an amiodarone randomized controlled trial, reporting that cardiovascular and total cause mortality were significantly elevated in the low-adherence amiodarone treatment group (relative risk 2.34-2.49).

DISCUSSION

This systematic review of studies that link medication adherence to coronary artery disease cost and mortality outcomes yielded a mix of observational studies with a few post hoc analyses of randomized controlled studies and one prespecified randomized controlled trial. Most studies were retrospective in nature and analyzed claims databases from large insurers or pharmacy benefit managers from North America, Europe, and Israel. Most studies examined adherence to statins or antihypertensive medications, either alone or in combination. These studies used a variety of adherence measures, from medication possession ratio, proportion of days covered, direct pill counts, and patient survey questions. They also used a wide mix of techniques to attempt to adjust for potential confounders, primarily focused on relevant sociodemographic, insurance, and comorbidity characteristics. The quality of studies was generally good per the Newcastle Ottawa Quality Scale.

Overall, our review of the published literature showed a consistent trend toward benefits in reduced coronary artery disease-related events, mortality, readmissions, and costs across a variety of adherence measures and medication classes. In general, despite specific method heterogeneity, a similar overall analytic approach was used: the authors identified patients as adherent or nonadherent based on refill claims data and evaluated the relationship between adherence category and health outcomes (hospitalizations, costs, or death). All of the studies reviewed found that adherence significantly improves health outcomes, and those that analyzed costs found reduced total annual coronary artery disease costs (consistently between $294 and $868 per patient, equating to 10.1%-17.8% cost reductions between high- and low-adherence groups).

Results from one previous systematic review and meta-analysis of studies[2] reported findings that were generally similar to the newer articles listed here. However, this study[2] was a systematic review of all types of behaviors for a host of chronic diseases and was conducted before the publication of many of the papers we analyzed; including the recent papers that directly linked cost analyses to adherence, as well as the prespecified randomized controlled trial.

One key problem with this literature base is that, in the overwhelming majority of these studies (except for Rasmussen et al,[25] Ho et al,[19] and Choudhry et al[14]), the authors did not consider the healthy adherer effect. The magnitude of the mortality and hospitalization benefits for better adherence is a function of whether the study controlled well for this potentially confounding effect. Patients who adhere to their medications also may be more likely to adhere to a healthier diet, exercise more frequently, and pursue a healthier lifestyle. Dormuth et al[31] found a strong relationship between statin adherence and motor vehicle accidents, for which there is little biologic plausibility. This research raises questions about the validity of the magnitude (but less likely the direction) of relationships between adherence and outcomes in observational studies that do not control for other healthy behaviors. Interestingly, the study on amiodarone use found large mortality reduction benefits (adjusted odds ratio ~2.4) for highly adhering patients, which is notable considering that a 2009 meta-analysis of amiodarone trials concluded that amiodarone use after myocardial infarction does not reduce all-cause deaths.[32] Nonetheless, while the literature is not ideal, and a definitive study has not been performed, there is a preponderance of evidence that suggests the presence of a strong relationship between adherence to essential coronary artery disease prevention medications and both improved health outcomes and cost reductions.

These results have a number of policy and research implications. First, although the direction of the associations all point to significant coronary artery disease cost and outcome improvement with better adherence, only two studies we found directly controlled for the healthy adherer effect (and one indirectly controlled for it by virtue of being a randomized trial). Thus, there is a critical need for better studies with healthy user controls, especially as payers and purchasers are starting to apply large resources towards adherence improvement and thus need more precise estimates for return on investment analyses. One good example of a recent study that controlled for this effect was Roebuck et al,[4] which used advanced econometric techniques to address this effect in claims data through elimination of unmeasured confounders if they did not change over time. Findings from Roebuck et al[4] also were consistent in direction and magnitude with the studies we identified in this review, although it focused on cardiovascular and other metabolic diseases in general and not on coronary artery disease specifically.

