Impact of Medication Nonadherence on Coronary Heart Disease Outcomes

A Critical Review

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A critical review of published literature was performed to assess the impact of medication adherence on morbidity and mortality among patients with or at risk for coronary artery disease and congestive heart failure. Twenty-one original research articles that met our inclusion criteria and related medication adherence to morbidity and mortality are summarized. No clinical trials that specifically tested the impact of a compliance-enhancing intervention on outcome in coronary heart disease were identified. Among 12 studies that compared hospitalization rates and mortality between adherers and nonadherers, 7 showed a significant relationship between medication adherence and outcomes. Three studies showed that adherence to placebo was associated with improved outcomes, suggesting that adherent behavior may be a marker of better prognosis or confers a protective effect on patients with coronary heart disease. Further study is necessary to determine whether adherent behavior can be taught and whether compliance-enhancing strategies improve outcomes in coronary heart disease.

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Coronary artery disease and congestive heart failure are common among the elderly and have important prognostic implications. Approximately 1.5 million Americans sustain a myocardial infarction each year, and up to 500 000 die before receiving medical attention.[1] Among men and women aged 65 years and older with a history of myocardial infarction, approximately 7% will sustain another myocardial infarction and 40% will die within the next year.[2] In the Multicenter Postinfarction Research Group,[3] approximately one third of patients with a history of myocardial infarction had an ejection fraction of less than 40%. Among these patients, total mortality was 60% during 1 to 3 years of follow-up and the relative mortality risk was 2.4. The prognosis of congestive heart failure is dismal, with 85% of men and 65% of women dying within 6 years of their congestive heart failure diagnosis.[4]

Within the last 2 decades, significant advances have been made in primary and secondary prevention of coronary heart disease. Pharmacological interventions have been identified that prevent coronary heart disease events among those at risk either because of atherosclerotic risk factors or prior coronary artery disease. For example, pharmacological therapy for hypercholesterolemia reduces the risk of coronary artery disease events and mortality among patients without known coronary artery disease.[5] Aspirin may prevent first myocardial infarction in older men.[6] Among patients with established coronary artery disease, aspirin, β-blockers, and therapy for hypercholesterolemia reduce morbidity and mortality.[7-9] For patients with coronary artery disease complicated by left ventricular systolic dysfunction, angiotensin-converting enzyme inhibitors combined with digoxin and diuretics improve survival and reduce hospital admissions.[10] However, the full benefits of these

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pharmacological interventions at various stages in the course of coronary artery disease will not be realized if patients are not compliant with prescribed therapies.

Establishing the prevalence and impact of medication nonadherence on outcomes for patients with varying stages of coronary artery disease is important, since the magnitude and significance of nonadherence will determine the degree to which the potential benefits of drug therapy are unrealized in congestive heart failure and coronary artery disease. Most of the adherence literature has focused on measuring intermediate outcomes such as pill counts, blood pressure control, or reduction in cholesterol levels. Studies addressing the impact of medication adherence on more clinically important outcomes, such as morbidity and mortality, are scarce. We therefore performed a critical review of the literature to determine the relationship between nonadherence and cardiovascular morbidity and mortality among patients at risk for coronary heart disease events. We evaluate the effect of adherence to pharmacological interventions targeted at various stages in the coronary artery disease and congestive heart failure continuum. We specifically sought to answer the following questions for patients with and at risk for coronary artery disease and congestive heart failure. First, does medication adherence affect survival? Second, does medication adherence have an impact on hospitalization and readmission rates? Finally, if adherence influences outcomes, which adherence-enhancing strategy has the greatest impact on reducing hospitalization, readmission, and mortality? We include adherence studies of (1) patients at risk for coronary artery disease and congestive heart failure because of atherosclerotic risk factors, (2) patients with coronary artery disease, and (3) patients with congestive heart failure as a consequence of coronary artery disease.

