

# Long-Term Outcomes of Optimized Medical Management of Outpatients With Stable Coronary Artery Disease

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The objective of this study was to assess long-term clinical outcomes and their correlates in medically managed outpatients with stable angina pectoris, healed myocardial infarction (MI), or documented asymptomatic coronary artery disease (CAD). Management strategy emphasized maximally tolerated medical therapy and modification of coronary risk factors. Referral to invasive coronary interventions followed stricter criteria than standard published guidelines. Primary study outcomes were all-cause mortality or nonfatal myocardial infarction. Secondary study outcomes included cardiac death, unstable angina, or coronary revascularization. A total of 693 men and women with proved CAD (mean age 67 years at entry, 85% men, 41% with history of MI) were enrolled. The annual incidence of nonfatal MI, cardiac

mortality, and total mortality was 2.2%, 0.8%, and 1.4%, respectively, during an average follow-up of 4.6 years. Coronary revascularization was performed in 24% of subjects; unstable or progressive anginal symptoms were the most common reasons for revascularization. In patients with documented stable CAD, a management strategy based on intensive medical therapy and modification of established coronary risk factors was associated with excellent long-term outcomes. Thus, coronary interventions can be safely delayed until clinical instability ensues, without increased risk of MI or death. This treatment approach represents a viable alternative to invasive strategies. ©2004 by Excerpta Medica, Inc.

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Previous retrospective research has suggested that patients with documented stable coronary artery disease (CAD) fare well with a conservative medical therapy-based approach.<sup>1,2</sup> The present study was designed to prospectively study the effectiveness of this approach.

## METHODS

**Patient recruitment:** Study subjects were recruited from patients examined by board-certified cardiologists at an outpatient cardiology clinic affiliated with a tertiary medical center and a medical school. Between December 1992 and June 2000 patients with CAD were screened and subsequently enrolled according to prespecified criteria. Men and women of all ages were included in the study if they satisfied  $\geq 1$  of the following criteria: history of documented myocardial infarction (MI), angiographically documented CAD, or history of typical exertional angina pectoris with a positive exercise treadmill test with or without nuclear imaging. In the absence of angina pectoris, previous angiography or MI, abnormal exercise treadmill test

results with abnormal imaging findings confirmed the presence of CAD. Patients were excluded from the study if they had previously undergone coronary revascularization (percutaneous intervention or coronary artery bypass grafting [CABG]); were in congestive heart failure (New York Heart Association class III or IV) at study recruitment; had advanced valvular heart disease; had severe or life-limiting noncardiac morbidities; or were examined for a 1-time consultation about their cardiac status. The study was approved by an institutional review board and informed consent was obtained from all participants.

**Management protocol:** The medical treatment strategy followed in this study emphasized individually tailored, maximally tolerated medical therapy. For example,  $\beta$  blockers were targeted to slow heart rate to  $\leq 60$  beats/min, if tolerated. Frequently, multiple antianginal therapies were prescribed. In addition to long-acting nitrates, liberal use of sublingual nitroglycerin, including prophylactic administration, was encouraged. Universal use of aspirin was attempted. During the study, use of medical and invasive interventions was modified to reflect new evidence on the benefit of such therapies, especially lipid-lowering agents, primarily statins. Risk factor modification, including exercise, dietary changes, and the psychosocial aspects of illness, received special attention. Patients were scheduled for a 1-hour initial visit and a half-hour follow-up visit. Whenever possible, the patient's spouse or partner was asked to accompany the patient to the examination to help devise and implement the management plan.

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Periodically, patients underwent symptom-limited exercise tests, with or without imaging studies (stress echocardiography or nuclear), to assess the presence, severity, and extent of myocardial ischemia. Patients also underwent echocardiographic or nuclear imaging to assess left ventricular systolic function and continuous electrocardiographic monitoring to detect cardiac arrhythmias.

