NONMEDICAL TREATMENT OF ISCHEMIC HEART DISEASE, 2002
RECENT ADVANCES, LINGERING PROBLEMS

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Dr. Hillis has no financial interests or other relationships with commercial concerns related directly or indirectly to this program. He will not be discussing off-label uses in his presentation.

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Dr. Hillis has had a longstanding (25 years) interest in ischemic heart disease. His research efforts, based primarily in the Catheterization Laboratory, have focused on the pathophysiology, diagnosis, and treatment of myocardial ischemia and infarction. From the "early days" of contemporary cardiology, he has observed and studied the evolution of the medical therapy of myocardial ischemia and infarction, including, among others, the testing and FDA approval of calcium antagonists, the study of thrombolytic therapy for acute myocardial infarction, and the determination of optimal management strategies for patients hospitalized with acute coronary syndromes. In addition, he has witnessed and actively participated in the evolution of nonmedical therapy, both percutaneous and surgical.

A BRIEF HISTORY OF THE MEDICAL AND NONMEDICAL TREATMENT OF ISCHEMIC HEART DISEASE (TABLE 1)

A. The Beginnings: In 1960, Mason Sones (at the Cleveland Clinic) first performed selective coronary angiography. Over the next 8 to 10 years, angiography provided an assessment of the extent and severity of epicardial coronary artery disease (CAD), but treatment options were extremely limited. A handful of patients with limiting angina pectoris underwent the so-called Vineberg procedure, whereby the left internal mammary artery was dissected free from the chest wall and was implanted into the anterior wall of the left ventricle. Interestingly, about one-third of subjects undergoing the Vineberg procedure became angina-free, attesting to the powerful placebo-effect of a midline sternotomy. The overwhelmingly majority of patients were treated medically, which in the 1960s consisted of (a) QID propranolol and (b) sublingual prn nitroglycerin (Table 2, next page). Aspirin obviously was available, but it was not used routinely in subjects with vascular disease until the 1980s. Long-acting nitrate preparations, such as isosorbide dinitrate, also were available, but they were seldom prescribed, since most physicians were convinced that they had no therapeutic efficacy. Long-acting/selective beta-adrenergic blockers, calcium antagonists, ACE inhibitors, and effective hypolipidemic agents (particularly statins) were not available.

TABLE 1: A CHRONOLOGY OF IMPORTANT EVENTS IN THE DIAGNOSIS & TREATMENT OF CAD

1960	Selective coronary angiography first performed
1968	First CABG performed
1972-82	Enrollment in randomized trials comparing medical Rx and CABG in patients with stable and unstable angina
1977	1st PTCA performed
1978-88	PTCA performed largely in patients with single vessel CAD
1988	Increasing use of PTCA in patients with multivessel CAD
1990-95	Randomized comparisons of PTCA and CABG in patients with single and multivessel CAD
1987	Coronary stenting first described
1990	Stenting begins to gain in efficiency, success, and popularity
1995-0	Stenting becomes widely applied, being used in most patients having percutaneous Rx
2002	Sirolimus-eluting stents are described

B. Coronary Artery Bypass Grafting: In 1968, Favaloro [1] performed the first coronary artery bypass operation (CABG), and by the early 1970s many cardiothoracic surgeons had begun to perform the procedure. Similar to medical therapy, CABG in its early days, in many respects, was quite primitive. First, with the exception of a handful of medical centers, arterial conduits (i.e., internal mammary arteries) were seldom, if ever, employed; all grafting in the early days was accomplished with reversed saphenous veins. Subsequent studies clearly have demonstrated that long-term patency is markedly better with arterial than with saphenous venous conduits [2]. Second, antiplatelet therapy (with aspirin) was never used; in fact, the surgeons went to great lengths to discontinue aspirin 7 to 10 days before CABG, in order to reduce the magnitude of intra- and postoperative bleeding. Only later (in the early 1980s) would it become clear that perioperative aspirin substantially improved short- and long-term graft patency. Third, myocardial preservation during cardiopulmonary bypass often was incomplete and inadequate (Table 2). As a result, it was not unusual that patients entered the Operating Room with reasonably good left ventricular (LV) systolic function, yet exited with worsened systolic function. In short, in the 1970s, both the medical and the surgical treatments of CAD – by 2002 standards – were quite primitive (Table 2).

TABLE 2: TREATMENT OF CAD IN THE 1970s

AVAILABLE AND UTILIZED

MEDICAL	SURGICAL
Sublingual NTG	Saphenous Vein Conduits
QID Propranolol	Poor Cardioplegia

NOT AVAILABLE OR UTILIZED

Antiplatelet Agents	Antiplatelet Agents
Long-Acting/Selective B-Blockers	Arterial Conduits
ACE Inhibitors	Adequate Cardioplegia
Calcium Antagonists	Long-Term Operative Experience
Statins	

C. Randomized Comparisons of Medical Rx and CABG in Stable Angina: In the setting, therefore, of somewhat primitive medical and surgical treatment of CAD, several randomized comparisons of medical therapy and CABG were performed in the 1970s. In patients with **stable** angina, 3 such randomized comparisons were performed: the Veterans Administration Cooperative Study [3], the Coronary Artery Surgery Study

(CASS)[4], and the European Coronary Surgery Study [5]. In Table 3 (below) are displayed the "nuts and bolts" of these 3 trials.

TABLE 3
RANDOMIZED COMPARISONS OF MEDICAL Rx & CABG IN STABLE ANGINA

	VA Cooperative [3]	CASS [4]	European [5]
# patients	686	780	767
# women	0	76	0
Yrs of enrollment	1972-74	1975-79	1973-76
Patient age (yrs)	27-68	$\leq$ 65	< 65
LV Ejection Fraction	Normal in 80% 20-49% in 20%	Normal in 80% 35-49% in 20%	Normal
Operative Mortality	5.8%	1.4%	3.2%

By 2002 standards, these trials were (a) small, with a **total** enrollment of slightly > 2200 subjects; (b) almost completely devoid of female participation (a total of only 76 female subjects); (c) devoid of patients with severely depressed LV systolic function (i.e., almost all subjects had LV ejection fractions > 35%); and (d) largely devoid of elderly subjects (almost all subjects were < 65 years of age). As noted, both treatment strategies were primitive and limited. Thirty years later, one wonders if the results of these trials are, in any way, relevant.