METHODS

ARTICLE SELECTION

To be included in the critical review, manuscripts were required to meet the following inclusion criteria. First, all manuscripts were required to describe original research. Second, manuscripts were required to relate medication compliance to specific outcomes. These outcomes were defined before beginning data collection and consisted of new cardiovascular events, documented progression of atherosclerosis, hospitalizations, and/or survival. Third, all manuscripts were required to include patients with or at risk for congestive heart failure or coronary artery disease. Patients were considered at risk for congestive heart failure or coronary artery disease if they had hypertension, diabetes mellitus, or hypercholesterolemia. Articles that did not meet these criteria were excluded. Additionally, letters, abstracts, and manuscripts published in non–peer-reviewed journals were excluded.

Candidate articles were identified with the help of an experienced librarian who performed a MEDLINE search in the May 1996 MEDLINE update for articles published beginning in 1966. Headings used for the search were the following: *coronary disease*, *explode coronary disease*, *heart failure, congestive*, *patient compliance*, *patient readmission*, *patient dropouts*, *cooperative behavior*, *treatment refusal*, *patient education*, and *treatment outcome*. Text words searched were *compliance*, *noncompliance*, and *heart failure*. Additionally, MEDLINE searches were performed using these medical subject heading headings and text words in conjunction with the phrase "development of any coronary heart disease." An Ovid search was performed using the keywords *diabetes*, *hypertension*, and *hypercholesterolemia*. Bibliographies of all selected articles were reviewed to identify additional pertinent studies. Articles published in languages other than English were included. In addition to the MEDLINE search, we contacted several experts in cardiology and drug compliance to identify unpublished studies of compliance and coronary heart disease or congestive heart failure.

ARTICLE REVIEW

Identified abstracts were reviewed independently by 2 of us (M.M.M. and B.S.). All manuscripts deemed potentially eligible for inclusion by either of us were pulled. All manuscripts were reviewed independently by 2 of us (M.M.M. and B.S.) for study eligibility. Discrepant decisions regarding study eligibility were discussed and resolved by consensus.

A data collection form was developed prior to article review to standardize and organize the abstraction of pertinent data from each manuscript undergoing a full review. Articles were methodologically categorized according to study design. To determine study generalizability, we evaluated cohort descriptions: age, gender, and subject selection criteria (sampling and allocation). To determine study validity, we assessed whether adherence and outcomes were objectively defined and blindly assessed. Differences in methodological assessment were discussed and resolved by consensus.

Articles written in foreign languages were interpreted by one of us (E.W.), who completed a data collection form. The results of these data collection forms were reviewed and evaluated for inclusion by 2 of us (M.M.M. and B.S.).

DATA ANALYSIS

Because various outcomes were used and different at-risk conditions were included in the identified studies, a pooled quantitative analysis was not considered appropriate, and a qualitative analysis was performed.

RESULTS

We identified 289 articles by the MEDLINE search and bibliographic review. Abstracts of these articles were independently reviewed by 2 of us (M.M.M. and B.S.), and a subset of articles were pulled for full review. Additional manuscripts were obtained after review of each article's reference list. A total of 179 articles were pulled for full review.

We identified 21 published manuscripts that met our inclusion criteria.[11-31] These 21 manuscripts included a report relating medication adherence to outcomes among subjects in the Cardiac Arrhythmia Suppression Trial (CAST).[11] The medications studied in CAST (encainide and flecainide) were associated with a higher mortality rate compared with subjects in the placebo group.[11] The negative effects of the study drugs on

survival were considered likely to confound the relationship between medication adherence and survival, and the CAST adherence study is therefore summarized separately in the "Comment" section.

Among the remaining 20 studies, 6 consisted of patients with coronary artery disease or myocardial infarction,[12-17] 9 included patients with congestive heart failure,[18-26] 2 included patients with hypertension,[27,28] 1 included patients with hypercholesterolemia,[29] and 2 included patients with coronary heart disease or consecutive patients admitted to a cardiology service.[30,31]

STUDY DESIGNS

As shown in **Table 1**, 9 studies[12-15,17-20,29] were either clinical trials or prospective cohort studies performed among subjects participating in clinical trials. Among the 11 remaining studies, 4 were prospective cohort studies,[16,21,22,30] 4 were cross-sectional,[23-25,31] 2 were case-control,[27,28] and 1 was a retrospective cohort study.[26] The compliance definition and method of compliance assessment are shown for each study in Table 1.