Although medical therapy was emphasized as the cornerstone of management, invasive interventions were recommended, when indicated. Referral criteria for invasive procedures were similar to published guidelines<sup>3,4</sup> but used higher thresholds. Criteria included recurrent angina at rest or after MI; level of angina not acceptable to patients on the maximally tolerated medical regimen; ischemic-induced pulmonary edema or malignant ventricular arrhythmia; left ventricular systolic dysfunction (ejection fraction <35%) in the presence of ischemia; substantially reduced exercise capacity due to cardiac symptoms; exertional hypotension associated with ischemia; and intolerance of medications or as mandated by employment description. Once an indication for angiography was met, the decision whether or not to intervene was left to the managing physician and the patient.

The primary end points of the study were occurrence of nonfatal MI and all-cause mortality. Secondary end points included cardiac mortality, coronary revascularization, and unstable angina. End points were ascertained through information provided by physicians, supplemented with reviews of inpatient and outpatient medical records.

**Data collection:** Upon study enrollment, both patients and physicians provided extensive data about sociodemographic, psychological, and clinical characteristics. Patients completed follow-up questionnaires annually. Physicians provided yearly information on interim testing data and changes in patients' symptoms, clinical condition, and medications. A research assistant performed quality control checks through review of medical records, supplemented by contact with the physicians and patients.

**Data analysis:** Chi-square or Fisher's exact tests were used for comparison of proportions, and the *t* test or rank-sum tests were used for between-group comparison of continuous variables. Cox proportional hazard regression models were used to identify sociodemographic, medical history, and clinical predictors of our principal study outcomes while controlling for varying duration of follow-up. Univariate associations of different covariates with primary outcome were initially examined. Statistically significant or clinically plausible variables were entered into a multivariate regression model, and the most parsimonious predictive models were identified. Intermediary outcomes, such as coronary revascularization, were treated as time-varying covariates to remove their potentially confounding effects. A significance level of 0.05 was used, and all reported *p* values were 2-sided.

**TABLE 1** Baseline Characteristics of Study Patients With Documented Stable Coronary Artery Disease (n = 693)

Characteristics	
Age (mean) (yrs) (range)	67.3 (39.6–97.4)
Men	566 (81.7%)
Second opinion patients (%)	381 (56.0%)
Body mass index (mean) (kg/m <sup>2</sup> )	27.0
Left ventricular ejection fraction (mean)	59.0%
Total cholesterol (mean) (mg/dl)	204
LDL cholesterol (mean) (mg/dl)	125
HDL cholesterol (mean) (mg/dl)	41
Creatinine (mean) (mg/dl)	1.1
MI (remote)	291 (42.1%)
Systemic hypertension	340 (54.4%)
Diabetes mellitus	109 (16.0%)
Smoke (ever)	406 (64.3%)
Smoke (current)	33 (5.9%)
Angina pectoris (ever)	545 (79.0%)
Angina pectoris (present)	386 (56.0%)
Angina pectoris class (%)	
I	236 (61.5%)
II	132 (33.9%)
III	16 (4.1%)
IV	2 (0.5%)
Use of various medications (%)	
β blockers	502 (70%)
Calcium channel antagonists	389 (55%)
Aspirin	580 (81%)
Nitrates	284 (41%)
Lipid lowering agents	243 (35%)
Angiotensin-converting enzyme inhibitors	76 (11%)

HDL = high density lipoprotein; LDL = low-density lipoprotein.

## RESULTS

**Patient enrollment:** Between December 1992 and June 2000, 2,598 subjects presenting to the clinic were screened. A total of 761 eligible subjects consented to study participation and formed the present study sample. The most common reasons for exclusion were history of coronary revascularization (42%), lack of objective evidence of CAD (31%), and consultation intended for a single visit (8%). The present analysis includes data from 693 patients with ≥1 year of follow-up by June 2001. Of the remaining 68 subjects, 34 did not complete 1 year of follow-up, 19 patients withdrew after the initial consent, and 15 patients left the practice. Of the 693 patients, 132 had documented asymptomatic CAD without previous MI, 390 patients had angina without previous MI, 171 had a previous MI, and 120 patients had both.

