CORONARY ARTERY BYPASS SURGERY, 1993:
RISKS AND BENEFITS, REALISTIC AND UNREALISTIC EXPECTATIONS

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OUTLINE

I. CASE PRESENTATION

A.G. first presented to PMH at age 60 with exertional angina. He had worked for 30 years as a carpenter. An exercise tolerance test was consistent with ischemia at a moderate workload, and he was placed on diltiazem, 360 mg/day, and isosorbide dinitrate, 30 mg/day. Despite this, he continued to have limiting angina, and, therefore, he was referred for coronary angiography. It revealed 3 vessel coronary artery disease and a left ventricular ejection fraction of 0.65. He was referred for elective CABG.

His CABG was performed without incident. An internal mammary graft was placed in his left anterior descending, and saphenous vein grafts were placed in his posterior descending artery and a large obtuse marginal branch of the circumflex. He sustained a perioperative inferior Q wave infarction on the third postoperative day. He was discharged home on postoperative day # 10, on aspirin and dipyridamole. His convalescence at home proceeded normally. Although he felt well within 3 months of CABG, he decided not to return to work, but rather to retire.

He was angina-free for 10 years. At age 70, however, he began to have limiting angina, which worsened over several months despite the reinitiation of adequate medical therapy. Repeat coronary angiography revealed that his internal mammary graft was patent, but both saphenous vein grafts were occluded. His ejection fraction was 0.47. A repeat CABG was recommended. It was technically difficult, due to extensive scarring of the previously opened pericardium. As a result, the operation was lengthy, with considerable blood loss. He died with persistent low cardiac output 2 hours after being transferred from the Operating Room to the Intensive Care Unit.

As we shall discover over the next hour, this patient serves to highlight many of the classic events in patients who undergo coronary artery bypass grafting: (a) he obtained complete relief of his angina with his first CABG; (b) he sustained a perioperative myocardial infarction; (c) despite becoming pain-free with his initial operation, he decided to retire early and not to return to work; (d) he was angina-free for 10 years, when he developed recurrent limiting angina; (e) repeat angiography revealed that his mammary graft was patent, but his saphenous vein grafts were occluded; and (f) a repeat CABG was technically difficult and resulted in his death.

II. INTRODUCTION

Since its introduction by Favaloro et al in 1969 [1], coronary artery bypass grafting (CABG) has become the most completely studied operation in the history of medicine. Over the past 25 years, it has been performed in millions of patients, both here and abroad. Major improvements in surgical technique, including frequent use of the internal mammary artery and better cardioprotection during surgery, have improved its long-term results and led to its more effective use in patients with substantial left ventricular dysfunction. It is highly efficacious in (a) relieving angina pectoris and (b) improving survival in patients with extensive coronary artery disease and left ventricular systolic dysfunction. At the same time, it has been performed in many subjects for unproven indications, and in these individuals its results have often been disappointing. My purpose today is to provide an overview of CABG in 1993, with particular emphasis on (a) recent developments in technique, (b) risks, and (c) proven benefits.

III. ADVANTAGES AND DISADVANTAGES OF VARIOUS CONDUITS

A. Saphenous Vein Grafts: In the modern era, saphenous vein conduits are utilized mainly for grafting of accessible branches of the right or circumflex coronary arteries. In addition, they may be used in sequential fashion for grafting of these vessels and diagonal branches of the left anterior descending coronary artery [2]. In emergency situations, most surgeons prefer the saphenous vein because it can be harvested and inserted rapidly. Thus, for example, in the patient who undergoes emergent CABG after a failed coronary angioplasty, a saphenous vein (rather than an internal mammary artery) is often used. Venous conduits harvested from the patient's arms have not proven as effective as saphenous veins or internal mammary arteries [3,4].

Following the implantation of saphenous vein grafts, closure occurs in some within hours or days and in others over the ensuing years. In general, saphenous graft closure that occurs during the first postoperative year is due to thrombosis; that which occurs during postoperative years 2 to 7 is caused by intimal hyperplasia; and that which occurs after the 7th postoperative year is due to graft atherosclerosis (Figure 1, top of page 5). Campeau et al [5] performed repetitive angiography at 1, 5 to 7, and 10 to

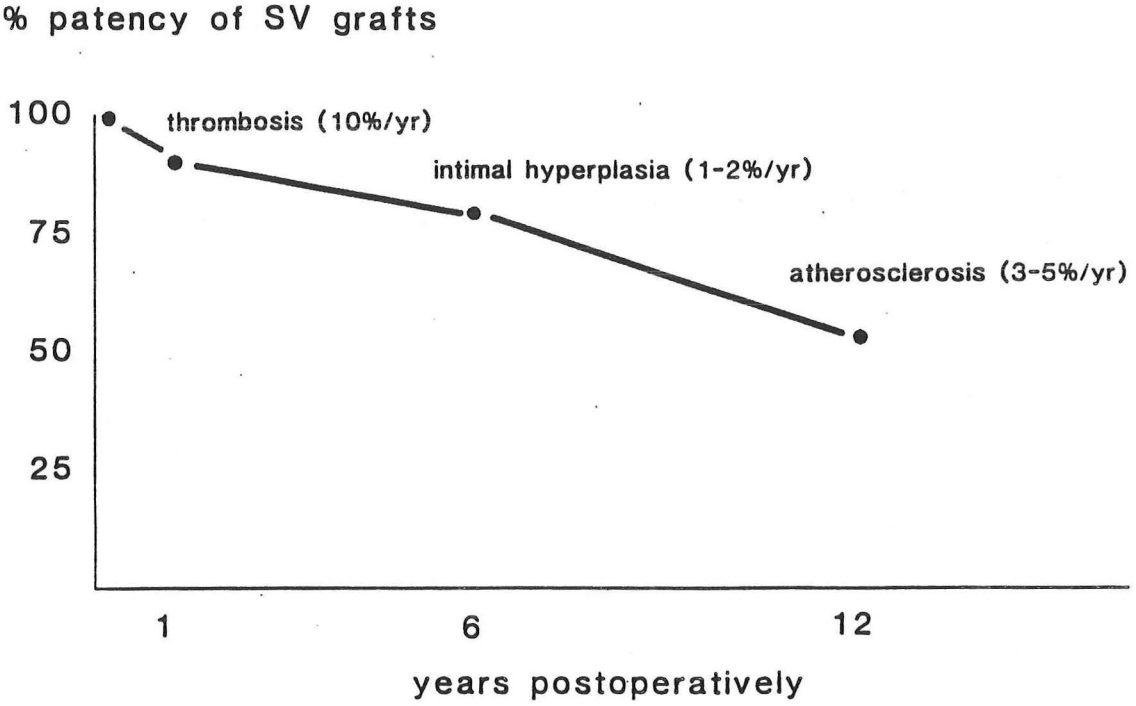

Figure 1: A schematic display of the patency of saphenous vein (SV) grafts over time. During the first year postoperatively, thrombosis occurs in about 10% of SV grafts. For the next 5 to 6 years, occlusion occurs uncommonly (1 to 2%/year) and is due to intimal hyperplasia. For the next 5 to 6 years, occlusion occurs more commonly (3 to 5%/year) and is due to atherosclerosis.

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12 years postoperatively in 60 patients with 109 saphenous vein grafts who underwent CABG from 1969 to 1972. At 1 year, 11 (10%) were occluded; at 5 to 7 years, 21 (19%) were occluded; and at 10 to 12 years, 44 (40%) were occluded (Table 1, below).

Table 1: Attrition of Saphenous Vein Grafts

Years postoperative	% closure/year	Cause of closure
1	10	thrombosis
2 to 7	1-2	intimal hyperplasia
7 to 12	3-5	atherosclerosis

From reference # 5

Shortly after implantation in the arterial circulation, much of the saphenous vein's endothelium disappears. Although early occlusion (i.e., within hours, days, or weeks of surgery) is occasionally caused by (a) technical factors (for example, kinking of the saphenous conduit) or (b) poor distal vessel runoff, it is usually caused by thrombosis of the saphenous vein graft. Chesebro et al [6] randomly and blindly assigned 407 patients undergoing CABG to placebo or dipyridamole (begun 2 days preoperatively) and aspirin (begun 7 hours postoperatively). From 7 days to 6 months (median, 8 days) postoperatively, 360 (88%) of them underwent angiography to assess saphenous vein graft patency. Dipyridamole/aspirin reduced the incidence of occluded saphenous grafts in the ensuing weeks to months (Table 2, below and Figure 2, top of page 7).

Table 2: Beneficial Effect of Dipyridamole/Aspirin on Saphenous Vein Graft Patency after CABG

	Placebo	Dip/Aspirin	P
Occlusion rate/graft at 1 month	38/362 (10%)	10/351 (3%)	<0.001
Occlusion rate/graft at 6 months	79/520 (15%)	19/488 (4%)	<0.001
Occlusion rate/pt at 1 month	27/130 (21%)	10/130 (8%)	0.003
Occlusion rate/pt at 6 months	56/184 (30%)	17/176 (10%)	<0.001

From reference # 6

In short, the major advantages of saphenous vein conduits are (a) their relative abundance and (b) the speed and ease with which they can be harvested and used. Their main disadvantage is their longevity, in that approximately half are occluded within 10 to 12 years of insertion. Although perioperative dipyridamole and aspirin appear to reduce the incidence of saphenous vein thrombosis within the first 6 months of CABG, they exert no demonstrable effect on the intimal hyperplasia or graft atherosclerosis that occur during the subsequent 2 to 12 years.