All 3 randomized trials yielded remarkably similar "bottom line" results. First, CABG was superior to medical Rx in relieving angina, improving exercise tolerance and so-called "quality of life," and alleviating the need for antianginal drug therapy. Second, in comparison to medical Rx, CABG improved survival in patients with severe, multivessel CAD, particularly in the setting of depressed LV systolic function (ejection fraction < 50%). The specific subgroups in whom CABG was superior to medical Rx in improving survival were those with (a) 3 vessel CAD + an LV ejection fraction < 50% [3,4] and (b) 2 or 3 vessel CAD with normal LV systolic function if, as a part of the 2 or 3 vessel CAD, the proximal portion of the left anterior descending coronary artery was significantly narrowed [5].

D. Randomized Comparisons of Medical Rx and CABG in Unstable Angina: During this same time period, 2 randomized comparisons of medical Rx and CABG were performed in patients hospitalized with **unstable** angina pectoris: the NIH-sponsored Cooperative Study of Unstable Angina [6] and the Veterans Affairs Cooperative Study of Unstable Angina [7] (Table 4, next page). As with the 3 randomized comparisons of medical Rx and CABG in patients with stable angina, these trials were (a) remarkably small (a total of 756 patients), (b) almost completely devoid of female participation (a

total of only 46 female subjects), (c) devoid of subjects with severely depressed LV systolic function, and (d) devoid of patients > 70 years of age.

TABLE 4
RANDOMIZED COMPARISONS OF MEDICAL Rx & CABG IN UNSTABLE ANGINA

	VA Cooperative [7]	NIH-Sponsored [6]
# patients	468	288
# women	0	46
Years of enrollment	1976-82	1972-76
Patient age (yrs)	< 70	< 70
LV Ejection Fraction	Normal in 71% 30-49% in 29%	> 30%
Operative mortality	4.1%	5%

The 2 trials yielded similar results. In comparison to medical Rx, CABG was more effective at relieving angina and reducing the incidence of repeat hospitalization over the ensuing months for recurrent unstable angina. Interestingly, the incidence of myocardial infarction was similar in the 2 groups. The survival data were similar to those of the 3 randomized trials of subjects with stable angina: those with severe, multivessel CAD, usually in conjunction with depressed LV systolic function, had a better survival with CABG.

E. Randomized Comparisons of Medical Rx and PTCA: Although PTCA was first performed in late 1977 and became widespread by the early to mid 1980s, randomized comparisons of PTCA and medical Rx were not performed until the late 1980s and not reported until the 1990s. Even to date, the number and magnitude of such direct comparative studies are very small. Parisi and the ACME Investigators [8] randomly assigned 212 male subjects with single vessel CAD to medical Rx (n = 107) or PTCA (n = 105) between 1987 and 1990. Although angina improved substantially in both groups, greater relief of angina was observed in those who had PTCA (Figure 1, next page). Twice as many of the PTCA patients were free of angina 1 month after treatment; at 6 months, 64% of the PTCA subjects and 46% of the medical Rx patients were angina-free. MI occurred in 5 PTCA patients and in 3 medically treated subjects. Death occurred in 1 medically managed subject and none of those in whom PTCA was performed.

Hueb et al [9] randomly assigned 214 subjects (58% male, 42% female) with isolated disease of the proximal left anterior descending coronary artery to (a) CABG (with a left internal mammary artery conduit)(n = 70), (b) PTCA (n = 72), or (c) medical Rx (n = 72). During an average follow-up period of 3 years, a primary end-point (defined as cardiac death, MI, or refractory angina requiring revascularization) occurred in only 2 subjects

assigned to CABG, whereas it occurred more often in those treated with medical Rx or PTCA (Table 5, below). All 3 management strategies resulted in a similar incidence of death and MI during follow-up.

Figure 1: Percentage of patients who were free of angina each month after randomization. B = before. At 1, 2, 3, 4, 5, and 6 months, those having PTCA (hatched bars) were more likely than those treated medically (clear bars) to be free of angina. From reference # 8.

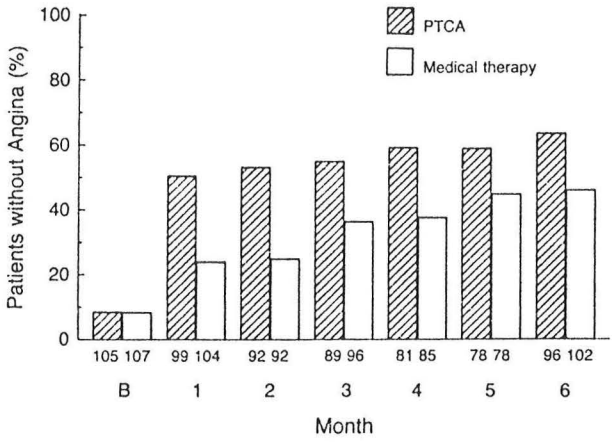


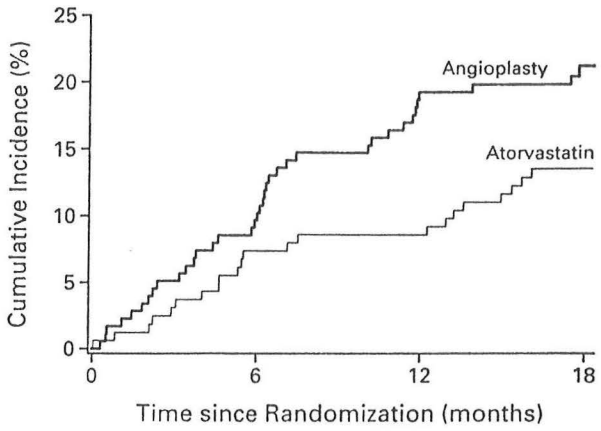
TABLE 5
RESULTS OF THE MEDICINE, ANGIOPLASTY OR SURGERY STUDY (MASS)

	Medical Rx (n=72)	PTCA (n=72)	CABG (n=70)
Cardiac death	0	1	1
Myocardial Infarction	2	2	1
Refractory Angina	7	27	0
Stroke	0	0	0

