SMH ST. MICHAEL'S HOSPITAL Cardiology
UNIVERSITY OF TORONTO
A REPORT BY THE DIVISION OF CARDIOLOGY
ST. MICHAEL'S HOSPITAL, UNIVERSITY OF TORONTO
Scientific Update™

Current Understanding of Pathophysiology and Treatment of Single Vessel Coronary Artery Disease

Originally presented by: BERNARD J. GERSH, MB, ChD, DPhiL, FRCP

American College of Cardiology 46th Annual Scientific Session
March 16-20, 1997, Anaheim, California

Reported and discussed by: **SHAUN GOODMAN, MD**

Previously, the majority of symptomatic patients with single-vessel coronary artery disease were treated with medical therapy, particularly in view of the results of randomized clinical trials comparing coronary artery bypass surgery with medical therapy. However, during the 1980's, the use of percutaneous transluminal coronary angioplasty (PTCA) arose as a third alternative. Although randomized trial data with long-term follow-up has been limited to date, PTCA has often been employed as the treatment of choice, particularly after a trial of medical therapy.

The Atherosclerotic Plaque

Atherosclerotic plaques typically consist of a lipid-rich core in the central portion of the eccentrically thickened intima (Fig. 1). The lipid core is bounded on its luminal aspect by a fibrous cap, at its edges by the "shoulder" region, and on its abluminal aspect by the base of the plaque. The central, lipid-rich core of the typical lesion contains many lipid-laden macrophage foam cells derived from blood monocytes. Once they reside within the arterial wall, these cells imbibe lipid, which accounts for their foamy cytoplasm. These foam cells can produce large amounts of tissue factor, a powerful coagulant that potently stimulates thrombus formation when in contact with blood.[1,2]

The integrity of the fibrous cap overlying this lipid-rich core fundamentally determines the stability of an atherosclerotic plaque. Rupture-prone plaques tend to have thin, friable, fibrous caps (Fig. 1a). Plaques not liable to precipitate acute myocardial events tend to have thicker fibrous caps to protect the blood compartment in the arterial lumen from contact with the underlying thrombogenic lipid core (Fig. 1b).

Figure 1a: The "Vulnerable" Atherosclerotic Plaque

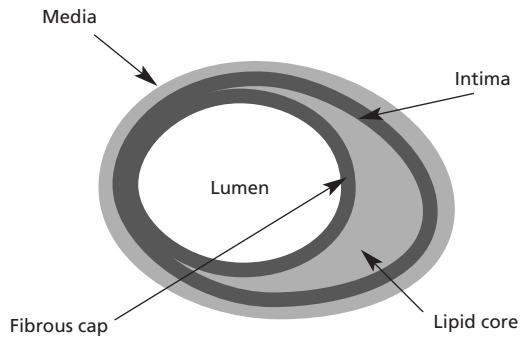
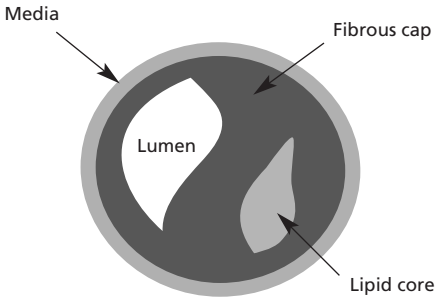


Figure 1b: The "Stable" Atherosclerotic Plaque



Adapted from Libby P[2]

St. Michael's Hospital
30 Bond St., Suite 701A
Toronto, Ontario M5B 1W8
Fax: (416) 864-5330