OUTCOME MEASURES

As shown in Table 1, mortality was an outcome measure in 7 reports.[14-18,26,27] Coronary restenosis after percutaneous transluminal coronary angioplasty was the main outcome measure in 2 studies,[12,13] hospital admissions and/or readmissions were outcome measures in 11 studies,[18-26,28,31] and coronary heart disease events or signs and symptoms of congestive heart failure were outcome measures in 6 studies.[16,18,22,27,29,30]

STUDY FINDINGS

We did not identify any randomized controlled clinical trials designed specifically to assess the effect of adherence-enhancing strategies alone on outcomes among patients with or at risk for coronary heart disease. However, 3 clinical trials[18-20] included medication adherence-enhancing strategies as one component of a multidisciplinary intervention to reduce hospitalizations and/or mortality among elderly patients with congestive heart failure. Of these, 2 clinical trials[18,20] (1 randomized) showed a favorable impact of the intervention on morbidity and mortality. The third study,[19] a randomized controlled clinical trial, showed no significant impact of the multidisciplinary intervention, including interventions aimed at adherence, on readmissions. However, this latter study did not have sufficient power to show a statistically significant improvement in outcomes.

There were 6 clinical drug trials[12-15,28,29] in which assessment of the relationship between adherence and morbidity and/or mortality was a secondary aim. Using data from the Beta-Blocker Heart Attack Trial (BHAT),[14] the Coronary Drug Project Research Group (CDPRG),[17] and the Lipid Research Clinics Program (LRCP) study,[29] 4 reports[14,15,28,29] (2 from BHAT) described the effect of drug adherence on mortality among patients randomized to the intervention and placebo arms respectively of these drug therapy clinical trials. The remaining 2 drug therapy clinical trials[12,13] performed subset analyses of adherence among patients randomized to the intervention arm of clinical trials assessing the efficacy of drug therapy in preventing coronary artery restenosis after coronary angioplasty.

ADHERENCE TO PLACEBO IS ASSOCIATED WITH REDUCED MORBIDITY AND MORTALITY

Investigators in the CDPRG, the BHAT, and the LRCP collected data on adherence for subjects randomized to the placebo and active drug therapy arms of these trials. As shown in Table 1, data from the CDPRG and BHAT show that nonadherence with either placebo or active drug was associated with higher mortality rates.[14,15,17] Investigators from the LRCP did not find that adherence was significantly related to coronary heart disease incidence in the placebo arm or in the active drug arm after controlling for cholesterol level.[29]

Among 1103 men participating in the CDPRG, subjects adherent to either clofibrate or placebo had better survival rates than subjects who were nonadherent to these drugs.[17] These findings were especially intriguing because clofibrate had no overall effect on survival rate in the CDPRG. At 5 years of follow-up, mortality rates for nonadherers vs adherers to clofibrate were 25% vs 15%. Among subjects randomized to the placebo group, mortality rates were 28% vs 15% for nonadherent vs adherent subjects. The relative mortality risks among subjects nonadherent to clofibrate and placebo were 1.7 and 1.9, respectively, compared with subjects adherent to clofibrate and placebo ($P<.001$ for each relative risk). Similar relationships were documented when analyses were adjusted for 40 baseline clinical characteristics.

However, among 1906 men with hypercholesterolemia participating in the LRCP trial, adherence to placebo was not associated with a reduction in coronary heart disease incidence. In univariate analysis, compliance to cholestyramine was associated with a reduction in coronary heart disease events. However, this relationship was not maintained after controlling for the cholesterol level in regression analysis.[29]

The BHAT investigators collected data on psychological and social characteristics of participants that might account for the relationships observed between adherence and survival in the CDPRG. Among 2176 male BHAT participants, all of whom had survived a myocardial infarction, a beneficial effect of adherence on survival was observed for participants in both the placebo and the propranolol study arms. Mortality rates were 5.4% among nonadherers and 2.2% among adherent subjects at 1-year follow-up. After adjusting for severity of the myocardial infarction, smoking status, and sociodemographic and psychological factors, nonadherence to propranolol was associated with an odds ratio for mortality of 2.8 ($P=.13$) and nonadherence to placebo was associated with an odds ratio for mortality of 2.7 ($P=.10$). When data from both the propranolol and placebo groups were combined, the adjusted odds ratio for mortality among nonadherers was 2.5 ($P=.03$).