From reference # 9

Finally, Pitt et al [10] randomly assigned 341 subjects with stable 1 or 2 vessel CAD, normal LV systolic function, mild to moderate angina, and a serum LDL concentration $\geq$ 115 mg% to (a) continued antianginal Rx + atorvastatin (lipitor), 80 mg QD, or (b) PTCA + antianginal Rx, as needed. These patients had been referred for percutaneous revascularization. Atorvastatin induced an average 46% reduction in the serum LDL concentration. Over an 18-month period of follow-up, 13% of those given atorvastatin and 21% of those having PTCA had an ischemic event (defined as cardiac death, nonfatal MI, required CABG or PTCA, or worsening angina necessitating hospitalization)($p < 0.05$)(Figure 2, next page). Therefore, in relatively "low-risk" subjects with stable CAD, aggressive lipid-lowering therapy is at least as effective as PTCA in reducing the incidence of ischemic events.

Figure 2: Cumulative incidence of first ischemic events with PTCA or atorvastatin. From reference # 10.



CABG VERSUS PERCUTANEOUS THERAPY IN PATIENTS WITH STABLE OR UNSTABLE ANGINA

A. CABG Versus PTCA: Several (a total of 8) randomized trials, beginning in the late 1980s and concluding in the mid-1990s, compared CABG and PTCA in patients with single [9, 11,12] or multivessel CAD [12-17]. The results of these 8 trials were remarkably similar and consistent. First, the periprocedural mortality was similar for the 2 procedures, averaging 1.0 to 1.5%. Second, the periprocedural morbidity was somewhat higher in those having CABG: they required a substantially longer hospitalization (average, 14 days for CABG, 4 days for PTCA) and period of convalescence, and the incidence of periprocedural Q wave MI was higher in the CABG patients (4.6% to 10.3% in the various studies) than in those undergoing PTCA (2.1% to 6.3% in the various studies). Third, long-term survival for all participating subjects was similar for the 2 treatment strategies. As will be discussed subsequently, those with treated diabetes mellitus had a better survival with CABG than with PTCA. Fourth, the surgically treated patients enjoyed better relief of angina and fewer antianginal medications, and those having PTCA were much more likely to require repeat coronary angiography and a further revascularization procedure (Table 6, below, and Figures 3 and 4, next page).

TABLE 6: THE MAIN FINDINGS OF CABG VS PTCA TRIALS

	CABG = PTCA	CABG Better	PTCA Better
1. Periprocedural mortality	xxxx		
2. Periprocedural morbidity			xxxx
3. Long-term survival	xxxx		
4. Angina relief/no need for repeat procedures		xxxx	

Figure 3: Survival of patients with multivessel CAD treated with CABG or PTCA. From reference # 15.

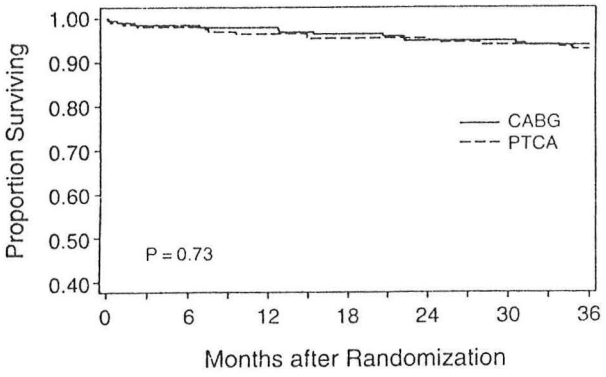
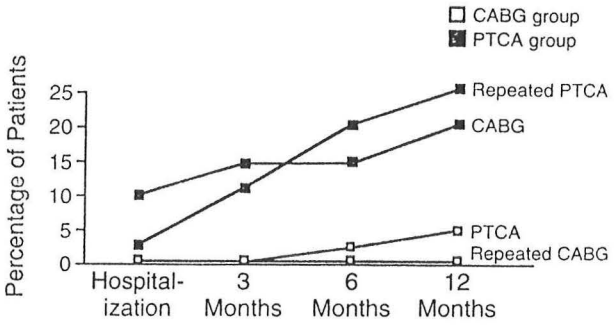


Figure 4: Rate of further interventions in the 2 treatment groups. From Reference # 14.



In a meta-analysis of all 8 trials, Pocock et al [18] summarized their results succinctly; these data are displayed in Table 7, below.

TABLE 7: RESULTS OF THE 8 RANDOMIZED COMPARISONS OF CABG & PTCA
(Average period of follow-up = 2.7 years)

	CABG (n = 1661)	PTCA (n = 1710)
Death	4.4%	4.6%
Death or nonfatal MI	9.3%	9.9%
Additional procedure required within 1 year of randomization	3.0%	34.0% *

* $p < 0.001$ in comparison to CABG

From reference # 18.

B. CABG Versus PTCA in Patients with Diabetes Mellitus: Of the 8 randomized comparisons of PTCA and CABG previously enumerated and discussed, the largest was BARI (Bypass Angioplasty Revascularization Investigation)[17]. The BARI investigators randomly assigned 1829 subjects with multivessel CAD to CABG (n = 914) or PTCA (n = 915), after which they were followed for an average of 5.4 years. The overall results of BARI are displayed in Table 8 (next page). As compared with CABG, PTCA did not compromise 5 year survival in patients with multivessel CAD, although subsequent revascularization was required more often with PTCA. **For treated diabetics (who comprised 20% of the study population), five-year survival was better with CABG** (Figure 5, next page).