Severity of Coronary Artery Disease Prior to Myocardial Infarction

Serial angiographic studies indicate that the more obstructive a plaque is, the more frequently it progresses to coronary occlusion[3] and/or gives rise to myocardial infarction.[4,5] For example, in the Coronary Artery Surgery Study (CASS), 2,938 non-bypassed coronary segments were prospectively evaluated in 298 patients.[3] These segments were divided by the stenosis severity at baseline; <5% (n=2,161), 5-49% (n=430), 50-80% (n=258), and 81-95% (n=89) (Fig. 2a). During the 5-year follow-up period, those segments with the most severe stenosis (81-95%) became occluded 23.6% of the time; in contrast, those with less severe stenosis at baseline (e.g., 50-80%) occluded at a lower rate (10%). However, although an individual with severe stenosis became occluded more frequently than did an individual with less severe stenosis, the less obstructive plaques (<80% stenosis at baseline) gave rise to more total occlusions than did the severely obstructive plaques (52 vs. 21) because of their much greater number (Fig. 2a). Thus, coronary occlusion in myocardial infarction most frequently evolved from mild to moderate stenoses, as initially reported by Ambrose et al[6] and Little et al[7] and later confirmed by others.[4,5] This has given rise to the concept that less obstructive plaques are more lipid-rich and vulnerable to rupture than larger plaques. The smaller plaques, however, could be most dangerous just because of their greater number – they by far outnumber the severely obstructive plaques. Furthermore, the smaller rather than larger plaques are more likely to lead to acute clinical events in the case of abrupt occlusion, because they are less frequently associated with a protective collateral circulation.[8]

Treatment of Single Vessel Disease

Coronary bypass surgery versus medical therapy

Long-term outcome in patients with stable angina and single-vessel disease has been evaluated in trials in which patients were randomly assigned to coronary artery bypass surgery or medical treatment. Yusuf et al[9] combined seven such studies as part of the Coronary Artery Bypass Graft Surgery Trials Collaboration. Overall, 10% of patients in these seven trials had only one vessel involvement of >50% stenosis. Not surprisingly, mortality was lowest among this subgroup at 5 years, (9.9% vs. 11.7% for two vessel, 17.6% for three vessel, and 36.5% for left main disease) in the medically treated group. In contrast, those patients with single-vessel disease who underwent bypass surgery had a lower (but not statistically significant) mortality rate at 5 years [odds ratio (OR) 0.54, 95% confidence interval (CI) 0.22-1.33; p=0.18]. Of note, those with proximal left anterior descending (LAD) involvement tended to have an increased 5-year mortality rate in the medically treated patients (8.3% without LAD disease vs. 14.6% with proximal LAD involvement in those patients with one- or two-vessel disease). Among those patients with one- or two-vessel disease who had proximal LAD involvement, there was a statistically significant benefit at 5 years for bypass surgery over medical treatment (OR 0.58, 95% CI 0.34-1.0; p = 0.05).

At 10 years, those with one- or two-vessel disease assigned to the coronary artery bypass surgery, as compared to the medically treated arm, had a nonsignificant 1.8 (standard error ±3.0) months increase in survival. While these analyses suggest a modest 5-year benefit of bypass surgery over medical treatment in single-vessel disease, particularly among those with proximal LAD involvement, the longer term outcome (at 10 years) appears comparable between these two treatment options.

There are several limitations to these analyses, including the fact that: (1) approximately 40% of patients in the overall medically treated group crossed over to bypass surgery by 10 years (although most commonly among those in the more severe disease categories); (2) medical treatment in these studies would not be considered similar to that administered today (for example, much lower rates of beta-blocker, antiplatelet, and cholesterol-lowering drug use); and (3) percutaneous transluminal coronary angioplasty (PTCA) was introduced since these studies were performed.