In a report describing the relationship between adherence and mortality among 505 female participants

Table 1. Characteristics and Results of Studies Relating Medication Adherence to Morbidity and Mortality Among Patients With or at Risk for Coronary Artery Disease and Congestive Heart Failure (CHF)*

Source, y	No. of Subjects	Study Design	Cohort Description	Adherence Assessment	Outcomes	Results
Rich et al,[18] 1995	282	RCCT	Hospitalized patients with CHF; mean age, 79 y	Pill count†	(1) Event-free survival (2) Readmissions (3) Quality-of-life score	Event-free 90-d survival rates were 64% in the intervention group and 54% in the treatment group (P=.09). Among patients discharged alive, event-free 90-d survival was 67% in the treatment group vs 54% in the control group (P=.04). Ninety-day readmission rates were 29% in the intervention group and 42% in the control group (P=.03). Quality-of-life score increased by 22 points in the intervention group and 11 points in the control group (P<.01).‡
Rich et al,[19] 1993	98	RCCT	Patients with CHF; mean age, 79 y	Not specifically assessed	(1) Rehospitalizations (2) Total days of hospitalization	Ninety-day readmission rates were 33% in the intervention group and 46% in the control group; however, this did not represent a significant difference.‡
Rosenberg,[20] 1981	100	NRCCT	Outpatients with CHF; age range, 31-89 y	Not specifically assessed	Hospital readmissions	The 50 subjects in the intervention group had fewer hospitalizations (35 vs 12, P=.01) and fewer total hospitalized days (600 vs 148, P=.01) during the 0.9 y following the intervention compared with the 0.9 y preceding the intervention. Of 29 subjects in the intervention group who were matched by sex, age, disease origin and severity with 29 control subjects, there were 5 vs 9 readmissions, respectively (P=.01), during 1.4 years of follow-up. Number of days hospitalized in the intervention vs control groups was 82 vs 238 (P=.01).
The Coronary Drug Project Research Group,[17] 1980	1103	Prospective cohort§	Men with coronary heart disease; age not stated	Quarterly pill count (clofibrate and placebo)†	Total mortality	At 5-y follow-up, subjects compliant with clofibrate or placebo had significantly improved survival over noncompliant subjects. The overall relative risk of mortality for nonadherers was 1.7. Among subjects treated with clofibrate, nonadherers had a relative risk for mortality of 1.6 compared with adherers (P<.001). Among subjects treated with placebo, nonadherers had a relative mortality risk of 1.9 (P<.001). Clofibrate was not significantly associated with improved survival in the Coronary Drug Project.‡

Table 1. Characteristics and Results of Studies Relating Medication Adherence to Morbidity and Mortality Among Patients With or at Risk for Coronary Artery Disease and Congestive Heart Failure (CHF)* (cont)