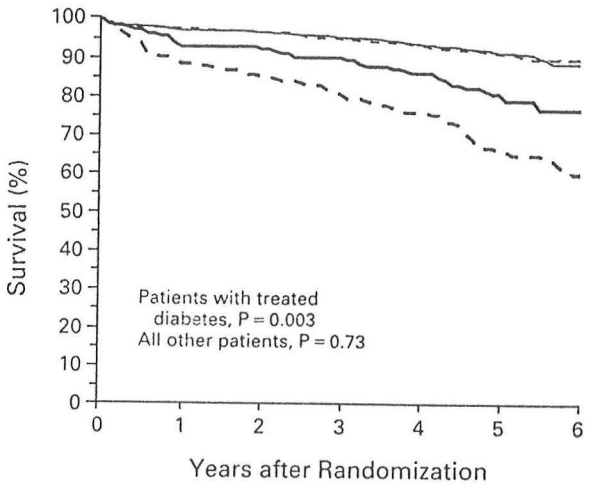
TABLE 8: RESULTS OF BARI

	CABG (n=914)	PTCA (n=915)
In-hospital mortality	1.3%	1.1%
Periprocedural Q wave MI	4.6%	2.1% *
Periprocedural stroke	0.8%	0.2%
Five year survival (all patients)	89.3%	86.3%
Five year survival free of Q wave MI	80.4%	78.7%
Additional revascularization procedure within 5 years	8.0%	54.0% *
Five year survival (treated diabetics)	80.6%	65.5% *

* $p < 0.01$ compared to CABG

From reference # 17

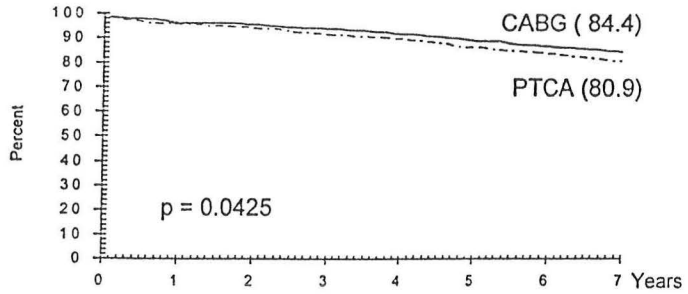
Figure 5: Survival among patients being treated for diabetes mellitus (heavy lines) and all other patients (light lines). CABG patients are represented by solid lines, PTCA patients by dashed lines. From reference # 17.



Recently, the 7-year results of BARI have been published [19]. These data are summarized in Figure 6 (next page). At 7 years, the treated diabetics had a substantially better survival with CABG than with PTCA. In contrast, those without treated diabetes mellitus had an excellent survival regardless of treatment strategy.

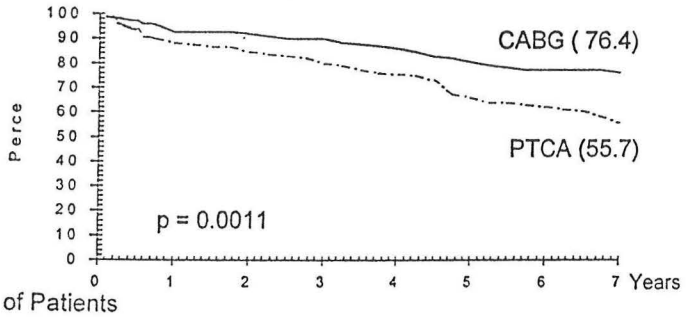
Figure 6: 7-year survival in BARI for all subjects (panel A), those with treated diabetes mellitus (panel B), and those without treated diabetes mellitus (panel C). Survival at 7 years was similar for CABG or PTCA in those without treated diabetes mellitus, whereas those with treated diabetes mellitus had a much better survival with CABG than with PTCA. From reference # 19.

A. Survival-All Patients



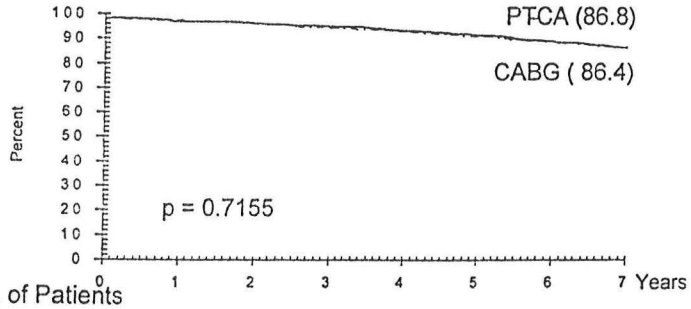
No. of Patients			
CABG	914	860	590
PTCA	915	842	579

B. Survival-Patients with Treated Diabetes



No. of Patients			
CABG	180	161	100
PTCA	173	139	70

C. Survival-Patients without Treated Diabetes



No. of Patients			
CABG	734	699	490
PTCA	742	703	509

As discussed previously, CABG was shown to be superior to medical Rx in improving survival in subjects with (a) 3 vessel CAD + an LV ejection fraction < 50% [3,4] and (b) 2 or 3 vessel CAD with normal LV systolic function if, as a part of the 2 or 3 vessel CAD, the proximal portion of the left anterior descending coronary artery was significantly narrowed [5]. Are the results of percutaneous Rx similar to those of CABG in these patient populations? The answer appears to be "yes." Berger et al [20] examined the results of BARI in nondiabetic patients with these specific anatomic features. As depicted in Figures 7 and 8 (below), the actuarial survival curves over a 7 year period of observation were similar for CABG and PTCA.

Figure 7: Actuarial survival of nondiabetic patients with 3 vessel CAD and a depressed LV ejection fraction. From reference # 20.