Second, patient-centered medical home and accountable care organization delivery pilots need to have more fine-grained understanding and evaluation of how they might improve adherence before they begin targeting it. Studies such as those reviewed here can help evaluators and policymakers make better estimates of expected outcome or cost improvements that may be achieved in federal shared savings pilots or private-payer care-delivery demonstrations (we found cost reductions in the range of 10%-18%). Furthermore, efforts to explicitly improve adherence will need to determine which domains of adherence to target (eg, cognitive, cost), and how to best measure the putative end points of these experiments. As Choudhry et al[14] showed, reducing cost barriers can improve adherence to secondary prevention medications and potentially reduce some unwanted outcomes. Whether interventions that address other adherence barriers (such as smart pillboxes for cognitive barriers) can achieve similar improvements remains to be rigorously evaluated on a large scale.

Many key delivery system reforms will increasingly rely on projected medication adherence improvements through team-based provider efforts, financial incentive alignment, or better technical support of patients at home in order to achieve important cost and outcome targets. Given the pace of delivery innovation throughout the US, and the magnitude of possible benefits from improved medication adherence, renewed efforts at the private and national levels to better understand and support increases in medication adherence are urgently needed.[33] While the promise of improved adherence around chronic disease such as coronary artery disease is large, much methodological and implementation work remains before we can conclusively quantify these benefits.

References

1. Heidenreich PA, Trogdon JG, Khavjou OA, et al. Forecasting the future of cardiovascular disease in the United States: a policy statement from the American Heart Association. *Circulation*. 2011;123(8):933-944.
2. DiMatteo MR, Giordani PJ, Lepper HS, Croghan TW. Patient adherence and medical treatment outcomes: a meta-analysis. *Med Care*. 2002;40(9):794-811.
3. Salas M, Hughes D, Zuluaga A, et al. Costs of medication nonadherence in patients with diabetes mellitus: a systematic review and critical analysis of the literature. *Value Health*. 2009;12(6):915-922.
4. 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.
5. Bechtel C, Ness DL. If you build it, will they come? Designing truly patient-centered health care. *Health Aff (Millwood)*. 2010;29(5):914-920.
6. Bouchard MH, Dragomir A, Blais L, et al. Impact of adherence to statins on coronary artery disease in primary prevention. *Br J Clin Pharmacol*. 2007;63(6):698-708.
7. Breekveldt-Postma NS, Penning-van Beest FJ, Siiskonen SJ, et al. The effect of discontinuation of antihypertensives on the risk of acute myocardial infarction and stroke. *Curr Med Res Opin*. 2008;24(1):121-127.
8. Corrao G, Conti V, Merlino L, et al. Results of a retrospective database analysis of adherence to statin therapy and risk of nonfatal ischemic

