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Medical versus interventional therapy in the management of stable angina pectoris

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INTRODUCTION

Untreated coronary heart disease (CHD) generally results in progressive angina, myocardial infarction (MI), left ventricular dysfunction, and ultimately death [1]. Although some patients with CHD remain asymptomatic or have only chronic stable exertional angina, these patients are at increased risk for sudden cardiac death. The goals of therapy in patients with stable angina are to alleviate symptoms, delay or prevent the progression of coronary disease, and prevent adverse outcomes such as death or myocardial infarction. This is usually accomplished with medical therapy, with revascularization being performed in selected patients. Revascularization can be accomplished with percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG). Interventional therapy ameliorates symptoms but generally does not improve mortality. There are two main indications for revascularization: a. Patients with unacceptable angina; b. Patients deemed likely to have a survival benefit from revascularization, based upon the location and severity of the lesion, the number of diseased vessels, and the presence of left ventricular dysfunction. The efficacy of medical versus interventional therapy in patients with stable angina will be reviewed here. The choice between PCI and CABG when intervention is required is discussed separately.

LIMITATIONS OF CLINICAL TRIALS

Before publication of the COURAGE trial cited below, recommendations for the treatment of stable angina were largely based upon older clinical trials comparing interventional to medical therapy and PCI to CABG. There are, however, a number of important limitations concerning the applicability of the results of these initial trials and even later trials to current clinical practice. The number of patients entered into the trials was only a small percentage of the number screened and is therefore not reflective of the general population. As an example, most patients had preserved left ventricular function and focal atherosclerotic coronary disease. Thus, extrapolation of these data to patients with diffuse CHD and/or left ventricular dysfunction is inappropriate. In early trials of PCI versus medical therapy, the majority of patients underwent percutaneous transluminal coronary angioplasty alone, without stenting. For patients in later trials who received a bare-metal stent, current antithrombotic regimens (eg, clopidogrel and glycoprotein IIb/IIIa inhibitors) were not employed. In the most recent trial, COURAGE, drug-eluting stents that markedly reduce the rate of restenosis and therefore repeat revascularization (figure 1) were used in only 15 percent of patients [2]. Most CABG trials were conducted at a time when saphenous vein graft use was prevalent rather than internal mammary (thoracic) arteries or other arterial conduits that are associated with improvements in long-term graft patency and patient survival (figure 2A-B) [3].

AGGRESSIVE RISK FACTOR REDUCTION

Even among patients who undergo interventional therapy, progression of native coronary disease is an important determinant of clinical outcome with time. This was illustrated in an analysis from the BARI trial, which compared PCI and CABG [4]. At five years, progression of disease in previously untreated vessels accounted for two-thirds of the increase in myocardium at risk, regardless of which procedure had originally been performed.

This observation demonstrates the importance of aggressive risk factor reduction in all patients with CHD, including those with stable angina pectoris. This includes low-dose aspirin, reaching treatment goals for hypertension and serum lipids, avoidance of smoking, and, in diabetic patients, controlling the serum glucose. These issues are discussed in detail separately. Optimal medical therapy was not used in any of the trials prior to COURAGE [2].

BYPASS SURGERY VERSUS MEDICAL THERAPY

CABG provides more symptomatic relief and improved survival when compared to medical management in selected patients with stable angina [5]. The following discussion will review data related to conventional CABG; the efficacy of minimally invasive CABG is discussed separately)

Relief of angina

Approximately 95 percent of patients have an improvement in or complete relief of angina immediately after CABG. The Coronary Artery Surgery Study (CASS) performed in the late 1970s and early 1980s showed that more patients remained symptom-free after CABG compared to medical therapy at one year (66 versus 30 percent) and five years (63 versus 38 percent) [6]. By 10 years, this difference had disappeared (47 versus 42 percent). This was due both to recurrence of symptoms by 10 years after CABG and to the performance of surgery in a significant proportion of the medically treated patients at a later date. The long-term success of CABG is limited by two factors: a. Progression of atherosclerosis in other vessels. B The development of bypass graft disease (ie, stenosis). The reoperation rate for recurrent symptoms was 6 to 8 percent per year in CASS, and the mortality rate within the first five years after bypass surgery was approximately 1 percent per year [6]. In older studies with saphenous vein grafts, survival at 10 years was approximately 80 percent, and 50 percent had recurrent angina; only 15 percent were angina-free at 15 years (figure 3) [7]. However, both graft patency and patient survival are significantly higher with internal mammary artery grafts (figure 2A-B) [3]. Effects on survival — CABG offered no significant overall mortality benefits compared to medical therapy alone in trials from the 1970s [8-11]. However, survival was improved in selected patients with severe CAD who were at high risk because a large amount of myocardium was supplied by the diseased vessel or because of significant underlying left ventricular dysfunction. These included patients with (table 1): a. Left main coronary artery stenosis or left main equivalent disease; b. Three vessel disease, particularly with a reduced left ventricular ejection fraction (LVEF, usually < 40 percent) [11-15]; c Two vessel disease when there was more than a 75 percent stenosis in the left anterior descending (LAD) artery proximal to the first major septal artery (figure 4) [11,16]. Patients with proximal LAD disease have a worse prognosis than those with more distal stenoses within the LAD, and the presence of proximal LAD plus concurrent right coronary disease is associated with a prognosis similar to that of left main disease [17]. Prognosis is also worse when either the LVEF <50 percent or ischemia is present on noninvasive testing. In addition to these three categories of patients, the 2004 ACC/AHA guidelines on CABG concluded that patients with stable angina and the following criteria also benefit from revascularization with CABG [18]: a. One or two vessel disease without significant proximal LAD disease, but with a large area of viable myocardium demonstrated on noninvasive imaging and with high risk criteria on stress testing. Patients with a moderate area of viable myocardium have possible benefit; b. Significant proximal (single vessel) LAD disease; c. Disabling angina while on maximal medical therapy. With the exception of left main disease, the survival benefit from CABG compared to medical therapy tends to disappear with prolonged follow-up in these groups [12,19]. A limitation to these observations is that currently recommended aggressive risk factor reduction was not performed.

Severity of angina

The severity of angina influences the outcome of medical therapy even among patients with similar angiographic findings. Nonrandomized data from the CASS registry found that five-year survival was lower in medically compared to surgically treated patients with both class III or IV angina (Canadian Cardiovascular Society classification) (table 2) and three vessel disease whether they had normal left ventricular function (74 versus ≥92 percent) or reduced left ventricular function (52 versus 82 percent) [20]. Strongly positive stress test — Among patients able to undergo exercise stress, the duration of exercise and the ST segment response during exercise testing have been used by the CASS registry and investigators at Duke to stratify medically treated patients into those with an annual mortality of 5 percent per year and those with an annual mortality of 1 percent per year [21,22]. Low-risk patients according to the Duke treadmill score for exercise testing are likely to have either no coronary stenosis ≥75 percent or single vessel disease [22]. Although 9 percent of low-risk patients in one report had three vessel or left main disease, five-year mortality for all patients in the low-risk group was only 3 percent (0.6 percent per year). Radionuclide myocardial perfusion imaging (rMPI) can also be used to determine which patients with stable angina are more likely to have a survival benefit from revascularization as opposed to medical therapy [23,24]. The potential predictive value of rMPI was illustrated in a retrospective evaluation of more than 10,000 consecutive patients without prior MI or revascularization who underwent exercise or adenosine rMPI [24]. Of these, 671 underwent revascularization within 60 days after rMPI; the remainder was treated medically. At two years, mortality was significantly lower with revascularization in patients with inducible ischemia of >10 percent of

total myocardium (2.6 versus 5.4 percent). In contrast, mortality was significantly lower with medical therapy in patients with inducible ischemia of ≤10 percent of total myocardium (0.9 versus 3.3 percent).