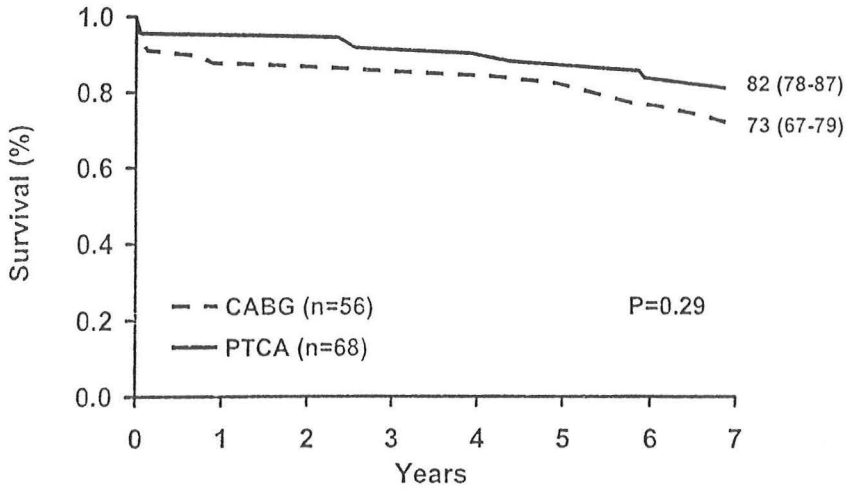
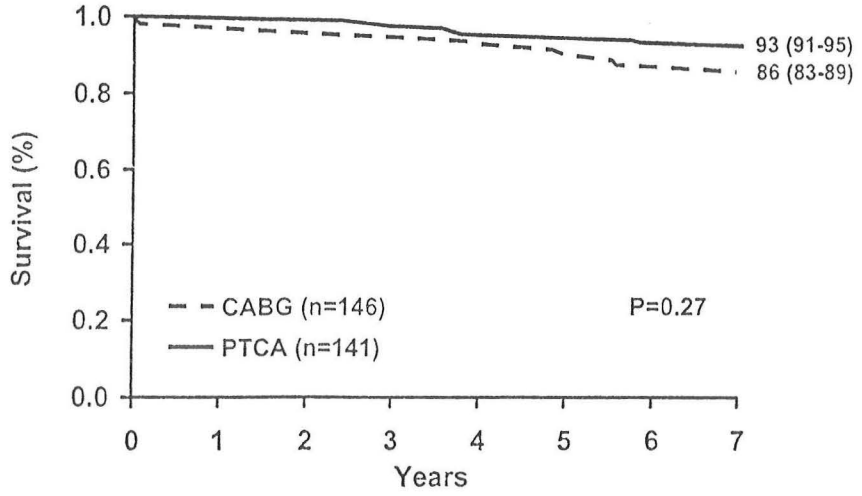


Figure 8: Actuarial survival of nondiabetic subjects with 2 vessel CAD, including narrowing of the proximal left anterior descending coronary artery. From reference # 20.



C. CABG Versus Stenting: By the early 1990s, so-called "POBA" – plain old balloon angioplasty – began to be supplanted by stenting, and by 1995, stenting was used in the majority of patients undergoing percutaneous revascularization. At present, it is estimated that 75 to 80% of all percutaneous revascularization procedures involve stenting. The clear advantage of stenting over POBA is a reduced incidence of restenosis and, as a result, a reduced need for additional revascularization procedures. Specifically, the incidence of symptomatic restenosis with POBA is roughly 35%, whereas with stenting it is 20 to 25%. From April, 1997 to June, 1998, Serruys et al [21] randomly assigned 1205 patients with stable angina and multivessel CAD to CABG (n = 605) or stenting (n = 600). Two-thirds of the patients had 2 vessel CAD, the other third 3 vessel CAD. As the data in Table 9, below, indicate, at 1 year the 2 groups were similar in the incidence of death, stroke, and MI. During the 1 year of follow-up, the stented patients were more likely to undergo a second revascularization procedure.

TABLE 9: CABG VERSUS STENTING IN STABLE ANGINA & MULTIVESSEL CAD CLINICAL END-POINTS AT 1 YEAR

	CABG (n = 605)	Stenting (n = 600)
Death	2.8%	2.5%
Cerebrovascular accident	2.1%	1.7%
Myocardial infarction	4.8%	6.2%
Repeat revascularization	3.8%	21.0% *

* $p < 0.01$ in comparison to CABG From reference # 21

In this study, Surruys et al [21] also examined monetary costs. The cost for the initial procedure averaged $4,212 less for stenting than for CABG, but this difference was reduced during follow-up because of the increased need for repeat revascularization procedures in those undergoing stenting. After 1 year, the net difference in favor of stenting was estimated to be $2,973 per patient.

De Feyter et al [22] randomly assigned 450 patients with **unstable angina** and multivessel CAD to stenting (n = 226) or CABG (n = 224). The results were similar to those described previously for subjects with stable angina and are displayed in Table 10 (next page).

Although some patients with multivessel CAD are excellent candidates for percutaneous revascularization (PTCA or stenting), CABG – quite appropriately – will continue to be the preferred revascularization procedure for many of them. Many subjects with multivessel CAD are less than optimal candidates for percutaneous Rx. In all the comparisons of CABG and percutaneous Rx, an overwhelming majority of patients were

TABLE 10: CABG VS STENTING IN UNSTABLE ANGINA & MULTIVESSEL CAD CLINICAL END-POINTS AT 1 YEAR

	CABG (n = 224)	Stenting (n = 226)
Death	2.2%	2.7%
Cerebrovascular accident	3.1%	0.4% *
Myocardial infarction	5.8%	5.8%
Repeat revascularization	3.6%	16.8% *

* $p < 0.01$ in comparison to CABG

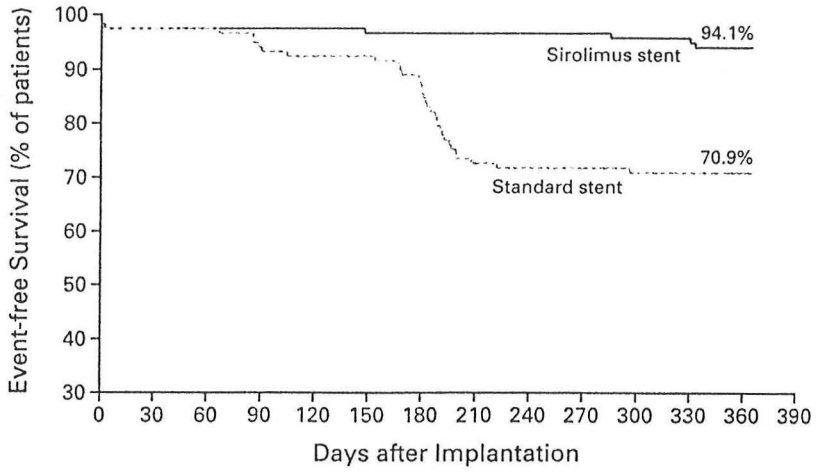
From reference # 22

excluded from enrollment because of factors that would make percutaneous Rx unsafe or unlikely to be successful, most commonly (a) chronically occluded coronary arteries, (b) anatomically complex coronary arterial stenoses, or (c) some degree of narrowing of the left main coronary artery. This "fact of life" is unlikely to change unless better percutaneous methods are developed for patients with chronically occluded arteries or disease of the left main coronary artery. For these individuals, CABG will continue to be the preferred revascularization strategy.