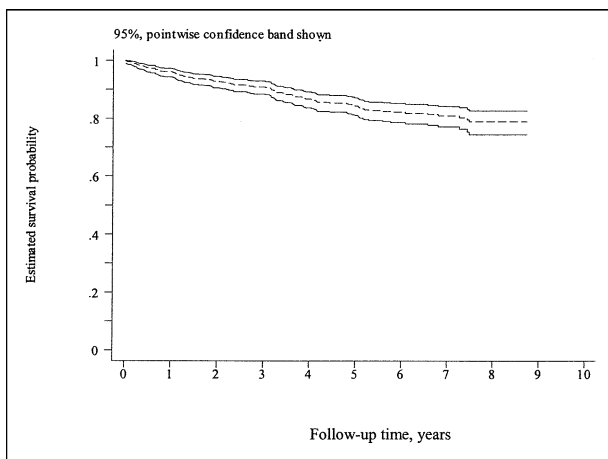
**Cohort characteristics:** Table 1 lists the baseline characteristics of the study sample. The cohort was mostly elderly white men of high socioeconomic status. Coronary risk factors, such as diabetes, hypertension, and hyperlipidemia, were common in the study sample. The subjects, on average, had preserved left ventricular systolic function, and most had low-grade angina.

**Use of medical therapies:** Use of cardiac medications increased during follow-up. Use of lipid-lowering agents, primarily statins, increased from 35% at entry to 68% during follow-up. This corresponded to a marked reduction in the average total cholesterol values by 17% (204 mg/dl at baseline to 170 mg/dl

**TABLE 2** Incidence of Clinical End Points in Study Patients During Follow-up\* (n = 693)

Outcome	Total With Outcome	Annualized Percentage
Nonfatal MI	72 (10.4%)	2.2%
All-cause death	46 (6.6%)	1.4%
Nonfatal MI or death	104 (15.0%)	3.2%
Cardiac death	26 (3.8%)	0.8%
Unstable angina pectoris	187 (27.0%)	6.8%
Heart failure	59 (8.5%)	1.8%
Coronary revascularization (CABG and percutaneous)	170 (24.5%)	6.0%

\*Average follow up, 4.7 years.



**FIGURE 1.** Kaplan-Meier estimates of survival free from nonfatal MI or death.

during follow-up) and an increase in average high-density lipoprotein cholesterol by 12% (from 41 to 46 mg/dl, respectively). Use of  $\beta$  blockers in more optimal doses increased from 70% at entry to 80% during follow-up. Similarly, use of angiotensin-converting enzyme inhibitors increased from 11% to 37%. The use of antiplatelet agents, mainly aspirin, increased from 81% at baseline to 89% during follow-up. Use of calcium channel antagonists decreased from 55% to 47% over this period.

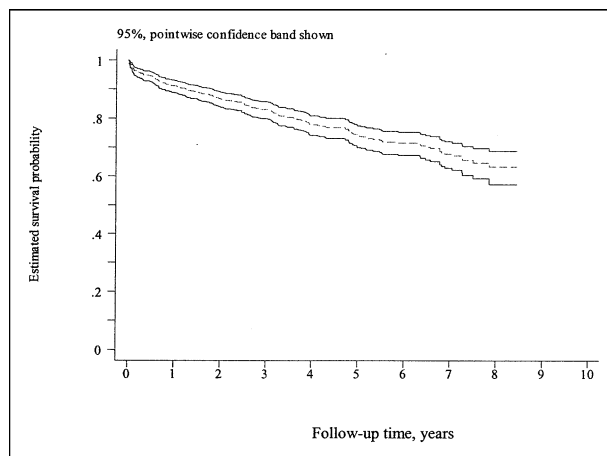
**Outcomes:** Crude and annualized rates for primary and secondary study end points during an average follow-up of 4.6 years are listed in Table 2. Cardiac event rates were low, with annualized cardiac death and MI rates of 0.8% and 2.2%, respectively. Cardiac death accounted for 57% (26 of 46 patients) of all deaths observed in this cohort. Figure 1 shows the survival rates free from nonfatal MI or death. To identify potentially high-risk patient groups, we compared the characteristics of patients who developed any of the primary study end points with those who did not (Table 3).