B. Internal Mammary Arteries: The left internal mammary artery is used for grafting of the left anterior descending or its major diagonal branches. Even in elderly patients, it is usually remarkably free of atherosclerosis.

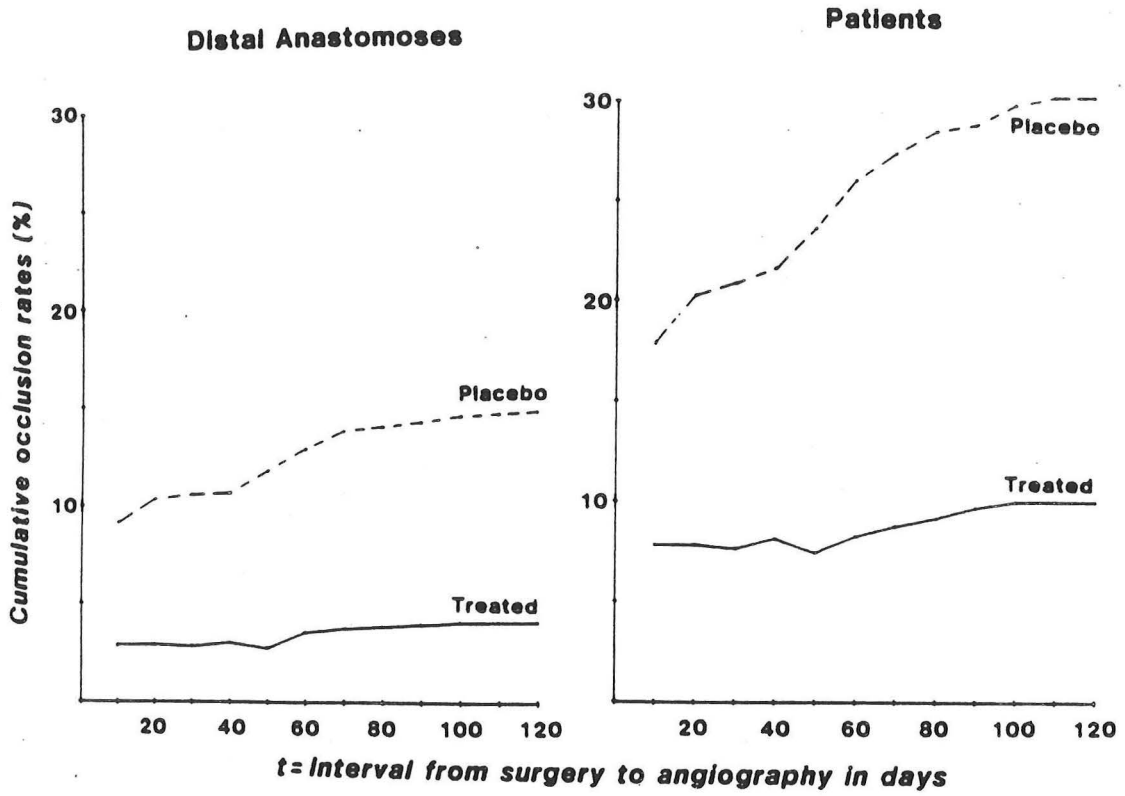


Figure 2: Cumulative occlusion rate of saphenous vein grafts, expressed as %, during the 120 days after CABG for those given placebo (dotted lines) or dipyridamole/aspirin ("treated," solid lines). The left panel displays the occlusion rate per graft, and the right panel displays the occlusion rate per patient. From reference # 6

In the decade after its anastomosis with a coronary artery, it rarely develops intimal hyperplasia or atherosclerosis. In comparison to saphenous vein grafts, therefore, it offers a substantial improvement in short and long-term patency. As a result, its use appears to be associated with an improved survival. Loop et al [7] from the Cleveland Clinic compared graft patency and survival in a very large number of patients in whom (a) only saphenous vein grafts were inserted (n = 3625) or (b) an internal mammary artery was used alone or in combination with saphenous vein grafts (n = 2306). As the data in Table 3 (top of page 8) demonstrate,

Table 3: 10 Year Survival of Patients Undergoing CABG With or Without a Left Internal Mammary Conduit

	Saph Veins Only	Int Mam + Saph Veins	P
LAD disease only	88%	93%	0.05
2 vessel CAD	80%	90%	< 0.001
3 vessel CAD	71%	83%	< 0.001
CAD & mild LV impairment	79%	88%	< 0.001
CAD & severe LV impairment	60%	77%	< 0.001

From reference # 7

those in whom an internal mammary artery was utilized had an improved survival (Figures 3, 4, and 5, pages 9 and 10).

Of this very large patient cohort, a relatively small number underwent angiography in the postoperative period. The patency of their internal mammary and saphenous vein grafts are displayed in Table 4, below.

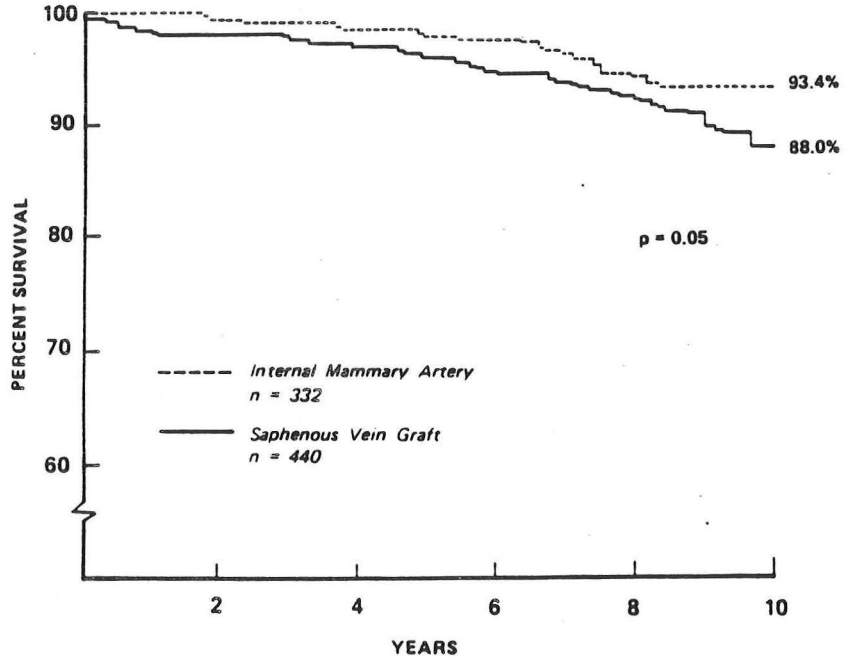
Table 4: Patency of Left Internal Mammary and Saphenous Vein Grafts

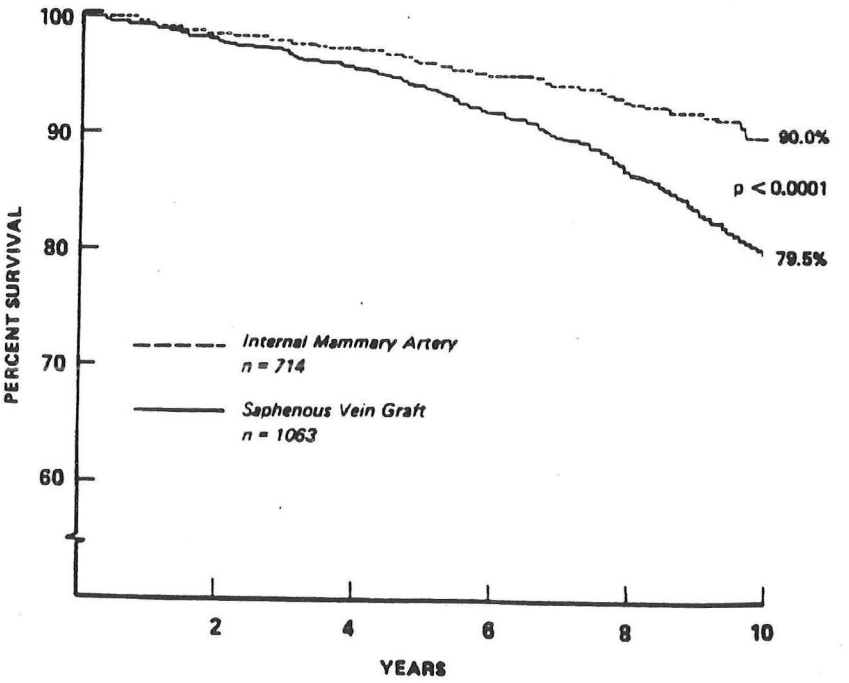
Years After CABG	Int Mam Grafts	Saph Vein Grafts
1	98%	87%
3	98%	88%
5	96%	78%
8	96%	64%
11	98%	52%