heart disease in daily clinical practice in Italy. *Clin Ther*. 2010;32(2):300-310.
9. Pittman DG, Chen W, Bowlin SJ, Foody JM. Adherence to statins, subsequent healthcare costs, and cardiovascular hospitalizations. *Am J Cardiol*. 2011;107(11):1662-1666.
10. Perreault S, Dragomir A, Blais L, et al. Impact of better adherence to statin agents in the primary prevention of coronary artery disease. *Eur J Clin Pharmacol*. 2009;65(10):1013-1024.
11. Amin AP, Mukhopadhyay E, Nathan S, et al. Association of medical noncompliance and long-term adverse outcomes, after myocardial infarction in a minority and uninsured population. *Transl Res*. 2009; 154(2):78-89.
12. Aubert RE, Yao J, Xia F, Garavaglia SB. Is there a relationship between early statin compliance and a reduction in healthcare utilization? *Am J Manag Care*. 2010;16(6):459-466.
13. Chapman RH, Yeaw J, Roberts CS. Association between adherence to calcium-channel blocker and statin medications and likelihood of cardiovascular events among US managed care enrollees. *BMC Cardiovasc Disord*. 2010;10:29.
14. Choudhry NK, Avorn J, Glynn RJ, et al. Full coverage for preventive medications after myocardial infarction. *N Engl J Med*. 2011;365(22): 2088-2097.
15. Corrao G, Parodi A, Nicotra F, et al. Better compliance to antihypertensive medications reduces cardiovascular risk. *J Hypertens*. 2011; 29(3):610-618.
16. Gallagher EJ, Viscoli CM, Horwitz RI. The relationship of treatment adherence to the risk of death after myocardial infarction in women. *JAMA*. 1993;270(6):742-744.
17. Gehi AK, Ali S, Na B, Whooley MA. Self-reported medication adherence and cardiovascular events in patients with stable coronary heart disease: the heart and soul study. *Arch Intern Med*. 2007;167(16): 1798-1803.
18. Ho PM, Spertus JA, Masoudi FA, et al. Impact of medication therapy discontinuation on mortality after myocardial infarction. *Arch Intern Med*. 2006;166(17):1842-1847.
19. Ho PM, Magid DJ, Shetterly SM, et al. Importance of therapy intensification and medication nonadherence for blood pressure control in patients with coronary disease. *Arch Intern Med*. 2008;168(3):271-276.
20. Ho PM, Magid DJ, Shetterly SM, et al. Medication nonadherence is associated with a broad range of adverse outcomes in patients with coronary artery disease. *Am Heart J*. 2008;155(4):772-779.
21. Irvine J, Baker B, Smith J, et al. Poor adherence to placebo or amiodarone therapy predicts mortality: results from the CAMIAT study. Canadian Amiodarone Myocardial Infarction Arrhythmia Trial. *Psychosom Med*. 1999;61(4):566-575.
22. Kleiner SA, Vogt WB, Gladowski P, et al. Beta-blocker compliance, mortality, and reinfarction: validation of clinical trial association using insurer claims data. *Am J Med Qual*. 2009;24(6):512-519.
23. Newby LK, LaPointe NM, Chen AY, et al. Long-term adherence to evidence-based secondary prevention therapies in coronary artery disease. *Circulation*. 2006;113(2):203-212.
24. Pittman DG, Tao Z, Chen W, Stettin GD. Antihypertensive medication adherence and subsequent healthcare utilization and costs. *Am J Manag Care*. 2010;16(8):568-576.
25. Rasmussen JN, Chong A, Alter DA. Relationship between adherence to evidence-based pharmacotherapy and long-term mortality after acute myocardial infarction. *JAMA*. 2007;297(2):177-186.
26. Shalev V, Chodick G, Silber H, et al. Continuation of statin treatment and all-cause mortality: a population-based cohort study. *Arch Intern Med*. 2009;169(3):260-268.
27. Spertus JA, Kettelkamp R, Vance C, et al. Prevalence, predictors, and outcomes of premature discontinuation of thienopyridine therapy after drug-eluting stent placement: results from the PREMIER registry. *Circulation*. 2006;113(24):2803-2809.
28. Sun SX, Ye X, Lee KY, et al. Retrospective claims database analysis to determine relationship between renin-angiotensin system agents, rehospitalization, and health care costs in patients with heart failure or myocardial infarction. *Clin Ther*. 2008;30(Pt 2):2217-2227.
29. Wei L, Wang J, Thompson P, et al. Adherence to statin treatment and readmission of patients after myocardial infarction: a six year follow up study. *Heart*. 2002;88(3):229-233.
30. Dragomir A, Cote R, White M, et al. Relationship between adherence level to statins, clinical issues and health-care costs in real-life clinical setting. *Value Health*. 2010;13(1):87-94.
31. Dormuth CR, Patrick AR, Shrank WH, et al. Statin adherence and risk of accidents: a cautionary tale. *Circulation*. 2009;119(15):2051-2057.
32. Piccini JP, Berger JS, O'Connor CM. Amiodarone for the prevention of sudden cardiac death: a meta-analysis of randomized controlled trials. *Eur Heart J*. 2009;30(10):1245-1253.
33. Goldman L, Epstein AM. Improving adherence–money isn't the only thing. *N Engl J Med*. 2011;365(22):2131-2133.