Left ventricular dysfunction

Optimal therapy for patients with multivessel coronary disease and left ventricular dysfunction has not been formally addressed in the large randomized trials [11] and a left ventricular ejection fraction (LVEF) less than 30 percent was an exclusion criterion in the COURAGE trial described below [2]. Despite these limitations, reduced left ventricular systolic function is one of the most important determinants of prognosis in medically treated patients with stable angina (table 1) and may be an indication for revascularization [12,14,15,18]. The following observations from the CASS registry are illustrative: a. In patients treated with medical therapy only, single vessel disease with poor left ventricular function and three vessel coronary disease with good left ventricular function had a similar prognosis [25]; b. Among patients with an LVEF between 35 and 49 percent, survival at seven years in patients with three vessel disease was associated with a significant improvement with CABG (88 versus 65 percent) [14]. No benefit from CABG could be identified in patients with one or two vessel disease. There are limited data on patients with lower ejection fractions. One study analyzed the outcome of 135 consecutive patients with an LVEF below 30 percent (mean 24 percent) who underwent CABG; most had multivessel disease [26]. The in-hospital mortality rate was 5.2 percent. The LVEF improved from 24 percent preoperatively to 34 percent postoperatively, and the three year survival rate was 81 percent. As demonstrated in the latter study, left ventricular dysfunction may be partially reversible in patients with coronary disease [26]. This may reflect hibernating myocardium, which refers to an ischemia-induced impairment in cardiac contractility that can be reversed over several days or weeks after revascularization. CABG may improve survival in patients with left ventricular dysfunction and hibernating myocardium, a benefit that is not expected in those with irreversibly scarred myocardium [27]. This finding suggests that myocardial viability should be adequately assessed prior to recommending CABG in patients with moderate to severe left ventricular dysfunction in whom there are significant stenoses in arteries supplying markedly hypokinetic or akinetic myocardium. Left main disease — Patients with untreated left main and left main equivalent disease have worse outcomes with medical therapy alone because of the large amount of myocardium at risk. Coronary artery bypass graft surgery (CABG) is the preferred approach for revascularization of a left main lesion, particularly if unprotected (absence of patent bypass graft in the left anterior descending or circumflex artery). There is some role for PCI that may increase with drug-eluting stents that markedly reduce restenosis. The management of these patients is discussed separately. Resumption of normal activities — Convalescence after CABG is lengthy, even among those who are successfully treated. Nevertheless, approximately 70 to 80 percent of patients eventually return to work. However, studies assessing return to function found no difference in employment or recreational status between those treated medically or surgically at two, five, and ten years of follow-up [6,28,29]. The presence or absence of posttreatment angina was the major predictive factor for return to work [28].

PCI VERSUS MEDICAL THERAPY — PCI has been compared to both limited and optimal medical interventions. Individual trials have demonstrated better outcomes with high-dose atorvastatin compared to percutaneous transluminal coronary angioplasty (PTCA) alone with usual (less aggressive) care (AVERT trial) [30] and with exercise training plus medical therapy compared to PCI with stenting plus medical therapy [31]. However, these trials have little relevance to current practice since all patients should receive optimal multicomponent medical therapy and lifestyle interventions, whether or not they are revascularized. A number of trials have compared the efficacy of PCI to optimal medical therapy in patients with stable angina. Many of these trials, such as RITA-2 and MASS II, used PTCA as the form of revascularization [32-41]. The general findings were that patients undergoing PTCA had similar rates of death and MI as those on medical therapy and were less likely to have angina during the first few years [32,33]. However, these trials were performed before the use of current optimal medical therapy or coronary artery stents. COURAGE trial — The data most applicable to current practice come from the COURAGE trial in which 2287 patients (mean age 62) with stable CHD were randomly assigned to either aggressive medical therapy alone or aggressive medical therapy plus PCI with bare-metal stenting [2]. Patients were required to have both objective evidence of ischemia and significant disease in a least coronary artery; 87 percent were symptomatic and 58 percent had Canadian Cardiovascular Society [CCS] class II or III angina (table 2). Exclusion criteria included CCS class IV angina, ≥50 percent left main disease, a markedly positive treadmill test (significant ST segment depressions and/or a hypotensive response during stage I of the Bruce protocol), an LVEF less than 30 percent, and coronary lesions deemed unsuitable for PCI. All patients received optimal, tolerable antiischemic therapy with beta blockers, calcium channel blockers, and nitrates, as well as antiplatelet therapy with either aspirin or clopidogrel, and aggressive lipid-lowering therapy, including administration of a statin (attained median LDL-cholesterol was 72 mg/dL [1.87 mmol/L] at five years). Exercise was recommended to achieve further improvements in the lipid profile when necessary. Lisinopril or losartan were

used as standard secondary prevention, although the specific efficacy of angiotensin inhibition remains unproven in the absence of a low LVEF or a prior MI. The following observations were made at a median follow-up of 4.6 years: a. There was no significant difference between the two treatment strategies for the primary endpoint of death from any cause and non-fatal MI (approximately 19 percent in both groups). This outcome remained unchanged when periprocedural MIs (most defined as CK-MB or troponin elevations) were excluded; b. There was no significant difference in the rates of hospitalization for ACS (approximately 12 percent in both groups); c. Patients in the PCI group underwent significantly fewer subsequent revascularization procedures (21 versus 33 percent, hazard ratio 0.60, 95% CI 0.51-71).The issue of whether patients who receive PCI plus optimal medical therapy have a better quality of life in general, and less angina in particular, than those who receive optimal medical therapy was addressed in a separate report from COURAGE [42]. Validated health surveys (Seattle Angina Questionnaire and RAND-36) were administered to patients at baseline, at 1, 3, 6, and 12 months, and then yearly [42]. The following findings were noted: a. At baseline, 22 percent of patients were free of angina. At three months, significantly more patients who received PCI were free of angina (53 versus 42 percent); however, there was no significant difference at 36 months (59 versus 56 percent); b. Patients in both groups showed significant improvements from baseline values in various measures of quality of life. The percent of patients with clinically significant improvement in parameters such as physical limitation, angina stability, angina frequency, and overall quality of life was significantly higher in the PCI group by six months but not at 36 months; c. The greatest benefit with PCI for most measures of quality of life occurred in the subgroup of patients with more severe angina at baseline. For patients similar to those enrolled in COURAGE, PCI with bare-metal stents plus optimal medical therapy and initial, optimal medical therapy with revascularization as necessary lead to similar outcomes.

Meta-analyses

The results of COURAGE discussed above have been echoed in two meta-analyses: a. A 2009 meta-analysis evaluated the rates of death and MI for PCI and medical therapy, using data from 61 PCI trials that compared any two of four interventions (PTCA, bare-metal stents, drug-eluting stents, or medical therapy) in over 25,000 patients with non-acute coronary artery disease [43]. In all direct or indirect comparisons, there was no significant difference between the rates of death or MI using any form of PCI or medical therapy; b. A 2010 meta-analysis of 14 randomized trials with over 7800 patients which compared PCI to medical therapy found that more patients were angina free after PCI than medical therapy alone (odds ratio [OR]1.69, 95% CI 1.24-2.30) [44]. However, when only trials performed in 2000 or after were evaluated, there was no significant difference in relief of angina between PCI and medical therapy (OR 1.13, 95% CI 0.76-1.68).

BOTH PCI AND CABG VERSUS MEDICAL THERAPY

The Medicine, Angioplasty, or Surgery Study (MASS) and MASS II trials directly compared PCI, CABG, and medical therapy for the management of stable angina [45-48]. However, the conclusions of MASS have uncertain applicability to current practice as it was performed prior to the current era of aggressive antithrombotic regimens (particularly around the time of PCI), the routine use of stenting (often with drug-eluting stents) at the time of PCI, the more frequent use of complete revascularization both with PCI and CABG, aggressive lipid lowering with statins, and a greater awareness of the importance of risk factor intervention. While the same limitations apply to the MASS II trial, patient management was more current than in MASS. MASS II randomly assigned 611 patients with multivessel disease (58 percent had triple vessel disease and 92 percent had left anterior descending artery disease) and stable angina (CCS II or III) to CABG, PCI (with bare-metal stenting in 72 percent and PTCA alone in 28 percent), or relatively aggressive medical therapy [45]. Patients who received CABG had an average of 3.3 vessels bypassed, while patients who underwent PCI had an average of 2.1 vessels dilated, and 73 percent received multivessel PCI. The primary endpoint was freedom from all cause death, MI or refractory angina requiring revascularization. At one year, the following observations were made: a. The incidence of the primary endpoint was significantly lower with PCI than with medical therapy or CABG (76 versus 88 and 93 percent respectively); b. One-year mortality was significantly lower with medical therapy than with PCI or CABG (1.5 versus 4.5 and 4.0 percent). At five-year follow-up [48]: a. The incidence of the primary endpoint was significantly higher with CABG than with medical therapy or PCI (79 versus 64 and 67 percent respectively); b. There was no significant difference in survival among the three groups (88 to 92 percent). At ten-year follow-up [49]: a. The incidence of the primary endpoint was significantly higher with CABG than with PCI or medical therapy (73 versus 55 versus 49 percent respectively). b. There was no significant difference in survival among the three groups (69 to 75 percent). The lack of mortality benefit from intervention supports the findings in COURAGE.

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SUMMARY AND RECOMMENDATIONS

All patients with coronary heart disease, including those with stable angina, should be treated with aggressive risk factor reduction. All patients with stable angina should undergo risk stratification with stress testing, and some need an assessment of left ventricular systolic function. This information is used to determine whether a patient is at high risk, defined as a large amount of viable myocardium at risk (as determined by noninvasive imaging or suggested by a strongly positive treadmill test) or significant underlying left ventricular dysfunction. We recommend coronary angiography followed by revascularization, to improve survival and/or symptoms, for two groups of patients with stable angina (Grade 1A): a. Patients in whom maximal medical therapy has not satisfactorily improved anginal symptoms or who are intolerant of medical therapy; b. Patients with high-risk criteria and selected patients with intermediate-risk criteria on noninvasive testing, regardless of anginal severity. For patients with stable angina that is not significantly interfering with the quality of life, and for whom revascularization is not indicated to prolong life, we suggest medical therapy rather than immediate revascularization (Grade 2A). In such patients, patient preference may be important.