Figure 2a

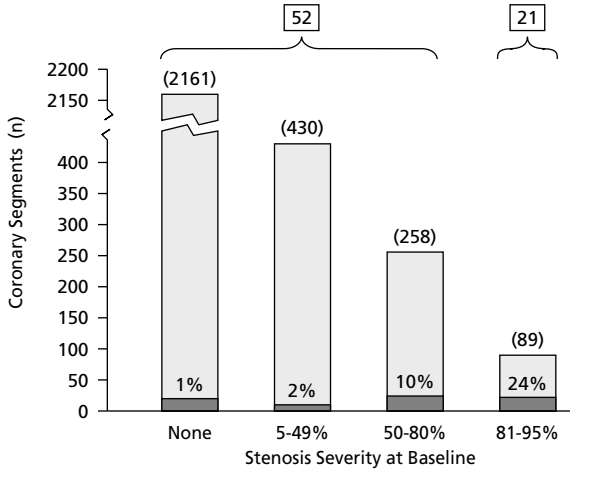
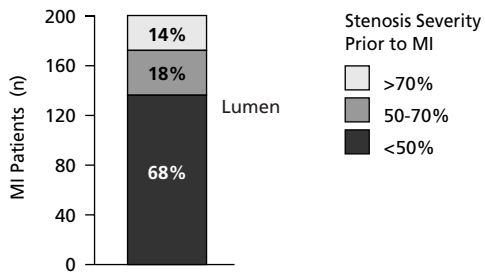


Figure 2b



Adapted from Falk et al[1]

Coronary angioplasty versus medical therapy

In 1992, Parisi et al[10] published the results of the only randomized clinical trial comparing PTCA to medical therapy in patients with single-vessel coronary disease and stable angina. Patients with 70-99% stenosis in the proximal two-thirds of one epicardial coronary artery and with exercise-induced myocardial ischemia were randomly assigned either to undergo PTCA (n=103) or receive medical therapy (n=107). PTCA was clinically successful in 80 of 100 patients who actually had the procedure, with an initial reduction in mean percent stenosis from 76 to 36%. Two patients in the PTCA group required emergency coronary artery bypass surgery. By 6 months after the procedure, 16 patients (16%) had undergone repeat PTCA. Myocardial infarction occurred in 5 patients assigned to PTCA and in 3 patients assigned to medical therapy. Only one death occurred in a patient assigned to the medical treatment group. At 6 months, 64% of the patients in the PTCA group were free of angina, as compared to 46% of the medically treated patients ($p<0.01$). The patients in the PTCA group were able to increase their total duration of exercise more than the medical patients (2.1 vs. 0.5 minutes, $p<0.0001$) and were able to exercise longer without angina on treadmill testing ($p<0.01$).

Two hundred and four of the 208 total patients underwent repeat coronary angiography at 6 months. In the medical-therapy group, the mean percent stenosis of the index lesions decreased from 77% at baseline to 75% at follow-up ($p=0.86$). The mean percent stenosis of the index lesions in the PTCA group decreased from 76% at baseline to 36% immediately after dilation, then increased to 54% at follow-up ($p<0.001$). A similar proportion of both groups had evidence of progression to 70% stenosis in other vessels on the 6-month coronary angiogram (10 of 98 patients in the medical-therapy group and 7 of 94 patients in the PTCA group, $p=0.05$).

The overall psychological well-being score improved by 8.6 for patients in the PTCA group and 2.4 for patients in the medical-therapy group ($p=0.03$). While an advantage for PTCA over medical therapy was evident in the subscores for general health and vitality ($p<0.05$), employment rates were not substantially changed at follow-up. The number of hospital days was greater for patients in the PTCA group, although patients assigned to PTCA had a mean decrease of 15 episodes of angina per month as compared with 7 fewer episodes per month for those assigned to medical therapy ($p=0.06$).

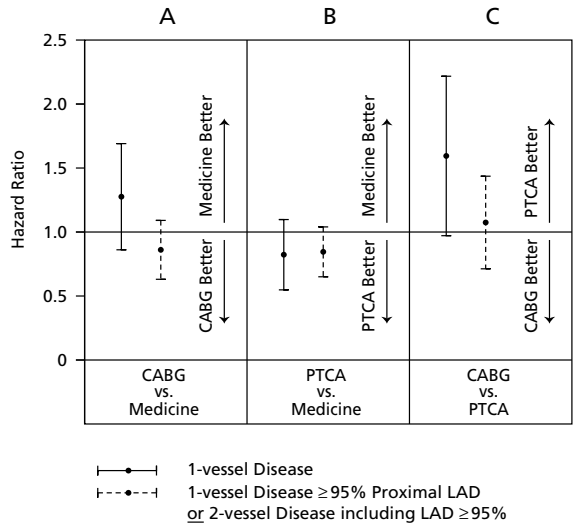
Thus, the ACME Investigators concluded that for patients with single-vessel disease, PTCA offers earlier and more complete relief of angina than medical therapy and is associated with better performance on the exercise test. However, PTCA initially costs more than medical treatment and is associated with a higher frequency of complications. Given the small sample size and short duration of follow-up, this trial was not powered to address differences between these treatment modalities in the prevention of death or myocardial infarction.