Source, y	No. of Subjects	Study Design	Cohort Description	Adherence Assessment	Outcomes	Results
Lipid Research Clinics Program,[29] 1984	1906	Prospective cohort§	Men with hypercholesterolemia; mean age, 35-59 y	Bimonthly pill count (cholestyramine)	Coronary heart disease incidence	Adherence to cholesterol-lowering therapy, but not adherence to placebo, was associated with a reduction in coronary heart disease incidence at 7-y follow-up. In regression analysis, cholesterol level reduction but not adherence was independently associated with a reduction in coronary heart disease incidence (specific risk reduction not provided).‡
Whitworth et al,[12] 1986	204	Prospective cohort§	Subjects aged 21-75 y undergoing percutaneous coronary transluminal angioplasty (PTCA)	Pill count (nifedipine)‖	(1) Angiographically proven coronary restenosis (2) Positive exercise test	At 4.3-4.4–y follow-up, recurrence of coronary stenosis occurred in 27% of subjects taking nifedipine vs 27% taking placebo. Restenosis occurred in 27% of subjects compliant to nifedipine and 32% of subjects compliant to placebo. Restenosis rates were not directly compared between compliant and noncompliant subjects in the placebo and active drug group.
Reis et al,[13] 1989	124	Prospective cohort§	Subjects undergoing PTCA	Pill count (fish oil)‖	(1) Angiographically proven coronary restenosis (2) Positive exercise test	At 6-mo follow-up, coronary restenosis developed in 34% of subjects taking fish oil and 23% of subjects taking placebo. Relative risk, 1.7 (95% confidence interval [CI], 0.9-3.4). Drug adherence had no impact on outcome for subjects in the fish oil group. Restenosis rates were 19% for subjects taking <25% of prescribed fish oil vs 40% for subjects taking >75% of prescribed fish oil. The effect of adherence on outcome was not assessed for subjects in the placebo group.
Beta-Blocker Heart Attack Trial Research Group,[14] 1982	2176 men	Prospective cohort§	Men aged 30-69 y who were survivors of an acute myocardial infarction	Quarterly pill count of propranolol and placebo‖	Total mortality	At 25-mo follow-up, adherence to placebo or propranolol was associated with improved survival. Overall, nonadherers to placebo or active drug were 2.6 times more likely to die than those who adhered to their treatment regimen (95% CI, 1.2-5.6). For patients nonadherent to propranolol, the odds ratio for mortality was 3.1 (95% CI, 0.9-10.3); for patients nonadherent to placebo, the odds ratio for mortality was 2.5 (95% CI, 0.9-7.0).‡
Gallagher et al,[15] 1993	505 women	Prospective cohort§	Women aged 30-69 y who were survivors of an acute myocardial infarction	Quarterly pill count (propranolol and placebo)‖	Total mortality	Overall adherence to propranolol and active drug, respectively, was associated with improved survival. Relative mortality risk among all nonadherers, 2.4 (95% CI, 1.1-5.6). Relative mortality risk among subjects nonadherent to propranolol, 1.9 (95% CI, 0.5-8.1); relative mortality risk among subjects nonadherent to placebo, 2.8 (95% CI, 1.0-7.6). Median follow-up, 26 mo.‡

(Continued)

Table 1. Characteristics and Results of Studies Relating Medication Adherence to Morbidity and Mortality Among Patients With or at Risk for Coronary Artery Disease and Congestive Heart Failure (CHF)* (cont)

Source, y	No of Subjects	Study Design	Cohort Description	Adherence Assessment	Outcomes	Results
Vinson et al,[21] 1990	161	Prospective cohort	Hospitalized patients with CHF; mean age, 81 y	Adherence was assessed by study physicians and nurses, in part based on patient report¶#	Readmissions	There was no evaluation of medication adherence among patients not rehospitalized. Among patients rehospitalized for CHF within 90 d because of a potentially preventable contributing event, 15% were noncompliant with medications.
Romm et al,[22] 1976	122	Prospective cohort	Outpatients with CHF; mean age, 63 y	Self-report#**	(1) CHF symptoms (2) Hospitalizations for CHF	There was no relationship between errors in medication taking and symptoms of CHF or activity level at 6-mo follow-up (specific results not provided).‡
Sampson and Arbona,[30] 1980	37	Prospective cohort	Patients with cardiac disease in a cardiac clinic; age range, 20 to >75 y	Patient report and medical record review[5,7]#††	Cardiac disease–related signs and symptoms or evidence of cardiac disease regression (defined as "patient welfare")	At 14-mo follow-up among 4 patients with poor adherence, 2 were categorized with fair and 2 were categorized with poor welfare. Of 26 patients with good adherence, 19 were categorized with good, 4 with fair, and 3 with poor welfare. The relationships between adherence and patient welfare were significant at $P<.05$.
Stegman et al,[16] 1987	157	Prospective cohort	Patients after myocardial infarction; mean age, 57 y	Defined by the Health Adherence Scale[34]¶#	(1) Cardiovascular morbidity (2) Overall mortality	Adherence was not related to cardiovascular morbidity or total mortality at 2.8-y follow-up (specific data not reported).‡
Ghali et al,[23] 1988	101	Cross-sectional	Hospitalized patients with CHF; mean age, 59 y	Self-report#‡	CHF hospitalizations	Forty-three percent of patients hospitalized for CHF were noncompliant with medications.
Pentimone and Del Corso,[24] 1993	10	Cross-sectional	Hospitalized patients with CHF; mean age, 76.3 y	Self-report¶#	Hospital admissions	Nonadherence with medications and dietary recommendations was 1 of 2 most common reasons for hospital admissions (specific numerical results not provided).
Wagdi et al,[25] 1993	111	Cross-sectional	Patients with CHF; mean age, 76 y	Self-report¶#	Hospital admissions	One of 3 identified common and preventable causes of readmission was medication and dietary nonadherence. Thirty-one percent of patients admitted with CHF were noncompliant to medication.
Davidsen et al,[31] 1988	426	Cross-sectional	Consecutive admissions to a cardiology service	Self-report§§	Cardiac-related hospitalizations	Among patients taking medications before admission, 5.2% were admitted because of drug nonadherence.
Psaty et al,[27] 1990	1085	Case-control	Outpatients with hypertension, aged 30-79 y	Computerized pharmacy database#	(1) First cases of coronary heart disease (2) Death from coronary heart disease	Relative risk of coronary heart disease within 30 d after stopping β-blocker therapy was 5.97 (95% CI, 1.7-20.96; $P=.005$). After adjusting for confounders, the relative risk of coronary heart disease among those stopping β-blocker therapy was 6.35 (95% CI, 1.67-24.21).‡