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Optimal Medical Therapy with or without PCI for Stable Coronary Disease

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ABSTRACT

BACKGROUND

In patients with stable coronary artery disease, it remains unclear whether an initial management strategy of percutaneous coronary intervention (PCI) with intensive pharmacologic therapy and lifestyle intervention (optimal medical therapy) is superior to optimal medical therapy alone in reducing the risk of cardiovascular events.

METHODS

We conducted a randomized trial involving 2287 patients who had objective evidence of myocardial ischemia and significant coronary artery disease at 50 U.S. and Canadian centers. Between 1999 and 2004, we assigned 1149 patients to undergo PCI with optimal medical therapy (PCI group) and 1138 to receive optimal medical therapy alone (medical-therapy group). The primary outcome was death from any cause and nonfatal myocardial infarction during a follow-up period of 2.5 to 7.0 years (median, 4.6).

RESULTS

There were 211 primary events in the PCI group and 202 events in the medical-therapy group. The 4.6-year cumulative primary-event rates were 19.0% in the PCI group and 18.5% in the medical-therapy group (hazard ratio for the PCI group, 1.05; 95% confidence interval [CI], 0.87 to 1.27; P=0.62). There were no significant differences between the PCI group and the medical-therapy group in the composite of death, myocardial infarction, and stroke (20.0% vs. 19.5%; hazard ratio, 1.05; 95% CI, 0.87 to 1.27; P=0.62); hospitalization for acute coronary syndrome (12.4% vs. 11.8%; hazard ratio, 1.07; 95% CI, 0.84 to 1.37; P=0.56); or myocardial infarction (13.2% vs. 12.3%; hazard ratio, 1.13; 95% CI, 0.89 to 1.43; P=0.33).

CONCLUSIONS

As an initial management strategy in patients with stable coronary artery disease, PCI did not reduce the risk of death, myocardial infarction, or other major cardiovascular events when added to optimal medical therapy. (ClinicalTrials.gov number, NCT00007657.)

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*Members of the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial are listed in the Appendix and in the Supplementary Appendix, available with the full text of this article at www.nejm.org.

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During the past 30 years, the use of percutaneous coronary intervention (PCI) has become common in the initial management strategy for patients with stable coronary artery disease in North America, even though treatment guidelines advocate an initial approach with intensive medical therapy, a reduction of risk factors, and lifestyle intervention (known as optimal medical therapy).[1,2] In 2004, more than 1 million coronary stent procedures were performed in the United States,[3] and recent registry data indicate that approximately 85% of all PCI procedures are undertaken electively in patients with stable coronary artery disease.[4] PCI reduces the incidence of death and myocardial infarction in patients who present with acute coronary syndromes,[5-10] but similar benefit has not been shown in patients with stable coronary artery disease.[11-15] This issue has been studied in fewer than 3000 patients,[16] many of whom were treated before the widespread use of intracoronary stents and current standards of medical management.[17-28]

Although successful PCI of flow-limiting stenoses might be expected to reduce the rate of death, myocardial infarction, and hospitalization for acute coronary syndromes, previous studies have shown only that PCI decreases the frequency of angina and improves short-term exercise performance.[11,12,15] Thus, the long-term prognostic effect of PCI on cardiovascular events in patients with stable coronary artery disease remains uncertain. Our study, the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial, was designed to determine whether PCI coupled with optimal medical therapy reduces the risk of death and nonfatal myocardial infarction in patients with stable coronary artery disease, as compared with optimal medical therapy alone.

METHODS

STUDY DESIGN

The methods we used in the trial have been described previously.[29,30] Sponsorship and oversight of the trial were provided by the Department of Veterans Affairs Cooperative Studies Program. Additional funding was provided by the Canadian Institutes of Health Research. Supplemental corporate support from several pharmaceutical companies included funding and in-kind support. All support from the pharmaceutical industry consisted of unrestricted research grants payable to the Department of Veterans Affairs.

The study protocol was approved by the human rights committee at the coordinating center and by the local institutional review board at each participating center. An independent data and safety monitoring board oversaw the conduct, safety, and efficacy of the trial. Data management and statistical analyses were performed solely by the data coordinating center with oversight by the trial executive committee, whose members, after unblinding, had full access to the data and vouch for the accuracy and completeness of the data and the analyses. The companies that provided financial support, products, or both had no role in the design, analysis, or interpretation of the study.

STUDY POPULATION

Patients with stable coronary artery disease and those in whom initial Canadian Cardiovascular Society (CCS) class IV angina subsequently stabilized medically were included in the study. Entry criteria included stenosis of at least 70% in at least one proximal epicardial coronary artery and objective evidence of myocardial ischemia (substantial changes in ST-segment depression or T-wave inversion on the resting electrocardiogram or inducible ischemia with either exercise or pharmacologic vasodilator stress) or at least one coronary stenosis of at least 80% and classic angina without provocative testing. Exclusion criteria included persistent CCS class IV angina, a markedly positive stress test (substantial ST-segment depression or hypotensive response during stage 1 of the Bruce protocol), refractory heart failure or cardiogenic shock, an ejection fraction of less than 30%, revascularization within the previous 6 months, and coronary anatomy not suitable for PCI. A detailed description of the inclusion and exclusion criteria is included in the Supplementary Appendix (available with the full text of this article at www.nejm.org). Patients who were eligible for the study underwent randomization after providing written informed consent.

TREATMENT

Patients were randomly assigned to undergo PCI and optimal medical therapy (PCI group) or optimal medical therapy alone (medical-therapy group). A permuted-block design was used to generate

random assignments within each study site along with previous coronary-artery bypass grafting (CABG) as a stratifying variable. All patients received antiplatelet therapy with aspirin at a dose of 81 to 325 mg per day or 75 mg of clopidogrel per day, if aspirin intolerance was present. Patients undergoing PCI received aspirin and clopidogrel, in accordance with accepted treatment guidelines and established practice standards. Medical antiischemic therapy in both groups included long-acting metoprolol, amlodipine, and isosorbide mononitrate, alone or in combination, along with either lisinopril or losartan as standard secondary prevention. All patients received aggressive therapy to lower low-density lipoprotein (LDL) cholesterol levels (simvastatin alone or in combination with ezetimibe) with a target level of 60 to 85 mg per deciliter (1.55 to 2.20 mmol per liter). After the LDL cholesterol target was achieved, an attempt was made to raise the level of high-density lipoprotein (HDL) cholesterol to a level above 40 mg per deciliter (1.03 mmol per liter) and lower triglyceride to a level below 150 mg per deciliter (1.69 mmol per liter) with exercise, extended-release niacin, or fibrates, alone or in combination.

In patients undergoing PCI, target-lesion revascularization was always attempted, and complete revascularization was performed as clinically appropriate. Success after PCI as seen on angiography was defined as normal coronary-artery flow and less than 50% stenosis in the luminal diameter after balloon angioplasty and less than 20% after coronary stent implantation, as assessed by visual estimation of the angiograms before and after the procedure. Clinical success was defined as angiographic success plus the absence of in-hospital myocardial infarction, emergency CABG, or death. Drug-eluting stents were not approved for clinical use until the final 6 months of the study, so few patients received these intracoronary devices.

CLINICAL OUTCOME

Clinical outcome was adjudicated by an independent committee whose members were unaware of treatment assignments. The primary outcome measure was a composite of death from any cause and nonfatal myocardial infarction. Secondary outcomes included a composite of death, myocardial infarction, and stroke and hospitalization for unstable angina with negative biomarkers. The angina status of patients was assessed according to the CCS classification during each visit. Further analyses of other secondary outcomes — including quality of life, the use of resources, and cost-effectiveness — are being conducted but have not yet been completed.

The prespecified definition of myocardial infarction (whether periprocedural or spontaneous) required a clinical presentation consistent with an acute coronary syndrome and either new abnormal Q waves in two or more electrocardiographic leads or positive results in cardiac biomarkers. Silent myocardial infarction, as detected by abnormal Q waves, was confirmed by a core laboratory and was also included as an outcome of myocardial infarction.

STATISTICAL ANALYSIS

We projected composite 3-year event rates of 21.0% in the medical-therapy group and 16.4% in the PCI group (relative difference, 22%) during a follow-up period of 2.5 to 7.0 years. We also incorporated assumptions about crossover between study groups and loss to follow-up.[31] We estimated that the enrollment of 2270 patients would provide a power of 85% to detect the anticipated difference in the primary outcome at the 5% two-sided level of significance. A detailed description of the sample-size calculation is included in the Supplementary Appendix.

