Is medical treatment for angina the most cost-effective option?

J. G. F. Cleland* and A. Walker†

*Medical Research Council Clinical Research Initiative in Heart Failure, West Medical Building, University of Glasgow; †Health Economics Unit, Greater Glasgow Health Board, Glasgow, U.K.

A meta-analysis of the benefits of coronary artery bypass graft (CABG) surgery has been used as the basis of a model for comparing the costs and benefits of surgical and medical treatment of angina pectoris. In order to allow for the results of recent research, the economic model included the addition of aspirin and aspirin plus an HMG-CoA reductase inhibitor (statin) to medical management. The analysis indicates that in unselected patients the cost-effectiveness of CABG vs initial standard medical therapy over 5 years is towards the upper limit of what can be considered a cost-effective treatment both in terms of its effect on mortality (life-years gained) and morbidity (quality adjusted life-years). Addition of a statin to medical therapy reduced mortality and made coronary artery bypass graft surgery an expensive option in terms of improvement of quality of life. In patients with three-vessel disease or left ventricular dysfunction surgery appears fairly cost-effective in comparison with standard medical therapy but becomes relatively expensive when the benefits of aspirin or lipid-lowering therapy are added to medical treatment.

Key Words: Coronary artery bypass, angioplasty, anti-ischaemic drugs, cost-benefit analysis.

Introduction

Ischaemic heart disease is a serious common health problem that can cause major morbidity and it remains the major cause of death in industrialized countries. Because of the enormous scale of the problem, ischaemic heart disease is not only a significant health problem but also an important economic issue.

Revascularization can be justified for the relief of pain alone in patients with severe angina resistant to optimal drug therapy and it is likely to be a highly cost-effective way of improving their quality of life relative to other uses of resources. Recent studies suggest that doctors may have an inflated view of the benefits of coronary artery bypass graft surgery in terms of the effect of the procedure on prognosis. The clinical trials of surgery compared early CABG with medical treatment which was continued until it was considered that the patient needed surgery, mainly for the relief of symptoms. Patients entering these studies did not, by and large, have intractable angina and the trials were ideally designed to test the philosophy of operating for symptoms vs operating for anatomical disease.

Although only one of nine randomized, controlled studies comparing medical therapy with coronary bypass surgery showed a significant reduction in mortality with surgery, a recent meta-analysis including seven of the studies suggested that 'a strategy of early CABG surgery significantly reduces mortality compared with initial medical therapies'. Whether it is appropriate to evaluate the studies by an overview of the individual study results or by a formal meta-analysis is a matter of some dispute. Meta-analysis of the surgical trials must be considered in the light of evidence that meta-analyses including studies with small numbers of patients are unreliable.

Medical treatment for coronary disease has advanced dramatically in recent years and has produced prognostic benefits in the context of properly designed, randomized, controlled trials. Surgical techniques have also advanced but it is difficult to be sure that they have really reduced mortality since such comparisons are retrospective rather than concurrent. Even if the proportionate benefit from surgery were to increase, the falling mortality with optimal medical therapy will reduce the absolute benefits of surgery over medical treatment. Thus, the surgical trials are being superseded and their relevance to modern medical practice must be questioned.

The problem of the limited healthcare resources at our disposal is a further consideration. Although surgery will improve mortality in some patients, the cost may be so high that it precludes such treatment, either because the individual cannot pay or because the high costs would preclude insurance companies or...
Table 1 Sources of clinical variables

<table>
<thead>
<tr>
<th>Source</th>
<th>Quality of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality rates after 5, 7 and 10 years</td>
<td>Yusuf et al[3]</td>
</tr>
<tr>
<td>Operation rate at 5, 7 and 10 years</td>
<td>Yusuf et al[3]</td>
</tr>
<tr>
<td>Non-fatal MI rate at 5 years</td>
<td>Yusuf et al[3]</td>
</tr>
<tr>
<td>Drug management at 1 year</td>
<td>Yusuf et al[3]</td>
</tr>
<tr>
<td>Impact of aspirin</td>
<td>SAPAT[14]</td>
</tr>
<tr>
<td>Impact of simvastatin</td>
<td>4S[4]</td>
</tr>
<tr>
<td>Quality-of-life data</td>
<td>CASS[15]</td>
</tr>
</tbody>
</table>

4S=Scandinavian Simvastatin Survival Study; CASS=Coronary Artery Surgery Study; MI=myocardial infarction; RCT=randomized controlled trial; SAPAT=Swedish Angina Pectoris Aspirin Trial.

government-funded healthcare systems from treating other patients who may have a better claim on those resources.