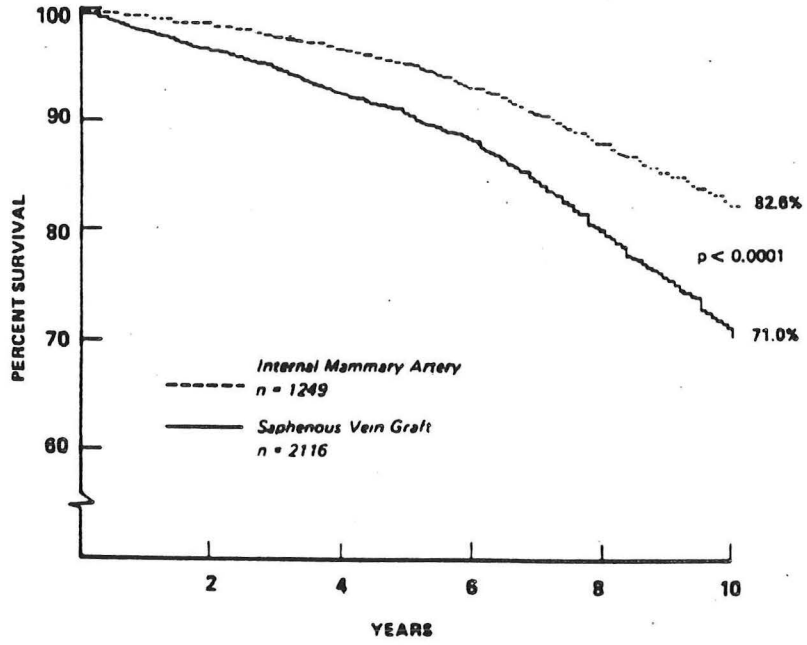
From reference # 7

The major advantage of left internal mammary conduits is their superior short and long-term patency, with a resultant improvement in survival when compared to patients

Figures 3, 4, and 5: Percent survival over 10 years for patients with 1 vessel (Figure 3), 2 vessel (Figure 4), and 3 vessel (Figure 5) coronary artery disease in whom an internal mammary graft was (dotted lines) or was not (solid lines) used.







with only saphenous vein grafts [8]. Their major disadvantages include (a) their limited number (1 per patient) and (b) the time and effort required to dissect the conduit free from the pleural surface of the left hemithorax, so that it can be attached to the left anterior descending or one of its diagonal branches.

The right internal mammary artery may be dissected free from the pleural surface of the right hemithorax and anastomosed to (a) the right coronary artery, including the proximal posterior descending artery, or (b) an obtuse marginal branch of the circumflex coronary artery. At present, no long-term data are available concerning the beneficial effect of routinely using both mammary arteries. Multiple internal mammary artery grafting is presently recommended in (a) patients without suitable venous conduits, (b) younger patients with accelerated vascular disease, and (c) patients undergoing repeat CABG in whom saphenous vein grafts have failed [9].

When both internal mammary arteries are dissected free and used as conduits, the incidence of postoperative sternal infections may increase. Morris et al [9] performed CABG with only the left internal mammary artery in 643 patients, 6 of whom (0.9%) had sternal infections. Of the 420 in whom both mammary arteries were utilized, 9 (2.1%) had sternal infections (NS). Obviously, if <u>both</u> mammary arteries are dissected free and used as conduits, the time and effort required are substantial.

C. Other Conduits: Rarely, other arterial conduits have been used for CABG. Limited data suggest that the right gastroepiploic artery offers similar advantages as the left internal mammary, in that it (a) is rarely diseased by atherosclerosis, (b) can be anastomosed effectively to the distal left anterior descending or the posterior descending coronary arteries, and (c) has an excellent chance of remaining patent for many years postoperatively [10,11]. Its long-term patency, in fact, appears to be similar to that of the left internal mammary artery.

In juxtaposition to the internal mammary and gastroepiploic arteries, the splenic artery is not an effective conduit, due to the fact that it is often (a) involved with atherosclerosis, (b) excessively big in diameter, and (c) tortuous [11]. As already noted, arm veins have not proven to be good conduits [3,4]. Although considerable work has been done on synthetic materials for CABG, all have been disappointing. In 8 patients, Chard et al [12] inserted a total of 28 polytetrafluoroethylene aortocoronary grafts. At 1 year postoperatively, 64% were patent; at 2 years, only 32% were patent; at 3 years, only 21% were patent; and at 45 months, only 14% were patent.

At present, then, there are no acceptable alternatives to internal mammary and saphenous vein conduits for CABG.

IV. OPERATIVE MORBIDITY AND MORTALITY

A. Myocardial Infarction: Perioperative myocardial infarction is usually due to (a) technical factors (i.e., kinking of a saphenous vein graft or mechanical obstruction at the distal anastomosis) or (b) thrombosis of the graft. Its exact incidence is unknown, due, at least in part, to the impaired ability of normally reliable techniques, such as electrocardiography and serum enzyme analyses, to identify myocardial damage in the immediate postoperative period. Thus, ST-T wave abnormalities and transient increases in creatine kinase often occur immediately postoperatively even in the most uncomplicated of patients; their occurrence is so ubiquitous that they are of limited use in identifying those in whom a non-Q wave infarction has occurred.

Perioperative Q wave myocardial infarction is more easily recognized, since the 12 lead electrocardiogram reveals Q waves that were absent preoperatively. In the 1970s, its incidence was reported to be 6 to 10% [13,14]. With improvements in cardioprotection intraoperatively and

the routine use of platelet inhibitors perioperatively, the incidence of perioperative myocardial infarction may now be lower, but there are no data to support such speculation. Even with perioperative platelet inhibition, graft occlusion within 6 months of CABG still occurs in 10% of patients (Table 2) [6]. Provided that these grafts are perfusing viable myocardium and that collateral perfusion is limited (2 reasonable assumptions), most of these graft occlusions result in some myocardial necrosis. In short, the incidence of peri-CABG myocardial infarction (Q wave or non-Q wave) -- even in the 1990s -- is 5% at an absolute minimum; realistically, it is probably closer to 10 or 12%.

More important than simply the occurrence of peri-CABG myocardial infarction is its influence on subsequent morbidity and mortality. Force et al [15] compared long-term morbidity and mortality after CABG in patients operated at the West Roxbury, MA Veterans Administration Medical Center (a Harvard-affiliated VA Hospital). Interestingly, these patients underwent CABG in 1981 to 1985, yet the incidence of peri-CABG Q-wave myocardial infarction was 10.5%. When they compared the long-term outlook of 59 patients with and 115 without perioperative myocardial infarction, they found that those with peri-CABG infarction were more likely to have recurrent cardiac events -- fatal and nonfatal -- in the subsequent 2 to 3 years (Table 5).

Table 5: Subsequent Morbidity and Mortality in Patients With and Without Peri-CABG Myocardial Infarction

	Peri-CABG MI	No peri-CABG MI	P
Number of pts	59	115	
Any cardiac event	31%	12%	< 0.01
Death, MI, CHF	25%	7%	< 0.01
Multiple events	19%	1%	< 0.01
Cardiac death	8%	4%	NS

From reference # 15

B. Cognitive/Intellectual Impairment: In the immediate postoperative period, many patients manifest impaired cognitive function in the absence of a perioperative cerebrovascular accident [16]. When tested 8 days after CABG, as many as 75% of patients exhibit subtle deficits. In the ensuing weeks, the majority of these resolve, so that by 3 months only about 10% of patients still have them. Their prevalance is unfavorably influenced

by postoperative anxiety and depression as well as by older age [17,18]. Only rarely are patients aware of or limited by these deficits.

C. Cerebrovascular Events: Gross neurologic deficits in the postoperative period most likely result from (a) embolization of atherosclerotic debris from the ascending aorta or (b) air embolization. In younger patients, they are reported in only about 0.5%. However, they occur in 5 to 8% of patients > 70 years old and in 8 to 10% of those > 75 years of age [19,20].

D. Mortality: Although peri-CABG mortality occasionally has been reported to be as low as 0.2 to 0.3% [21,22], data from larger multi-institutional studies suggest a considerably higher peri-CABG mortality: 6 to 7 % in many community hospitals and 2 to 4% in the best university settings [23]. In the Veterans Administration Cooperative Study of CABG, the 30-day operative mortality was 5.8% [14]. Not surprisingly, peri-CABG mortality varies substantially from institution to institution and from surgeon to surgeon. As a result, it is imperative that the physician who refers patients for CABG have a precise idea of his institution's and surgeon's mortality data.

Peri-CABG mortality is influenced by many factors. Most important among them are:

a. Left ventricular dysfunction
b. Left main coronary artery disease
c. Extracardiac vascular disease
d. Extracardiac concomitant disorders (COPD, diabetes mellitus, azotemia, obesity)
e. Age
f. Gender
g. Repeat CABG

Although data are limited, peri-CABG mortality appears to increase as left ventricular systolic function decreases. In the Coronary Artery Surgery Study (CASS), peri-CABG mortality for patients with left ventricular ejection fractions > 0.50 was only 1.4%. In contrast, it was 6.9% in patients with ejection fractions < 0.36 [24]. Similar data were reported by Wechsler and Junod [25], who noted that peri-CABG mortality increased in stepwise fashion as CHF worsened (Table 6, top of page 14).

Patients with left main coronary artery disease have a higher peri-CABG mortality than those with less severe disease [26,27]. Gomberg et al [27] reported a 9.1% peri-CABG mortality in 176 patients with left main disease operated between 1981 and 1986. Among those with left main stenoses, the operative mortality was especially high in women and in those necessitating emergency CABG.