Estimates of the cumulative event rate were calculated by the Kaplan–Meier method,[32] and the primary efficacy of PCI, as compared with optimal medical therapy, was assessed by the stratified log-rank statistic.[33] The treatment effect, as measured by the hazard ratio and its associated 95% confidence interval (CI), was estimated with the use of the Cox proportional-hazards model.[34] Data for patients who were lost to follow-up were censored at the time of the last contact. Analyses were performed according to the intention-to-treat principle. Categorical variables were compared by use of the chi-square test or the Wilcoxon rank-sum test, and continuous variables were compared by use of the Student t-test. Adjusted analysis of the primary outcome was performed with the use of a Cox proportional-hazards regression model with eight preidentified covariates of interest — age, sex, race, previous myocardial infarction, extent or distribution of angiographic coronary artery disease, ejection frac-

tion, presence or absence of diabetes, and health care system (Veterans Affairs or non–Veterans Affairs facility in the United States, or a Canadian facility) — as well as the stratifying variable of previous CABG. All other comparisons were unadjusted. A level of significance of less than 0.01 was used for all subgroup analyses and interactions.

RESULTS

BASELINE CHARACTERISTICS AND ANGIOGRAPHIC DATA

Between June 1999 and January 2004, a total of 2287 patients were enrolled in the trial at 50 U.S. and Canadian centers (Fig. 1). Of these patients, 1149 were randomly assigned to the PCI group and 1138 to the medical-therapy group. The baseline characteristics of the patients were recently published[35] and were similar in the two groups (Table 1). The median time from the first episode of angina before randomization was 5 months (median, three episodes per week, with exertion or at rest), and 58% of patients had CCS class II or III angina. A total of 2168 patients (95%) had objective evidence of myocardial ischemia, whereas the remaining 119 patients with classic angina (CCS class III) and severe coronary stenoses did not undergo ischemia testing (56 in the PCI group and 63 in the medical-therapy group). Among patients who underwent myocardial perfusion imaging at baseline, 90% had either single (23%) or multiple (67%) reversible defects for inducible ischemia. Two thirds of the patients had multivessel coronary artery disease.

Of the 1149 patients in the PCI group, 46 never underwent a procedure because the patient either declined treatment or had coronary anatomy unsuitable for PCI, as determined on clinical reassessment. In 27 patients (2%), the operator was unable to cross any lesions. PCI was attempted for 1688 lesions in 1077 patients, of whom 1006 (94%) received at least one stent. In the stent group, 590 patients (59%) received one stent and 416 (41%) more than one stent. Drug-eluting stents were used in 31 patients. On average, stenosis in the luminal diameter, as evaluated on visual assessment of angiograms, was reduced from a mean (±SD) of 83±14% to 31±34% in the 244 lesions not treated with stents and from 82±12% to 1.9±8% in the 1444 lesions treated with stents. After PCI, successful treatment as seen on angiography was achieved in 1576 of 1688 lesions (93%), and clinical success (i.e., all lesions successfully dilated and no in-hospital complications) was achieved in 958 of 1077 patients (89%).

MEDICATION AND TREATMENT TARGETS

Patients had a high rate of receiving multiple, evidence-based therapies after randomization and during follow-up, with similar rates in both study groups (Table 2). At the 5-year follow-up visit, 70% of subjects had an LDL cholesterol level of less than 85 mg per deciliter (2.20 mmol per liter) (median, 71±1.3 mg per deciliter [1.84±0.03 mmol per liter]); 65% and 94% had systolic and diastolic blood pressure targets of less than 130 mm Hg and 85 mm Hg, respectively; and 45% of patients with diabetes had a glycated hemoglobin level of no more than 7.0% (Table 2). Patients had high rates of adherence to the regimen of diet, regular exercise, and smoking cessation as recommended by clinical practice guidelines,[1,2] although the mean body-mass index did not decrease.

FOLLOW-UP PERIOD

The median follow-up period was 4.6 years (interquartile range, 3.3 to 5.7) and was similar in the two study groups, with a total of 120,895 patient-months at risk. Only 9% of patients were lost to follow-up in the two groups (107 in the PCI group and 97 in the medical-therapy group, P=0.51) before the occurrence of a primary outcome or the end of follow-up. Vital status was not ascertained in 194 patients (99 in the PCI group and 95 in the medical-therapy group, P=0.81).

PRIMARY OUTCOME

The primary outcome (a composite of death from any cause and nonfatal myocardial infarction) occurred in 211 patients in the PCI group and 202 patients in the medical-therapy group (Table 3). The estimated 4.6-year cumulative primary event rates were 19.0% in the PCI group and 18.5% in the medical-therapy group (unadjusted hazard ratio for the PCI group, 1.05; 95% CI, 0.87 to 1.27; P=0.62) (Fig. 2).

SECONDARY OUTCOMES

For the prespecified composite outcome of death, nonfatal myocardial infarction, and stroke, the event rate was 20.0% in the PCI group and 19.5%

Table 1. (Continued.)

Characteristic	PCI Group (N=1149)	Medical-Therapy Group (N=1138)	P Value
Angiographic			
Vessels with disease — no. (%)			0.72
1	361 (31)	343 (30)	
2	446 (39)	439 (39)	
3	341 (30)	355 (31)	
Disease in graft¶	77 (62)	85 (69)	0.36
Proximal LAD disease	360 (31)	417 (37)	0.01
Ejection fraction	60.8±11.2	60.9±10.3	0.86

* Plus–minus values are means ±SD. Baseline data were missing for one patient in each study group. CCS denotes Canadian Cardiovascular Society, CABG coronary-artery bypass grafting, and LAD left anterior descending artery.
† Race or ethnicity was reported by the patient at enrollment.
‡ Nuclear imaging could have been performed after either an exercise treadmill test or pharmacologic stress.
§ The percentage in this category is the proportion of patients who underwent imaging.
¶ The percentage in this category is the proportion of patients who had undergone previous CABG.

in the medical-therapy group (hazard ratio, 1.05; 95% CI, 0.87 to 1.27; P=0.62) (Table 3 and Fig. 2). The rates of hospitalization for acute coronary syndromes were 12.4% in the PCI group and 11.8% in the medical-therapy group (hazard ratio, 1.07; 95% CI, 0.84 to 1.37; P=0.56), and adjudicated rates of myocardial infarction were 13.2% and 12.3%, respectively (hazard ratio, 1.13; 95% CI, 0.89 to 1.43; P=0.33). For death alone, the rates were 7.6% and 8.3%, respectively (hazard ratio, 0.87; 95% CI, 0.65 to 1.16); the mortality curves for the two groups were virtually identical during the initial 4.6 years of the study. For stroke alone, the rate was 2.1% in the PCI group and 1.8% in the medical-therapy group (hazard ratio, 1.56; 95% CI, 0.80 to 3.04; P=0.19). When the primary end point was calculated with the exclusion of periprocedural myocardial infarction, the event rates were 16.2% and 17.9% (hazard ratio, 0.90; 95% CI, 0.73 to 1.10; P=0.29).

At a median follow-up of 4.6 years, 21.1% of patients in the PCI group had additional revascularization, as compared with 32.6% of those in the medical-therapy group (hazard ratio, 0.60; 95% CI, 0.51 to 0.71; P<0.001). In the PCI group, 77 patients subsequently underwent CABG, as compared with 81 patients in the medical-therapy group. Revascularization was performed for angina that was unresponsive to maximal medical therapy or when there was objective evidence of worsening ischemia on noninvasive testing, at the discretion of the patient's physician. The median time to subsequent revascularization was 10.0 months (interquartile range, 4.5 to 28.0) in the PCI group and 10.8 months (interquartile range, 3.2 to 30.7) in the medical-therapy group.

There was a substantial reduction in the prevalence of angina in both groups during follow-up. There was a statistically significant difference in the rates of freedom from angina throughout most of the follow-up period, in favor of the PCI group (Table 2). At 5 years, 74% of patients in the PCI group and 72% of those in the medical-therapy group were free of angina (P=0.35).

SUBGROUP ANALYSES

There was no significant interaction (P<0.01) between treatment effect and any predefined subgroup variable (Fig. 3). Of note, among patients with multivessel coronary artery disease, previous myocardial infarction, and diabetes, the rate of the primary end point was similar for both groups. When subgroup variables were included in a multivariate analysis, the hazard ratio for treatment was essentially unchanged (1.09; 95% CI, 0.90 to 1.33; P=0.77).