Coronary angioplasty versus coronary bypass versus medical therapy

Although no other randomized trials in single-vessel disease patients with stable angina have been performed, a large-scale, single-centre, prospective, observational treatment comparison of PTCA, bypass, and medicine was also published in 1994.[11] Patients with symptomatic coronary artery disease referred for cardiac catheterization to Duke University (1984-1990) without prior PTCA, bypass surgery, or significant (75%) left main disease were contacted up to 5 years later (97% follow-up). Of those initially treated medically (n=3,557), 43% had single-vessel disease; in contrast, 51% undergoing PTCA (n=2,626) and 6% of those undergoing bypass surgery (n=3,080) had single-vessel disease. Those with single-vessel disease involving the proximal LAD (stenosis 95%) were included with those with two-vessel disease, including 95% LAD stenosis (15%, 18%, and 15% in the medical-, PTCA-, and bypass surgery-treated groups). As this was not a randomized trial, it is not surprising that there were several other differences in baseline characteristics among the three treatment groups (e.g., PTCA patients had the best and medical patients had the worst left ventricular function). In both an unadjusted and adjusted (for differences in baseline characteristics) analysis, there was a very slight trend towards higher survival in patients with one-vessel disease treated with PTCA as compared to bypass surgery and medicine; however, this difference was small at the 5-year follow-up (adjusted 5-year survivals: PTCA 95%; bypass surgery 93%; medicine 94%).

Because the traditional classification of one-, two-, and three-vessel disease is not sufficiently detailed to reflect all of the important prognostic aspects of coronary anatomy, Mark et al[11] used a derived CAD index to calculate Cox model estimated hazard or mortality ratios for pairs of treatments against several different levels of coronary disease severity. In the least severe categories of CAD (e.g., one-vessel disease), there was a trend favouring medicine over bypass surgery; however, bypass surgery appeared somewhat better than medical treatment in patients with one-vessel disease of 95% proximal LAD or two-vessel disease with 95% LAD involvement (Fig. 3, panel A). When comparing PTCA to medical treatment, there was a trend for PTCA to reduce mortality by approximately 20% in both patients with one-vessel disease and those with one-vessel disease and 95% proximal LAD disease (Fig. 3, panel B). Finally, there was a trend for PTCA to reduce mortality relative to bypass surgery in patients with one-vessel disease; these two treatment strategies appeared equivalent in patients with proximal LAD disease alone or two-vessel disease including LAD involvement of 95% (Fig. 3, panel C). However, none of these trends was statistically significant since, in every case, the confidence limits crossed the 1.0 hazard ratio line of identity. It is important to note that this analysis compares treatment strategies rather than the "pure effects" of the treatments. For example, 18% of all patients who underwent PTCA required crossover to bypass surgery in addition to the frequent need for repeat PTCA to treat restenosis.

Figure 3



Adapted from Mark et al[11]

Summary

The limited but best available evidence to date suggests that an initial strategy of medical therapy for patients with single-vessel disease and stable angina is warranted. As there is no clear survival improvement in this group of patients with revascularization (PTCA or bypass surgery) and in view of the apparent inability to predict which "culprit" stenosis will ultimately lead to myocardial infarction and/or death, the main indication for revascularization in patients with single-vessel coronary disease is to alleviate symptoms refractory to medical therapy.

