from hospital specialists to general practitioners, and the presence of a general practitioner research group might stimulate a healthy state of affairs in which the hospital disciplines might learn something from general practice.

Some form of ethical control is needed for research in general practice. Ethical considerations should be included in the research element of vocational training courses, and advice is available through the Royal College of General Practitioners, but again a local body would be helpful. Local medical committees might see this as within their scope, or again postgraduate centres might be a focus for an ethical committee. Membership of such committees might include representatives of patient groups such as community health councils as well as general practitioners and hospital doctors. At present the only arbiters of ethical and scientific quality seem to be the journals to which completed papers are submitted for publication. Unfortunately, by then the damage may have already been done, both to the future enthusiasm of the researchers, who (with the best intentions) may have produced an ill conceived and poorly executed piece of research, and to the patients on whom it was carried out.

Many improvements are, therefore, possible both in motivating general practitioners to do good research and in providing them with facilities. Nevertheless, we should remember that good general practice is primarily concerned with providing medical services, both technological and humanitarian, to the patient, and that, though research can and should improve the ways in which this is done, it must not become the tail that wags the dog.

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Regular Review

Coronary artery bypass grafting for the reduction of mortality: an analysis of the trials

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A coronary artery bypass graft is without doubt highly effective for the relief of angina and should be considered in almost any patient whose angina does not respond adequately to medical treatment. What constitutes "adequate" control of angina is a highly subjective judgment which depends on the patient's lifestyle and on his expectations—and on the expectations of his doctors and his relatives. If symptomatic relief is the only benefit from a bypass then the provision of facilities for the operation should compete for funds with provision of other symptomatic treatments such as hip replacement and the care of the aged or mentally ill. However, if bypass grafts prolong life then the provision of adequate surgical facilities becomes a priority. We need, therefore, to consider whether or not there is convincing evidence that bypass grafts increase longevity. We need either uncontrolled evidence that is so clear cut as to make a clinical trial both unnecessary and unethical or we must depend on the results of randomised trials.

This article reviews the mortality results of the three randomised trials so far published, those of the Veterans Administration,[1-4] of the European Coronary Surgery Group,[5-7] and of the Coronary Artery Surgery Study (CASS).[8,9] Results of small trials based on only about 100 patients have been reviewed elsewhere.[10]

The Veterans Administration study

This study shows the importance of carrying out an investigation of a new form of treatment while it is still at an early stage of development, before attitudes harden and studies begin to be thought "unethical." At the same time it shows how difficult it can be to conduct a study before the participating centres have become familiar with a new treatment.

Patients were recruited for the Veterans Administration study between 1970 and 1974 with 13 centres admitting 1015 patients. No details have been published about the population from which these patients were drawn.

The inclusion criteria for the study were a stenosis of at least half of the diameter of at least one coronary artery; provided the anatomical lesions were suitable for operation there were apparently few exclusion criteria other than the presence of a left ventricular aneurysm or of left ventricular failure. The patients' characteristics would be expected to put them at high risk: 92% had at least moderate angina (New York Heart Association class 2 or 3) and 61% had had a previous myocardial infarction. Thirteen per cent had disease of the left main coronary artery, and 53%, 33%, and 14% respectively had three, two, and single vessel disease. Eighty per cent either had radiographic evidence of left

ventricular enlargement or had an ejection fraction of less than 45%. Nearly half of the patients had both three vessel disease and abnormal left ventricular function.

The patients were randomly allocated to medical or surgical treatment (508 and 507 patients respectively), and one of the remarkable things about this study was that almost all the patients continued to receive the treatment they had been allocated: only 20 of the patients assigned to surgical treatment were not operated on, and only in 42 of those assigned to medical treatment was surgery later considered necessary.

With such a potentially high risk group the study should have been big enough to detect a reduction of mortality by surgical treatment of about 30%, and with a low "cross over" rate the answer from the trial should have been unequivocal. Unfortunately the trial failed to give a clear result because there was an unacceptable operative mortality in the surgical group. In 1970-2 the surgical mortality was so high that the patients admitted to the trial in this period were excluded from the analysis of results after four years of follow up.[3] The published four year survival data thus referred to a subgroup formed at the end of the trial, made up of 332 patients treated surgically (operative mortality 5·6%) and 354 patients treated medically. In these the four year mortality was 14% and 17% respectively, a difference not statistically significant.

