Heart
A; HD

PROLONGATION OF LIFE
IN
ISCHEMIC HEART DISEASE

Medical Grand Rounds

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October 18, 1984

. . . Seeing that death, a necessary end,
Will come when it will come.

William Shakespeare Julius Caesar
II, ii, 32

Cardiovascular disease is still responsible for approximately one-half of all deaths in the United States each year. Over the past two decades there has been significant advances into the treatment of these patients. There has been a significant decline in mortality over these two decades (Figure 1).

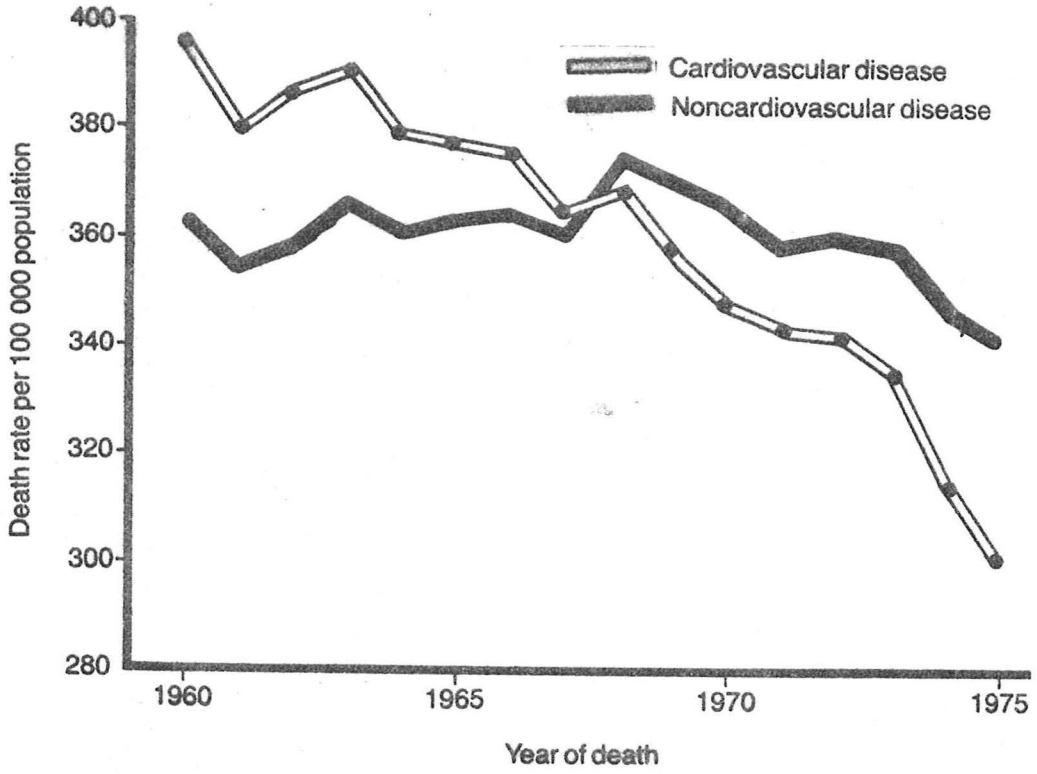

Figure 1. The decrease in cardiovascular disease between 1960 and 1976. (Levi R: Progress towards prevention of cardiovascular disease, a thirty year prospective. Modern Concepts of Cardiovascular Disease 1978; 48: No. 10 by American Heart Association, Inc.

Between 1960 and 1975 there was an almost 25% decline in cardiovascular death rates. Since 1975 the decline has continued, but due to changes in reporting methods an exact comparison is not available.[1]

There are many potential causes for this decline. Dr. Blumenthal in his introduction to the *Proceedings of the Conference on the Decline in Coronary Heart Disease Mortality* suggested some potential causes. Causes he enumerated included artifact, coronary care units, emergency medical services/CPR, surgery, Medicare-Medicaid, less smoking, blood pressure control, diet change, cholesterol change, exercise, environmental and socio-economic factors. Recently several drugs have also been

mentioned as possibilities in reducing cardiovascular deaths. This review will try to examine those factors that might be affecting longevity in Coronary Heart Disease (i.e., secondary prevention). [2]

Before we start looking at specific studies, a short review of statistical methods is in order so that we can understand the significance of these studies. To design a study to look at survival from a multi-system disease is difficult at best. We obviously would like to have prospective, blinded, randomized trials. At times these trials are impossible. Where a trial is possible, there are problems in study design and numbers of patients. The most significant problem is a statistical problem. The mortality from Coronary Heart Disease is relatively low. The low mortality greatly affects the number of patients needed for a study. Dr. Joan Reisch of our school has calculated the number of patients needed to show statistical significance at various mortalities. We are assuming that an intervention will reduce mortality by 35% as compared to placebo. We are assuming a 20% dropout (this is average for long term studies).

Placebo Mortality	Intervention Mortality	Number of Patients for 70% Chance of Proving Difference	Number of Patients for 90% Chance of Proving Difference
20%	13.0%	890	1514
10%	6.5%	1946	3320
6%	3.9%	3356	5730
2%	1.3%	10400	17782

As the annual mortality for most subgroups of Coronary Heart Disease is between 2% and 6%, the problem with setting up studies is obvious. Large numbers of patients are needed, and these patients would have to be followed over long times. The longer the study the more dropouts occur, due to lack of interest, patient moving, etc. A commonly used compromise is three years. [3-5]

Another way of looking at this is that if an intervention causes a 35% reduction in mortality and the placebo mortality is 10% and you have ten studies each with 1620 patients, from a statistical standpoint you would expect seven studies to show a significant difference and three studies to be negative, just due to chance and the low number of patients. If each study had 2940 patients, then nine studies would be positive and one negative from the statistical point of view. Similarly, any subgroup would need the same number of patients in the subgroup for a reasonable chance of proving statistical significance for that subgroup. The splitters who try to analyze subgroups from these studies often do the study a disservice and make claims of lack of significances which are unjustified due to inadequate numbers in the group.

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Beta-Adrenergic Blocking Agents

There have now been 17 trials using beta-adrenergic blocking agents after myocardial infarction. The post-myocardial infarction model has been the model selected by most investigators in order to have a chance to reach statistical significance. Post myocardial infarction patients are a more homogeneous population than angina patients (due to less errors in diagnosis) and have a higher mortality in the first year than the angina population; these two factors increase the likelihood of a successful study with a smaller number of patients. [6]

The following table summarizes the major trials with various beta adrenergic blocking agents. Three of these beta blockers are available in the United States: metoprolol, propranolol, and timolol. The three agents available in the United States are among the best studied drugs for prolongation of life.

Major Beta-Adrenergic Blocking Agent Trials

Post Myocardial Infarction

Drug	Dose (mg/day)	Patients (Number)	Total Deaths (%)	Change In Treated Group (%)		
				Total Mortality	Sudden Death	Reinfarction
Alprenolol [7]	400	230	9%	- 50%	- 70% *	0
Alprenolol [8]	400 (< 65 y/o)	282	15%	- 54% *	-	-
	(> 65 y/o)	198	42%	+ 22%	-	-
Metoprolol [9-20]	200	1395	7%	- 36%*	- 48% *	- 35% *
Oxprenolol [21-22]	?	?	?	- 16%	?	?
Practolol [23-24]	400	3053	4%	- 38% *	- 45% *	- 22%
Propranolol [25]	120	720	8%	0	-	0
Propranolol [26]	180 - 240	3837	8%	- 26% *	- 28% *	-
Sotolol [27]	320	1456	8%	- 18%	- 15%	- 41% *
Timolol [28]	20	1884	13%	- 36% *	- 45% *	- 28% *

* $p < 0.05$
\- Not reported
? Unable to locate paper

As can be seen, the majority of studies have shown a beneficial reduction in total mortality. If you lump all of the studies together, the beta blockers have reduced total mortality by 26% with a range of 15 - 35% ($p < 0.00001$). Further, if you look at those studies that have more than 1000 patients, four of five have shown a statistically significant reduction in total mortality. From the death rates and numbers of patients in these studies, this is exactly the distribution of positive and negative studies that we would expect. Hence, the evidence that beta-adrenergic blocking agents reduce mortality after myocardial infarction is extremely strong. Additional studies will not shed further light on total mortality.