DISCUSSION

As an initial management strategy, PCI added to optimal medical therapy did not reduce the primary composite end point of death and nonfatal

Table 3. Primary and Secondary Outcomes.*

Outcome	Number of Events		Hazard Ratio (95% CI)†	P Value†	Cumulative Rate at 4.6 Years	
	PCI Group	Medical-Therapy Group			PCI Group	Medical-Therapy Group
					%	
Death and nonfatal myocardial infarction‡	211	202	1.05 (0.87–1.27)	0.62	19.0	18.5
Death§	68	74				
Periprocedural myocardial infarction	35	9				
Spontaneous myocardial infarction	108	119				
Death, myocardial infarction, and stroke	222	213	1.05 (0.87–1.27)	0.62	20.0	19.5
Hospitalization for ACS	135	125	1.07 (0.84–1.37)	0.56	12.4	11.8
Death§	85	95	0.87 (0.65–1.16)	0.38	7.6	8.3
Cardiac	23	25				
Other	45	51				
Unknown	17	19				
Total nonfatal myocardial infarction	143	128	1.13 (0.89–1.43)	0.33	13.2	12.3
Periprocedural myocardial infarction	35	9				
Spontaneous myocardial infarction	108	119				
Death, myocardial infarction, and ACS	294	288	1.05 (0.90–1.24)	0.52	27.6	27.0
Stroke	22	14	1.56 (0.80–3.04)	0.19	2.1	1.8
Revascularization (PCI or CABG)¶	228	348	0.60 (0.51–0.71)	<0.001	21.1	32.6

* ACS denotes acute coronary syndrome, PCI percutaneous coronary intervention, and CABG coronary-artery bypass grafting.
† The hazard ratio is for the PCI group as compared with the medical-therapy group, and P values were calculated by the log-rank test and are unadjusted for multiple variables.
‡ The definition of myocardial infarction was the finding of new Q waves at any time; a spontaneous creatine kinase MB fraction of at least 1.5 times the upper limit of normal or a troponin T or I level of at least 2.0 times the upper limit of normal; during a PCI procedure, a creatine kinase MB fraction of at least 3 times the upper limit of normal or a troponin T or I level of at least 5.0 times the upper limit of normal, associated with new ischemic symptoms; and after CABG, a creatine kinase MB fraction or a troponin T or I level of at least 10.0 times the upper limit of normal. If periprocedural myocardial infarction is excluded from the primary outcome, the hazard ratio is 0.90 (95% CI, 0.73 to 1.10; P=0.29).
§ Some patients had a nonfatal myocardial infarction before their subsequent death so that the number of deaths overall is greater than the number of deaths in the primary outcome analysis, which includes the time until the first event.
¶ Values exclude the initial PCI procedure in patients who were originally assigned to the PCI group.

myocardial infarction or reduce major cardiovascular events, as compared with optimal medical therapy alone, during follow-up of 2.5 to 7.0 years, despite a high baseline prevalence of clinical coexisting illnesses, objective evidence of ischemia, and extensive coronary artery disease as seen on angiography. Although the degree of angina relief was significantly higher in the PCI group than in the medical-therapy group, there was also substantial improvement in the medical-therapy group. All secondary outcomes and individual components of the primary outcome showed no significant differences between the study groups, nor was there a significant interaction between treatment effect and any prespecified subgroup variable. For the primary outcome, the 95% CI excludes a relative benefit of more than 13% in the PCI group. Thus, it is highly unlikely that we missed a prognostically important treatment benefit in favor of the initial PCI strategy.

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Prognostic value of peak and post-exercise treadmill exercise echocardiography in patients with known or suspected coronary artery disease

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Aims Although peak may have higher sensitivity than post-treadmill exercise echocardiography (EE) for the detection of coronary artery disease (CAD), its prognostic value remains unknown. We sought to assess the relative values of peak and post-EE for predicting outcome in patients with known/suspected CAD.

Methods and results We studied 2947 patients who underwent EE. Wall motion score index (WMSI) was evaluated at rest, peak, and post-exercise. Ischaemia was defined as the development of new or worsening wall motion abnormalities with exercise. Separate analyses for all-cause mortality and major cardiac events (MACE) were performed. Ischaemia developed in 544 patients (18.5%). Among them, ischaemia was detected only at peak exercise in 124 patients (23%), whereas 414 (76%) had ischaemia at peak plus post-exercise imaging and six patients (1%) had ischaemia only at post-exercise. During follow-up, 164 patients died. The 5-year mortality rate was 3.5% in patients without ischaemia, 15.3% in patients with peak ischaemia alone, and 14% in patients with post-exercise ischaemia ($P < 0.001$ normal vs. ischaemic groups). In the multivariate analysis, post-exercise WMSI was an independent predictor of MACE [hazard ratio (HR) 1.87, 95% confidence interval (CI) 1.09–2.19, $P = 0.02$]. Peak exercise WMSI was an independent predictor of MACE (HR 2.19, 95% CI 1.30–3.69, $P = 0.003$) and mortality (HR 1.58, 95% CI 1.07–2.35, $P = 0.02$). The addition of peak EE results to clinical, resting echocardiography, exercise variables, and post-EE provided incremental prognostic information for MACE ($P = 0.04$) and mortality ($P = 0.04$).

Conclusion Peak treadmill EE provides significant incremental information over post-EE for predicting outcome in patients with known or suspected CAD.

Keywords Exercise testing • Exercise echocardiography • Prognosis

Introduction

Exercise echocardiography (EE) is a recognized method for diagnosis and risk stratification of patients with known or suspected coronary artery disease (CAD).[1–10] Its accuracy and prognostic value are similar to those of nuclear myocardial perfusion imaging.[9–10] Nevertheless, as the cost is lower and safety is higher, an expansion of this method is likely expected. Exercise echocardiography should be the first choice for patients referred to stress echocardiography who are able to exercise,[11–12] and within the EE modalities, treadmill EE is widely used. However, one of the pitfalls of this latter technique, when compared with pharmacological stress echocardiography or semi-supine bicycle, is that images are not acquired at peak exercise. This may lead to underestimation of the ischaemic burden, as heart rate and blood pressure can rapidly recover after cessation of exercise,[13] particularly in young patients and patients under the effect of beta-blockers or other drugs. In fact, current guidelines state that imaging at peak exercise is not feasible with treadmill.[11–12] Nevertheless, our group has demonstrated that peak treadmill EE is feasible and

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has higher sensitivity and accuracy than post-exercise treadmill imaging.[14–16] However, the prognostic value of this method has not been evaluated. In particular, it is unknown whether ischaemia limited to peak exercise has the same prognostic significance as ischaemia detected at both peak and post-exercise imaging. Also it is unknown whether the prognostic information offered by peak imaging enhances that of post-EE. Therefore, the aim of this study was to assess whether peak treadmill EE increases the value of the traditionally performed post-treadmill EE to predict mortality and major adverse cardiac events (MACE) in patients with confirmed or suspected CAD.

Methods

Patients

A total of 3000 consecutive patients with a first treadmill EE performed at our institution between 1 August 2002 and 15 September 2006 were considered for inclusion. Patients were included if they had a complete EE study available, including peak and post-exercise images; in addition, post-exercise images had to be acquired within 40 s after the end of exercise. Of the 3000 patients, 53 (1.8%) were excluded: 14 because peak imaging was unfeasible due to premature cessation of exercise or technical problems and five because the complete post-exercise study was not acquired within the first 40 s of the end of the exercise. In addition, 34 patients referred for evaluation of valvular disease or cardiomyopathies were also excluded. Therefore, the final patient's group was made up of 2947 patients. All of them gave informed consent before testing.

Main reasons for referring these patients to EE included chest pain in 2178 patients (73.9%), functional evaluation after myocardial infarction and/or revascularization procedures in 554 patients (18.8%), functional assessment of known coronary lesions in 58 patients (2%), previous non-diagnostic ECG exercise testing in 79 patients (2.7%), and other reasons in 78 patients (2.6%).

Whenever possible, beta-blocker therapy was discontinued for at least 48 h before testing. However, 6.6% of the patients were still under the influence of beta-blocker drugs at the time of their tests.

Exercise treadmill testing

Heart rate, blood pressure, and a 12-lead electrocardiogram were obtained at baseline and at each stage of the exercise protocol. Patients were encouraged to perform a treadmill exercise test (Bruce protocol 86.6%, modified Bruce 4.2%, modified Bruce for sportive people 8.6%, Naughton 0.6%), until they reached an endpoint. Exercise endpoints included physical exhaustion, significant arrhythmia, severe hypertension (systolic blood pressure $>$240 mmHg or diastolic blood pressure $>$110 mmHg), or severe hypotensive response (decrease $>$20 mmHg in systolic blood pressure from baseline). Ischaemic ECG abnormalities during the test were defined as the development of ST-segment deviation of $\geq$1 mm which was horizontal or sloping away from the isoelectric line 80 ms after the J point, in patients with normal baseline ST-segment. The resting ECG was considered non-diagnostic in the presence of left bundle branch block, pre-excitation, paced rhythm, repolarization abnormalities, or treatment with digoxin.