Such subset analysis may be useful for generating hypotheses to be tested by later clinical trials, but it cannot be used as a basis for clinical practice. The published data leave some uncertainties, but the mortality results at four years seem to have been very similar in the original medical and surgical groups. Thus we can only conclude that in patients with multivessel disease and impaired left ventricular function surgery of the standard available between 1970 and 1974 had no advantage over the medical treatment of the day.

One further subset analysis did, however, show a dramatic result.[1 3] Of the patients with disease of the left main coronary artery who were recruited between 1972 and 1974, those treated medically (44 patients) had a four year mortality of 33%, while among the 46 patients treated surgically the four year mortality was 7%. This difference was "statistically significant," even though the number of patients was small. Results obtained by subset analysis in this way must be treated with caution because in general the more subsets that are formed retrospectively the greater the chance of an apparently "significant" difference being detected. Coupled with a mass of uncontrolled observations showing the same thing, however, the evidence that surgery is the preferred treatment for left main coronary disease is clinically acceptable, even if not academically totally sound.[11 12]

The European study and Coronary Artery Surgery Study

The recruitment period for these two studies overlapped that of the Veterans Administration study, but since they were begun a little later there had been time for surgical expertise to improve, and high risk patients could be identified with greater confidence. Both studies were aimed at patients with less severe heart disease than those in the Veterans Administration study, and since both have been fully reported with five year follow up data it is on these that our clinical practice should be based. Nevertheless, we have to appreciate that both refer to patients and the state of the medical and surgical art nearly 10 years ago.

After five years of follow up of all the patients the results of the two trials are apparently conflicting—and are certainly confusing. In the European study 30 deaths were reported among the 395 patients initially allocated to surgical treatment (five year mortality 7·6%) compared with 61 deaths among the 373 patients initially allocated to medical treatment (16·3%), a difference that was statistically highly significant ($p<0·001$). In CASS the comparable death rates were 7·4% (29 of 390) among those patients treated surgically and 9·2% (36 of 390) in the medically treated group, a difference that could easily have occurred by chance.

Which (if either) of these trials has revealed the "truth" on which we should base our approach to patients, and on which we should plan our future services? The answer is not immediately obvious. The results of the two trials are in fact statistically compatible, for the 95% confidence intervals overlap. Thus in CASS the observed reduction in mortality in the surgical group was 19% (placebo group mortality of 9·2% reduced by 1·8%) and we can be 95% certain that the "true" result lies somewhere between a 61% reduction in mortality and a 13% increase in mortality associated with surgical treatment. In the European study surgery caused a 53% reduction in mortality, and the 95% confidence interval is 25% to 81%. These wide confidence intervals show that the results of both trials must be treated with caution, but they are the only trials we have. If we assume that their results are indeed different, we need to compare the two trials carefully to see why the different results might have occurred.

Patients

Table I compares the inclusion criteria in the two studies. In the European study the severity of angina was not clearly defined, whereas in CASS the patients were symptomatically in Canadian Cardiovascular Society class 1 or 2, which means that they could climb a flight of stairs without pain. All the patients in the European study were required to have angina, but patients in CASS could be free of angina if they had had a previous myocardial infarction.

TABLE I—*Comparison of inclusion criteria in the European study and CASS*

European study	CASS
Men	Men and women
Age <65	Age <65
Stable angina for 3 months	Angina class 1 or 2
>50% stenosis in 2 or 3 vessels including left main coronary artery	>70% stenosis in at least 1 vessel, 50-70% stenosis of left main coronary artery
Good left ventricular function; ejection fraction >50%	Impaired left ventricular function acceptable, provided ejection fraction >35% and provided the patient did not have heart failure grade 3 or 4

The extent of coronary disease shown angiographically suggested that the European study was aimed at the more severely affected patients: at least two vessels had to be affected, while patients in CASS might have disease only in a single vessel. All the patients in the European study, however, had to have good left ventricular performance (ejection fraction better than 50%) while those in CASS could have impaired left ventricular function. Since left ventricular function is a major predictor of mortality in

patients with coronary disease the patients in CASS might have been expected to have a higher risk than those in the European study.

A comparison of the groups of patients who were actually included in the two studies is essential to any attempt to understand their different results, and table II shows this.

Although CASS allowed the inclusion of women, 90% of the patients were men. The European patients were a little older than those in CASS. The severity of angina in the two groups cannot be compared, but fewer of the European patients had previously had a myocardial infarction. On angiographic assessment the European group had disease in more vessels but had better left ventricular function with a mean ejection fraction of 62%; 20% of the patients in CASS had an ejection fraction less than 50% (mean result not stated).