The mechanisms of reduction in mortality are more difficult to establish. When we try to look at mechanism of death we are dealing with smaller numbers than for Total Mortality, and the chances of reaching statistical significance are much less than for Total Mortality. In spite of this, five of six studies that evaluated sudden death found a reduction in sudden death which ranged from 15% to 70%. Hence, reduction in sudden death certainly appears to be one mechanism in reducing mortality after myocardial infarction. [7, 9-11, 16, 17, 23-25, 27-28]

A second mechanism that has been evaluated is reinfarction. Reinfarction could certainly increase mortality. However, reinfarction causing death has not been effectively evaluated. Morbidity from reinfarction has been investigated in several of the studies. It is important to recognize that reinfarction was only analyzed in those patients who remained alive long enough to have ECG's and enzyme studies performed. Six studies have looked at reinfarction rates, and three have shown a significant reduction in reinfarction rate. It should be noted that two of the negative studies had insufficient numbers of patients from a statistical viewpoint. Of the four studies with more than 1000 patients, all showed reductions of 22% to 41%, with three of the studies reaching statistical significance. Hence, we have strong evidence that beta-adrenergic blocking agents reduce the reinfarction rate post myocardial infarction. As the reinfarction rate is decreased, then probably this also has influenced the reduction in total mortality, though we have no direct information on this point. [7, 9-11, 13, 16-17, 23-24, 26, 28]

A third potential mechanism is limitation in infarct size. Peter et al showed a significant reduction in peak creative Kinase when propranolol was administered in the first four hours after infarction. To date there are two good studies involving infarct size. The Goteborg Metoprolol Trial looked at heat stable lactate dehydrogenase in 1375 patients measured at 12 hour intervals for 48 to 108 hours. For all 1375 patients metoprolol showed a 10% lower LDH which was not significant ($p = 0.054$). For the 936 patients who received metoprolol or placebo within 12 hours of onset of symptoms, a 19% reduction in LDH was found ($p = 0.009$). In 747 patients who received drugs within eight hours, a 16% reduction in LDH was found ($p = 0.018$). In 343 patients who received drugs within four hours, the 13% reduction in LDH was not significant ($p = 0.167$). In the Goteborg Metoprolol Trial there was also a reduction in infarct size by ECG mapping techniques. A recent study with propranolol vs. placebo (MILIS) failed to show a change in infarct size in 269 patients. In the MILIS study, no change was seen in left ventricular ejection fraction, extent of area involved in pyrophosphate uptake, R-wave loss on electrocardiograms, or mortality at three years. Hence, the MILIS trial, which is the best designed trial to date, failed to show any effect of beta-adrenergic blocking agents in the first eight hours or later after onset of symptoms. It should be noted that only 124 patients were seen within eight hours in MILIS, while the Goteborg Metoprolol Trial had 747 patients within eight hours, though the methods were superior in the MILIS trial. The answer concerning

infarct size remains in doubt, and hopefully two large on-going studies with atenolol and metroprolol will shed more light on infarct size. It should be noted that the MILIS trial only gave beta-adrenergic blocking agents for nine days after infarction and the mortality data is only used as an index of infarct size, not on long term survival. [14-15, 29-30]

Though other mechanisms may play a role in the reduction of mortality with beta-adrenergic blocking agents, there is no data that addresses these other mechanisms in man. Hence, we can safely say beta-adrenergic blocking agents reduce total mortality after myocardial infarction for up to three years. We have no data after three years. A part of this reduction is a reduction in sudden death. A second part of this reduction is probably due to a lower reinfarction rate. Whether infarction size is a factor remains to be proven or not, and we must await further studies.

Another issue involving beta-adrenergic blocking agents are adverse reactions. The surprising aspect of all these studies were the low incidence of side effects. Hypotension occurred more frequently with beta-adrenergic blocking agents.

	Hypotension All Episodes		Hypotension Causing Withdrawal	
	Placebo	Drug	Placebo	Drug
Metoprolol [20]	20.2%	26.7% *	1.4%	3.7%
Propranolol [26]	-	-	0.3%	1.2% *
Sotolol [27]	0.7%	2.3% +	0.7%	2.1% +
Timolol [28]	2.8%	5.8% *	1.2%	2.8% *

* $p < 0.05$
\+ No statistics reported

Congestive heart failure, however, was not more frequent in patients receiving beta-adrenergic blocking agents.

Congestive Heart Failure

	All Episodes		Causing Withdrawal	
	Placebo	Drug	Placebo	Drug
Metoprolol [20] †	29.6%	27.4%	1.0%	0.6%
Propranolol [26]	-	-	3.5%	4.0% +
Sotolol [27]	4.1%	3.5% +	3.8%	2.6% +
Timolol [28]	9.8%	13.1%	2.3%	3.7%

* $p < 0.05$
\+ No statistics reported
† Acute administration of drug or placebo

It should be noted that the metoprolol study was started on Day One of infarction, and the other three studies after day five, accounting for the higher incidence of congestive heart failure. While beta-adrenergic blocking causes a decrease in heart rate in most patients, bradycardia which required withdrawal from the study was low.

Bradycardic Caused Withdrawal

	Placebo	Drug
Metoprolol [20]	0.7%	2.6% *
Propranolol [26]	0.3%	0.7% +
Sotolol [27]	0	4.4% +
Timolol [28]	0.2%	3.9% *

* $p < 0.05$
\+ No statistics reported

Atrioventricular block (2^{o}or 3^{o}) also did not seem to be aggravated by beta adrenergic blocking agents.

Atrioventricular Block (2^{o} or 3^{o})

	All Episodes		Causing Withdrawal	
	Placebo	Drug	Placebo	Drug
Metoprolol [20] †	4.8%	5.4%	1.6%	2.3%
Propranolol [26] +	-	-	0.1%	0.1%
Sotolol [27]	-	-	-	-
Timolol [28]	0.9%	0.7%	0.3%	0.3%

* $p < 0.05$
\+ No statistics reported
† Acute administration of drug or placebo

It should be noted that patients who had 2^0 or 3^0 atrioventricular block at randomization were excluded from all of the studies. The higher incidence of atrioventricular block in the metoprolol study was due to the fact that drug or placebo was given on Day One of infarction while never before Day Five in the other three studies. Serious ventricular ectopy was higher in the placebo group than with the beta-adrenergic blocking agents.

Serious Ventricular Ectopy

	All Episodes		Causing Withdrawal	
	Placebo	Drug	Placebo	Drug
Metoprolol [17]	9.8%	2.9% *	-	-
Propranolol [26]	-	- +	1.0%	0.3% * +
Sotolol [27]	1.6%	1.5%	1.4%	1.4%
Timolol [28]	4.0%	1.4% *	4.0%	1.4% *

* $p < 0.05$
\+ No statistics reported

When you look at total withdrawals from each of the studies, the differences between placebo and drug were small.

Total Withdrawals

	Placebo	Drug
Metoprolol [20]	19.1%	19.1%
Propranolol [26]	9.3%	12.7% *
Sotolol [27]	20.8%	25.4% *
Timolol [28]	23.3%	29.1% *

* $p < 0.05$

Hence, the incidence of side effects was greater with beta-adrenergic blocking agents, but the difference was small.

Hence, it appears that beta-adrenergic blocking agents are beneficial after myocardial infarction at reducing mortality and the increase in risk of side effects is small. As seen in the following figure, there is some suggestion that the earlier the beta-adrenergic blocking agent is given, the greater the overall survival; but this is only a suggestion. As the potential mechanisms for decreased mortality with beta-adrenergic blocking agents are also present in all patients with coronary artery disease, the question should be raised whether this protective effect might be common to all patients with coronary artery disease, though no data is available except during the first three years after myocardial infarction. From currently available data no subgroup can be identified that has more or less percent reduction in mortality than any other subgroup; the lack of statistical significance in various subgroups may be explained by inadequate number of patients.