D. Summary: The management of the patient with (a) single vessel CAD (regardless of LV systolic function), (2) 2 vessel CAD not involving the proximal left anterior descending coronary artery (regardless of LV systolic function), and (c) 3 vessel CAD and normal LV systolic function can be individualized and "symptom-driven." For some of these subjects, medical Rx will be sufficient, in that it will substantially or completely alleviate symptoms. If nonmedical Rx is chosen, the decision of whether to use percutaneous or surgical Rx should be reached "with the understanding that CABG is associated with greater initial morbidity but results in more effective relief of angina and freedom from repeat procedures in the ensuing years. On the other hand, percutaneous Rx is associated with a lower rate of initial morbidity but a greater likelihood of recurrent angina, with the need for antianginal medications and subsequent revascularization procedures"[23]. The patient with (a) 3 vessel CAD and depressed LV systolic function or (b) 2 or 3 vessel CAD with narrowing of the proximal left anterior descending coronary artery (regardless of LV function) should be encouraged to undergo percutaneous or surgical revascularization (irrespective of symptoms), in order to achieve an improved survival. If the patient is diabetic, CABG probably should be chosen. If he or she is not diabetic and has coronary anatomy amenable to a percutaneous or surgical approach, the decision of whether to use percutaneous or surgical therapy, once again, can be based of the preferences of the patient, with appropriate input from his/her physician.

E. Future Prospects: In all the above-cited comparisons of CABG and percutaneous Rx for patients with 1, 2, or 3 vessel CAD (regardless of LV systolic function), the consistent (and only) disadvantage of percutaneous management has been the substantial percentage of patients who require repeat coronary angiography followed by CABG or repeat percutaneous Rx, an occurrence caused by the process known as restenosis. As stated previously, symptomatic restenosis occurs in about 35% of subjects in the 1 to 12 months after successful POBA and in 20 to 25% of those who have had successful stenting. If one could effectively prevent restenosis, this one major disadvantage of percutaneous Rx would be alleviated, thereby making percutaneous Rx much more atttractive than CABG (provided, of course, that there are no contraindications to percutaneous Rx). Preliminary data [24] suggest that sirolimus-eluting stents are seldom, if ever, complicated by restenosis. Specifically, of 238 patients randomly assigned to receive a standard (n = 118) or a sirolimus-eluting (n = 120) stent, 27% of the former and 0% of the latter group developed restenosis within 6 months ($p < 0.001$) (Figure 9, below). These incredibly positive results await confirmation in larger studies. If they are valid, percutaneous Rx will supplant CABG in patients whose coronary anatomy allows it.

Figure 9: Event-free survival during 1 year of follow-up for patients receiving a standard or a sirolimus-eluting stent. From reference # 24.



OFF-PUMP CORONARY ARTERY BYPASS GRAFTING

Although peri-CABG morbidity and mortality have improved since the 1970s, the basic approach to the procedure has not changed: as with the first CABG, the patient is exposed to (a) a median sternotomy, (b) full heparinization, (c) cardiopulmonary bypass with aortic cross-clamping, (d) global ischemic cardiac arrest with or without cooling, (e) saphenous vein harvest and aortic side-clamping, and (f) an anesthetic regimen specific to cardiopulmonary bypass-supported CABG. Clearly, the "classic CABG" is not free of

complications, particularly in elderly subjects. In the United States in 1996, the Society of Thoracic Surgeons reported that 170,895 CABGs were performed. The overall operative mortality was 2.9% (2.5% for men, 4.0% for women), In only 65% of the procedures were no complications reported [25]. Of the 101,812 patients $\geq$ 65 years of age undergoing CABG in the United States in 1993, 4.3% died in hospital, 3.6% were discharged to a non-acute-care facility, and 10.2% were discharged to home > 14 days postoperatively (the delay being due to complications). In short, only 82% were discharged to home < 14 days postoperatively [26].

Cardiopulmonary bypass is associated with several problems, including (a) substantial blood loss, with required replacement of blood products; (b) inadequate or incomplete myocardial preservation during global ischemic cardiac arrest; and (c) discrete cerebrovascular events or sustained neurocognitive dysfunction [27]. Particularly troubling and frequent in elderly subjects are cerebrovascular catastrophic events or sustained neurocognitive impairment. Following cardiopulmonary bypass, many subjects manifest impaired cognitive function. Newman et al [28] demonstrated cognitive decline in 53% of post-CABG patients at the time of hospital discharge, 36% at 6 weeks, 24% at 6 months, and 42% at 5 years. Roach et al [29] evaluated 2108 patients from 24 American institutions who underwent "classic CABG." Adverse cerebral outcomes occurred in 129 (6.1%), with half being type I (fatal cerebral injury or nonfatal stroke) and the other half being type II (new deterioration in intellectual function or new-onset seizures). In comparison to those without, the 6.1% of subjects with an adverse cerebral outcome were more likely to die, to have a prolonged hospital stay, and to be discharged to an intermediate or long-term care facility. Older age was the most important predictor of an adverse cerebral outcome (type I or II) (Table 11, below).

TABLE 11: ADVERSE CEREBRAL OUTCOMES IN PATIENTS HAVING CABG

	Type I Outcome (n = 66)	Type II Outcome (n = 63)	No Adverse Outcome (n = 1979)
Death during hosp	21%	10%	2%
Duration of ICU stay (days)	11	7	3
Duration of hosp (days)	25	21	10
Discharged home	32%	60%	90%

From reference # 29

The neurologic complications related to cardiopulmonary bypass may be caused by (a) macroembolism (large embolic material, such as air, intracardiac or intravascular thrombus, or atherosclerotic debris from the ascending aorta which is dislodged during aortic cross-clamping); (b) microembolism ("small" embolic material, such as gaseous emboli or platelet aggregates); and (c) the so-called "systemic inflammatory response syndrome" [30]. Cardiopulmonary bypass induces the release of numerous proinflammatory cytokines, including tumor necrosis factor alpha, IL-1, IL-6, and IL-8.