Approximately one-quarter of the patients underwent cardiac revascularization during follow-up; most (79%) underwent CABG, whereas the remaining patients underwent percutaneous coronary interventions.

**TABLE 3** Characteristics of Patients According to Whether Subjects Developed Primary End Points During Follow-up

	Primary End Points During Follow-up	
	No (n = 589)	Yes (n = 104)
Age (mean) (yrs)	66.8	70.5*
Men	484 (82.2%)	82 (78.9%)
Second opinion patients	320 (54.3%)	61 (58.7%)
Body mass index (mean) (kg/m <sup>2</sup> )	27.1	27.2
Ejection fraction (mean)	60.1%	54.0%*
Total cholesterol (mean) (mg/dl)	204	208
LDL cholesterol (mean) (mg/dl)	124	131
HDL cholesterol (mean) (mg/dl)	41	39*
Creatinine (mean) (mg/dl)	1.1	1.1
Healed MI	239 (40.5%)	53 (51.0%)*
Systemic hypertension	312 (52.9%)	65 (62.8%)*
Diabetes mellitus	82 (13.9%)	28 (26.9%)*
Smoke (ever)	370 (62.8%)	76 (72.9%)*
Smoke (current)	36 (6.1%)	5 (4.7%)
Angina pectoris (ever)	458 (78%)	87 (84.0%)*
Angina pectoris (present)	349 (59.3%)	62 (59.6%)
Angina pectoris class (%)		
I	221 (63.3%)	32 (52.4%)*
II	113 (32.4%)	26 (41.3%)*
III	13 (3.7%)	4 (6.4%)*
IV	2 (0.6%)	0 (0.0%)*
Use of antianginal medications (%)		
$\beta$ blockers	438 (74.4%)	64 (61.5%)*
Calcium channel antagonists	321 (54.5%)	68 (65.4%)*
Aspirin	501 (85.1%)	79 (76.0%)*
Nitrates	230 (39.0%)	51 (49.0%)*
Lipid-lowering agents	277 (47.0%)	30 (29.0%)*

\*p < 0.05.  
Abbreviations as in Table 2.



**FIGURE 2.** Kaplan-Meier estimates of survival free from coronary revascularization.

The event rate in the 132 asymptomatic patients without prior MI was 2.4/100 years compared with 3.4 in the group with angina, previous MI, or both (p = 0.20). Of the 291 patients with previous MI (with or without angina), 53 patients reached an end point. Of the 171 asymptomatic patients with previous MI, 26 developed angina (rate of 3.6/100 years) and 19 underwent revascularization. Of the 390 patients with angina, 136 became unstable, 50 developed MI, and

**TABLE 4** Annual Rates of Study End Points According to Whether Patients Met Criteria for Coronary Intervention

	Met Criteria for Interventions During Follow-up	
	No (n = 413)	Yes (n = 280)
Nonfatal MI	4 (1.0%)	11 (3.9%)
Nonfatal MI or death	9 (2.2%)	13 (4.6%)
Cardiac death	3 (0.8%)	2 (0.7%)
Unstable angina pectoris	8 (2.0%)	41 (14.6%)
Heart failure	4 (1.0%)	8 (2.8%)
Coronary revascularization	5 (1.1%)	40 (14.2%)

122 were revascularized. Figure 2 shows survival estimates free of coronary revascularization during follow-up.

**Criteria for coronary interventions and need for revascularization:** The criteria used for coronary interventions in this study were correlated with the subsequent development of primary outcomes or the need for coronary revascularization (Table 4). Compared with subjects who did not meet the criteria for intervention, patients who satisfied the criteria had an increased risk of developing primary and secondary outcomes.

During follow-up, 186 subjects (26.8%) underwent coronary angiography, and 170 subjects (24.5%) eventually underwent revascularization. The most common reasons for intervention were worsening angina despite therapy adjustment (48%), development of unstable coronary syndrome (15%), and development of angina in the recovery phase after MI (7%). Findings at coronary angiography showed 2-vessel CAD in 24% of patients and 3-vessel CAD in 61% of patients. Consequently, most of the revascularization procedures (79%) were CABG. Single-vessel CAD was seen in only 13% of patients and nonobstructive CAD was seen in only 2% of patients.