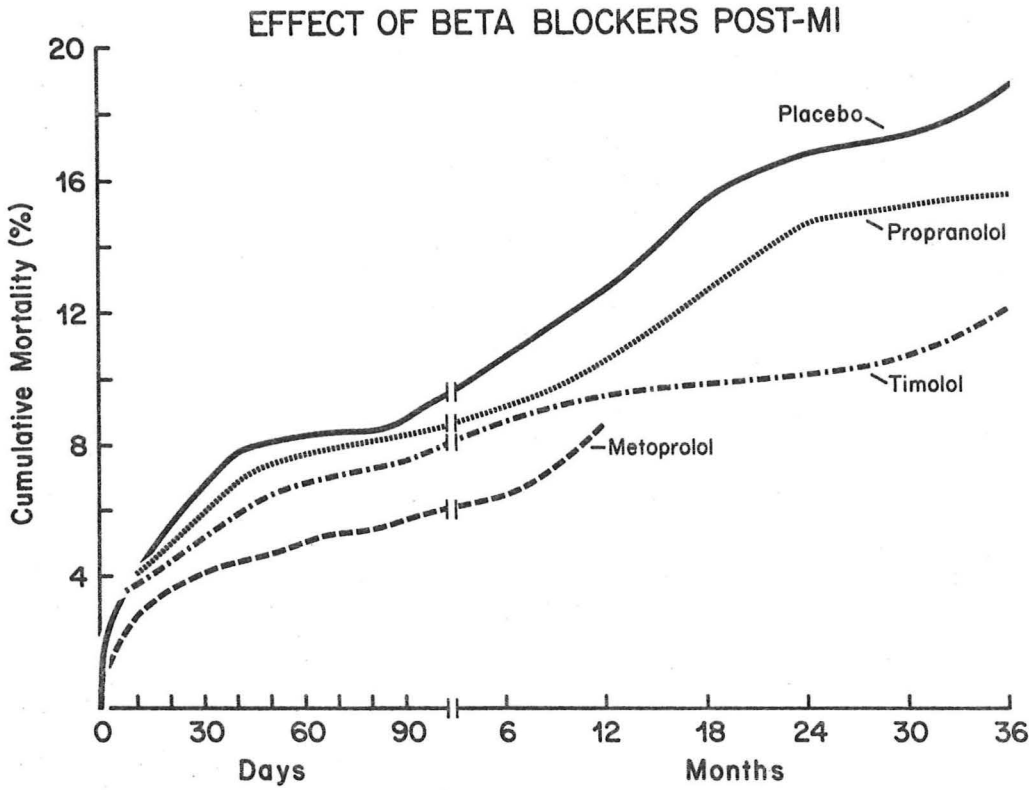

Figure 2. Placebo survival is estimated by averaging all studies. Drug curves are estimated by the reductions from placebo in each study using the normalized placebo curve. Each curve starts on the average day of randomizations.

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Antiplatelet Agents

Aspirin and other antiplatelet agents have been touted as being of benefit in coronary artery disease. Agents such as aspirin might decrease platelet clumping which could decrease the incidence of thrombosis, thereby decreasing the reinfarction rate and secondarily decreasing mortality. Recently new work has brought about the suggestion that antiplatelet agents might alter platelet prostaglandin release such as decreased levels of thromboxane A_2, thereby diminishing the likelihood of spasm; less spasm could in turn reduce the reinfarction rate. [32-36]

For these reasons large studies with three antiplatelet agents have been performed. Six studies have been performed using various doses of aspirin. One trial combined aspirin with dipyridamole (Persantine), and two trials evaluated sulfinpyrazone (Anturane). These studies are summarized in the following table.[37-45]

Antiplatelet Agents in Ischemic Heart Disease

Drug	Dose (mg)	Total Patients	Total Deaths (%)	Change From Placebo		
				Total Mortality	Cardiovascular Mortality	Reinfarction
Aspirin [37]	300	1239	9.6%	- 24%	- 18%	- 21%
Aspirin [38]	972	1529	7.1%	- 30%	- 31%	- 21%
Aspirin [39]	900	1682	13.5%	- 22%	- 23%	- 30%
Aspirin [40]	1500	626	9.4%	- 28%	- 29%	- 36%
Aspirin [41]	1000	4524 +	10.3%	+ 10%	+ 6%	- 20%
Aspirin [42]	972	1216 +	11.3%	- 18%	- 21%	- 24%
Dipyridamole	225					
Aspirin [42]	972	1216 +	11.4%	- 16%	- 24%	- 25%
Sulfinpyrazone [43]	800	727	5.6%	- 5%	- 5%	- 56% *
Sulfinpyrazone [44-45]	800	1558	6.8%	- 28%	- 30%	-

* $p < 0.05$
\+ Placebo - 406 patients only

Of the six studies using aspirin alone, five out of six studies showed a reduction in total mortality, but this reduction was not statistically significant. It should be noted that the reduction in mortality in these five studies ranged in the 20 - 25% range; and as the total mortality was less than 10% in three studies and 13.5% and 11.3% in the other two studies, the number of patients was inadequate to have a reasonable chance of proving significance. Only the AMIS trial had potentially enough mortality and number of patients to hope for statistical significance; and this study showed no change in mortality, though the trend was toward a 10% higher mortality than placebo. To have a 70% chance of a successful study, 10,496 patients would be needed. [37-42]

When cardiovascular mortality was analyzed a similar result was found. Five of six studies had a reduction in cardiovascular mortality, and one study had a slight increase. None of these changes were statistically significant. [37-42]

All six studies revealed a reduction in reinfarction rate with aspirin which ranged from 20 - 36%, but none of these reductions were significant. As the reinfarction rate is less than the mortality rate, there was little hope in any of these studies of reaching statistical significance. [37-42]

Hence, there is no conclusive data that supports that aspirin might reduce reinfarction and/or mortality. However, there is a fairly consistent trend which suggests that aspirin reduces the reinfarction rate and mortality. Peto, initially, and several other authors have pooled the results from the six aspirin trials. The pooled results reveal a 21% reduction in reinfarction rate which is significant ($p < 0.001$). By pooling cardiovascular mortality, aspirin reduced mortality by 16% as compared to placebo ($p < 0.01$). Hence, there is evidence that aspirin has a small but significant effect on reducing mortality and reinfarction rate. However, we must be careful at drawing too strong an opinion from pooled data, because these studies had different entry criteria and different dosages of aspirin. In spite of these problems, we can say that there is fair evidence which supports the use of aspirin in the post-myocardial infarction patient. The dose of aspirin is not known. From studies on platelet function it has been shown that daily doses of 160 mg of aspirin may be sufficient to alter platelet activity. [46-50]

Dipyridamole (Persantine) has not been independently studied. There is one trial that utilized dipyridamole and aspirin in combination (PARIS trial). This trial revealed that there was a 24% reduction in cardiovascular mortality and a 25% reduction in reinfarction rate. Neither reduction was statistically significant. The aspirin only group in this study had an almost identical reduction. This study is plagued by a poor statistical design for this type of study; 1/5 of the patients were randomized to placebo, 2/5 to aspirin, and 2/5 to dipyridamole and aspirin. This randomization only allowed 406 patients to be evaluated on placebo, hence the chance of statistical significance was very low. Hence, there is no evidence that dipyridamole and aspirin is any better than aspirin alone. [42]

Another antiplatelet agent, sulfinpyrazone (Anturane) has also been studied with two prospective randomized trials. The first trial revealed a 5% reduction in mortality, which was not significant; a significant 56% reduction in reinfarction rate was found in this study. While all of the other trials reported reductions in reinfarction rate, this is the only reduction that is statistically significant. A second major trial was the Anturane Reinfarction Trial Research Group. This study was designed to look at reinfarction rates primarily and mortality rates secondarily. The reinfarction rate is not reported for this study.

There was a reduction in total mortality and cardiovascular mortality in this study. The p-value was 0.057 for cardiovascular mortality. When deaths were categorized there was a statistically significant reduction in sudden deaths. Heavy criticism has been raised by this study. First the statistical approach was challenged. A subsequent followup with recalculated statistics was unchanged from the initial analysis; hence reanalysis corroborated that there was a reduction in sudden death rate. However, one major methodological problem remains. The study was not designed to evaluate sudden death; hence the groups were not properly screened to see if the placebo and Anturane groups were similar in the incidence arrhythmias. Thus, the position of Anturane remains in doubt. 43-45

Hence, there is fair support for the concept of giving patients 160 mg/day of aspirin, though this evidence is not conclusive.