In an attempt to avoid the potential problems associated with cardiopulmonary bypass, many cardiac surgeons have become increasingly enthusiastic about the so-called **OPCAB**: **O**ff-**P**ump **C**oronary **A**rtery **B**ypass grafting. Although CABG on the beating heart without cardiopulmonary bypass was first reported in the late 1960s, problems with (a) cardiac motion and (b) limited (if any) access to the posterior, inferior, and lateral surfaces of the heart rendered the procedure suboptimal. In the early days of CABG, therefore, as cardiopulmonary bypass improved, OPCAB was largely abandoned in the United States, but it continued to be used in some other countries, where its use was limited to patients needing bypass of only the left anterior descending and/or right coronary arteries.

In the 1990s, the few surgeons who performed OPCAB attempted to achieve target coronary artery stabilization/immobilization with drug-induced bradycardia or intermittent temporary asystole (accomplished with intermittent bolus injections of adenosine). However, graft patency was inferior to that of cardiopulmonary bypass-assisted CABG, due to frequent problems with the anastomosis of the graft to the native coronary artery. In the mid-1990s, so-called "mechanical stabilizers" were developed, with which one could effectively limit target artery motion. With these stabilizing devices, graft patency improved. At the same time, techniques and devices for cardiac positioning made it possible to graft multiple epicardial coronary arteries, even those on the posterior, inferior, and lateral surfaces of the heart.

The technique of OPCAB can be summarized briefly, as follows. Following exposure of the heart via a median sternotomy (or occasionally through a smaller intercostal incision at the left or right sternal border), each coronary artery to be grafted is dissected free from the surrounding tissue and held with 2 sutures a short distance (1 to 2 cm) proximal and distal to the site of graft anastomosis. A stabilizing device, which is attached to the operating table, is placed on the cardiac surface in the area surrounding the dissected epicardial coronary artery. When pressed gently against the epicardial surface of the heart, this device allows the surgeon to immobilize the coronary artery of interest without substantially compromising overall pump function. Special effort is made to use arterial conduits (i.e., the left and/or right internal mammary arteries and/or the gastroepiploic artery). Numerous reports of sizable anecdotal experiences have suggested that OPCAB is safe and effective (Table 12, below). Importantly, they also have suggested

TABLE 12: INITIAL RESULTS OF OPCAB

	# patients	operative death	operative MI	graft patency
Diegeler et al [31]	209	0.5%	1.9%	97%
Jansen et al [32]	100	0%	4.0%	95%
Tasdemir et al [33]	2052	1.9%	2.9%	NA
Hart et al [34]	1582	1.0%	1.2%	NA

that graft patency is comparable to that achieved with cardiopulmonary bypass-assisted CABG.

Over the past 2 years, several cardiac surgeons have reported large single or multicenter experiences with OPCAB and have compared its results to those of cardiopulmonary bypass-assisted CABG [35-38]. These **nonrandomized** comparisons suggest strongly that OPCAB offers advantages in morbidity and mortality. The data from the largest of these comparisons [38], which are taken from the database of the American Thoracic Society for calendar years 1998 and 1999, are displayed in Table 13 (below). It is important to emphasize that, if anything, those undergoing OPCAB were deemed (by standard criteria) to be "sicker" than those undergoing on-pump CABG, in that the OPCAB subjects were older, more likely to be female, and more likely to have certain comorbid conditions, including chronic obstructive pulmonary disease, azotemia, and cerebrovascular disease.

TABLE 13: NONRANDOMIZED COMPARISON OF OPCAB & ON-PUMP CABG

	OPCAB (n=11,717)	ON-PUMP (n=106,423)
In-hospital mortality	2.3%	2.9% *
Perioperative stroke	1.3%	2.0% *
Acute renal failure	3.9%	4.3% *
Prolonged ventilation	4.1%	6.5% *
Reoperation for bleeding	2.1%	2.8% *
Mediastinitis	0.6%	0.7%
Length of hospital stay (days)	6	7 *

* $p < 0.01$ in comparison to OPCAB From reference # 38

Recently, van Dijk et al [39] and Angelini et al [40] have published the first randomized comparisons of OPCAB and on-pump CABG. Van Dijk et al [39] randomly assigned 281 patients, mean age 61 years, to off-pump or on-pump CABG. Mortality and "substantial" morbidity (stroke, MI) were low – and similar in incidence – in both groups. As displayed in Table 14 (next page), those who had OPCAB (a) were less likely to require blood products perioperatively, (b) had a somewhat smaller release of CK into the blood, and (c) were discharged from hospital slightly (average, 1 day) sooner. Angelini et al [40] randomly assigned 200 subjects to OPCAB and 201 to on-pump CABG. As in the study of van Dijk et al [39], mortality and substantial morbidity were low in both groups. The OPCAB patients (a) required less blood products perioperatively, (b) were less likely to require inotropic support postoperatively (presumably a reflection of less myocardial "stunning" with OPCAB), and (c) left the ICU and the hospital somewhat sooner. These data are similar to those of Pfister et al [41], who compared 220 OPCAB patients with

220 retrospectively matched on-pump control subjects. In comparison to the on-pump controls, those who had OPCAB were less likely to require blood products (73% of OPCAB subjects and 55% of on-pump patients were not transfused), and the OPCAB patients were less likely to have a postoperative low-output state (reflective of less myocardial "stunning" in those not having cardiopulmonary bypass).

For several reasons, OPCAB is considerably less expensive (monetarily) than on-pump CABG. First, intraoperative equipment, materials, and personnel are more limited. Second, time in the ICU is reduced. Third, transfusion requirements are less. Fourth, total time in-hospital is reduced. Ascione et al [42] demonstrated that OPCAB was substantially less costly than on-pump CABG.