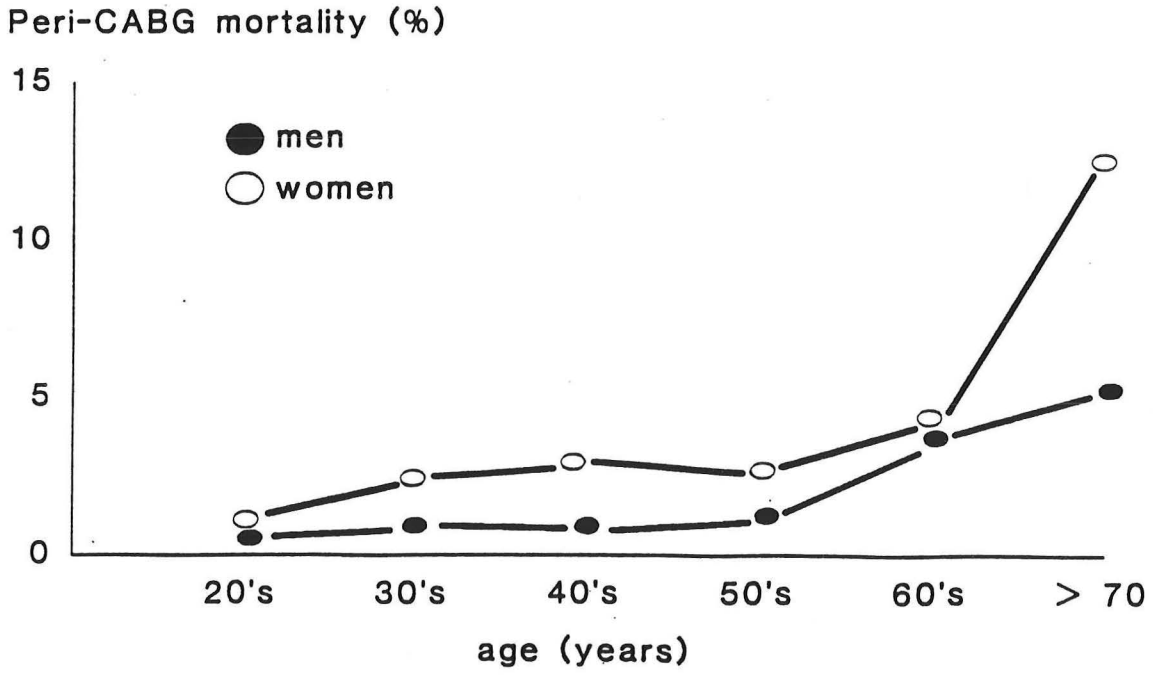
Table 6: Peri-CABG Mortality According to CHF Class (Data from Duke University Medical Center)

CHF Class	Peri-CABG Mortality
0	3.0%
1	2.5%
2	4.2%
3	8.0%
4	14.9%

From reference # 25

Patient age substantially influences peri-CABG mortality. In the CASS registry, mortality rose steadily with age: the overall peri-CABG mortality was 2.3%, increasing to 7.9% in patients > 70 years old [28] (Figure 6, below). Horneffer et al [29] reviewed all CABGs

Figure 6: Influence of age and gender on peri-CABG mortality. From reference # 28.



performed at Johns Hopkins from 1980 to 1985, dividing the 684 patients into 3 age groups (< 55, 55 to 69, and > 70 years). The elderly patients (a) were more often female, (b) were more likely to have severely limiting or rest angina, and (c) were more likely to have concomitant peripheral and cerebrovascular disease. In the postoperative period, as the data in Table 7 (below) indicate, the patients > 70 years old were more likely to experience a myriad of operative complications, including death.

Table 7: Preoperative and Perioperative Data According to Patient Age

Variable	< 55 (n=228)	55-69 (n=228)	> 70 (n=228)	P
Female	22%	21%	34%	0.002
Unstable angina	27%	31%	48%	0.001
Cerebrovascular disease	8%	13%	28%	0.001
Peripheral vascular disease	12%	18%	26%	0.001
Reop for bleeding	1%	4%	7%	0.004
Wound infection	4%	4%	13%	0.001
Stroke	0%	3%	8%	0.001
Dialysis	0%	1%	3%	0.025
Long ventilation	2%	4%	8%	0.007
Length of stay after CABG (days)	9	11	14	0.001
Mortality	2%	2%	9%	0.001

From reference # 29

Recently the Mayo Clinic has reported their surgical results for 191 consecutive patients ≥ 80 years of age undergoing a variety of cardiac surgical procedures, including CABG. Of this total, 62 had CABG alone, with an operative mortality of 13% [30]. In short, regardless of the institution or the surgeon, patient age is a very important determinant of peri-CABG mortality. This is due,

at least in part, to the fact that elderly patients more often have concomitant morbid conditions (i.e., cerebro- and peripheral vascular disease, lung disease, and renal insufficiency) than younger ones.

In the CASS registry, 6630 patients underwent CABG from 1975 to 1979. Of this total, 5569 were men, and 1061 were women. Among the men, the peri-CABG mortality was only 1.9%; in marked contrast, it was 4.5% for the women ($p < 0.001$) [28]. Similarly, Hall et al [31] reviewed the CABG experience from the Texas Heart Institute, reporting the outcome in 22,284 consecutive patients operated from 1970 to 1981. Peri-CABG mortality was 2.6% for men and 5.3% for women ($p < 0.001$). Other studies have suggested that the peri-CABG mortality in women is higher than in men simply because women are more likely to be smaller in body size, with resultant smaller epicardial coronary arteries.

Increasingly in the 1990s, patients are requiring repeat CABG for angina refractory to maximal medical therapy. The perioperative mortality associated with repeat CABG appears to be substantial. Christakis et al [32] reported on 7334 patients undergoing CABG from 1982 to 1986 at a group of hospitals affiliated with the University of Toronto. Those undergoing first CABG had an operative mortality of 3.2%, whereas those undergoing repeat CABG had a mortality of 9.1% ($p < 0.01$). In their multivariate analysis, this was the most significant predictor of increased peri-CABG mortality. For all CABGs performed in New York State in 1986, the mortality for repeat operations was 11.7% -- more than 4 times the mortality associated with the initial procedure [33].

In summary, peri-CABG mortality, even in the best of hands and the healthiest of patients, appears to be in the range of 2 to 4%, and in many institutions it is undoubtedly higher. From this "best-case" figure, peri-CABG mortality rises with the presence of a variety of associated conditions, including left ventricular dysfunction, concomitant peripheral vascular disease, concomitant extravascular disease, age, gender, and the need for repeat CABG.

V. RESULTS OF CABG IN PATIENTS WITH STABLE ANGINA

A. Relief of Angina Pectoris: CABG effectively relieves angina, at least for several years. The Veterans Administration Cooperative Study of CABG enrolled 686 men with stable angina pectoris for $\geq$ 6 months from 1972 to 1974

at 13 clinical sites; they were randomly assigned to medical (n = 354) or surgical (n = 332) therapy. All had a left ventricular ejection fraction > 0.25, and the majority had

Table 8: Relief of Angina with CABG or Medical Therapy (Veterans Administration Cooperative Study)

	Medical Rx (n=354)	CABG (n=332)	P
Pre-CABG			
mild/no angina	32%	28%	NS
severe angina	27%	33%	NS
1 Yr Post-CABG			
mild/no angina	38%	78%	0.001
severe angina	28%	5%	0.001
5 Yrs Post-CABG			
mild/no angina	49%	64%	0.001
severe angina	24%	18%	unstated

From reference # 34

normal left ventricular function. As noted previously, the 30-day operative mortality was 5.8%. As shown in Table 8 (above), CABG was substantially better than medical therapy at relieving angina.

In the randomized portion of the Coronary Artery Surgery Study (CASS), 780 patients (704 men and 76 women, all aged ≤ 65 years) with mild angina or previous myocardial infarction were randomly assigned to medical (n = 390) or surgical (n = 390) therapy. This study was performed from 1975 to 1979 at 11 clinical sites. The majority of patients had normal left ventricular ejection fractions, though 160 had ejection fractions of 0.35 to 0.49. As noted previously, the peri-CABG mortality was only 1.4%. In light of the fact that these patients were (a) minimally symptomatic or even asymptomatic, (b) likely to have normal left ventricular function, and (c) ≤ 65 years of age, this peri-CABG mortality is not inconsistent with other data.

As the data in Table 9 (top of page 18) indicate, CABG was better than medical therapy at relieving angina irrespective of the severity of underlying coronary artery disease (Table 10, page 18).

In these same studies, CABG was superior to medical therapy in improving exercise performance. Specifically, treadmill time was improved, and the percentage of patients who developed ischemia with exercise was reduced

substantially with CABG. As a result, CABG was better than medical therapy at reducing the need for antianginal

Table 9: Relief of Angina with CABG or Medical Therapy (Coronary Artery Surgery Study)

	Medical Rx (n=390)	CABG (n=390)	P
Angina-free at:			
1 year	27%	68%	< 0.001
3 years	38%	66%	< 0.001
5 years	35%	57%	< 0.001

From reference # 35

medications after randomization. Of those treated medically, 65% continued to require beta blockers, and 52% required nitrates. In contrast, of those treated surgically, only 37% continued to require beta blockers, and 22% required nitrates ($p < 0.001$ in comparison to medical therapy for both agents).

Table 10: Relief of Angina with CABG or Medical Therapy (Coronary Artery Surgery Study)

1 Vessel Coronary Artery Disease

	Medical Rx (n=107)	CABG (n=107)	P
Angina-free at:			
1 year	26%	56%	< 0.03
3 years	43%	63%	< 0.03
5 years	41%	58%	NS

3 Vessel Coronary Artery Disease

	Medical Rx (n=135)	CABG (n=126)	P
Angina-free at:			
1 year	33%	69%	< 0.01
3 years	37%	66%	< 0.01
5 years	32%	59%	< 0.01

From reference # 35

The efficacy of CABG in relieving angina, which is convincingly demonstrated by the data cited in Tables 8-10, appears to dissipate 10 years postoperatively (Table 11).