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Anticoagulant Therapy

The use of anticoagulant therapy in the post-myocardial infarction remains controversial and inconclusive. Intermittent reports have shown some benefit on in-hospital mortality after infarction. The mechanism of these benefits is not clear. In an acute myocardial infarction, low dose heparin has been shown to decrease the deep vein thrombosis and pulmonary embolism. If mural thrombi are present, anticoagulation has been shown to reduce the incidence of cerebral embolization from 10% to 4%. There is also some evidence of benefit in high risk patients (marked obesity, ventricular aneurysm, cardiogenic shock, low output, or thrombophlebiteis). [51-59]

The role of long term anticoagulation after hospitalization is even more controversial. A review by an international review group was published in *Lancet* in 1970. This review covered the nine randomized trials that were performed prior to 1970. Of the nine studies, the anticoagulant used was bishydroxycoumarin in six, phenprocoumon in four, phenindione in one, and sodium warfarin in one; three of the studies mixed two different anticoagulants. The control group had no therapy in one study an ineffective dose of the anticoagulant in three studies, and placebo in five studies. None of these studies reached statistical significance. By lumping the nine series together there was a 20% reduction in mortality in men only (no difference was found in women). When different periods were observed there was intermittent significance; for example, the reduction in mortality in men < 55 years of age at two and three years was significant, but not at one, four, or five years. In men over 55 years of age, the reduction was significant at years three and four but not at one, two, or five years. There are major problems with this combination of studies; different drugs, dosages, groups of patients, and controls were used. It is interesting to note that two authors disagreed with the interpretation of the data in the conclusion of the paper. [60-69]

A study in the Netherlands in the 1960's showed a significant reduction in mortality with anticoagulation. Phenprocoumon was given to 68 patients and one died. Placebo was given to 70 patients and eight died. This was significant by Chi square. However, the number of deaths are small and may be chance. [70]

Another Dutch study randomized 250 men who had a myocardial infarction more than one year previously and who had been well controlled on phenprocoumon for at least 12 months with no complications. Half of the patients were continued on phenprocoumon and half were switched to placebo. Cardiovascular deaths were 4.8% in the anticoagulant group and 7.2% in the placebo group, which was significant. No difference in complications or reinfarction rate was found. Hence, it appears that anticoagulation can reduce mortality in those patients who can take anticoagulants for a long period of time without complications. [71]

Based upon the two studies reported in *Acta Scandinavia*, physicians in the Netherlands routinely anticoagulate all post-myocardial infarction patients for life. During the 1970's controversy arose concerning the older patients who seemed to have more intracranial bleeds. In this study 912 patients over 60 years of age were randomized, and anticoagulation or placebo was begun 30 days later. In the interval three patients died, 20 withdrew, and 11 had other events that excluded them. There were deviations from protocol (withdrawal) in 25% of the patients. Thus, only 597 patients were analyzed. Analysis of mortality is shown on the next table.

Mortality

	Placebo	Anticoagulant
No deviations in protocol	13.4%	7.6% *
Deviations from protocol	15.7%	11.6%

* $p < 0.05$

Reinfarction rate was lower in the anticoagulant group 3.6% as compared to placebo 7.7%; the number of patients was too small to reach statistical significance. Hemorrhagic events causing major protocol deviations were 6.2% in the anticoagulant group and 0.7% in the placebo group, a significant difference. Hence, when you eliminate protocol deviations, some of which are adverse reactions, anticoagulants in this study showed a reduction in mortality and reinfarction rate; but when protocol deviations are considered, there is no significant difference in mortality. It should be pointed out, however, that the number of patients in this study is borderline to show significance. [72]

Thus, the answer to anticoagulation remains unclear. There is fair evidence that anticoagulation reduces the reinfarction rate. There is good evidence that those individuals who can take long term anticoagulation at a pro times > 20 seconds without complications will have a lower mortality. But, when you add complications into the analysis, the reduction in mortality is not significant. Inadequate numbers of patients have been studied to determine if mortality is reduced when complications are considered.

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Antiarrhythmic Agents

There have been few long term trials with antiarrhythmics after myocardial infarction. There is considerable data on the effects of antiarrhythmics in the first 48 hours after infarction, and many agents have been shown to reduce the number of PVC's, incidence of ventricular tachycardia, and death in the acute setting. However, there is little data in the post myocardial infarction patient after discharge. [73]

The following table summarizes the double-blind controlled studies.

Antiarrhythmic Therapy After Myocardial Infarction

Drug	Dose (mg/day)	Length Of Study	Patients (Number)	Deaths (Number)	Mortality (%) Placebo	Mortality (%) Drug
Aprindine [74-75]	100-200	1 year	305	31	12.5%	7.8%
Mexiletine [76]	600-750	3 months	344	43	11.7%	13.3%
Phenytoin [77]	300-400	1 year	568	49	8.1%	9.2%
Phenytoin [78]	variable	2 years	150	32	18.4%	24.3%
Procainamide [79]	1500-2000	2 years	78	6	9.8%	3.7%
Tocainide [80]	1200	6 months	112	10	8.9%	8.9%
Tocainide [81]	1200	6 months	146	7	4.1%	5.6%

* $p < 0.05$

The overall goal of the majority of these studies was to evaluate effectiveness of new antiarrhythmics as far as PVC's/hour were concerned. Mortality was secondary. These newer drugs have insufficient numbers of patients to prove an effect on mortality. There are two studies with phenytoin which is a very weak antiarrhythmic at best. The remaining study was with procainamide, but the dose was 500 mg TID or QID. This low dose of procainamide along with its short half life makes likelihood of success of this study very dubious. Hence, there is no data that supports or refutes the use of antiarrhythmics after myocardial infarction except in the acute situation. There is some data in patients with complex ectopy, but no large controlled randomized trials have been performed due to ethical reasons. [73-81]

73. Myerburg, RJ., Zaman, L., Luceri, R., Kessler, KM., Kayden, D., and Castellanos, A.: Antiarrhythmic drug therapy after myocardial infarction. In *The First Year After a Myocardial Infarction* eds: Kulbertus, HE., Wellens, HJJ. Futura Publishing Co, Mount Kisco, New York, 1983, p 321-339.

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76. Chamberlain, DA., et al: Oral mexiletine in high-risk patients after myocardial infarction. *Lancet* 2:1324, 1980.

77. Collaborative Group: Phenytoin after recovery from myocardial infarction: Controlled trial in 568 patients. *Lancet* 2:1055, 1971.

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79. Kosowsky, BD., Taylor, J., Lown, B., Ritchie, RD.: Long-term use of procainamide following acute myocardial infarction. *Circulation* 47:1204, 1973.

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81. Bastian, BC., et al.: Chronic tocainide therapy studies: a prospective randomized trial of tocainide in patients following myocardial infarction. *Am. Heart J.* 100;1017, 1980.

Calcium Channel Blocking Agents

No studies involving alterations in mortality have been performed using calcium channel blocking agents. There is some potential for calcium channel blocking agents because of some of their effects. Verapamil has favorably changed ventricular fibrillation threshold after experimental coronary occlusion. Both verapamil and nifedipine have favorably changed ventricular fibrillation threshold after experimental reperfusion. Some beneficial effects have been described in dogs with diltiazem. Also, alterations in myocardial perfusion, neurocardiac interactions, and platelet function may also be beneficial. Though of potential theoretical benefit, no large scale randomized controlled trials have been performed. [82-84]

82. Verrier, RL., Raeder, EA., Lown, B.: Use of calcium channel blockers after myocardial infarction: potential cardioprotective mechanisms. In *The First Year After a Myocardial Infarction* eds: Kulbertus, HE., Wellens, HJJ. Futura Publishing Co, Mount Kisco, New York, 1983, p 341-352.

83. Verrier, RL., Lown, B.: Contrasting effects of verapamil and nifedipine on vulnerability to ventricular fibrillation in the normal and ischemic heart. In *Calcuim Antagonism in Cardiovascular Therapy: Experience with Verapamil* eds: Zanchetti, A., Krikler, DM., Exerpta Medica, Amsterdam, 1981, p 326.