What are the limitations and potential problems with OPCAB? First, since each surgical anastomosis consumes more time than if it were performed on the arrested heart, the total number of anastomoses that can be performed with OPCAB is only 3 or 4. Second, in an occasional subject, the left anterior descending coronary artery is intramyocardial rather than on the epicardial surface. Obviously, such an intramyocardial artery would not be graftable in the setting of a beating heart. Third, despite attempts to make the surgical area of interest completely motionless (with a stabilizing device of some sort), a minimal amount of motion usually remains. As a result, concerns exist about the

TABLE 14: RANDOMIZED COMPARISON OF ON-PUMP & OFF-PUMP CABG

	off-pump (n=142)	on-pump (n=139)
# of distal anastomoses	2.4	2.6
use of arterial conduits only	84%	76%
mortality	0	0
stroke	1	1
MI	5	5
Survival free of CV events	93%	94%
Use of blood products	3%	13% *
CK release	164	277 *
# days to discharge	6	7 *

From reference # 39 * $p < 0.01$ in comparison to off-pump

adequacy of graft flow as well as long-term graft patency. Will those in whom grafting was accomplished on the beating heart have a lower incidence of long-term graft

patency when compared to those in whom the anastomoses were performed on an arrested, motionless heart? Preliminary anecdotal data suggest that the patency of off-pump LIMA to the left anterior descending coronary artery is similar (> 90%) to that of on-pump grafting [43]. In this regard, encouraging data have been published by Angelini et al [40], who reported that the incidence of death or myocardial infarction during 2 years of follow-up was similar in their 200 OPCAB and their 201 on-pump CABG subjects.

TRANSMYOCARDIAL LASER REVASCULARIZATION (TMR)

An occasional patient with far-advanced CAD and severe angina is not a candidate for CABG or percutaneous intervention, most often because of extremely diffuse atherosclerotic CAD. These individuals have frequent angina, limited exercise tolerance, and a poor quality of life. So-called transmyocardial laser revascularization (TMR), performed surgically or with catheter-based technology, was developed to treat such patients. In 1965, Sen et al [44] proposed the creation of transmural channels in the LV wall to permit direct perfusion of ischemic myocardium with oxygenated LV blood. This concept was based on the model of the reptilian heart, in which the LV myocardium is perfused directly from endothelium-lined channels that radiate out from the LV cavity. Subsequently, Mirhoseini et al [45,46] advanced the concept by using laser (rather than mechanical) energy to create the transmural channels, after which several reports of anecdotal experiences [47,48] suggested that TMR improved angina in patients who were not candidates for CABG or percutaneous therapies.

To perform TMR surgically, the surgeon exposes the beating heart through a left lateral thoracotomy, places a laser (carbon dioxide or holmium) on the epicardial surface of the LV, and applies sufficient energy to create small channels from the epicardial to the endocardial surfaces. During a typical procedure, 10 to 50 such channels are created. Initially, as noted, these small, laser-created transmyocardial channels were thought to improve the perfusion of ischemic myocardium by providing it with direct access to oxygen-rich LV blood, but it was subsequently found that the channels quickly occlude after the procedure [49].

On the basis of the previously noted anecdotal reports, 4 multicenter, randomzied, controlled trials – 1 in the United Kingdom and 3 in the United States – have now compared surgical TMR with medical therapy in patients with severe, refractory angina [50-53]. Obviously, these trials were randomized and controlled **but not blinded**. As the data in Table 15 (next page) demonstrate, these 4 studies provided results that, by and large, were consistent with one another. In comparison to medical therapy, surgical TMR was more likely to induce an improvement in the severity of angina, but there was little **objective** evidence that TMR was superior to medical therapy, and in none of the studies was surgical TMR associated with an improvement in LV systolic function or survival.

TABLE 15: RANDOMZIED COMPARISONS OF SURGICAL TMR AND MEDICAL Rx

	Schofield [50]	Burkhoff [51]	Frazier [52]	Allen [53]
# patients	188	182	192	275
Angina improved @ 1 yr				
TMR	25%	48%	72%	76%
Medical Rx	4%	14%	13%	32%
Perioperative mortality	5%	1%	3%	5%
Survival @ 1 yr				
TMR	89%	95%	85%	84%
Medical Rx	96%	90%	79%	89%

The placebo effect of a thoracotomy should not be underestimated, particularly in patients for whom all therapeutic options have been exhausted and particularly when the procedure is combined with the use of a laser device. In all 4 trials, patients were eligible for enrollment only if they had severe, activity-limiting angina despite aggressive antianginal medical therapy and only if CABG and percutaneous revascularization were considered to be impossible. Such patients often are eager to embrace any procedure that offers hope of improvement. For laypersons and physicians alike, the word "laser" is synonymous with state-of-the-art, highly successful therapy. This inherent prejudice in favor of laser therapy is impossible to quantify. In all the studies, crossover from medical Rx to TMR "was allowed as an incentive for patients assigned to maximal medical Rx to remain in the study if medical Rx failed" [52], thereby implying a bias on the part of the investigators that TMR was more effective than medical Rx [54].

Recently, Stone et al [55] have reported the first randomized and **double-blind** comparison of maximal medical Rx and **percutaneous** TMR in subjects with refractory angina. A total of 141 subjects were studied; 70 received TMR (and continued medical Rx, as needed), whereas 71 had a sham-TMR and continued medical Rx. At 6 months, angina severity improved by 2 or more classes in 49% of the TMR subjects and 37% of those given only medical Rx ($p = 0.33$). Exercise duration increased 64 seconds in the TMR group and 52 seconds in the medical Rx only group ($p = 0.73$). During the 6 months of follow-up, MI was documented in 4.3% on the TMR patients and 2.9% of the medical Rx subjects; death occurred in 8.6% and 8.8% of the TMR and medical Rx patients, respectively. These completely negative results led some investigators to conclude that **"DMR (Direct Myocardial Revascularization) is DNR."**

At present, the final word on TMR has not been written. The surgeons argue vehemently that surgical TMR is more effective than percutaneous TMR in creating truly transmural channels; as a result, they argue that surgical TMR is a better procedure. If, in fact, TMR has some efficacy aside from its marked placebo effect, how might it do so? As summarized in Table 16, several possible mechanisms have been proposed, though none is supported by substantial objective data. For example, although studies in

TABLE 16: POSSIBLE MECHANISMS BY WHICH TMR IS EFFICACIOUS

1. Marked placebo effect of a thoracotomy
2. Angiogenesis (growth of new blood vessels)
3. Denervation of ischemic myocardium
4. Infarction of ischemic myocardium

experimental animals showed that TMR induced a highly disorganized pattern of neovascularization at the periphery of laser-created channels that had occluded, the evidence that TMR, in fact, improves perfusion of ischemic myocardium in inconsistent and unpersuasive.

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