**Predictors of adverse outcomes:** Table 5 lists the crude hazard ratios of the primary study outcomes associated with selected variables. Coronary revascularization and meeting criteria for interventions during follow-up were handled as time-varying covariates. The findings of this analysis are consistent with the results of previous studies. Self-reported regular intake of alcohol, use of aspirin,  $\beta$  blockers, or lipid-lowering agents (most of which were statin drugs), and higher ejection fraction were all protective of adverse events; in contrast, increasing age, male gender, previous MI, history of diabetes or hypertension, and higher total cholesterol levels were predictive of adverse outcomes. These variables were also predictive of secondary cardiac end points, such as combined cardiac death and nonfatal MI, with only minor changes in the hazard ratios.

## DISCUSSION

The findings of this large, prospective longitudinal study support an approach based on intensive medical therapy, risk factor modification, and stricter criteria for coronary intervention that is not based merely on

the presence of CAD or ischemia. The findings confirmed that such a management strategy in selected patients with documented stable CAD is associated with excellent long-term outcomes. Postponing invasive coronary interventions until medical therapy fails or instability ensues was safe and was not associated with higher risk of death or MI.

Overall, the incidence of these outcomes was low and compared favorably with results reported from observational and experimental studies. For example, the annualized cardiac mortality among our patients with a history of MI was 0.9% compared with 3% to 5% among survivors of MI in 2 large population-based studies.<sup>5,6</sup> Similarly, the incidence of nonfatal MI and cardiac deaths in our study (2.2%, 0.8% per year, respectively) compares favorably with rates in either the atorvastatin (2.4%, 0.6%, respectively) or percutaneous coronary intervention arms (2.8%, 0.6%, respectively) of the Aggressive Lipid-Lowering Therapy compared with angioplasty in stable coronary artery disease (AVERT) study (per 18 months of follow-up).<sup>7</sup> These findings were observed despite the fact that, compared with AVERT subjects, our subjects were older, had more advanced CAD, and were followed for longer duration, allowing for more cardiac events to develop.

Our findings confirm the safety of our conservative strategy as a viable alternative to a rushed invasive approach in many patients with documented stable CAD. Moreover, with the ongoing progress in both medical therapies and invasive interventions, even the favorable outcomes demonstrated in this study could be further improved. Initial employment of state-of-the-art medical interventions may obviate the need for interventions all together in some patients, as well as provide others with safer, more advanced, and durable revascularization procedures when they become necessary.

The occurrence of unstable or crescendo angina, despite optimal medical therapy, was the most common reason for coronary interventions. However, holding off coronary interventions until indicated by clinical instability did not result in an increased risk of complications. Patients' symptomatic status predicted the need for coronary revascularization as well as the risk of subsequent MI or death. Among patients with stable symptoms, normal left ventricular function, and adequate exercise tolerance, rates of nonfatal MI or death were very low, regardless of the presence of demonstrable ischemia by objective testing.

Previous studies comparing medical therapy with revascularization have shown comparable results when hard cardiac outcomes were considered, despite only limited use of comprehensive medical therapy. For patients in whom revascularization improved hard outcomes in these studies, such as those with depressed left ventricular systolic function in the presence of ischemia, revascularization was also advised in our study. Reducing angina is an important goal of management. Although CABG reduces angina the most, it comes at a higher financial cost and is associated with potentially serious complications. Although percutaneous coronary intervention results in

**TABLE 5** Crude and Adjusted Hazard Ratios (HR) for Selected Predictors of Nonfatal Myocardial Infarction (MI) or All-cause Death