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Coronary Artery Bypass Grafts

The evaluation of CABG in the treatment of coronary artery disease is complex, and many factors have to be evaluated. The main determinants relating to mortality after CABG as compared to medical therapy include the number of vessels involved, which vessels are involved, the degree of stenosis, left ventricular function, and the clinical status of the patient.

First let us look at left main coronary lesions. In every major study where surgical vs. medical therapy was evaluated, survival has been significantly better with surgical therapy. In the following figure the results of the three major trials of medical and surgical therapy are shown.

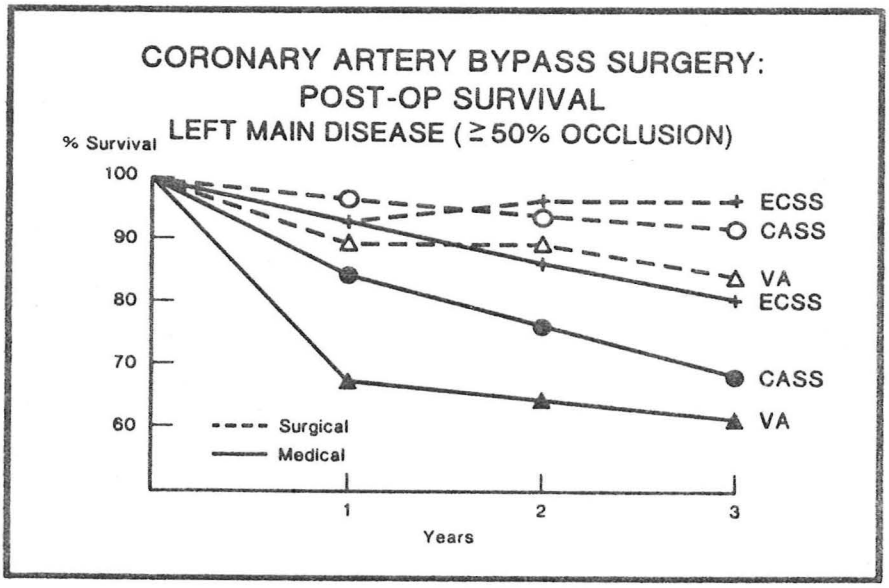

Figure 3. Cumulative three year survival rates of medically and surgically treated patients with left main coronary artery disease in three studies: the collaborative study (CASS), the European study (ECSS) and the Veterans Administration (VA) study. In the European study, only patients less than 65 years old with an ejection fraction of 0.5 or greater were entered. In CASS, a larger spectrum of disease severity is represented. From: Chaitman, BR., Fisher, LD., Bourassa, MG., et al: Effects of coronary artery bypass surgery on survival patterns in subsets of patients with left main coronary disease: report of the collaborative study in coronary artery disease (CASS). Am. J. Card. 48:765-777, 1981.

As can be clearly seen, there is a significant improvement in survival at one, two, and three years with the surgical management of left main coronary disease greater than or equal to 50% occlusion. In the CASS study (1492 patients with left main disease) surgical management was significantly better than medical management in all three age groups analyzed (< 50 years, 50-64 years, $\geq$ 65 years). The improvement in survival was greatest in the over 65 age group. When left ventricular function was analyzed, all groups had a significant improvement with surgery. In general the worse the left ventricular function, the greater the improvement in survival with surgery. When the degree of stenosis over 50% was analyzed, all groups had a significant improvement with surgery; however, the greater the stenosis the greater the improvement in survival with surgery. There was significant improvement in patients with a right dominant or balanced circulation with surgery. If a patient had a left dominant circulation with his/her left main disease, the improvement was not statistically significant, due to a high initial surgical mortality and an insufficient number of patients in the medical group. In the CASS study if you look at multiple risks, the greater the number of "bad" parameters (LV function, degree of stenosis, age, type of circulation) the greater the survival with surgery; but even the lowest risk group did significantly better with surgery. In the VA study, left main coronary disease patients in the high risk tercile had the greatest improvement in survival. Patients in the low and mid risk terciles were not significantly improved with surgery, but the numbers of patients involved were too small to achieve significance with the differences found (terciles will be described later in this section). [85--87]

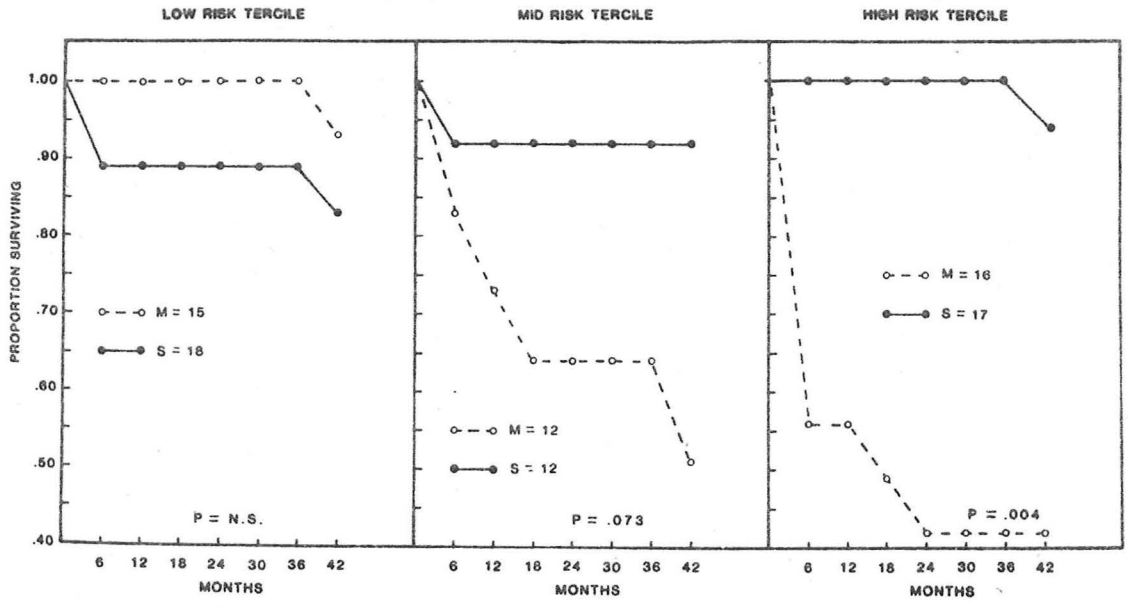

Figure 4. Cummulative survival rates in risk terciles by treatment assigned. M = Medical; S = surgical. From: Detre, KM., Hultgren, HN., Murphy, ML.: Survival in subgroups of patients with left main coronary artery disease: Veterans Administration cooperative study of surgery for coronary arterial occlusive disease. Circulation 66:14-22, 1982.

When you analyze the data for one, two, and three vessel coronary artery disease in patients with stable angina pectoris, surgery appears to be of benefit in three vessel coronary disease as a whole. Significance for three vessel coronary disease was obtained in the ECSS and CASS studies for the group as a whole. When the VA study was analyzed using only the ten centers with a good operative mortality, surgery was of significant benefit for three vessel coronary artery disease. In all three studies, no significant difference was found for one vessel coronary artery disease or two vessel coronary artery disease. The VA study is shown in the following figure.