Meta-analysis has proved, to the satisfaction of some, that surgery is effective in reducing mortality[3] but it does not tell us at what price the benefit can be obtained. The aim of this paper is to address this issue.

**Methods**

Comparisons of percutaneous transluminal coronary angioplasty and coronary artery bypass graft surgery

Several studies have compared the costs of percutaneous transluminal coronary angioplasty (PTCA) and CABG over 2–3 years and shown that PTCA may be marginally less expensive[5-13]. The long-term comparative costs of a strategy of revascularization by PTCA or CABG have not been tested but it is likely that the costs of PTCA are similar to, or higher than, CABG over a 5–10 year period[5-13]. We have assumed that the longer-term costs of CABG and PTCA will be similar and have only formally compared the costs of CABG vs medical treatment. The costs of PTCA could be substituted for those of CABG.

Comparisons of medical treatment and revascularization

The costs and benefits were assessed for a hypothetical cohort of 100 patients using a spreadsheet model constructed using data from the literature. This followed the meta-analysis by analysing on an ‘intention-to-treat’ basis. The main outputs of this model were the health service costs per annum and quality adjusted survival estimates. Variables used and data sources are shown in Table 1.

The basic data for the model were derived from a meta-analysis of published randomized, controlled trials[3]. This approach posed two problems for an economic model because the focus of the meta-analysis was on benefits rather than costs and the outcome measure was limited to survival gain, but quality of life is also relevant.

**Quality-of-life estimation**

In order to estimate quality adjusted survival, data from the Coronary Artery Surgery Study (CASS)[15] were combined with weighting to reflect the value of life-years spent in less than perfect quality-of-life. The latter were derived from published sources using generic health status measures[16]. Mild activity restriction was assumed to give health status that was 95% as good as normal, while moderate to severe restriction (the classification used in the source work) was valued at 80% of normal.

**Addition of aspirin and simvastatin to the model**

The meta-analysis was based on trials conducted in the 1970s, yet the current analysis attempts to draw implications for current practice. Since the trials were designed, medical management in particular has progressed. Allowance was made for the following research findings:

1. Aspirin (75 mg daily) reduced non-fatal myocardial infarction (MI) (P<0.006) rate by 39% after 5-year follow-up in the Swedish Angina Pectoris Aspirin Trial (SAPAT) study[14]. It was assumed that there was no mortality benefit from aspirin as this has not been proven in patients with angina.

2. The HMG-CoA reductase inhibitor simvastatin reduced all-cause mortality by 30% after 5 years of follow-up (P<0.0003) in the Scandinavian Simvastatin Survival Study (4S)[4], as well as reducing the need for coronary surgery by 37% and non-fatal myocardial infarctions by 30% (both P<0.00001). The dose of simvastatin in the trials was 20 mg.day^{-1} in 63% of patients and 40 mg in 37%.
Cost-effectiveness in angina

Table 2 Sources for U.S. cost data

<table>
<thead>
<tr>
<th></th>
<th>U.S. cost</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>CABG</td>
<td>$11,364</td>
<td>Mark et al. [17]</td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>$3,007</td>
<td>Mark et al. [17]</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>$0.10/day</td>
<td>Roberts [18]</td>
</tr>
<tr>
<td>Aspirin</td>
<td>$0.10/day</td>
<td>Pro rata to statin</td>
</tr>
<tr>
<td>ß-blockers</td>
<td>$0.15/day</td>
<td>Pro rata to statin</td>
</tr>
<tr>
<td>Digitalis</td>
<td>$0.19/day</td>
<td>Pro rata to statin</td>
</tr>
<tr>
<td>Diuretics</td>
<td>$0.19/day</td>
<td>Pro rata to statin</td>
</tr>
<tr>
<td>Outpatient clinic</td>
<td>$4.5</td>
<td>Mark et al. [17]</td>
</tr>
</tbody>
</table>

CABG = coronary artery bypass graft; MI = myocardial infarction.

The economic model thus consisted of three variants on the medical option: (1) medical management alone as described in the meta-analysis; (2) medical management plus aspirin; (3) medical management plus aspirin plus an HMG-CoA reductase inhibitor (statin).

The benefits of statins were assumed to be additional to those of aspirin. The quality-of-life and cost gains of avoiding a non-fatal myocardial infarction in 4S and SAPAT [16, 14] were also included. The quality-of-life data were adjusted by reducing the proportion with moderate or severe activity restrictions and increasing the proportion with no problems by a factor reflecting the number of non-fatal myocardial infarctions avoided.