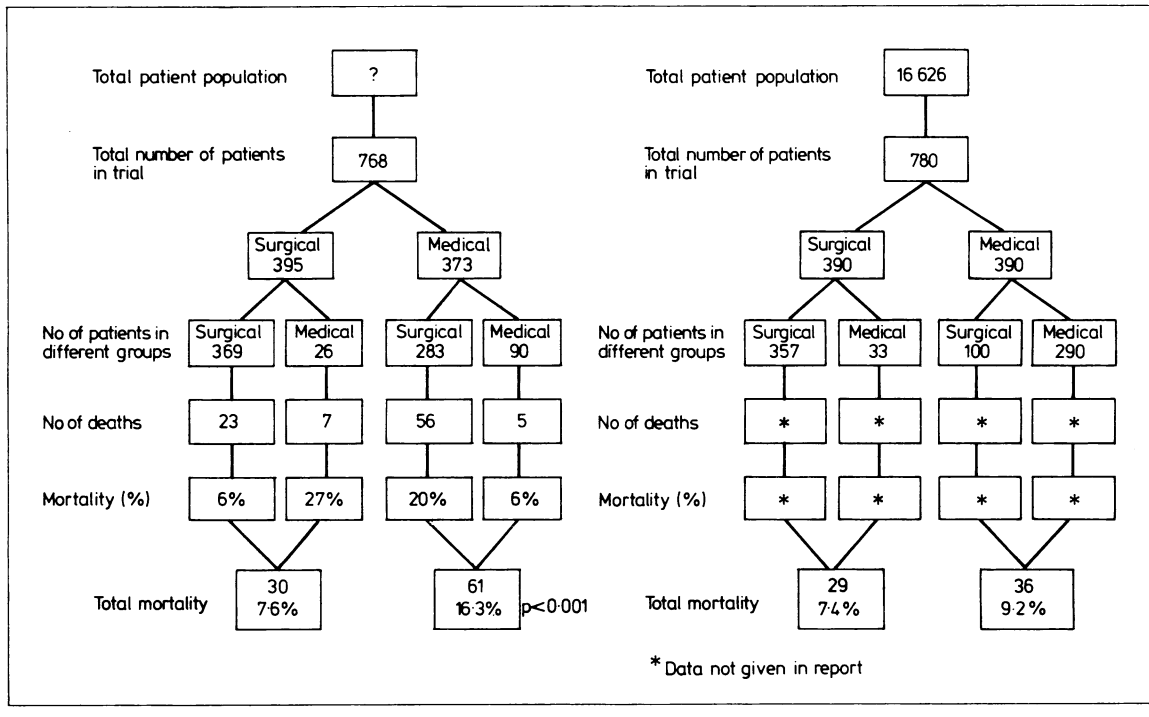

FIG 1—Results of European Coronary Surgery Study (five year follow up).

FIG 2—Results of Coronary Artery Surgery Study (CASS).

So in some ways the European patients might seem at greater risk (greater age, more left main and three vessel disease) while in others the CASS patients might be expected to have the worse prognosis (more with previous myocardial infarctions, worse left ventricular function). Comparison of the patients in the two studies does not seem to explain the difference in the results.

Results of the trials

Figures 1 and 2 show the results of the European study and CASS in a common format.[13] The main weakness of the European study is that nothing is known about the original population from which the trial patients were drawn. On the other hand one of the main problems with CASS is that we *do* know about the original population: the patients in the trial represented only 5% of those initially registered in the participating centres. Most of the exclusions were, however, required by the protocol: of the original 16 626 patients 37% had angina that required surgical treatment for relief of symptoms (that is, the patients were unable to climb a flight of stairs, though the extent of their medical treatment is not clear), 28% were found to have minimal or no coronary disease at angiography, 5% were technically inoperable, 2% had left main coronary disease, and 16% were excluded for other protocol reasons such as a previous coronary artery bypass graft. This left 2099 eligible patients, and of these 780 (37%) were randomly allocated to medical or surgical treatment.