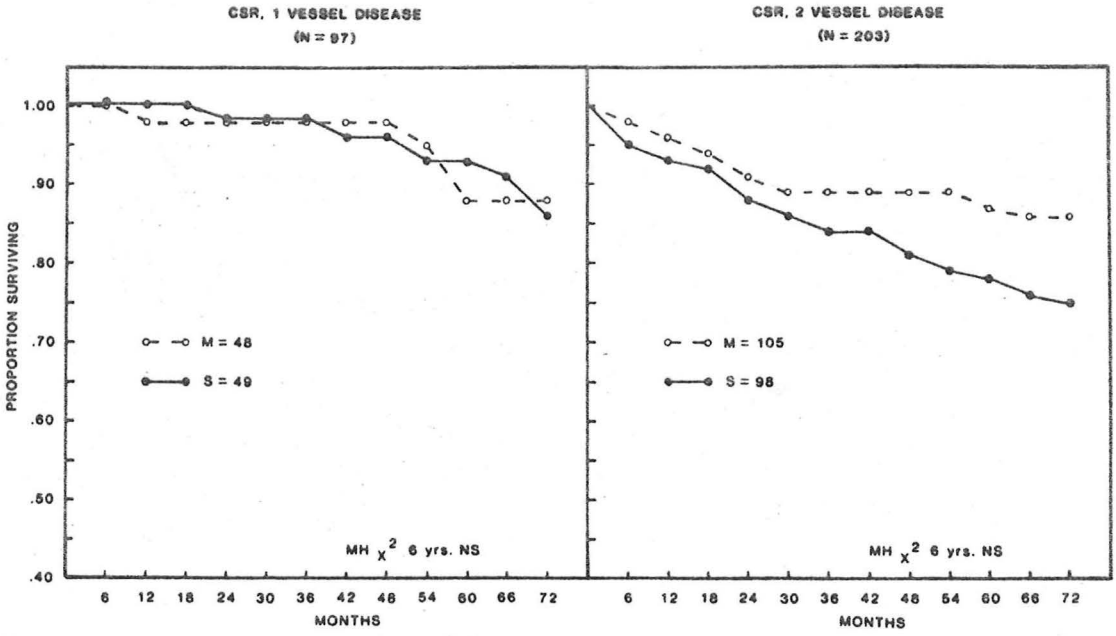

FIGURE 5. *Cumulative survival rates in 97 patients with one-vessel disease and 203 patients with two-vessel disease who entered the study between 1972 and 1974. See figure 3 for abbreviations.*

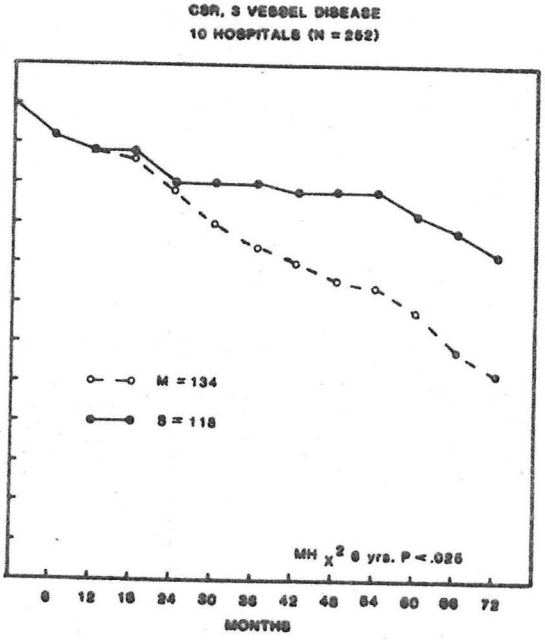

Figure 5. Cummulative survival rates in 97 patients with one vessel disease, 203 patients with two vessel disease, and 252 patients with three vessel disease who entered the study between 1972 and 1974. In this figure, analyses are presented by treatment assigned, counting patients as lost to follow-up at the time of the treatment change. M = patients assigned to medical treatment; S = patients assigned to surgical treatment; MH $\chi 2$ = Mantel-Haenszel chi-square statistic. From: Takaro, T., Hukgren, HN., Detre, KM. et al: The Veterans Administration cooperative study of stable angina: current status. Circulation 65: II-60-67, 1982.

The presence of a proximal left anterior descending lesion in two or three vessel disease significantly effected survival. With two vessel coronary artery disease there was no difference in survival with no proximal LAD disease. With two vessel disease and a proximal LAD lesion survival was significantly better in the ECSS study.

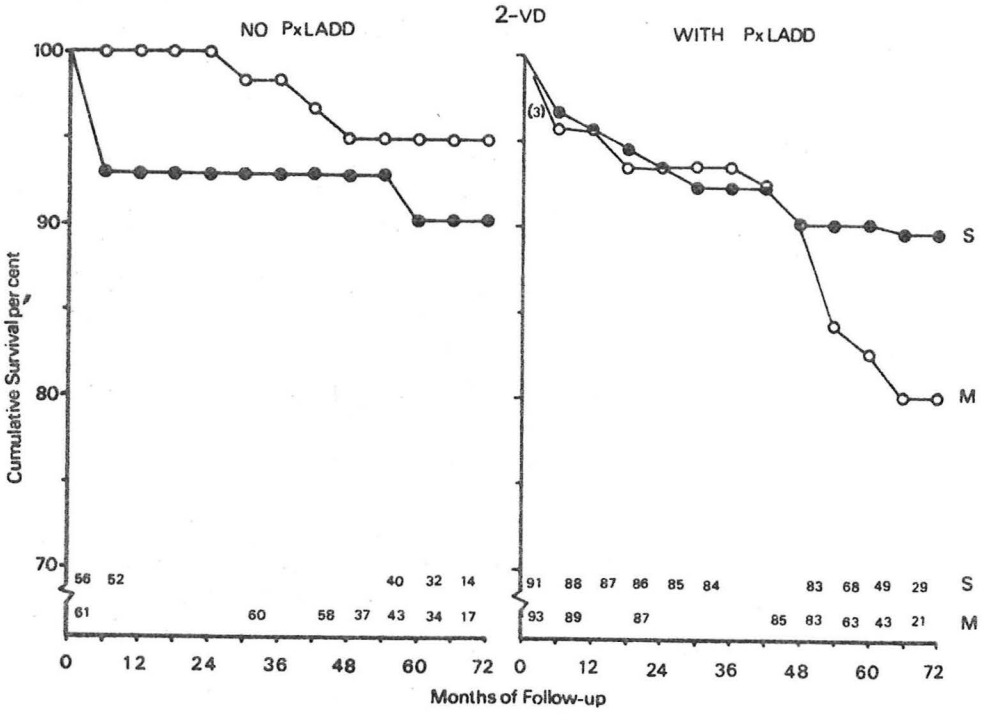

Figure 6. Cumulative survival curves for patients with two vessel disease (2-VD) subdivided into two subsets according to absence and presence of approximal left anterior descending disease (PxLADD). M = medical group; S = surgical group. From: European Coronary Surgery Study Group. Prospective randomized study of coronary bypass surgery in stable angina pectoris: a progress report on survival. Circulation 65 (suppl II) II-67-71, 1982.

The ECSS study also showed a greater surgical survival in those patients who had greater ST segment changes on exercise testing. Those patients who had greater than 1.5 mm ST segment depression on an exercise test had a better survival with surgery. [103]

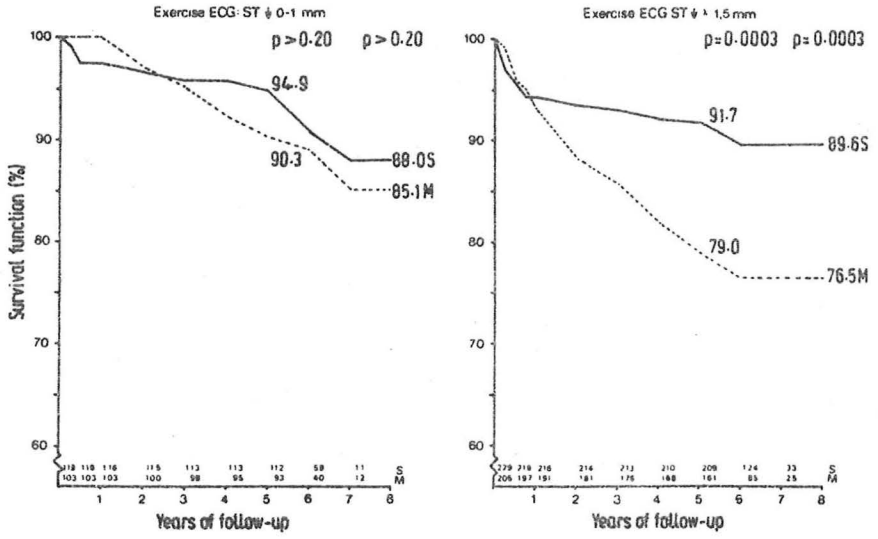

Figure 7. Survival curves for subset of patients with exertional ST-segment depression by 0-1 mm and the subset with > 1-5mm ST depression. From: European Coronary Study Group: Long-term results of prospective randomized study of coronary artery bypass surgery in stable angina pectoris. Lancet 2:1173-1180, 1982.