Appendix: Search Terms Used

"Epidemiologic Studies" [Mesh] OR "Epidemiological Studies" [tw] OR "Epidemiological Study" [tw] OR "Case-Control" [tw] OR "Case-Compeer" [tw] OR "Case-Comparison" [tw] OR "Case-Referent" [tw] OR "Case Base" [tw] OR "retrospective study" [tw] OR "retrospective studies" [tw] OR "Cohort Study" [tw] OR "Concurrent Studies" [tw] OR "Concurrent Study" [tw] OR "Cohort Analyses" [tw] OR "Cohort Analysis" [tw] OR "Incidence Studies" [tw] OR "Incidence Study" [tw] OR "Longitudinal Study" [tw] OR "Longitudinal Studies" [tw] OR "Longitudinal Survey" [tw] OR "Longitudinal Surveys" [tw] OR "Follow-Up Study" [tw] OR "Follow Up Studies" [tw] OR "Followup Study" [tw] OR "Followup Studies" [tw] OR "Prospective Study" [tw] OR "Prospective Studies" [tw] OR "Cross Sectional Studies" [tw] OR "Cross Sectional Study" [tw] OR "Cross-Sectional Study" [tw] OR "Cross-Sectional Studies" [tw] OR "Disease Frequency Surveys" [tw] OR "Disease Frequency Survey" [tw] OR "Cross Sectional Survey" [tw] OR "Cross Sectional Surveys" [tw] OR "Cross-Sectional Survey" [tw] OR "Cross-Sectional Survey" [tw] OR "Cross Sectional Analysis" [tw] OR "Cross Sectional Analyses" [tw] OR "Cross-Sectional Analysis" [tw] OR "Cross-Sectional Analyses" [tw] OR "Prevalence Study" [tw] OR "Prevalence Studies"

AND ("compliance" [tiab] OR "patient compliance" [mesh] OR "patient adherence" [tw] OR "patients adherence" [tw] OR "patient compliance" [tw] OR "medication adherence" [tw] OR "medication compliance" [tw] OR "treatment compliance" [tw] OR "treatment adherence" [tw] OR "treatment refusal" [mesh] OR "patient dropouts" [mesh] OR "treatment refusal" [tw] OR "patient dropout" [tw] OR "patient dropouts" [tw] OR "patient dropped" [tw] OR "drug adherence" [tw] OR "drug compliance" [tw] OR "persistence" [tiab]

AND ("drug therapy" [mesh] OR "drug therapy" [sh] OR "Pharmaceutical Services" [mesh] OR "Medication systems" [Mesh] OR "Drug Utilization Review" [mesh] OR "pharmacies" [mesh] OR "Pharmaceutical Preparations" [mesh] OR "prescription drugs" [tw] OR "prescription drug" [tw] OR "drug therapy" [tw] OR "drug treatment" [tw] OR (("drug" [tw] OR "drugs" [tw] OR "medicine" [tw] OR "medicines" [tw] OR "medication" [tw] OR "medications" [tw]) NOT medline[sb]) OR "Cardiovascular Agents/therapeutic use" [Mesh] OR "Hypoglycemic Agents/therapeutic use" [Mesh] OR "Antihypertensive agents/therapeutic use" [Mesh] OR "Antilipemic Agents/therapeutic use" [Mesh]) OR ("Cardiovascular Agents" [Mesh] OR "Cardiovascular Agents "[Pharmacological Action]) OR "Insulin" [Mesh] OR "insulin" [tw] OR "hypoglycemic agents" [Mesh] OR "hypoglycemic agents" [pa] OR "hypoglycemic agent" [tw] OR "antidiabetic" [tw] OR "hypoglycemic drug" [tw] OR "hypoglycemic agents" [tw] OR "antidiabetics" [tw] OR "hypoglycemic drugs"[tw]) OR ("Antihypertensive agents" [Mesh] OR "Antihypertensive Agents" [pa])