In the VA Cooperative Study [36], anginal severity was quantitated, resulting in a so-called "angina score." In light of what is known about the natural history of saphenous vein grafts, the gradual loss of efficacy with CABG is not surprising: at 10 years, 40 to 50% of saphenous vein conduits are occluded.

Table 11: "Angina Score" in the VA Cooperative Study

	Medical Rx	CABG	P
Pre-CABG	9.3	9.9	NS
1 yr post-CABG	8.7	4.2	< 0.00001
5 yrs post-CABG	7.8	6.0	< 0.0001
10 yrs post-CABG	6.5	6.6	NS

From reference # 36

B. Prevention of Myocardial Infarction: Although CABG is frequently performed with this indication in mind, there are no data to suggest that, in fact, it reduces the incidence of subsequent myocardial infarction. There are at least 2 reasons that CABG does not prevent infarction. First, as discussed previously, about 10% of patients sustain a perioperative infarction. A severely narrowed epicardial coronary artery that perfuses viable myocardium is grafted, and in the ensuing hours, days, or weeks -- probably because of the absence of a perfusion pressure gradient across the intrinsic stenosis -- the native artery occludes at the site of previous narrowing, so that the distal artery's perfusion is now totally dependent on graft patency. Within the ensuing weeks or months, the graft thromboses or occludes because of intimal hyperplasia, leading to infarction of the myocardium fed by the artery.

Second, recent data demonstrate that the majority of myocardial infarctions occur in epicardial coronary arteries that are not significantly narrowed by atherosclerosis. Little et al [37] reviewed the coronary angiograms of 42 consecutive patients who underwent angiography before and within 1 month after myocardial infarction. On the second angiogram, 29 of the 42 had an occluded infarct artery. When this artery was evaluated on the pre-infarction angiogram, it was found to have < 50% luminal diameter narrowing in 19 of the 29 (66%). If, then, these 29 patients had undergone CABG after the first angiogram, the (subsequent) infarct artery would not have been grafted in 2/3 of them. Ambrose et al [38] published very similar data: of 23 patients who had coronary angiography before and

after myocardial infarction, the site of occlusion was not significantly narrowed before infarction in 18 (78%). In summary, coronary arterial thrombosis, with resultant myocardial infarction, is often the result of disruption of a mild or moderate atheroscleortic coronary plaque. Since most of these arteries would not be sufficiently narrowed to require grafting, CABG would not prevent a subsequent ischemic event.

C. Return to Gainful Employment: In comparison to medical therapy, CABG does not improve the chance that the patient will return to gainful employment. In the huge Texas Heart Institute experience of > 22,000 patients who underwent CABG [31], follow-up information revealed that only 45% returned to full-time employment; 12% were holding part-time jobs; 24% were retired; 11% were classified as "disabled"; and 7% were "confined to the home." In the randomized portion of CASS, a similar percentage of patients in the medical and surgical groups were employed at 1, 3, and 5 years postoperatively (Table 12, below).

Table 12: Return to Full or Part-Time Employment After Entry into the CASS Randomized Trial

	Medical Rx (n=390)	Surgical Rx (n=390)	P
1 year	66%	69%	NS
3 years	56%	61%	NS
5 years	50%	51%	NS

NS = not significant.

From reference # 35

Several factors may contribute to the somewhat disappointing employment data for the patients who undergo CABG. First, many of them have surgery at or near retirement age, so that CABG serves as a "catalyst" for retirement. Second, many of them are unemployed or disabled for an extended period preoperatively because of limiting angina or myocardial infarction. Some studies have suggested that the likelihood of a return to work is indirectly proportional to the duration of disability preoperatively.

D. Relief of Congestive Heart Failure/Improvement in Left Ventricular Function: An occasional patient has impaired left ventricular systolic function, with resultant symptoms of congestive heart failure, because of "hibernating" myocardium (i.e., persistent left ventricular dysfunction because myocardial perfusion is chronically

reduced but is adequate to maintain tissue viability). In these individuals, surgical revascularization leads to improved systolic function and amelioration of congestive symptoms. Unfortunately, the vast majority of patients with substantial left ventricular systolic dysfunction -- and resultant congestive heart failure -- have had one or more previous myocardial infarctions, with resultant necrosis of myocardium. In these patients, improved perfusion of the epicardial coronary arteries does not alter myocardial function. In short, CABG is usually not efficacious in influencing left ventricular performance or alleviating symptoms of congestive heart failure, since the pathophysiology of left ventricular dysfunction is irreversible myocardial necrosis.

E. Amelioration of Ventricular Tachyarrhythmias and Sudden Cardiac Death: Data from the CASS registry suggest that CABG reduces the incidence of sudden cardiac death, especially in patients with (a) extensive coronary artery disease and/or (b) left ventricular dysfunction. In this large, nonrandomized registry, 6260 patients with coronary artery disease were treated medically, 323 (5.2%) of whom had sudden cardiac death. In contradistinction, of 7216 patients who underwent CABG, only 129 (1.8%) had sudden cardiac death during a similar period of follow-up [39]. As noted, the difference between medical and surgical therapy in the percentage of patients without sudden cardiac death was most marked in those with 3 vessel coronary artery disease and a history of congestive heart failure (i.e., probable left ventricular systolic dysfunction): after 5 years of follow-up, 91% of the surgical patients had not had sudden death, whereas only 69% of those treated medically had not experienced sudden death ($p < 0.0001$) (Table 13).

Table 13: Percentage of Patients with a History of CHF Without Sudden Death After 5 years Follow-up

	Medical Rx	Surgical Rx	P
2 vessel CAD	83%	98%	< 0.0001
3 vessel CAD	69%	91%	< 0.0001

From reference # 39

Our own retrospective analysis of survivors of myocardial infarction suggests that CABG or PTCA of occluded infarct arteries improves long-term survival by reducing the likelihood of sudden death [40]. Of 200 survivors of a first myocardial infarction (137 men, 63 women, aged 25 to 76 years) with a persistently occluded infarct artery and no other coronary artery disease, 148 were treated medically,

and 52 underwent single vessel CABG (n = 20) or PTCA (n = 32). Over an average 4 years of follow-up, 24 (16%) of the 148 medically treated patients died, with 23 experiencing sudden death. Of the 52 who had CABG or PTCA, only 1 (2%) died (p = 0.008). The difference between the groups was especially marked in those in whom the occluded artery was the left anterior descending or left circumflex (i.e., those most likely to have associated left ventricular systolic dysfunction). Of 78 survivors of myocardial infarction with an occluded left anterior descending or circumflex who were treated medically, 20 (26%) died within 3 to 4 years of follow-up; of 39 with an occluded anterior descending or circumflex who had CABG or PTCA, only 1 (3%) died (p < 0.05). Figure 7 (below) is a life table survivorship analysis for those treated medically (Group I) and those undergoing CABG or PTCA (Group II).

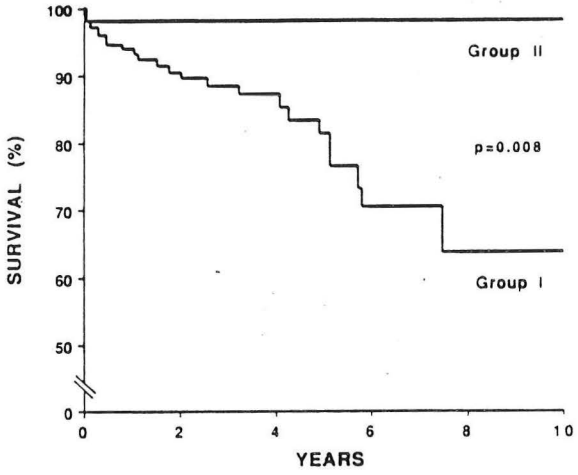


Figure 7: A life table survivorship of patients with an occluded infarct artery treated medically (Group I) or with PTCA or CABG (Group II). See text for details. From reference # 40.

As I have discussed previously at these Grand Rounds, survivors of myocardial infarction with a persistently occluded infarct artery have a substantially worse long-term prognosis than those with a patent artery, even though the magnitude of left ventricular dysfunction is similar. The <u>combination</u> of a persistently occluded infarct artery and depressed left ventricular function (ejection fraction < 0.50) portends an especially poor prognosis. Interestingly, almost all the patients who die do so suddenly. The restoration of antegrade flow in the persistently occluded infarct artery -- via mechanisms as yet unknown -- appears to render these patients less "electrically unstable" [41]. It is possible, then, that CABG will prolong life in survivors of myocardial infarction with a persistently occluded infarct artery because it diminishes the incidence of arrhythmic events in the weeks, months, and years after infarction.

F. <u>Prolongation of Life</u>: Our current approach to CABG for improving survival is based almost completely on the

results of 3 large, randomized trials: the Veterans Administration Cooperative Study of CABG, the European Coronary Surgery Study, and the randomized portion of the Coronary Artery Surgery Study (CASS).

The VA Cooperative Study of CABG enrolled 686 men with stable angina for ≥ 6 months. They were randomly assigned to medical (n = 354) or surgical (n = 332) therapy in 1972 to 1974 at 13 clinical sites. Those with left main coronary artery disease were excluded. Also excluded were patients with (a) myocardial infarction within 6 months, (b) refractory diastolic hypertension (> 100 mmHg), (c) left ventricular aneurysm, (d) other "serious cardiac disease," (e) other organ-system disease making surgery inadvisable or limiting life expectancy to < 5 years, (f) unstable angina, or (g) uncompensated congestive heart failure. All had left ventricular ejection fractions > 0.25. The perioperative mortality was 5.8%, and the incidence of perioperative Q wave infarction was 9.9%.