The VA study reevaluated patients based on risk terciles. Patients with main left coronary lesions were excluded. The remaining patients were analyzed for several other risk factors including presence of angina NYHA Class III or IV, history of hypertension, history of myocardial infarction, and ST-segment depression on resting ECG. By multivariable analysis, patients were divided into risk terciles. The groupings of these risk terciles are given in the following table. [93]

Clinical Patterns and Probabilities - 1972-1974 Cohort*

Probability of Dying	Clinical Pattern †	Total Patients
Low Tercile		
0.067230	----	60
0.087612	N---	61
0.123349	-H--	30
0.147773	--M-	85
Middle Tercile		
0.159230	NH--	26
0.181650	---S	9
0.189953	N-M-	121
0.232106	N--S	19
High Tercile		
0.261005	-HM-	23
0.315585	-H-S	11
0.328661	NHM-	44
0.369083	--MS	20
0.393206	NH-S	10
0.454904	N-MS	43
0.581557	-HMS	9
0.682660	NHMS	18
	UNK	6

* Patients with left main disease are excluded.

Abbreviations: N = New York Heart Association class III or IV;
H = History of hypertension;
M = History of myocardial infarction;
S = ST-segment depression on resting ECG;
UNK = Pattern unknown because of missing data.

In the high risk tercile surgical survival was significantly greater than medical survival. In the middle risk tercile there was no difference, and in the low risk tercile medical survival was significantly greater than medical survival. [93]

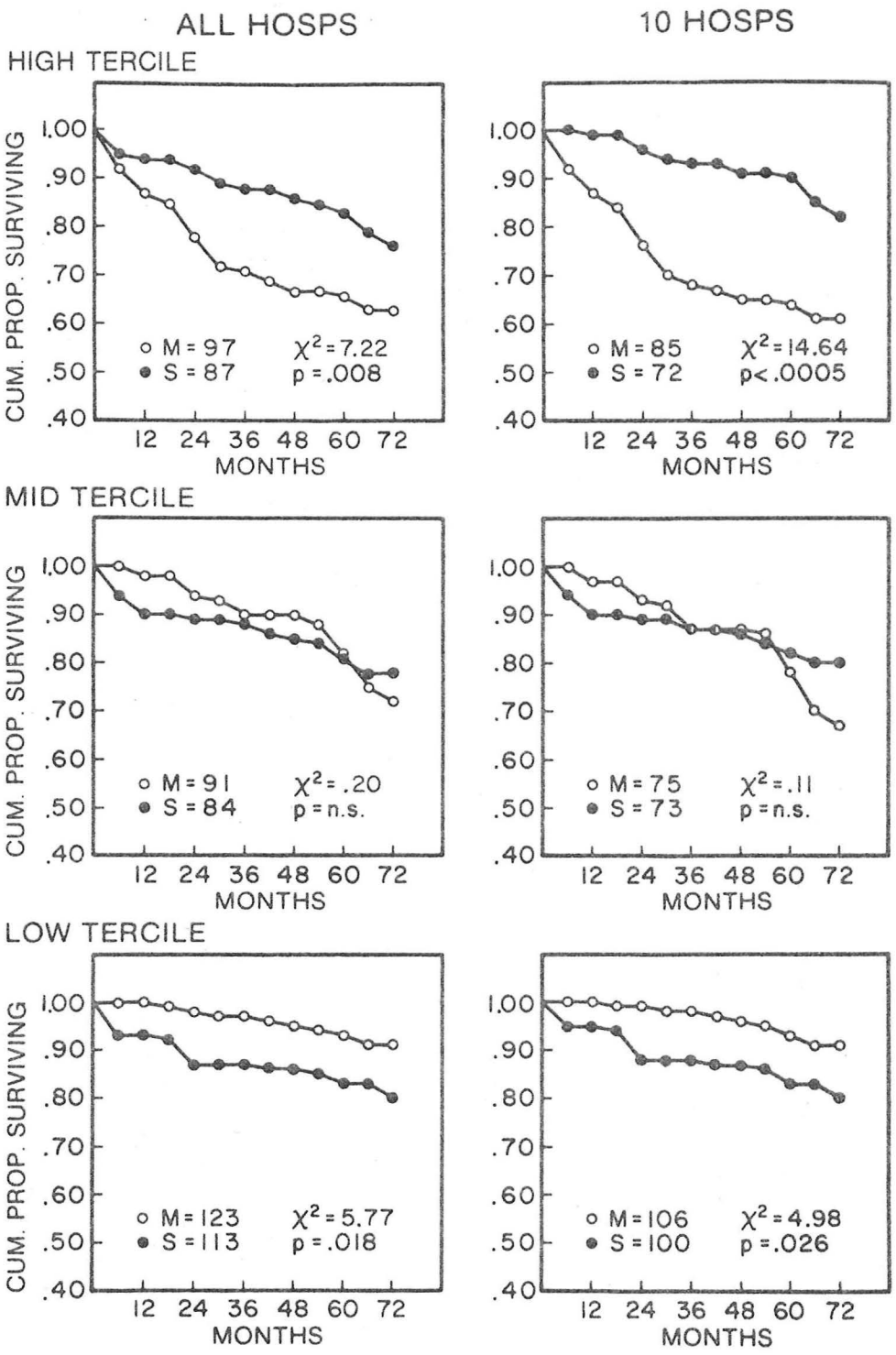

Figure 8. Cumulative survival rates in each risk tercile for all 1972-1974 patients without left main disease. Patients with missing data were included in the high-risk tercile and survival rates were determined by the crossover method. The Mantel-Haenszel chi-square statistic was used to compare survival rates in the two treatment groups at five years. Results are shown separately for all hospitals and for the ten hospitals with low operative mortality rates. From: Detre K., Peduzzi, P., Murphy, M., et al: Effect of bypass surgery on survival in patients in low-and high-risk subgroups delineated by the use of simple clinical variables. Circulation 63: 1329-1338, 1981.

One significant study was performed in unstable angina pectoris. Patients with unstable angina were catheterized and randomized to medical or surgical therapy. If patients in the medical group continued to have Class III or IV angina, then they were later sent to surgery. In patients who were operated acutely, the operative mortality was high (5%). The initial inhospital mortality was 5% in the surgical group and 3% in the medical group. The inhospital infarction rate was 17% in the surgical group and 8% in the medical group ($p < 0.05$). There was no difference in survival over the next four years between the medical only group and the surgical group as shown in the following figure. [104]

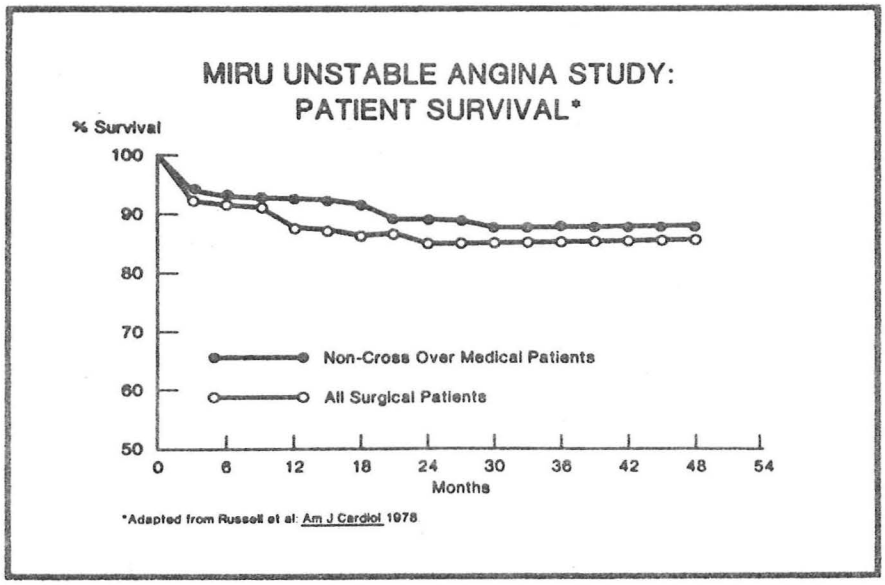

Figure 9. Survival of patients randomized to medical and surgical therapy. From: Russell, RO., Karp, R., Rackley, LE., et al: Unstable angina pectoris: national coperative study group to compare surgical and medical therapy: II. In Hospital experience and initial follow-up results in patients with one, two, and three vessel disease. Am. J. Card. 42:839-848, 1978.