AND ("Diabetes Mellitus" [Mesh] OR "diabetes" [tw] OR "Blood Pressure" [Mesh]) OR "Cardiovascular Diseases" [Mesh] OR "Heart arrest" [mesh] OR "Heart arrest" [tw] OR "Heart arrests" [tw] OR "Cardiac Arrest" [tw] OR "Cardiac Arrests" [tw] OR "Asystole" [tw] OR "Asystoles" [tw] OR "Cardiopulmonary Arrest" [tw] OR "Cardiac Sudden Death" [tw] OR "Sudden Cardiac Death" [tw] OR "circulation arrest" [tw] OR "circulatory arrest" [tw] OR "heart standstill" [tw] OR "Ventricular Fibrillation" [mesh] OR "Ventricular Fibrillation" [tw] OR "Ventricular Fibrillations" [tw] OR "Myocardial Ischemia" [mesh] OR "Myocardial Ischemias OR "Myocardial Ischemia" [tw] OR "Ischemic Heart Disease" [tw] OR "Ischemic Heart Diseases" [tw] OR "Acute Coronary Syndromes" [tw] OR "Acute Coronary Syndrome" [tw] OR "Stenocardia" [tw] OR "Stenocardias" [tw] OR "Angor Pectoris" [tw] OR "Angina" [tw] OR "Anginas" [tw] OR "Myocardial Preinfarction" [tw] OR "Cardiac Syndrome X" [tw] OR "Coronary Diseases" [tw] OR "Coronary Disease" [tw] OR "Coronary Heart Disease" [tw] OR "Coronary Heart Diseases" [tw] OR "Coronary Aneurysms" [tw] OR "Coronary Aneurysm" [tw] OR "Coronary Artery Diseases" [tw] OR "Coronary Artery Disease" [tw] OR "Arteriosclerosis" [tw] OR "Arterioscleroses" [tw] OR "Coronary Occlusions" [tw] OR "Coronary Occlusion" [tw] OR "Coronary Artery Stenosis" [tw] OR "Coronary Stenosis" [tw] OR "Coronary Stenoses" [tw] OR "Coronary Artery Stenoses" [tw] OR "Coronary Restenoses" [tw] OR "Coronary Restenosis" [tw] OR "Coronary Thromboses" [tw] OR "Coronary Thrombosis" [tw] OR "Coronary Vasospasms" [tw] OR "Coronary Vasospasm" [tw] OR "Coronary Artery Vasospasm" [tw] OR "Coronary Artery Vasospasms" [tw] OR "Myocardial Infarctions" [tw] OR "Myocardial Infarction" [tw] OR "Myocardial Infarct" [tw] OR "Myocardial Infarcts" [tw] OR "Heart Failure" [mesh] OR "Heart Failure" [tw] OR "Cardiac Failure" [tw] OR "Myocardial Failure" [tw] OR "Heart Decompensation" [tw] OR "Paroxysmal Dyspnea" [tw] OR "Paroxysmal Dyspneas" [tw] OR "Paroxysmal Nocturnal Dyspnea" [tw] OR "Cardiac Asthma" [tw] OR "Cardiac Edemas" [tw] OR "Cardiac Edema" [tw] OR "Heart Failures" [tw] OR "backward failure" [tw] OR "cardiac backward failure" [tw] OR "cardiac decompensation" [tw] OR "cardiac incompetence" [tw] OR "cardiac insufficiency" [tw] OR "cardial decompensation" [tw] OR "cardial insufficiency OR "heart insufficiency" [tw] OR "decompensatio cordis" [tw] OR "heart incompetence" [tw] OR "heart insufficiency" [tw] OR "insufficientia cardis" [tw] OR "myocardial insufficiency" [tw] OR "Ventricular Dysfunction" [mesh] OR "Ventricular Dysfunctions" [tw] OR "Ventricular Dysfunction" [tw] OR "ventricle insufficiency" [tw] OR "ventrical failure" [tw] OR "ventricular insufficiency" [tw] OR "ventricular failure" OR "Cerebrovascular Disorders" [mesh] OR "Cerebrovascular Disorder" [tw] OR "Cerebrovascular Insufficiency" [tw] OR "Cerebrovascular Insufficiencies" [tw] OR "Cerebrovascular Occlusion" [tw] OR "Cerebrovascular Occlusions" [tw] OR "Lenticulostriate Vasculopathy" [tw] OR "Lenticulostriate Vasculopathies" [tw] OR "Basal Ganglionic Hemorrhage" [tw] OR "Basal Ganglia Hematoma" [tw] OR "Putamen Hemor-