Of note in this regard are the American Heart Association/American College of Cardiology published guidelines for the use of coronary angioplasty.[12] For example, in patients with stable angina, the guidelines state that for angioplasty to be performed, there must be "objective evidence of myocardial ischemia while on medical therapy during laboratory testing".[12] However, analysis of recent coronary angioplasty practice in the United States suggests that such guidelines have *not* been adopted. For example, among 2,201 patients who underwent PTCA during 1988-1989 in the U.S., 2,117 (96%) underwent single-vessel PTCA and only 29% of these patients had undergone an antecedent stress test within three months of the procedure. This finding demonstrates the practice of performing angioplasty primarily on the basis of coronary anatomic findings. However, a single angiographic examination of stenosis severity does not reliably identify lesions which will lead to future clinical events. Therefore, therapy in single-vessel disease needs to be individualized and based on patients' lifestyle and ability to tolerate medical therapy and the severity of their symptoms. An intrinsic aspect of such a policy is meticulous attention to risk factor modification with its attendant benefits on progression of coronary disease, plaque stabilization, and subsequent clinical events.

References

1. Falk E, Shah PK, Fuster V. Coronary plaque disruption. *Circulation* 1995;92:657-71.
2. Libby P. Molecular bases of the acute coronary syndromes. *Circulation* 1995;91:2844-50.
3. Alderman EL, Corley SD, Fisher LD, Chaitman BR, Faxon DP, Foster ED, Killip T, Sosa JA, Bourassa MG, CASS participating investigators and staff. Five-year angiographic follow-up of factors associated with progression of coronary artery disease in the Coronary Artery Surgery Study (CASS). *J Am Coll Cardiol* 1993;22:1141-54.
4. Nobuyoshi M, Tanaka M, Nosaka H, Kimura T, Yokoi H, Hamasaki N, Kim K, Shindo T, Kimura K. Progression of coronary atherosclerosis: is coronary spasm related to progression? *J Am Coll Cardiol* 1991;18:904-10.
5. Giroud D, Li JM, Urban P, Meier B, Rutishauser W. Relation of the site of acute myocardial infarction to the most severe coronary arterial stenosis at prior angiography. *Am J Cardiol* 1992;69:729-32.
6. Ambrose JA, Tannenbaum MA, Alexopoulos D, Hjemdahl-Monsen CE, Leavy J, Weiss M, Borrico S, Gorlin R, Fuster V. Angiographic progression of coronary artery disease and the development of myocardial infarction. *J Am Coll Cardiol* 1988;12:56-62.
7. Little WC, Constantinescu M, Applegate RJ, Jutcher MA, Burrows MT, Kahl FR, Santamore WP. Can coronary angiography predict the site of a subsequent myocardial infarction in patients with mild-to-moderate coronary artery disease? *Circulation* 1988;78:1157-66.
8. Danchin N. Is myocardial revascularization for tight coronary stenoses always necessary? *Lancet* 1993;342:224-5.
9. Yusuf S, Zucker D, Peduzzi P, et al. Effect of coronary artery bypass graft surgery on survival: overview of 10-year results from randomised trials by the Coronary Artery Bypass Graft Surgery Trialists Collaboration. *Lancet* 1994;344:563-70.
10. Parisi AF, Folland ED, Hartigan P, on behalf of the Veterans Affairs ACME investigators. A comparison of angioplasty with medical therapy in the treatment of single-vessel coronary artery disease. *N Eng J Med* 1992;326:10-16.
11. Mark DB, Nelson CL, Califf RM, et al. Continuing evolution of therapy for coronary artery disease. Initial results from the era of coronary angioplasty. *Circulation* 1994;89:2015-25.
12. ACC/AHA Task Force Report. Guidelines for percutaneous transluminal coronary angioplasty: a report of the American College of Cardiology/American Heart Association Task Force on Assessment of Diagnostic and Therapeutic Cardiovascular Procedures (Subcommittee on Percutaneous Transluminal Coronary Angioplasty). *J Am Coll Cardiol* 1988;12:529-45.