Those patients who had medical management early and then elective surgery for continued Class III or IV angina later had a better survival than those patients operated acutely; the operative mortality was similar to that for stable angina pectoris. Thus, it appears that in unstable angina pectoris, intensive medical therapy should be initially given, and if the patient remains Class III or IV with angina, the patient should have surgery later. [104]

Thus, certain groups have a better survival with surgery. Those groups which have a better survival with surgery include main left coronary lesions, three vessel coronary artery disease, two vessel coronary artery disease with a proximal LAD lesion, greater than 1.5 mm ST-segment depression on exercise test, and the VA high risk tercile. The VA low risk tercile and unstable angina (at least initially) have a better survival with medical therapy.

85. Chaitman, BR., Fisher, LD., Bourassa, MG. et al: Effects of coronary bypass surgery on survival patterns in subsets of patients with left main coronary artery disease: report of the collaborative study in coronary artery surgery (CASS). *Am. J. Card.* 48:765-777, 1981.

86. Takaro, T., Peduzzi, P., Detre, KM., et al: Survival in subgroups of patients with left main coronary artery disease: Veterans Administration cooperative study of surgery for coronary arterial occlusive disease. *Circulation* 66:14-22, 1982.

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88. Detre, KM., Hultgren, HN., Takaro, T., and Participants of the Veterans Administration Cooperative Study Group: Veterans Administration Cooperative Study of Surgery for Coronary Arterial Occlusive Disease. III. Methods and baseline characteristics, including experience with medical treatment. *Am. J. Card.* 40:212, 1977.

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90. Bhayana JN., Gage, AA., Takaro, T., and Participants of the Veterans Administration Coronary Bypass Surgery Cooperative Study Group: Long-term results of internal mammary artery implantation for coronary artery disease: a controlled trial. *Ann. Thorac. Surg.* 29:234, 1980.

91. Morphy, M., Hultgren, HN., Detre, K., Thomsen, J., Takaro T., and Participants of the Veterans Administration Cooperative Study: Treatment of chronic stable angina. A preliminary report of survival data of the randomized Veterans Administration Cooperative Study. *N. Eng. J. Med.* 297: 621, 1977.

92. Read, RC., Murphy, ML., Hultgren HN., Takaro, T: Survival of men treated for chronic stable angina pectoris: a cooperative randomized study. *J. Thorac. Cardiovasc. Surg.* 75:1, 1978.

93. Detre, K., Peduzzi, P., Murphy, M., Hultgren, H., Thomsen, J., Oberman, A., Takaro, T., and Participants of the Veterans Administration Cooperative Study Group for Surgery for Coronary Arterial Occlusive Disease: Effect of bypass surgery on survival of patients in low- and high-risk subgroups delineated by the use of simple clinical variables. *Circulation* 63:1329-1338, 1981.

94. Takaro, T., Hultgren, HN., Lipton, MJ., Detra, KM., Participants in the VA Study Group: The VA Cooperative Randomized Study for Coronary Arterial Occlusive Disease. II. Subgroup with significant left main lesions. *Circulation* 54 (suppl III): III-107, 1976.

95. Takaro, T., and the VA Cooperative Study Group for Surgery for Coronary Arterial Occlusive Disease: Low and high risk in left main disease. (abstr) *Circulation* 62 (suppl III): III-248, 1980.

96. Peduzzi, P. and Hultgran, HN.: Effect of medical vs. surgical treatment on symptoms in stable angina pectoris: The Veterans Administration Cooperative Study of Surgery for Coronary Arterial Occlusive Disease. *Circulation* 60:888, 1979.

97. Davis, K., Kennedy, JW., Kemp, HG, et al: Complications of coronary arteriography from the collaborative study of coronary artery surgery (CASS) *Circulation* 59:1105-1112, 1979.

98. The Principal Investigators of CASS and Their Associates: The National Heart, Lung and Blood Institute coronary artery surgery study (CASS) *Circulation* 63 (suppl I) I-1, 1981.

99. Kennedy, JW., Kaiser, FC., Fisher, LD, et al: Multivariate discriminant analysis of the clinical and angiographic predictors of operative mortality from the collaborative study in coronary artery surgery (CASS) *J. Thorac. Cardiovasc. Surg.* 80:876-887, 1980.

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RISK FACTOR MODIFICATION

Hypertension

There have been three studies that demonstrated that prognosis was worse after myocardial infarction in hypertensive patients who were untreated, poorly treated, and treated. Hence, it appears that treatment of hypertension decreases risk. However, no prospective randomized trials have been performed, and most feel that it would be unethical to perform such studies. [105-107]

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Smoking

Cessation of smoking has been shown in several studies to reduce subsequent mortality after myocardial infarction. The reduction in mortality has been in the 40 - 60% range with cessation of smoking. Even by multivariate analysis cessation of smoking is a major determinant of later risk. It is obvious that a prospective randomized trial is impossible. [108-116]

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Cholesterol

A recent study of cholesterol by the Lipid Research Clinics Program revealed that reducing cholesterol reduced risk. Patients with and without symptomatic heart disease and who had high cholesterols were placed on a low atherogenic diet, then randomized to cholestyramine or placebo. This study showed that cholestyramine lowered total cholesterol by 8.5% as compared to placebo. With this reduction in cholesterol there was a 24% reduction in cardiovascular mortality and a 19% reduction in reinfarction (all statistically significant). There was also a tendency for less progression of coronary artery disease on angiography though this was not significant. [117-119]

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Exercise

Exercise programs after myocardial infarction have been evaluated in 2019 patients. There has been a tendency toward lower mortality in those patients who exercise after myocardial infarction, but the number of patients is inadequate to prove statistical significance. Wilhelmsen reported a 22.3% mortality in the control group and a 17.5% mortality in the training group (a 22% reduction). [120-124]

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Summary

The following tables summarize our current knowledge of prolongation of life in ischemic heart disease.

Beta Adrenergic Blocking Agents

Post-MI reduction in mortality	Definite
Post-MI reduction in reinfarction	Definite
Reduction in mortality in angina	Possible-unknown
Recuction in mortality in asymptomatic	Unknown

Aspirin

Post-MI reudction in mortality	Probable
Post-MI reduction in reinfarction	Probable
Reduction in mortality in angina	Possible-unknown
Recuction in mortality in asymptomatic	Possible-unknown

Anticoagulation

Post-MI reduction in mortality	Questionable-no
Post-MI reduction in mortality excluding complications	Probable
Post-MI reduction in reinfarction	Probable
Reduction in mortality in angina	Doubtful-unknown
Reduction in mortality in asymptomatic	No

Antiarrhythmic Agents (Excluding First Five Days)

Post-MI reduction in mortality	Possible-unknown
Complex arrhythmias	Probable
Simple arrhythmias	Possible-unknown

Calcium Channel Blocking Agents

Possible effects	Unknown

Surgery (CABG)

Left main coronary disease	Definite
All three vessel CAD	Probable (asymptomatic unknown)
High risk three vessel CAD	Definite
Two vessel CAD	No
Two vessel CAD-high risk	Probable
Two vessel CAD + proximal LAD	Probable (low)
One vessel CAD	No
Low risk patients	No-possible
Unstable angina pectoris	No early

Hypertension

Post-MI reduction in mortality	Probable
Reduction in mortality in angina	Probable
Reduction in mortality in asymptomatic	Probable

Smoking

Post-MI reduction in mortality	Probable
Reduction in mortality in angina	Probable
Reduction in mortality in asymptomatic	Probable

Cholesterol

Post MI reduction in mortality	Probable-not proven
Reduction in mortality in angina	Probable-not proven
Reduction in mortality in asymptomatic	Probable

Exercise

Post-MI reduction in mortality	Possible-probable
Reduction in mortality in angina	Unknown
Reduction in mortality in asymptomatic	Probable-possible

Prolong human life only

when you can shorten its misery . . .

Stanislaw Jerzy Lec
More Unkempt Thoughts, 1962