rhage" [tw] OR "Putaminal Hematoma" [tw] OR "Putaminal Brain Hemorrhage" [tw] OR "Putaminal Brain Hemorrhages" [tw] OR "Brain Ischemias" [tw] OR "Brain Ischemia" [tw] OR "Ischemic Encephalopathy" [tw] OR "Ischemic Encephalopathies" [tw] OR "Cerebral Ischemia" [tw] OR "Cerebral Ischemias" [tw] OR "Brain Infarctions" [tw] OR "Brain Infarction" [tw] OR "Brain Venous Infarction" [tw] OR "Brain Venous Infarctions" [tw] OR "Lacunar Infarction" [tw] OR "Lacunar Infarctions" [tw] OR "Cerebral Circulation Infarction" [tw] OR "Brainstem Infarction" [tw] OR "Brainstem Infarctions" [tw] OR "Claude Syndrome" [tw] OR "Weber Syndrome" [tw] OR "Millard Gublar" [tw] OR "Top of the Basilar Syndrome" [tw] OR "Benedict Syndrome" [tw] OR "Foville Syndrome" [tw] OR "Lateral Medullary Syndromes" [tw] OR "Posterior Inferior Cerebellar Artery Syndrome" [tw] OR "Wallenberg's Syndrome" [tw] OR "Wallenbergs Syndrome" [tw] OR "Dorsolateral Medullary Syndrome" [tw] OR "Lateral Bulbar Syndrome" [tw] OR "Cerebral Infarctions" [tw] OR "Cerebral Infarction" [tw] OR "Subcortical Infarction" [tw] OR "Subcortical Infarctions" [tw] OR "Cerebral Artery Infarction" [tw] OR "Multi Infarct Dementias" [tw] OR "Multi Infarct Dementia" [tw] OR "Lacunar Dementia" [tw] OR "Lacunar Dementias" [tw] OR "ACA Infarction" [tw] OR "ACA Infarctions" [tw] OR "Cerebral Artery Circulation Infarction" [tw] OR "Cerebral Artery Distribution Infarction" [tw] OR "Heubner Artery Infarction" [tw] OR "Heubner's Artery Infarction" [tw] OR "Heubners Artery Infarction" [tw] OR "Cerebral Artery Syndrome" [tw] OR "MCA Infarction" [tw] OR "Cerebral Artery Embolus" [tw] OR "Cerebral Artery Occlusion" [tw] OR "Cerebral Artery Thrombotic Infarction" [tw] OR "Cerebral Artery Thrombosis" [tw] OR "Cerebral Artery Embolic Infarction" [tw] OR "PCA Infarction" [tw] OR "Brain Hypoxia Ischemias" [tw] OR "Brain Hypoxia Ischemia" [tw] OR "Hypoxic Ischemic Encephalopathy" [tw] OR "Hypoxic Ischemic Encephalopathy" [tw] OR "Hypoxic Ischemic Encephalopathies" [tw] OR "Ischemic Hypoxic Encephalopathy" [tw] OR "Ischemic Hypoxic Encephalopathies" [tw] OR "Anoxic Ischemic Encephalopathy" [tw] OR "Anoxic Ischemic Encephalopathies" [tw] OR "Cerebral Hypoxia-Ischemia" [tw] OR "Cerebral Hypoxia Ischemia" [tw] OR "Cerebral Ischemia Hypoxia" [tw] OR "Brain Ischemia Anoxia" [tw] OR "Brain Anoxia Ischemia" [tw] OR "Cerebral Ischemia Anoxia" [tw] OR "Cerebral Anoxia Ischemia" [tw] OR "TIA" [tw] OR "TIAs" [tw] OR "Transient Ischemic Attack" [tw] OR "Transient Ischemic Attacks" [tw] OR "Brain TIA" [tw] OR "Transient Brainstem Ischemia" [tw] OR "Transient Brainstem Ischemias" [tw] OR "Transient Cerebral Ischemia" [tw] OR "Transient Cerebral Ischemias" [tw] OR "Vertebrobasilar Insufficiencies" [tw] OR "Vertebrobasilar Insufficiency" [tw] OR "Vertebrobasilar Ischemia" [tw] OR "Vertebrobasilar Ischemias" [tw] OR "Vertebrobasilar Dolichoectasia" [tw] OR "Vertebrobasilar Dolichoectasias" [tw] OR "Vertebral Artery" [tw] OR "Basilar Artery" [tw] OR "Subclavian Artery Stenosis" [tw] OR "Subclavian Artery Stenoses" [tw] OR "Basilar Steal Syndrome" [tw] OR "Basilar Steal Syndromes" [tw] OR "Brachial Basilar Insufficiency Syndrome" [tw] OR "Subclavian Steal" [tw] OR "Brain Vascular Trauma" [tw] OR "Brain Vascular Injury" [tw] OR "Vascular Brain Injuries" [tw] OR "Vascular Brain Injury" [tw] OR "Subarachnoid Hemorrhages" [tw] OR "Subarachnoid Hemorrhage" [tw] OR "Intracranial Arterial Disease" [tw] OR "Intracranial Arterial Disorder" [tw] OR "Intracranial Arterial Disorders" [tw] OR "Arterial Brain Disease" [tw] OR "Arterial Brain Diseases" [tw] OR "Arterial Brain Disorder" [tw] OR "Arterial Brain Disorders" [tw] OR "Cerebral Arterial Disease" [tw] OR "Cerebral Arterial Diseases" [tw] OR "Cerebral Artery Diseases" [tw] OR "Cerebral Artery Disease OR "CADASILM" [tw] OR "Cerebral Amyloid Angiopathies" [tw] OR "Congophilic Angiopathy" [tw] OR "Congophilic Angiopathies" [tw] OR "Cerebral Amyloid Angiopathy" [tw] OR "Icelandic Type Amyloidosis" [tw] OR "ACA Infarction" [tw] OR "ACA Infarctions" [tw] OR "MCA Infarction" [tw] OR "PCA Infarction" [tw] OR "Progressive Intracranial Occlusive Arteropathy (Moyamoya)" [tw] OR "Moyamoya Syndrome" [tw] OR "Moya Moya Disease" [tw] OR "Intracranial Aneurysms" [tw] OR "Artery Aneurysm" [tw] OR "Berry Aneurysm" [tw] OR "Berry Aneurysms" [tw] OR "Brain Aneurysm" [tw] OR "Brain Aneurysms" [tw] OR "Cerebral Aneurysm" [tw] OR "Cerebral Aneurysms" [tw] OR "Intracranial Mycotic Aneurysm" [tw] OR "Intracranial Mycotic Aneurysms" [tw] OR "Intracranial Arterioscleroses" [tw] OR "Intracranial Atherosclerosis" [tw] OR "Intracranial Atherosclerоses" [tw] OR "Cerebral Arteriosclerosis" [tw] OR "Cerebral Arterioscleroses" [tw] OR "Cerebral Atherosclerosis" [tw] OR "Cerebral Atherosclerоses" [tw] OR "Vascular Dementias" [tw] OR "Vascular Dementia" [tw] OR "Arteriosclerotic Dementia" [tw] OR "Arteriosclerotic Dementias" [tw] OR "Binswanger Disease" [tw] OR "Binswanger Encephalopathy" [tw] OR "Chronic Progressive Subcortical Encephalopathy" [tw] OR "Binswanger's Encephalopathy" [tw] OR "Binswanger's Disease" [tw] OR "Binswangers Disease" [tw] OR "Subcortical Leukoencephalopathies" [tw] OR "Subcortical Arteriosclerotic Encephalopathy" [tw] OR "Subcortical Leukoencephalopathy" [tw] OR "Subcortical Arteriosclerotic Encephalopathies" [tw] OR "Intracranial Arteriovenous Malformation" [tw] OR "Intracranial Arteriovenous Malformations" [tw] OR "AVM Intracranial" [tw] OR "Cerebral Arteriovenous Malformation" [tw] OR "Cerebral Arteriovenous Malformations" [tw] OR "Galen Malformations Veins" [tw] OR "Carotid Artery Thromboses" [tw] OR "Carotid Artery Thromboses" [tw] OR "Carotid Thrombosis" [tw] OR "Brain Embolism" [tw] OR "Brain Emboli" [tw] OR "Brain Embolus" [tw] OR "Cerebral Embolism" [tw] OR "Cerebral Emboli" [tw] OR "Cerebral Embolus" [tw] OR "Intracranial Thromboses" [tw] OR "Intracranial Thrombus" [tw] OR "Cerebral Thrombosis" [tw] OR "Cerebral Thromboses" [tw] OR "Brain Thrombosis"