Exercise echocardiography and echocardiographic analysis

Two-dimensional echocardiography was performed in three apical views (long-axis, four-chambers, and two-chambers) and two parasternal views (long-axis and short-axis) at baseline, peak exercise,[14–16] and in the immediate post-exercise period. Peak and post-exercise images were obtained using a continuous imaging capture system, the former with the patient still exercising, the second lying in the table. Peak imaging was performed, when signs of exhaustion were present or an endpoint was achieved. If necessary, patients were asked to walk quickly rather than run, to decrease body and respiratory movements. The transducer was firmly positioned on the apical and parasternal area by applying slight pressure to the patient's back with the left hand, so maintaining the patient between the transducer and the left hand, to avoid movement. Imaging acquisition was performed online and stored on an optical disk. The images corresponding to each view having the best quality at peak and at post-exercise were chosen for comparison with rest images.

Echocardiographic two-dimensional analysis was performed on a digital quadscreen display system. Regional wall motion was evaluated with a 16-segment model of the left ventricle.[17] Each segment was graded on a four-point scale, with normal wall motion scoring = 1, hypokinetic = 2, akinetic = 3, and dyskinetic = 4. However, isolated hypokinesia of the infero-basal or septal basal segment were not considered abnormal, except when an adjacent segment was also abnormal.[18] Wall motion score index (WMSI) was calculated at rest, peak, and post-exercise as the sum of the scores divided by the number of segments. The changes in WMSI (ΔWMSI) from rest to peak exercise, from rest to post-exercise, and from peak to post-exercise (ΔWMSI Pk–Post) were also calculated. Left ventricular ejection fraction (LVEF) at rest, peak, and post-exercise was also visually estimated.[19] Reading of resting and peak images and reading of resting and post-exercise images were performed in separate days by two observers; in case of disagreement a third observer was required.

Ischaemia was defined as the development of new or worsening wall motion abnormalities (WMA) with exercise (i.e. ΔWMSI $>$ 0). The entire information about the clinical, ECG, haemodynamic, and echocardiographic response to exercise was provided to the clinicians in charge of the patients, with the exception of the specific time at which ischaemia was detected (peak, post-exercise, or both).

Patients with poor imaging quality were not excluded. The percentage of patients in whom $\leq$14 segments could be assessed was 3% at rest, 6.5% at peak exercise, and 6% at post-exercise.

Follow-up and endpoints

Follow-up was obtained by review of hospital databases, medical records, and death certificates, as well as by telephone interviews when necessary.

Endpoints were all-cause mortality and MACE, i.e. cardiac death and non-fatal myocardial infarction. Cardiac death was defined as death due to acute myocardial infarction, congestive heart failure, life-threatening arrhythmias, or cardiac arrest; unexpected, otherwise unexplained sudden death was also considered cardiac death. Myocardial infarction was defined as the appearance of new symptoms of myocardial ischaemia or ischaemic ECG changes accompanied by increases in markers of myocardial necrosis. Revascularization procedures during follow-up were collected, although they were not considered events as EE results might have influenced patient management.

Statistical analysis

Categorical variables were reported as percentages and comparison between groups based on the χ^2 test. Continuous variables were reported as mean $\pm$ standard deviation and differences were assessed with the unpaired *t*-test or Mann–Whitney *U* test as appropriate.

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CLINICAL RESEARCH **Clinical Trials**

The Medicine, Angioplasty, or Surgery Study (MASS-II): A Randomized, Controlled Clinical Trial of Three Therapeutic Strategies for Multivessel Coronary Artery Disease

One-Year Results

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OBJECTIVES We sought to evaluate the relative efficacies of three possible therapeutic strategies for patients with multivessel coronary artery disease (CAD), stable angina, and preserved ventricular function.

BACKGROUND Despite routine use of coronary artery bypass graft surgery (CABG) and percutaneous coronary intervention (PCI), there is no conclusive evidence that either one is superior to medical therapy (MT) alone for the treatment of multivessel CAD.

METHODS The primary end point was defined as cardiac mortality, Q-wave myocardial infarction (MI), or refractory angina requiring revascularization. All data were analyzed according to the intention-to-treat principle.

RESULTS A total of 611 patients were randomly assigned to either a CABG (n = 203), PCI (n = 205), or MT (n = 203) group. The one-year survival rates were 96.0% for CABG, 95.6% for PCI, and 98.5% for MT. The rates for one-year survival free of Q-wave MI were 98% for CABG, 92% for PCI, and 97% for MT. After one-year follow-up, 8.3% of MT patients and 13.3% of PCI patients underwent to additional interventions, compared with only 0.5% of CABG patients. At one-year follow-up, 88% of the patients in the CABG group, 79% in the PCI group, and 46% in the MT group were free of angina ($p < 0.0001$).

CONCLUSIONS Medical therapy for multivessel CAD was associated with a lower incidence of short-term events and a reduced need for additional revascularization, compared with PCI. In addition, CABG was superior to MT for eliminating anginal symptoms. All three therapeutic regimens yielded relatively low rates of cardiac-related deaths. (J Am Coll Cardiol 2004;43:1743–51)

The most appropriate treatment for patients with multivessel stable coronary artery disease (CAD) remains unknown. There is no recent evaluation of medical therapy (MT) versus surgical therapy in the modern era of pharmacologic treatment, since novel surgical techniques have been performed. Furthermore, the use of percutaneous coronary intervention (PCI) is increasing more rapidly than surgery, despite a lack of evidence regarding its superiority to either MT or surgical approaches.

See page 1752

Medical therapy for patients with multivessel CAD has changed considerably in recent years. Current therapeutic strategies, including aggressive modification of risk factors and intermittent use of nitrates, beta-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, and more recently, 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors, have improved the outcomes of patients with CAD (1,2). Nonetheless, the rate of major cardiovascular events is considerable in medically treated patients, particularly those with multivessel disease (3).

For patients with multivessel disease, the benefits of coronary artery bypass graft surgery (CABG) are well documented with respect to symptoms and, in some groups, mortality and morbidity (4–6). Refinements in PCI have improved the treatment of patients with CAD (7,8). However, the rapidly expanding use of PCI is based on a perceived benefit in comparison with the use of CABG or MT, but these perceptions are from selected subsets of patients (9). In fact, no study has demonstrated a mortality benefit over MT in patients with stable CAD (10).

The specific question of whether PCI or surgical treatment offers any advantage over MT in patients with stable

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5. Cutlip-UptoDate (truncated)

http://www.uptodate.com/contents/bypass-surgery-versus-percutaneous-intervention-in-the-management-of-stable-angina-pectoris-clinical-studies

Bypass surgery versus percutaneous intervention in the management of stable angina pectoris: Recommendations

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Section Editors: DO Williams, Gabriel S Aldea,
Deputy Editor: Gordon M Saperia.

INTRODUCTION — The treatment of atherosclerotic coronary artery disease (CAD) has evolved significantly due in part to advances in revascularization with both percutaneous coronary intervention (PCI) and coronary artery bypass graft surgery (CABG).

Among patients with stable angina, the goals of medical therapy, PCI, and CABG are to delay or prevent the complications of coronary disease in an effort to prolong life, decrease cardiac morbidity, and alleviate symptoms. Patient age, left ventricular function, and the severity of atherosclerosis and symptoms frequently affect the outcome and can influence the choice of a particular management strategy.

The recommended approach to choosing between bypass surgery and PCI in patients with stable angina pectoris who are candidates for intervention will be reviewed here. The major clinical trials that provide the evidence to support the recommendations, and recommendations for revascularization in patients with acute coronary syndromes are discussed separately. (See "Bypass surgery versus percutaneous intervention in the management of stable angina pectoris: Clinical trials" and "Selecting a reperfusion strategy for acute ST elevation myocardial infarction" and "Coronary arteriography and revascularization for unstable angina or non-ST elevation acute myocardial infarction".)

Regardless of which method of revascularization is used, aggressive risk-factor modification is necessarily in all patients.

INDICATIONS FOR REVASCULARIZATION — The decision to proceed with revascularization, as opposed to continuing medical therapy, is made in three groups of stable patients:

- Patients with activity-limiting symptoms despite maximum medical therapy
- Active patients who want PCI for improved quality of life compared to medical therapy, such as those who are not tolerating medical therapy well, or who want to increase their activity level.
- Patients with anatomy for which revascularization has a proven survival benefit such as significant left main coronary artery disease (greater than 50 percent luminal narrowing) or multivessel coronary artery disease (CAD) with a reduction left ventricular ejection fraction and a large area of potentially ischemic myocardium.

The supportive data are presented separately. (See "Medical versus interventional therapy in the management of stable angina pectoris".)

CABG VERSUS PCI — The choice of CABG versus PCI is dependent upon a number of factors, including the location and number of vessels involved, and the anatomic complexity of the lesions requiring revascularization [1-5]:

- PCI with drug-eluting stents has been preferred in patients with one or two vessel disease
- CABG has been preferred when there is a large amount of myocardium at risk, as with unprotected (no patent distal bypass grafts) left main coronary disease, intermediate-high SYNTAX scores and diffuse three-vessel coronary disease, particularly in patients with diabetes.