	Crude HR (95% CI)	Adjusted HR* (95% CI)
Age (10-yr increment)	1.51 (1.24–1.86)	1.26 (0.91–1.73)
Men	0.81 (0.51–1.28)	1.48 (0.63–3.47)
History of MI	1.51 (1.10–2.05)	0.85 (0.49–1.47)
Diabetes mellitus	2.23 (1.45–3.43)	1.62 (1.10–4.22)
Systemic hypertension	1.50 (1.0–2.25)	2.06 (1.12–3.81)
Regular exercise	0.58 (0.36–0.95)	0.91 (0.40–2.12)
Regular intake of alcohol	0.68 (0.46–1.0)	0.66 (0.37–1.18)
Total cholesterol (10-point increment)	1.03 (0.98–1.08)	1.13 (1.04–1.23)
HDL cholesterol (10-point increment)	0.89 (0.74–1.07)	0.91 (0.67–1.23)
Ejection fraction (10-point increment)	0.61 (0.52–0.72)	0.63 (0.52–0.77)
Use of aspirin	0.39 (0.26–0.58)	0.54 (0.28–1.04)
Use of $\beta$ blockers	0.47 (0.32–0.69)	0.59 (0.32–1.10)
Use of lipid-lowering agents	0.34 (0.23–0.52)	0.44 (0.24–0.82)

\*Adjusting for other variables listed in the table in addition to body mass index and revascularization. Revascularization was handled as a time-varying covariate.  
CI = confidence interval; other abbreviation as in Table 1.

less frequent angina compared with medical therapy, both achieved equal control of severe, limiting angina.<sup>8</sup> Furthermore, in a recent large randomized trial, medical therapy was as effective as revascularization in limiting angina and improving quality of life in elderly patients with advanced CAD.<sup>9</sup>

Recent studies have emphasized the different benefits of medical therapy in patients with CAD. Dakik et al<sup>10</sup> showed that intensive medical therapy was as effective as percutaneous coronary intervention in suppressing cardiac ischemia and in preventing ischemic events in stable survivors of MI. In the AVERT study, high-dose atorvastatin compared with percutaneous coronary intervention in patients with stable CAD was associated with reduction in ischemic events.<sup>7</sup> The Lyon Diet Heart Study<sup>11</sup> and Ornish et al<sup>12</sup> showed remarkable reductions in cardiac events by lifestyle modifications. In the Heart Outcomes Prevention Evaluation Study (HOPE), ramipril improved all cardiovascular outcomes and prevented progression of CAD, including reduced rates of revascularization procedures in high-risk subjects with established cardiovascular disease or diabetes.<sup>13,14</sup> Of note, these excellent outcomes were observed, although none of these studies, with the exception of the study by Dakik et al,<sup>10</sup> used a comprehensive strategy of intensive medical therapy, which might have further improved the observed results.

There are several limitations to the present study. Considering the select nature of the study population, the high socioeconomic status, and the under-representation of women and minority groups, our findings might not be generalizable. However, the clinical characteristics of this cohort are similar to those reported in other studies, thereby minimizing the potential impact of baseline differences. Our findings may not be extrapolated to patients with more symptomatic angina (only 5% of our subjects had class III to IV angina) and to those with previous revascularization (exclusion criteria in our study). Although this cohort represents a group with inherently good outcomes, many of these patients would have been subjected to

coronary revascularization had the standard approach to CAD been applied. Before study entry, more than half of the patients had already been advised to undergo coronary revascularization by other physicians. Finally, the management protocol was not compared with a randomly assigned group subjected to a more invasive approach. This was not done because investigators did not feel comfortable with such an alternative in stable patients with stable CAD; thus, this study was designed to be observational in nature. However, the outcomes of recent studies employing state-of-the-art invasive interventions substituted the control group with a reliable reference for comparison.<sup>7,9</sup>

This study has several strengths. In contrast to previous investigations in which medical therapy was defined vaguely as “usual practice” compared with state-of-the-art percutaneous coronary intervention or CABG, this prospective study used predefined medical treatments and preventive strategies that can be readily reproduced in actual clinical practice. The study sample was relatively large, with extended, almost complete follow-up. Finally, this study tested and demonstrated the safety of using stricter criteria for referral to revascularization procedures, leading to lower rates of coronary interventions without compromising long-term outcomes.

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