Of the 332 patients assigned randomly to CABG, 20 (6%) did not have the operation. Of the 354 assigned to medical therapy, 133 (38%) eventually had CABG during the 11 years of follow-up: 22 (6%) had left main disease and crossed over to CABG on an elective basis in accordance with a protocol amendment, whereas the remaining 111 (32%) underwent CABG because of angina refractory to medical therapy. Medical therapy consisted of nitrates and beta adrenergic blockers. Similar to countless other trials, survival in the 2 treatment groups was analyzed on an "intention to treat" basis: that is, patients remained in the treatment group (medical or surgical) to which they were originally randomly assigned regardless of whether, in fact, they actually received that therapy. Therefore, the 20 patients assigned to surgical therapy who did not have surgery nonetheless remained in the surgery group for the duration of the trial, and the same was true for the 133 patients assigned to medical therapy in whom CABG was eventually performed (that is, they remained a part of the medical group).

Table 14: Cumulative Survival of all Patients Without Left Main Disease

	Medical Rx	Surgical Rx	P
5 years	80%	82%	NS
7 years	72%	77%	NS
11 years	58%	58%	NS

From reference # 14

For all enrollees, survival at 5, 7, and 11 years was similar in the 2 groups (Table 14, above). Specifically, 11 years after randomization, 58% of each group were alive. Cumulative survival was similar in the medical and surgical patients with (a) 1 and 2 vessel coronary artery disease (regardless of left ventricular ejection fraction) and (b) 3 vessel coronary artery disease and a normal ejection fraction (Table 15, below).

Table 15: Cumulative Survival of Patients with 1 or 2 Vessel CAD or 3 Vessel CAD with a Normal Ejection Fraction

	Medical Rx	Surgical Rx	P
5 years	87%	82%	NS
7 years	82%	77%	NS
11 years	68%	61%	NS

From reference # 14

In contradistinction to these results, CABG prolonged life in patients with 3 vessel coronary artery disease and a depressed left ventricular ejection fraction, in large part because these patients fared so poorly on long-term medical therapy (Table 16, below and Figure 8, top of page 25).

Table 16: Cumulative Survival of Patients with 3 Vessel Coronary Artery Disease and an Ejection Fraction < 0.50

	Medical Rx	Surgical Rx	P
5 years	66%	83%	0.018
7 years	52%	76%	0.002
11 years	38%	50%	0.026

From reference # 14

In the VA Cooperative Study of CABG, 4 so-called "clinical risk variables" were prospectively identified, and their

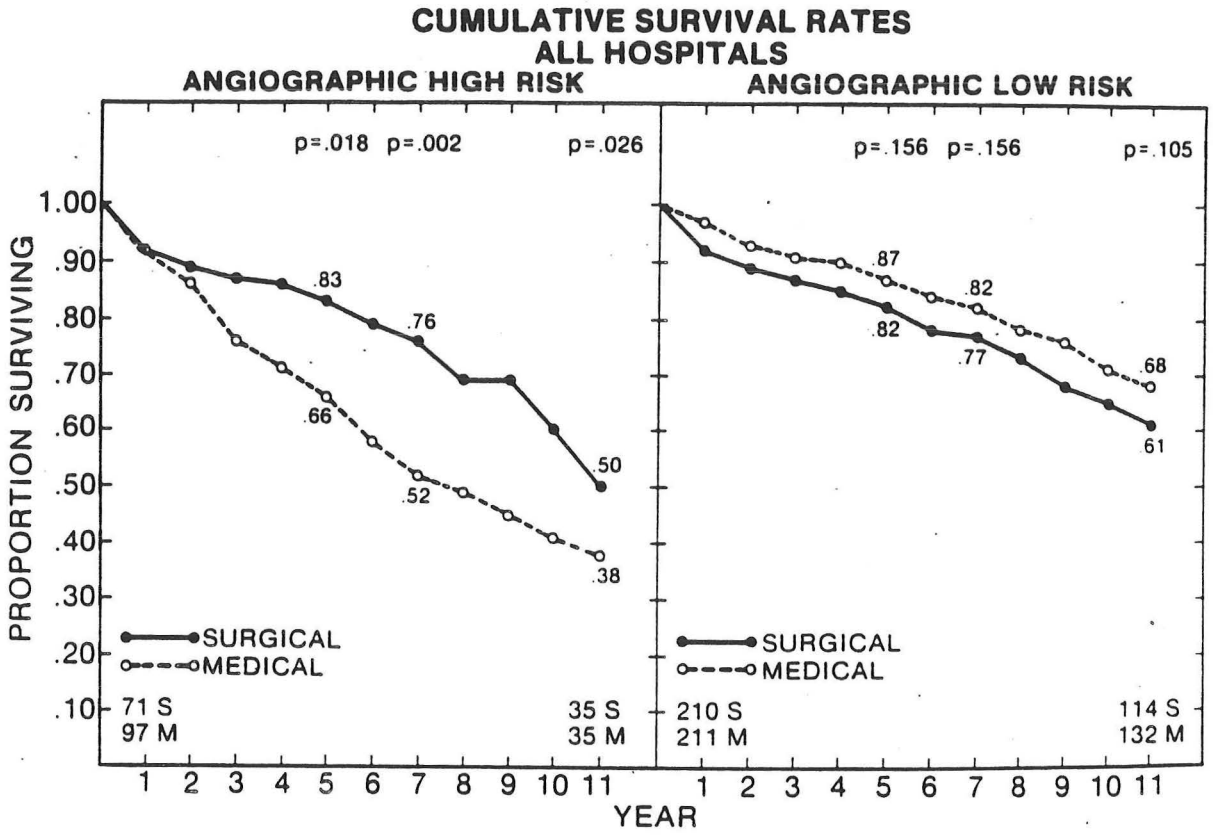


Figure 8: Cumulative survival in the Veterans Administration Cooperative Study for patients treated medically (open circles, dotted lines) or surgically (closed circles, solid lines). The left panel displays the data for patients with 3 vessel coronary artery disease and a left ventricular ejection fraction < 0.50; the right panel shows the results for all other patients (1 and 2 vessel disease regardless of ejection fraction as well as 3 vessel disease and an ejection fraction > 0.50). From reference # 14.

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influence on survival was assessed. They were:

a. NYHA functional classification
b. History of myocardial infarction
c. History of hypertension
d. ST depression on resting ECG

The presence or absence of these 4 risk variables profoundly influenced survival, most strikingly in patients with 3 vessel coronary artery disease and a depressed ejection fraction. As the data in Table 17 indicate, patients with 3 vessel disease, a low ejection fraction, and $\geq$ 1 of these 4 risk variables had a poor prognosis with medical therapy,

and they did substantially better with CABG. In contrast, those with 3 vessel disease, a depressed ejection fraction, but none of the 4 risk variables had a similar long-term prognosis with medical or surgical therapy.

Table 17: Survival at 11 Years of Patients with 3 Vessel CAD and a Depressed Ejection Fraction

	Medical Rx	Surgical Rx	P
> 1 risk variable	24%	54%	0.005
1 risk variable	40%	43%	NS
0 risk variables	62%	52%	NS

From reference # 14

The authors of the VA Cooperative Study of CABG concluded that CABG offers no survival benefit in comparison to medical therapy in patients with (a) 1 vessel coronary artery disease, (b) 2 vessel disease, or (c) 3 vessel disease with normal left ventricular function. CABG is superior to medical therapy in those with 3 vessel disease and a depressed ejection fraction, but this survival benefit appears to be particularly striking in those with "high clinical risk" (i.e., those with > 1 of the so-called "clinical risk variables" already outlined).

The European Coronary Surgery Study enrolled 767 men, aged < 65 years, with mild or moderate angina for $\geq$ 3 months. They were randomly assigned to medical (n = 373) or surgical (n = 394) therapy in 1973 to 1976. All had normal left ventricular ejection fractions (> 0.50). Patients with 1 vessel coronary artery disease were not enrolled, but those with 2 or 3 vessel disease or left main disease were eligible for enrollment. The perioperative mortality was 3.2%, a surprisingly high figure, considering that all patients were men < 65 years of age with normal left ventricular function.

For all patients, survival at 5 years was better in the surgical group than in the medical group (92% versus 83%, respectively, p = 0.0001). This survival advantage was maintained out to 12 years postoperatively, though the superiority of CABG was somewhat attenuated as time elapsed. As a result, at 12 years post-randomization, 71% of the surgical group were alive, and 67% of those treated medically were alive (p = 0.04)(Figure 9, top of page 27).