[tw] OR "Brain Thromboses" [tw] OR "Brain Thrombus" [tw] OR "Intracranial Hemorrhage" [tw] OR "Posterior Fossa Hemorrhage" [tw] OR "Posterior Fossa Hemorrhages" [tw] OR "Brain Hemorrhage" [tw] OR "Brain Hemorrhages" [tw] OR "Cerebrum Hemorrhage" [tw] OR "Cerebrum Hemorrhages" [tw] OR "Intracerebral Hemorrhage" [tw] OR "Intracerebral Hemorrhages" [tw] OR "Cerebral Hemorrhages" [tw] OR "Cerebral Hypertensive Hemorrhage" [tw] OR "Cerebral Hypertensive Hemorrhages" [tw] OR "Traumatic Intracranial Hematoma" [tw] OR "Traumatic Intracranial Hematomas" [tw] OR "SAH (Subarachnoid Hemorrhage)" [tw] OR "SAHs (Subarachnoid Hemorrhage)" [tw] OR "Subarachnoid Hemorrhages" [tw] OR "Subarachnoid Hemorrhage" [tw] OR "Strokes" [tw] OR "Stroke" [tw] OR "Brain Vascular Accident" [tw] OR "Brain Vascular Accidents" [tw] OR "CVA (Cerebrovascular Accident)" [tw] OR "CVAs (Cerebrovascular Accident)" [tw] OR "Apoplexy" [tw] OR "Cerebrovascular Accident" [tw] OR "Cerebrovascular Accidents" [tw] OR "Susac's Syndrome" [tw] OR "Susacs Syndrome" [tw] OR "Retinocochleocerebral Vasculopathy" [tw] OR "Retinocochleocerebral Vasculopathies" [tw] OR "Peripheral Vascular Disease" [mesh] OR "PAD" [tw] OR "Peripheral Vascular Disease" [tw] OR "Peripheral Vascular Disease" [tw] OR "Peripheral Angiopathies" [tw] OR "Peripheral Angiopathy" [tw] OR "Peripheral Arterial Disease" [tw] OR "Peripheral Arterial Disease" [tw] OR "peripheral arteriopathy" [tw] OR "peripheral blood vessel disease" [tw] OR "peripheral vascular disorder" [tw] OR "peripheral vasculopathy" [tw] OR "peripheral vessel disease" [tw] OR "Hypertension" [mesh] OR "hypertensive" [tw] OR "High Blood Pressure" [tw] OR "High Blood Pressures" [tw] OR "Hypertension" [tw] OR "Hypertensions" [tw] OR "Goldblatt Syndrome" [tw])