Table 1. Characteristics and Results of Studies Relating Medication Adherence to Morbidity and Mortality Among Patients With or at Risk for Coronary Artery Disease and Congestive Heart Failure (CHF)* (cont)

Source, y	No. of Subjects	Study Design	Cohort Description	Adherence Assessment	Outcomes	Results
Maronde et al,[28] 1989	150	Case-control	Patients with hypertension, aged 50-52 y	Pharmacy records¶#|||	Readmissions	At up to 18 mo of follow-up, the ratio of days without medication to the total number of study days was significantly higher among readmitted than nonreadmitted subjects (0.382 vs 0.108, $P<.001$).‡
Goldberger et al,[26] 1986	94	Retrospective cohort	Patients hospitalized with acute pulmonary edema; mean age, 74 y	Medical record report¶#	(1) Hospitalizations (2) Mortality	Seven percent of hospitalizations for acute pulmonary edema were precipitated by drug nonadherence. Survival and rehospitalization rates were no higher among noncompliant patients at 10-16 mo follow-up.

**RCCT indicates randomized controlled clinical trial; NRCCT, nonrandomized controlled clinical trial.*
†Adherence was defined as consumption of at least 80% of prescribed medications.
‡Results were adjusted for confounders.
§Denotes prospective studies performed within clinical trials.
\|\|Adherence was defined as consumption of at least 75% of prescribed medications.
¶No specific adherence definition provided.
#Adherence assessment was not focused on 1 specific medication.
***Nonadherence was defined as any errors in medication taking (commission, omission, or scheduling).*
††Adherence was subjectively rated by investigators into 1 of 3 categories: nonadherence, moderate adherence, and excellent adherence.
‡‡Nonadherence was defined as subjects who stopped taking medications or took medication intermittently. Also included subjects noncompliant with sodium restriction.
§§Nonadherence was defined as consumption of less than 50% of prescribed drugs.
\|\|\|The number of days subjects were without medication was used in analyses.

in BHAT, mortality among poor adherers was 13.6% vs 5.6% for adherent subjects. The relative mortality risk was 1.9 (95% confidence interval, 0.5-8.1) for nonadherers to propranolol and 2.8 (95% confidence interval, 1.0-7.6) for nonadherers to placebo compared with subjects adherent to propranolol and placebo, respectively. Median follow-up was 26 months. In multivariate analysis adjusting for psychological and social characteristics as well as treatment category and disease severity, the relationship between nonadherence and mortality was maintained.[15]