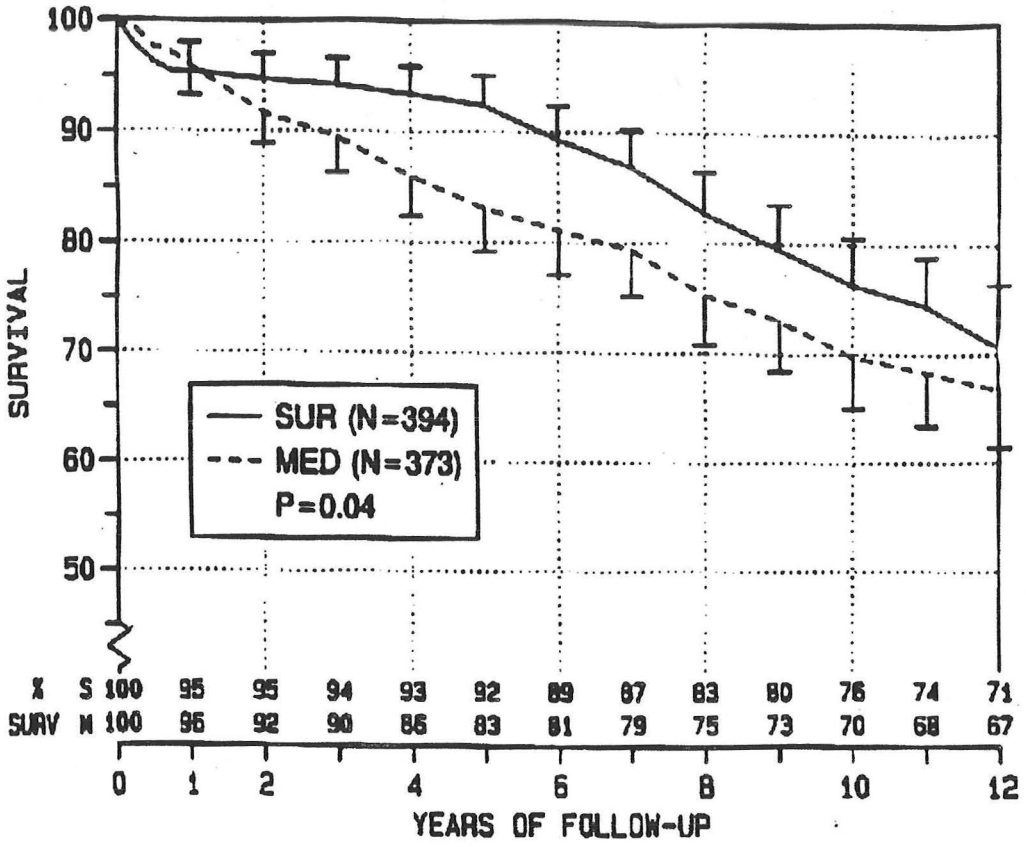

Figure 9: Survival in the European Coronary Surgery Study over 12 years of follow-up. The dashed line reflects those treated medically and the solid line those undergoing CABG. Survival was improved with surgery. From reference # 42.

A closer examination of the data from the European Coronary Surgery Study reveals that CABG improved survival only in those with significant narrowing of the proximal portion of the left anterior descending coronary artery. If the proximal left anterior descending was not diseased, survival was excellent in both treatment groups (Table 18, below and Figure 10, top of page 28).

Table 18: 10 Year Survival in Patients With or Without Proximal Left Anterior Descending Disease

	Medical Rx	Surgical Rx	P
Proximal LAD disease	66%	76%	0.007
No Proximal LAD disease	83%	81%	NS

From reference # 42

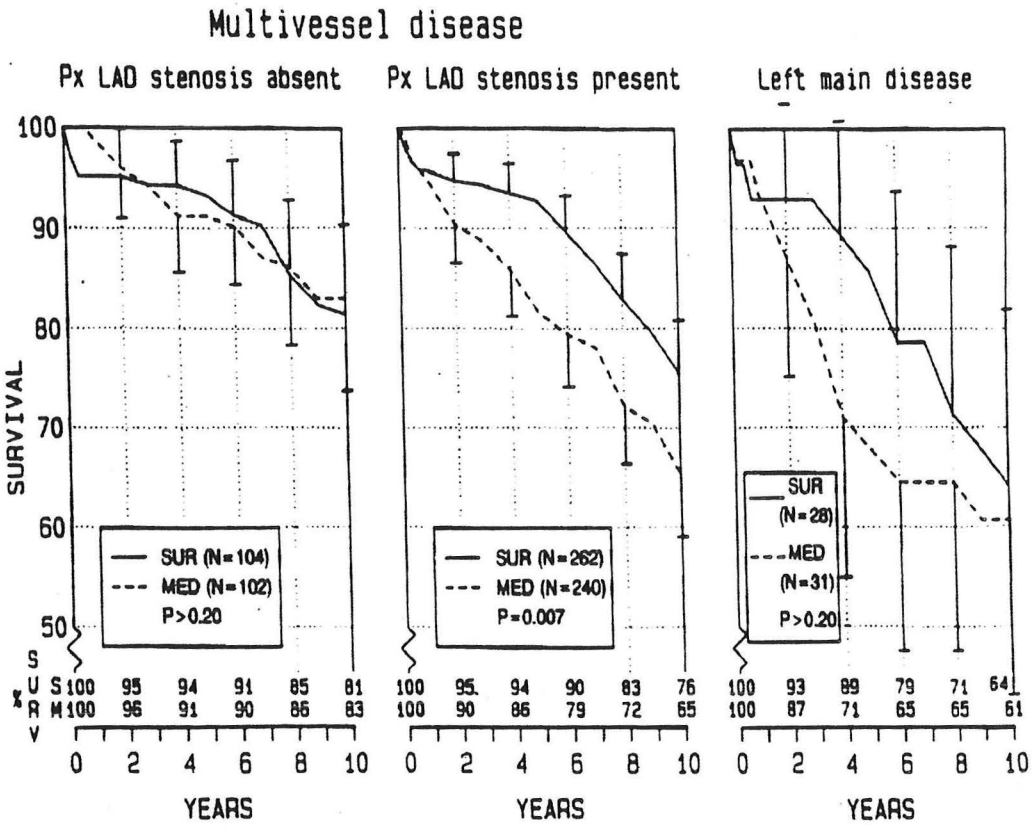

Figure 10: Survival in the European Coronary Surgery Study over 10 years of follow-up for those without proximal (Px) left anterior descending (LAD) disease (left panel), those with proximal LAD disease (middle panel), and those with left main disease (right panel). The dashed lines depict those treated medically, whereas the solid lines reflect those undergoing CABG. CABG improved survival in patients with proximal LAD disease (middle panel), but it did not do so in those without proximal LAD involvement (left panel). Interestingly, survival was similar with medical or surgical therapy in patients with left main disease (right panel).

Interestingly, in this study, patients with left main stenoses were enrolled and randomized to medical or surgical therapy. Although the numbers were not large (31 treated medically, 28 surgically), survival at 10 years was similar (61% in those treated medically, 64% in those managed surgically, NS).

The authors of the European Coronary Surgery Study concluded that CABG offered a survival benefit for 12 years in patients with stable angina pectoris and multivessel coronary artery disease, although this effect was somewhat attenuated after 5 years. This survival benefit was limited to those with narrowing of the proximal portion of the left anterior descending coronary artery.

The Coronary Artery Surgery Study (CASS) enrolled 780 patients (704 men, 76 women), aged ≤ 65 years, with mild angina (functional class II) or a previous myocardial infarction. The patients were randomly assigned to medical (n = 390) or surgical (n = 390) therapy at 11 clinical sites in the United States between 1975 and 1979. Subjects with left main narrowing ≥ 70% were excluded. Roughly 75% of the patients had left ventricular ejection fractions > 0.50, whereas the other 25% had ejection fractions of 0.35 to 0.49. The perioperative mortality was only 1.4%.

Of the 390 patients assigned to surgical therapy, 11% remained only on medical therapy for at least 6 months after randomization. Subsequently, about half of these underwent CABG, so that 6% of those assigned to CABG were, in fact, treated only medically. Of the 390 patients assigned to medical therapy, 40% eventually underwent CABG over the ensuing 10 years, almost all for angina refractory to medical therapy.

For all patients, survival at 10 years was similar in those randomized to medical therapy (79%) and those assigned to CABG (82%)(NS)[43]. For those with an ejection fraction > 0.50, both groups had an excellent 10-year survival: medical, 84%; surgical, 83% (NS). In contrast, those with depressed ejection fractions fared better with CABG: the 10-year survival was 61% in those assigned to medical therapy and 79% in those assigned to CABG ($p = 0.01$). This survival benefit was limited to those with 3 vessel coronary artery disease. In the patients with 3 vessel disease and an ejection fraction < 0.50, the 10-year survival for those assigned to medical therapy was 58%, wheras it was 75% in those assigned to CABG ($p = 0.08$).

In short, the results of CASS are remarkably similar to those of the VA Cooperative Study. Since the CASS patient population was ≤ 65 years of age, were minimally or even asymptomatic, and had a predominance of normal ejection fractions, its perioperative and long-term mortalities -- for both medical and surgical therapy -- were lower than those reported in the VA Cooperative Study. In the end, the patients who derived clear benefit from CABG were those with extensive coronary artery disease (3 vessel) and left ventricular systolic dysfunction (ejection fraction < 0.50).

VI. RESULTS OF CABG IN PATIENTS WITH UNSTABLE ANGINA

A. Relief of Angina Pectoris: Similar to the data presented above for stable angina, CABG is superior to medical therapy in alleviating pain in patients hospitalized with unstable angina.

The NIH-sponsored Cooperative Study of Unstable Angina enrolled 288 patients (242 men, 46 women) with unstable angina at 9 clinical sites between 1972 and 1976 [44]. All were < 70 years of age and were otherwise in good health. None had sustained a myocardial infarction within 3 months of entry. All had transient ST-T wave abnormalities during chest pain at rest. All had left ventricular ejection fractions > 0.30. Following coronary angiography and the demonstration of $\geq$ 70% luminal diameter narrowing of 1, 2, or 3 coronary arteries, each patient was randomly assigned to continued medical (n = 147) or surgical (n = 141) therapy. Medical therapy consisted of bed rest, beta adrenergic blockers, and oral nitrates (none received aspirin). The in-hospital mortality for those assigned to CABG was 5%.