The numbers of patients in the two studies were similar. It is not clear in either case whether this number was calculated in advance as being adequate; in fact it would have been sufficient to show with the usual level of statistical confidence a reduction in mortality of 50% in the surgical group compared with patients treated medically, provided that the medical group had at least a 15% death rate. In the European study the medical group did have this sort of mortality, but only on what seems to have been a

TABLE II—*Comparison of the patients recruited to the European study and to CASS*

	European study	CASS
Recruitment period	1973-6	1975-9
% of men	100	90
Mean age (years)	56	51
Severity of angina (%):		
None	—	21
Class 1	?	20
Class 2		59
Previous myocardial infarct (%)	45	60
Smoker (%)	44	88
Previous β blocker	55	43
Angiographic findings (%):		
Left main disease	8	—
3 vessel disease	53	27
2 vessel disease	39	40
1 vessel disease	—	33
Ejection fraction	Mean 62%	20% of patients <50% ejection fraction

basis of "multiple looks" at the results. In other words the results have been inspected and reported continuously up to a point where a significant difference between treatment groups was apparent. This way of analysing results is undesirable since the more frequently the data are analysed the more likely it is that a "statistically significant" difference will be detected. Nevertheless the European study may be defended on the grounds that the difference between the treatment groups has become progressively greater with the passage of time, so the result may be real. The CASS was a much better study in this respect, with a single report after a defined period. Unfortunately (from the trial point of view) the death rate among the patients treated medically was low at 9·2%: had it been appreciated in advance that this would be the case over 3000 patients would have had to be recruited for a 30% reduction in mortality to be shown with confidence, while even greater numbers would have been needed if the difference in results between the treatment groups had been expected to be smaller. Thus in terms of size and the way the trials were conducted neither was ideal.

The figures show that in both studies there was considerable "cross over" of patients between groups. In the European study 26 (3·7%) of the 395 patients randomised to surgical treatment were in fact treated medically, while 90 (29%) of those randomly allocated to receive medical treatment were in fact operated on within the study period. In the CASS 33 (8·4%) of the 390 patients allocated to surgical treatment were actually treated medically, while 100 (26%) of the 390 who were intended to be treated medically were eventually operated on.

The high rate of transfer of patients from medical to surgical treatment is thus a fault of both studies, and it makes interpretation of the results difficult. The CASS report states firmly (and correctly) that analysis by "intention to treat" is the only proper and meaningful method and does not state separately what happened to the transferred patients. Perhaps more sensibly the European study provides the data that allows both "explicative" and "intention to treat" analysis of the results; this showed that the patients transferred from the medical to the surgical group fared as well as those randomly assigned to surgery, while those who continued with medical treatment had a higher mortality than the medically treated group as a whole. It is comforting that in the European study "explicative" and "intention to treat" analyses give the same result, even if it would be wrong to claim that the "real" result is that obtained by explicative analysis.

Perhaps the greatest problem posed by this part of the results of both trials is to decide the point at which a high cross over rate makes a trial meaningless: clearly if none of the patients are treated in the way intended by the randomisation process the trial would be pointless, and whether a 25-30% cross over rate is acceptable is a moot point.

Subset analysis

Since analysis of the results from the overall groups in the two studies fails to account for their different results subsets of the patients may reasonably be formed to see if comparing them gives any clues. In doing this we must be clear that we are trying to generate hypotheses which could perhaps be a basis for future trials: we are not trying to identify particular types of patients who can be said on the basis of these trials to need medical or surgical treatment.

Subset analysis in the European study showed that a "significant" reduction in mortality was associated with surgical treatment only in those patients who had three vessel disease, and there was a suggestion that it was the presence of stenosis in the proximal left anterior descending artery that was important. The difference between treatment groups among patients with two vessel disease was small (five year mortality 15% in the medical and 13% in the surgical group). The difference in the patients with left main coronary disease was large (five year mortality 37% in the medical and 18% in the surgical group) but with relatively few patients (31 medical, 28 surgical) the difference did not achieve statistical significance. Subset analysis within the patients included in the CASS did not produce any clear indications of benefit, but the patients with impaired left ventricular function seemed to do better with surgery.

Since the inclusion criteria for the European study and the CASS were different, the results of the studies might be expected to be different. Nevertheless subset analysis can form groups from the two trials that should be more comparable than the total groups. Common to both studies are patients with two vessel and three vessel disease. Table III compares the outcome of patients with these angiographic findings treated medically and surgically in the two studies. If allowance is made for the higher operative mortality in the European study the five year results are

TABLE III—*Subset analysis of the European study and CASS. Five year mortality (%) in patients with disease of two and three coronary arteries, according to treatment group*

	European study	CASS
Medically treated patients		
2 vessel disease	15	6
3 vessel disease	22	10
Surgically treated patients		
2 vessel disease	8	5
3 vessel disease	13	8
(operative mortality	3·5	1·4)

very similar in the two groups of patients treated surgically. On the other hand, a considerable difference in outcome is seen in the medical groups, those in the European study having a much higher mortality than those in the CASS. This similarity in the surgical groups and dissimilarity in the medical groups is difficult to explain, but there are various possibilities.