In the 2 clinical trials[12,13] that assessed the impact of pharmacological therapy on restenosis after coronary angioplasty, neither the drugs under study nor adherence to these drugs had a significant impact on coronary restenosis rates. Among the remaining 4 prospective cohort studies, 2[16,22] showed no impact of medication adherence on outcome, 1[30] showed a reduction in cardiac signs and symptoms among adherers, and 1[21] did not provide sufficient data to allow a direct comparison between adherers and nonadherers. In 2 case-control studies[27,28] of patients with hypertension, development of coronary heart disease and hospitalizations were less frequent among patients who were more adherent to drug therapy. In a retrospective cohort study[26] of 94 patients hospitalized with congestive heart failure (mean age, 74 years), drug adherence was unrelated to symptoms of congestive heart failure or patient-reported activity level at 10 to 16 months of follow-up. The cross-sectional studies[23,25,31] reported that noncompliance with drug therapy contributed to 4% to 43% of hospitalizations for congestive heart failure or cardiac-related problems.

Table 2 summarizes cumulative results from studies that provided sufficient data to allow a direct comparison between adherers and nonadherers. Overall, 8 studies[14,15,17,18,20,27,28,30] showed an inverse relationship between medication adherence and outcomes, while 7[12,13,16,19,22,26,29] showed no relationship or a direct relationship between medication adherence and morbidity and mortality. Among the 13 prospective studies, 6[14,15,17,18,20,30] showed an inverse relationship between medication adherence and outcome, 6[12,13,16,19,22,29] showed no relationship between adherence and outcome, and 1[21] did not specifically allow for comparison between adherers and nonadherers.

COMMENT

Coronary artery disease and its consequence, congestive heart failure, are common causes of hospital admission and mortality. Significant resources, time, and effort have been expended in large clinical trials defining optimal drug therapy for congestive heart failure and coronary artery disease. If drug noncompliance is common and unfavorably affects outcomes, then compliance-enhancing strategies may be necessary to maximize the benefits reported in clinical trials. For example, in a study[32] of temporal trends in treatment patterns for patients with congestive heart failure,

Table 2. Summary of Outcomes Among Studies Linking Drug Adherence to Morbidity and Mortality in Patients With or at Risk for Coronary Artery Disease and Congestive Heart Failure

Study Design	Adherence Associated With Lower Morbidity and Mortality Rates	Adherence Not Associated With Improved Morbidity and Mortality
Randomized controlled clinical trial	2	1
Prospective cohort study	4	5*†
Case-control study	2	0
Retrospective cohort	0	1
Total	**8**	**7**

** In the Lipid Research Clinics Program,[29] better adherence to cholesterol-lowering therapy was associated with a reduction of cardiovascular events, but not independently of the cholesterol level.*

† Includes 2 studies that assessed adherence to medications shown not to be effective in reducing the rate of restenosis after angioplasty.

survival did not improve even while rates of angiotensin-converting enzyme inhibitor prescriptions increased. Noncompliance with medication may be one factor explaining the observed lack of mortality reduction over time.

DOES MEDICATION ADHERENCE AFFECT SURVIVAL?

In our critical review we identified no randomized controlled trials designed specifically to evaluate the impact of adherence-enhancing strategies on morbidity and mortality among patients with or at risk for congestive heart failure or coronary artery disease. Therefore, we cannot make conclusive statements based on available literature regarding the relationship between adherence-enhancing strategies and survival among the patient population studied. However, after an exhaustive literature review, we identified 21 studies assessing the relationship between medication adherence and outcomes among patients with or at risk for congestive heart failure and coronary artery disease. Of 7 studies[14-18,26,27] summarized in Table 1 that included mortality as an outcome, 4[14,15,17,18] showed a significantly favorable impact of medication adherence on survival.

DOES MEDICATION ADHERENCE HAVE AN IMPACT ON HOSPITALIZATION AND READMISSION RATES?

The available data from our comprehensive review also support a favorable relationship between medication adherence and hospitalization rates. Among the 6 studies[18-20,22,26,28] that compared hospital admission rates between adherent and nonadherent patients, 3[18,20,28] showed a significant impact of adherence on hospital readmission rates. Power was insufficient to demonstrate a significant impact of medication adherence on readmission rates in a fourth study.[19]

WHAT IS THE OPTIMAL STRATEGY TO MAXIMIZE ADHERENCE?