Primary Care Management of Chronic Stable Angina and Asymptomatic Suspected or Known Coronary Artery Disease: A Clinical Practice Guideline from the American College of Physicians

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In 1999, the American College of Physicians (ACP), then the American College of Physicians–American Society of Internal Medicine, and the American College of Cardiology/American Heart Association (ACC/AHA) developed joint guidelines on the management of patients with chronic stable angina. The ACC/AHA then published an updated guideline in 2002, which ACP recognized as a scientifically valid review of the evidence and background paper. This ACP guideline summarizes the recommendations of the 2002 ACC/AHA updated guideline and underscores the recommendations most likely to be important to physicians seeing patients in the primary care setting. This guideline is the second of 2 that provide guidance on the management of patients with chronic stable angina. This document covers treatment and follow-up of symptomatic patients who have not had an acute myocardial infarction or revascularization procedure in the previous 6 months. Sections addressing asymptomatic patients are also included. *Asymptomatic* refers to patients with known or suspected coronary disease based on a history or electrocardiographic evidence of previous myocardial infarction, coronary angiography, or abnormal results on noninvasive tests. A previous guideline covered diagnosis and risk stratification for symptomatic patients who have not had an acute myocardial infarction or revascularization procedure in the previous 6 months and asymptomatic patients with known or suspected coronary disease based on a history or electrocardiographic evidence of previous myocardial infarction, coronary angiography, or abnormal results on noninvasive tests.

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For author affiliations, see end of text.

In 1999, the American College of Physicians (ACP), then the American College of Physicians–American Society of Internal Medicine, and the American College of Cardiology/American Heart Association (ACC/AHA) developed joint guidelines on the management of patients with chronic stable angina (1). The ACC/AHA published an updated guideline in 2002 (2), which ACP recognized as a scientifically valid, high-quality review of the evidence and background paper. This ACP guideline summarizes the recommendations of the 2002 ACC/AHA updated guideline and underscores the recommendations most likely to be important to physicians seeing patients in the primary care setting. For more in-depth analysis and details, readers should refer to the full-text guideline at www.acc.org/clinical/guidelines/stable/stable.pdf. This guideline is the second ACP guideline on the management of patients with chronic stable angina. The first ACP guideline covered diagnosis and risk stratification (3). For guidance on revascularization, readers should refer to the 2002 ACC/AHA guidelines on chronic stable angina (2) and unstable angina (4).

This document covers treatment and follow-up for symptomatic patients who have not had an acute myocardial infarction (MI) or revascularization procedure in the previous 6 months. Sections also address asymptomatic patients with known or suspected coronary disease based on electrocardiographic evidence of previous MI, coronary angiography, or abnormal results on noninvasive tests. This in no way constitutes an endorsement of noninvasive testing in asymptomatic patients for the purposes of "screening" but rather acknowledges the clinical reality that patients often present after having undergone such an evaluation. Although this guideline covers pharmacologic therapy, physicians should always recommend lifestyle modifications, such as smoking cessation, appropriate diet, and exercise, to patients.

The target audience for this guideline is all clinicians who manage patients with chronic stable angina. The target patient population is patients without known coronary disease whose symptoms suggest chronic stable angina, patients who present with known chronic stable angina, and asymptomatic patients with evidence suggesting coronary disease on previous testing. This guideline does not apply to patients with unstable angina because they have a high to moderate short-term risk for an acute coronary event.

*This paper, written by Vincenza Snow, MD; Patricia Barry, MD, MPH; Stephan D. Fihn, MD, MPH; Raymond J. Gibbons, MD; Douglas K. Owens, MD; Sankey V. Williams, MD; Christel Mottur-Pilson, PhD; and Kevin B. Weiss, MD, MPH, for the American College of Physicians/American College of Cardiology Chronic Stable Angina Panel, was developed for the Clinical Efficacy Assessment Subcommittee of the American College of Physicians (ACP): Kevin B. Weiss, MD, MPH (*Chair*); Mark Aronson, MD; Patricia Barry, MD, MPH; Donald E. Casey Jr., MD, MPH, MBA; Thomas Cross Jr., MD, MPH; Nick Fitterman, MD; E. Rodney Hornbake, MD; Douglas K. Owens, MD; and Katherine D. Sherif, MD. Approved by the ACP Board of Regents in April 2004.

Methods

The ACP has traditionally developed evidence-based guidelines. The ACP bases guideline recommendations on the results of systematic reviews of high-quality evidence (several well-designed randomized, controlled trials) and meta-analyses where appropriate. Without good evidence from randomized trials, the ACP will not make recommendations but will underscore practices that are not supported by evidence. Since this document is based on the ACC/AHA guidelines, the College has maintained the levels of evidence as designated by the ACC/AHA in the recommendation statements: A level A recommendation is based on evidence from several randomized clinical trials with large numbers of patients; a level B recommendation is based on evidence from a limited number of randomized trials with small numbers of patients, careful analyses of nonrandomized studies, or observational registries; and a level C recommendation is based on expert consensus.

Pharmacologic Therapy

Overview of Treatment

The treatment of stable angina has 2 major purposes. The first is to prevent MI and death and thereby increase the length of life. The second is to reduce symptoms of angina and occurrence of ischemia, which should improve quality of life. Therapy directed toward preventing death has the highest priority. When 2 different therapeutic strategies are equally effective in alleviating symptoms of angina, the therapy with an advantage in preventing death should be recommended. Patient education, cost-effectiveness, and patient preferences are important components in this decision-making process. This section on pharmacologic therapy considers treatments to prevent MI and death first, then antianginal and anti-ischemic therapy to alleviate symptoms, reduce ischemia, and improve quality of life.

Antiplatelet Medications

Aspirin (75 to 325 mg daily) should be used routinely in all patients with acute and chronic ischemic heart disease with or without manifest symptoms and without contraindications. A meta-analysis of more than 200 trials showed that the reduction in vascular events was similar for dosages of 75 to 150 mg daily and 160 to 325 mg daily; however, daily doses less than 75 mg had less benefit (5–9). In a randomized trial that compared clopidogrel with aspirin in patients with previous MI, stroke, or symptomatic peripheral vascular disease (that is, those at risk for ischemic events), clopidogrel appeared to be slightly more effective than aspirin in decreasing the combined risk for MI, vascular death, or ischemic stroke (10). However, no further studies have confirmed the efficacy of clopidogrel in patients with stable angina; thus, clopidogrel is best reserved for patients who cannot take aspirin. Dipyridamole exerts vasodilatory effects on coronary resistance vessels and also has antithrombotic effects. However, the usual oral doses of dipyridamole can enhance exercise-induced myocardial ischemia in patients with stable angina (11). Therefore it should not be used as an antiplatelet agent.

β-Blockers

β-Blockers also reduce cardiac events when used as secondary prevention in postinfarction patients and reduce mortality and morbidity among patients with hypertension. On the basis of their potentially beneficial effects on morbidity and mortality, β-blockers should be strongly considered as initial therapy for chronic stable angina. They seem to be underused (12). Diabetes mellitus is not a contraindication to their use, and diabetic patients seem to benefit as much as or more than patients without diabetes.

Lipid-Lowering Agents

Many recent clinical trials, notably the Heart Protection Study (HPS) (13) and the Cholesterol and Recurrent Events (CARE) study (14), have documented that low-density lipoprotein cholesterol–lowering agents can decrease the risk for adverse ischemic events in patients with established coronary artery disease (CAD) (13–16). These clinical trials indicate that in patients with established CAD, including chronic stable angina, lipid-lowering therapy with a statin should be recommended even in the presence of mild to moderate elevations of low-density lipoprotein cholesterol levels.

Angiotensin-Converting Enzyme Inhibitors

Recently, several trials have proven that angiotensin-converting enzyme (ACE) inhibitors reduce cardiovascular death, MI, and stroke in patients who were at risk for or who had vascular disease (without heart failure). In the Heart Outcomes Prevention Evaluation (HOPE) study (17), the ACE inhibitor ramipril (10 mg/d) reduced cardiovascular death, MI, and stroke in patients who were at high risk for or who had vascular disease without heart failure. Furthermore, only a small part of the benefit could be attributed to a reduction in blood pressure (decrease of 2 to 3 mm Hg). The European trial on reduction of cardiac events with perindopril in stable CAD (called the EUROPA study [18]) enrolled a group of patients similar to the HOPE participants but also included those with positive stress test results. Patients with heart failure and diabetes were excluded. This study showed that an ACE inhibitor can have a vasculoprotective effect in patients at lower risk than those enrolled in the HOPE study. Whether this is a class effect is a subject of continuing controversy but can be argued on the basis of additional positive studies with enalapril (19, 20) and captopril (21). Moreover, using ACE inhibitors for secondary prevention in patients with diabetes and CAD seems to be particularly beneficial. Currently, evidence for the use of angiotensin-receptor blockers in chronic stable angina is insufficient.