In comparison to those treated surgically, those assigned to medical therapy were much more likely to have continuing limiting angina over the ensuing weeks, months, and years (Table 19). Of those assigned to medical

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Table 19: Percentage of Patients with Class III or IV Angina 1 Year After Randomization

	Medical Rx	Surgical Rx	P
1 vessel CAD	22%	3%	< 0.05
2 vessel CAD	40%	13%	< 0.01
3 vessel CAD	40%	15%	< 0.01

From reference # 44

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therapy, 36% underwent CABG for angina refractory to medical therapy within the ensuing 2 years. Only 3% required surgery during the initial hospitalization, but the remaining 33% required it within the subsequent 2 years.

The Veterans Affairs Cooperative Study of Unstable Angina enrolled 468 men < 70 years old who were hospitalized with unstable angina at 12 participating VA Hospitals between 1976 and 1982. They were randomly assigned to

medical (n = 237) or surgical (n = 231) therapy. Medical therapy consisted of nitrates, beta blockers and -- for the final 2 years of randomization -- calcium antagonists. Aspirin was not administered. The perioperative mortality was 4.1%.

CABG effectively reduced the severity of angina and dramatically reduced the incidence of rehospitalization over the ensuing months for recurrent unstable angina. Specifically, 80% of those assigned to CABG but only 58% of those assigned to medical therapy had an improvement in anginal frequency and severity ($p < 0.01$). At 1 year, more than twice as many patients in the medical group than in the surgical group had recurrent unstable angina [45].

B. Prevention of Myocardial Infarction: CABG does not prevent or reduce the incidence of nonfatal myocardial infarction in patients hospitalized with unstable angina. In the VA Cooperative Study, nonfatal infarction occurred during the first 2 years after randomization in 12% of those treated medically and in 12% of those assigned to CABG [46]. These are particularly interesting data, since those treated medically did not receive aspirin. With the present-day routine use of aspirin in patients with unstable angina, the incidence of nonfatal infarction in the 2 years after initiation of therapy is probably even lower than that reported above [47,48].

C. Prolongation of Life: The influence of CABG on survival in patients with unstable angina is remarkably similar to that already described for patients with stable angina. For all patients, the 3 year survival in those treated medically or surgically was excellent (86% in the medical group, 89% in those assigned to CABG; NS). In those with a left ventricular ejection fraction < 0.50, however, survival was substantially improved with CABG: the 3 year mortality was 17.6% for those treated medically and only 6.1% for those treated surgically ($p = 0.039$) [49](Figure 11, top of page 32).

VII. CONCLUSIONS

In comparison to medical therapy, CABG is more effective at relieving stable or unstable angina pectoris. First and foremost, then, it should be performed in patients with angina who have "failed" medical therapy and who are not candidates for coronary angioplasty. However, its efficacy in relieving angina does not last forever; as atherosclerotic disease in the native coronary arteries and

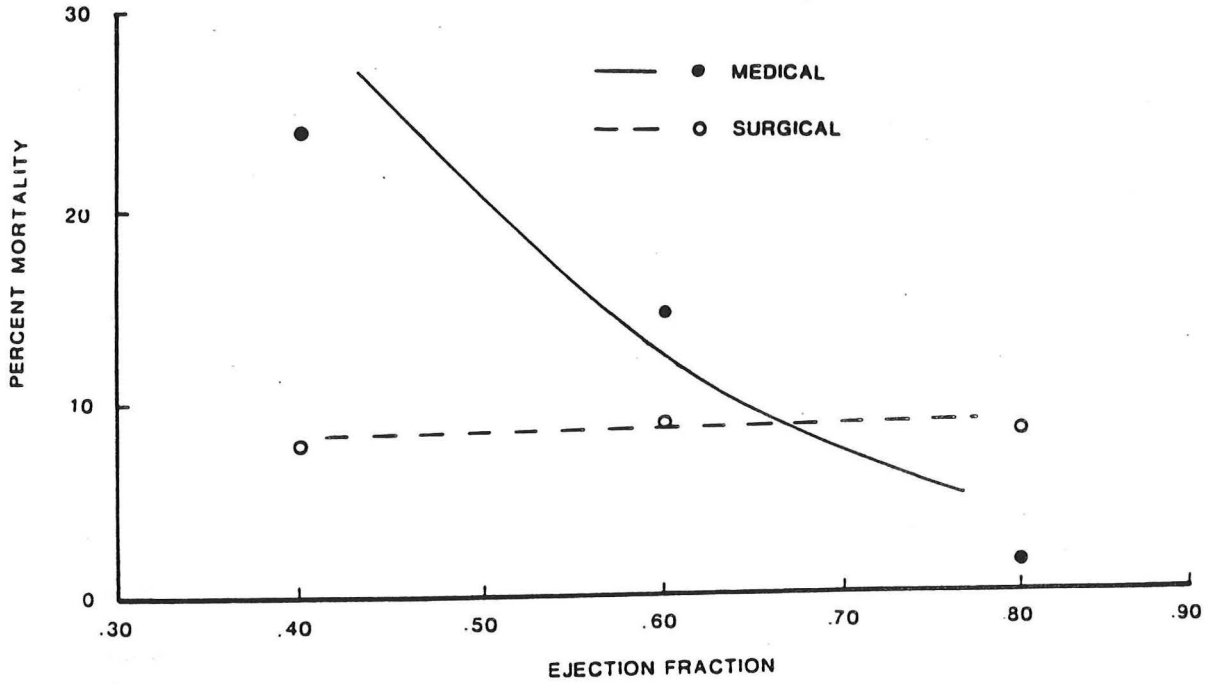

Figure 11: Percent mortality in patients with unstable angina treated medically (closed circles and solid line) or surgically (open circles and dashed line) as a function of left ventricular ejection fraction. From reference # 49.

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grafts slowly progresses, many post-CABG patients redevelop angina 8 to 12 years postoperatively.

In comparison to medical therapy, CABG improves survival only in a limited subset: those with (a) left main coronary artery disease and (b) 3 vessel disease and depressed left ventricular function. In fact, CABG appears to exert its maximal benefit on survival in those whose left ventricular function is most impaired. In patients with less extensive disease or those with 3 vessel disease and normal left ventricular function, survival is similar in those treated medically or surgically, due to the fact that these patients have a very good long-term prognosis without surgery. Despite the widespread misconceptions among laymen and physicians alike, atherosclerotic coronary artery disease -- 1, 2, or even 3 vessel -- is compatible with a prolonged survival. For example, data from the VA Cooperative Study [14], the European Coronary Surgery Study [42], and CASS [13] -- all acquired in the 1970s before the routine use of aspirin and calcium antagonists -- show that the annual mortality for patients with 3 vessel coronary

artery disease is only 2.9 to 5.0%. With modern medical therapy, these figures are probably even lower.

I shall speculate further that survival in patients with coronary artery disease whose arteries are only narrowed <u>but not occluded</u> is superb. All 3 major survival studies discussed above -- the VA Cooperative Study, the European Coronary Surgery Study, and CASS -- enrolled patients with angiographically proven coronary artery disease, some of whom had only narrowed arteries and others of whom had 1 or more persistently occluded arteries. I suspect that almost all the deaths in those treated medically occurred in those with persistently occluded arteries, whereas those with only narrowed arteries had an excellent prognosis. I base this speculation on our own data in survivors of myocardial infarction. In survivors of infarction with disease of only the infarct artery [50], those with antegrade flow in the artery had <u>0% mortality</u> over a follow-up period that averaged 4 years (Figure 12).

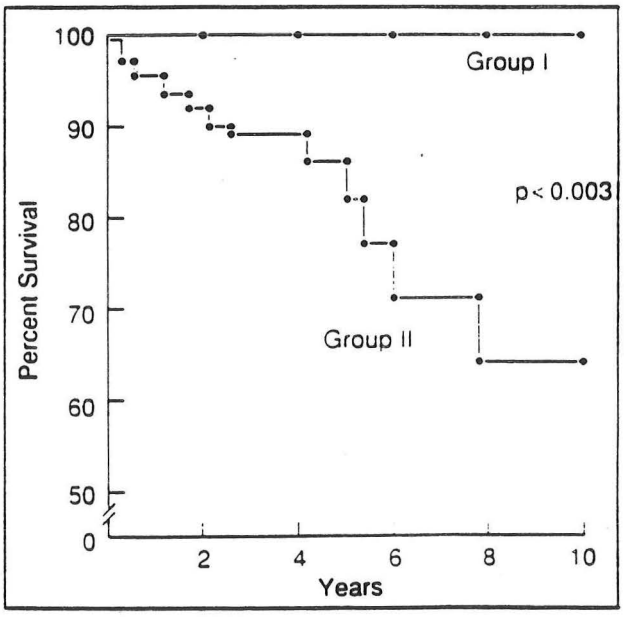

Figure 12: A life table survivorship for survivors of myocardial infarction with a patent (Group I) or occluded (Group II) infarct artery. From reference # 50.

In survivors of infarction with <u>multivessel</u> coronary artery disease [51], those with antegrade flow in the infarct artery had only a <u>6% total mortality</u> over a follow-up period of almost 4 years (i.e., a mortality of < 2% per year). In short, <u>patients with coronary artery disease whose arteries are only narrowed (and not occluded) have such a superb long-term prognosis with medical therapy that one cannot improve it with a nonmedical procedure, such as CABG or angioplasty</u>.

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