While we also sought to identify the optimal adherence-enhancing strategy to reduce morbidity and mortality among patients with coronary artery disease and congestive heart failure, none of the identified studies compared the impact of different adherence-enhancing strategies on outcome. Three studies[18-20] used adherence-enhancing strategies as part of multidisciplinary interventions to improve outcomes in congestive heart failure. The multidisciplinary interventions in these studies included review of medications and side effects with patients, simplification of the drug therapy regimen, and follow-up telephone calls to patients to encourage adherence. Patients were also given charts and/or medication dispensers specifying dosing intervals and frequencies, educated about diet and the signs and symptoms of congestive heart failure, and instructed to record daily weights. However, various methods of adherence-enhancing strategies have not been compared to identify the method that best prevents progression of coronary heart disease, hospitalizations, and/or mortality.

DOES GREATER ADHERENCE TO PLACEBO DRUGS FAVORABLY AFFECT OUTCOMES?

Results from the BHAT and the CDPRG suggest that adherent behavior may be a marker of patients with good prognosis or alternatively that adherence confers a protective effect on patients with coronary heart disease.[14,15,17] If patients who comply with placebo also incur a survival benefit compared with nonadherers, it seems likely that adherence is a marker of some unidentified health care behavior that is itself linked to prognosis. If this is the case, adherence strategies and interventions may not produce the desired outcomes. Therefore, it is important in trials involving patients with or at risk for congestive heart failure and coronary artery disease to measure adherence to medications, including placebo, and link adherence to important clinical outcomes.

Identifying the most optimal method of assessing adherence in large clinical trials is outside the scope of this critical review. However, the BHAT, the CDPRG, and the LRCP used pill counts to assess adherence. The validity of this method is underscored by the fact that all produced meaningful results. A portable electronic pill dispenser has been developed that records the time and date of medication removal from the dispenser.[33] Adherence with blood pressure medication as measured by the pill dispenser has been shown to correlate highly with the degree of blood pressure control among patients with hypertension.[34] If it can be established that adherence is significantly and independently predictive of important outcomes, then additional research is needed to explore strategies for adherence assessment for both clinical and economic purposes.

ADHERENCE IN THE CARDIAC ARRHYTHMIA SUPPRESSION TRIAL

We did not summarize the CAST adherence study[11] with the other identified adherence studies because the active medication in CAST was associated with a higher mortality rate compared with placebo. The negative

effect of active drug on survival would confound the assessment of medication adherence and outcome. Among CAST participants randomized to the active drug arm, arrhythmic deaths were significantly higher among subjects more adherent to encainide and flecainide than among less adherent patients.[11] These findings are interesting in light of the data summarized above showing a beneficial effect of adhering to placebo. Even if an adherence behavior confers a favorable outcome, that positive effect will be counteracted by a harmful medication.

MULTIDISCIPLINARY INTERVENTIONS FOR CONGESTIVE HEART FAILURE

Three studies[18-20] included in our critical review were clinical trials that implemented a multidisciplinary intervention to improve outcomes. These studies included adherence-enhancing strategies in their multidisciplinary interventions but did not specifically define medication adherence. Two showed significantly favorable effects of the multidisciplinary intervention on outcomes, including hospitalizations, event-free survival, and quality of life.[18,20] The third[19] showed a non–statistically significant reduction in rehospitalization rates among the intervention group. We have included these studies in Table 1 because they meet our inclusion criteria. However, the inability to determine the independent effect of medication adherence on outcomes is a limitation of our critical review.

In summary, our data show that although medication nonadherence is common among patients with congestive heart failure and is an important contributor to readmissions, the relationship between interventions designed specifically to enhance drug adherence and cardiovascular morbidity and mortality has not been adequately assessed among patients at highest risk for cardiovascular events because of atherosclerotic risk factors or past coronary heart disease. Some available data suggest that adherence to active drug or placebo is associated with improved survival and fewer hospitalizations, and this relationship warrants further study. We emphasize the need, in future trials, to collect data on medication adherence and evaluate its effects on morbidity and mortality. We suspect that patients adherent with medication regimens have other characteristics that confer a protective effect on survival. Identifying, and if possible, teaching these characteristics to nonadherers, might improve morbidity and mortality rates and conserve resources among patients with or at risk for coronary artery disease and congestive heart failure.

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