7. Robertson2010 (truncated)

Treatment Options for Angina

Interventional Cardiology Perspective

Michael A. Robertson, M.D.

10/30/10

Community Heart and Vascular

THE COURAGE TRIAL

- Enrolled 2287 patients with stable angina
  - 80% had CCS Class 0, 1, or II symptoms
  - Only 20% had CCS Class III symptoms
  - EF 60%.

- Randomization occurred **AFTER** coronary angiography
  - Stenosis of at least 70% in at least one proximal epicardial coronary artery and objective evidence of myocardial ischemia
  - Stenosis of at least 80% and classic angina without provocative testing
  - Approximately 30% had proximal LAD disease
  - Approximately 40% had two vessel CADdz
  - Approximately 30% had three vessel CADdz

Boden et al. NEJM; 356; 15; 1503-1516

The Prevalence Of Angina Biology Essay

The prevalence of angina according to Rose angina questionnaire increases from in women, respectively 2-5 in men aged 45-54, to 10-15 in women, respectively 10-20% in men aged 65-74. Untreated coronary heart disease results in progressive angina, myocardial infarction (MI), left ventricular dysfunction, and death. Therefore, the treatment of stable angina has two major purposes: to prevent MI and death (improvement in survival); to alleviate the symptoms of angina (improvement in quality of life). Before treatment, every patient with angina requires risk stratification using clinical evaluation, stress testing, and echocardiography. Then patients with high-risk at non-invasive tests require coronary arteriography. According to current guidelines, certain categories of patients require myocardial revascularization to improve prognosis: those with left main (LM) stenosis > 50%, proximal left anterior descending artery (pLAD) stenosis >50%, 2 or 3-vessel disease with impaired left ventricular (LV) function, proven large area of ischemia (>10% left ventricul), or single remaining pattent vessel > 50% stenosis. Recommendations for the treatment of stable angina were largely based upon older clinical trials comparing interventional to medical therapy and percutaneous coronary intervention (PCI) to coronary artery bypass grafting (CABG). There are, however, a number of important limitations concerning the applicability of these results to current clinical practice: no widespread use of modern medical treatment (MT) and intensive risk factor modification; no long term use of dual antiplatelet therapy after stenting; saphenous vein graft use was prevalent to internal mammary in surgical revascularizations. In our study, all patients received modern MT and most could benefit from drug-eluting stents and internal mammary artery grafting. Given the above, we sought to asses the value of these three

different therapeutic approaches in patients with stable coronary artery disease and high-risk for cardiovascular events. This study included 115 patients with Canadian Cardiovascular Society (CCS) class II-IV stable angina and/or evidence of myocardial ischemia on the resting electrocardiogram (ECG) or during stress test. All patients un- derwent coronary arteriography at the Department of Interventional Cardiology of the Institute of Cardiovascular Disease and Transplantation, Tîrgu Mureş between January 1, 2006 and March 31, 2008. Demographic, clinical and echocardiographical data, as well as coronarography results, were entered in our database at the time of the procedures and at subsequent admissions. The inclusion criteria were: LM stenosis > 50%, pLAD stenosis > 50%, 2 or 3-vessel disease with left ventricular ejection fraction (LVEF) ≤ 45% and objective evidence of myocardial ischemia (angina or substantial changes in ST-segment depression or T-wave inversion on the resting ECG or inducible ischemia with exercise stress). Exclusion criteria included LVEF <30% and severe comorbidities that affect survival. Patients were divided into three groups, according to the therapeutic approach: surgical (CABG), interventional (PCI) and medical therapy (MT) alone. Of these, 39 underwent PCI, 44 underwent CABG, both subgroups with modern MT, and 32 received MT alone. All patients received optimal antiischemic therapy, including beta-blockers, calcium channel blockers, and nitrates, alone or in combination, along with angiotensin converting enzyme inhibitors (ACEI), as well as antiplatelet therapy with either aspirin or clopidogrel. Patients also received lipid-lowering therapy, including administration of a statin, and glycemic control in diabetics. Target level of low-density lipoprotein (LDL) was 100 mg/dl and was achieved in about one third of cases in each group. Physical exercise was recommended to achieve further improvements in the serum lipid profile. Percutaneous coronary revascularization was followed by dual antiplatelet therapy for a minimum of nine month. 41% of patients use them both indefinitely and the rest use aspirin alone indefinitely. 56.4% of patients received drug eluting stents. CABG has been the preferred approach in patients with left main coronary disease and diffuse three-vessel coronary disease, particularly in patients with diabetes. The internal mammary artery was used to bypass the LM and LAD. Follow-up period was 4 years. Data were obtained by review of hospital databasis, subsequent admissions, ambulatory evaluations, as well as by telephone interviews. Primary end points were cardiac death and non fatal myocardial infarction. Cardiac death was defined as death due to acute

myocardial infarction, congestive heart failure, life-threatening arrhythmias, or cardiac arrest; unexpected, otherwise-unexplained sudden death was also considered cardiac death. Myocardial infarction was defined as the appearance of new symptoms of myocardial ischemia or ischemic ECG changes accompanied by increases in markers of myocardial necrosis. Secondary end points were the quality of life and persistent disabling angina (CCS class III-IV angina), as well as the need for repeated revascularization. Categorical variables were compared by use of the chi-square test and continuous variables were compared by use of the ANOVA test. A level of significance of less than 0.05 was used for all subgroup analyses and interactions. Clinical, echocardiographic and angiographical characteristics of the patients are summarized in Table I. The average age was about 60 years, and most patients were men (> 80%). The widespread of comorbidities (diabetes, periferal artery disease, and stroke) was similar in the three groups, with a lower incidence of hypertension in the CABG group. Most patients with left ventricular dysfunction belong to medical group (50%), while just about a third of patients treated invasivelly had impaired left ventricular function. Patients treated with MT alone either had a coronary anatomy unsuitable for revascularization, or refused surgery. Of these, 19% had 3-vessel disease, 19% had LM disease, and 37% had pLAD disease. In PCI group, most of patients had pLAD disease (77%), and just 5% had 3-vessel disease respectively LM disease. In CABG group, 48% had LM disease and 40% had pLAD disease. There was not a statistically significant difference between the three groups regarding cardiac death (p=0.07), however we found a trend of increased mortality in the medical group (15.63% MT, 2.56% PCI, 4.54 CABG). The primary outcome (a composite of cardiac death and nonfatal myocardial infarction) occurred in 25% of patients in the medical group, 5.12% of patients in the PCI group, and 4.54% in the CABG group (p=0.006). There was no difference between the two methods of revascularization (p=1.00), while primary event rate was significantly increased in the medical group (25%, p=0.006). Repeated revascularization was required in both groups, but the difference is statistically significant in favor of CABG (2.27% vs 15.38%, p = 0.04). In the PCI group 50% of patients who required revascularization received drug eluting stents. At a median follow-up of 4 years, about 9% of patients in the CABG group, 20% in the PCI group and 50% in the medical group had disabling angina. There was no statistically significant difference between the PCI and CABG group (p = 0.21). Conservatively treated patients had high rates of disabling angina versus PCI (p=0.01) and versus CABG (p=0.0001). Left main disease. Of the 6 patients with LM disease in the medical group, there was one death, while the remaining 5 survived free of myocardial infarction and with only mild symptoms. The 2 patients with LM in the PCI group survived both, but one developed disabling angina and required surgical revascularization. Most patients with LM disease (21) were in the CABG group. Of these, after 4 years of follow-up, 19 survived free of myocardial infarction and disabling symptoms, and 2 died. Current European and American guidelines stress that there is a category of patients who benefit in terms of prognosis (cardiac death, nonfatal myocardial infarction) from myocardial revascularization. The highest recommendation goes to surgical revascularization, but sometimes PCI is an option too. We summarized these recommendations in Table IV. In our study we selected these very patients to assess their outcome depending on chosen therapy. Among the most important contemporary studies that address this topic are SYNTAX, MASS II, and BARI 2D. Earlier studies did not benefit from modern treatment strategies, therefore are not mentioned here. SYNTAX trial enrolled 1800 patients with 3-vessel disease and/or LM disease, randomly assigned for surgical revascularization or drug eluting stenting (DES). Patients amenable for only one treatment approach formed PCI and CABG registries. Last reports (september 2010) are from a 3-years follow-up. CABG offered no significant overall mortality benefits compared to the PCI group in the randomized arm (6.7% vs 8.6%, p = 0.13). Also, the incidence of death/nonfatal MI and stroke was similar in the two groups (14.1 vs 12.0, p = 0.21). The need for repeated revascularization was significantly higher for patients in the PCI group (19.7% vs 10.7%, p < 0.001). MASS II was a single-center study (Brazil) where 611 patients were randomly assigned to CABG, PCI or medical treatment alone. This study included a ten years follow-up (till august 2010) of patients with multivessel