Firstly, the two groups of patients selected for the studies may have been initially comparable and in each trial the groups randomised to medical or surgical treatment may also have been comparable, but medical treatment in the European patients was inferior to that of the CASS patients. The two studies were conducted at the same time and European medical practice seems unlikely to have been much different from that in North America.

Secondly, the two original groups of patients may have been different, the European patients having a high risk and the CASS patients a low risk, so explaining the different outcomes in those treated medically. In the surgical groups, however, coronary artery bypass graft lowered mortality to a minimum level which, being irreducible, was the same in both studies. As we have seen, however, there is no convincing evidence that there was much difference between the two original groups of patients studied.

Thirdly, the two original groups may have been similar,

but owing to a failure of randomisation in the European study high risk patients were treated medically and low risk patients were treated surgically. Had this happened the patients treated by surgery in the European study should have had a lower mortality than the surgical patients in CASS, so this explanation seems unlikely to be true.

Fourthly, the two study groups of patients may have been comparable but the mortality among medical patients in the European study was spuriously high. Such chance results can occur in any trial, and the only way we can test this hypothesis is by asking what mortality might have been expected among the sort of patients who were admitted to these trials.

The prognosis of patients with angina

There are few published reports of patients with angina treated medically who might be comparable with the patients treated medically in the European and the CASS studies. The whole point of a randomised trial is, after all, to avoid invalid comparisons between groups of patients selected arbitrarily, so only the most general of conclusions can be drawn.

Superficially it might seem logical to compare the outcome in the trial patients with others whose coronary arteries had been shown at angiography to have a similar extent of disease. Unfortunately, patients studied by angiography but treated medically are unlikely to be representative of angina patients in general, for angiography is usually a prelude to surgery. A group of such patients treated medically is likely to include a variety of patients, ranging from those with trivial disease through those with inoperable lesions due to distal stenosis to those with severely impaired left ventricular function. Furthermore, identification of coronary disease as "single," "double," or "triple" vessel disease is simplistic. These limitations may help explain why patients with single, double, and triple vessel disease have been reported respectively to have a five year mortality of 14%, 37%, and 54%[14]—figures vastly in excess of the death rate seen in the medically treated groups of both trials. However, the outcome in patients who were included in the CASS registry but not in the randomised trial gives a different perspective.[15] Of those with good left ventricular function the overall four year mortality was 8% with medical treatment; patients with single, double, and triple vessel disease respectively had 6%, 9%, and 21% fatality rates.

In community studies patients with angina have been found to have an even better life expectancy. In the Whitehall survey of 18 236 middle aged men 3118 were found to have some evidence of ischaemic heart disease, and in this group the five year mortality was 4·5%.[16] The group was made up of patients with chest pain, patients known to their doctors to have heart disease, and patients found on electrocardiographic screening (limb leads only) to have ischaemic changes. In the small number to whom all three criteria applied the five year mortality was 20%; in those with chest pain who were under medical care the five year mortality was 6·0%.

Since the coronary artery bypass graft studies permitted the inclusion of patients with chest pain who had evidence of ischaemia on either a full (12 lead) electrocardiogram or on exercise it seems reasonable to suppose that the five year mortality of the patients treated medically would be nearer 6% than 20%. Thus the 16% mortality in the patients treated medically in the European group may well be "too high," while the 9·2% mortality for the patients treated medically in CASS could be "about right."

Conclusions

None of the three studies of coronary artery bypass grafting is perfect, and we cannot be certain whether surgical treatment prolongs the life of patients with angina. Statistically, the CASS and the European results are compatible. However, the Coronary Artery Surgery Study was a better trial than the European study. Probably the patients admitted to the two studies were similar, but we cannot be certain because the severity of angina in the European patients was poorly defined. Allowing for the differences in operative mortality, the outcome in the patients treated surgically was similar in the two studies. The difference between the patients treated medically and surgically in the European study was probably due to the mortality among the patients treated medically being "too high."

It seems reasonable to base our clinical practice on the results of CASS: patients whose angina is not adequately controlled should be considered for surgery, but those who can climb a flight of stairs without pain can be treated medically, for there is no good evidence that surgery will prolong their lives.

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