Costs

The following costs were included in this model: CABG, drug treatment, routine follow-up and non-fatal MI. The cost data were derived from a number of sources (Table 2).

Surgical rates

Following the meta-analysis [3], it was assumed that 94% of patients would be operated on in the first year in those randomized to surgery and that 5% per year of those randomized to medical treatment would be operated on each year for the first 5 years, and 2–3% thereafter. Following surgery, the annual rate of need for a second operation was 0.93% per annum, based on the rate in the European Coronary Surgery Study (ECSS). This was assumed to apply equally to the group who survived surgery but who had been randomized to initial medical management, i.e. the rate applied to all patients who survived surgery.

Follow-up costs

Follow-up was assumed to be twice as frequent for medical management to reflect the 'watchful waiting' aspect of managing a group of symptomatic patients.

Surgical patients were assumed to be seen twice per year in clinic, while all medical management resulted in four visits per annum.

Hospitalization

Rates of hospitalization were assumed to be the same in two groups as shown in the clinical trials.

Modelling assumptions

Where data were available for a limited number of years, a constant rate of change was assumed between these fixed points. For example, mortality in year 8 is not reported directly in the meta-analysis but is assumed equal to one-third of the difference between years 7 and 10. Where figures were only available for 5-year follow-up, an equal annual rate of increase was assumed for years 6–10.

Discounting and inflation

All costs and benefits were discounted to net present value at 6% per annum. Thus, quality of life saved in year 1 was valued more highly than quality of life or a life saved in year 5. Similarly, an operation performed in year 1 was considered more expensive than an operation in year 5. Health service inflation was assumed to be rising at 5% per annum. Drug costs, which have fallen in real terms over the last 5 years, were assumed to be static.

Subgroups

The above model was first run using data for all patients included in the meta-analysis. Results for subgroups of patients with particular diagnoses and characteristics were also constructed, although caution is required since sample sizes are reduced in subsets of the population studied in the randomized clinical trials. Wherever possible data specific to that subgroup were used; other results were estimated. For example, the 5-year mortality rate for three-vessel disease was 17–6% under medical management, 11% above the figure for all patients. Thus, it was assumed that the 7- and 10-year figures were also 11% higher. On this basis, the model was re-run for different patient groups.

Results

All patients in the meta-analysis

Medicine plus aspirin was as effective as medical management alone in terms of survival but was far cheaper because of the number of non-fatal MI prevented.

Eur Heart J, Vol. 18, Suppl B 1997
The questions of interest were thus: (1) what were the additional costs and benefits of CABG compared with medicine plus aspirin; (2) what were the additional costs and benefits of adding statins to an existing regime of medicine plus aspirin; (3) what were the additional costs and benefits of CABG in comparison with a medical regime that included aspirin and statins?

When and where did the (discounted) costs occur?

The cheapest option was standard medical therapy. The major cost over 5 years in the surgical and standard medical groups was that of surgery but if the costs of statins were added to the cost of medically-managed patients then drug therapy became the major cost. Over 5 years, the addition of statins was about $3500 per patient less expensive than surgery (Fig. 1a). Over 10 years, standard medical therapy was least expensive and surgery or medical therapy with statins had similar costs (Fig. 1b). Note that most of the costs of surgery were incurred immediately and therefore the cost of surgery fell with time relative to the costs of the medical strategies.

What were the benefits?

Overall, over 5 years, surgery compared with medical treatment led to a gain of 10 life-years per 100 patients (i.e. effectively two more people lived for 5 years with surgery than with medical treatment for 100 operations).
Cost-effectiveness in angina

Figure 3  Estimated quality-adjusted life years gained per 100 patients (a) at 5 years and (b) at 10 years. • shows the gain in all cases, ◇ the gain with mild angina, □ the gain with severe angina, ◆ the gain with three-vessel disease and □ the gain with poor left ventricular function.

(Fig. 2a). Life-year gain per 100 patients with surgery was reduced to 2 by the addition of a statin to medical therapy (Fig. 2a). Patients at higher risk, for instance those with severe angina or those with three-vessel disease, derived greater absolute benefit from surgery but in no group did the gain in life-years per 100 patients with surgery exceed 7 when surgery was compared with aspirin and a statin. Similar results were found over 10 years, with surgery increasing the number of life-years gained compared with standard medical therapy to 57 per 100 patients at most in those patients with poor left ventricular function (Fig. 2b). With the addition of a statin to medical therapy the additional life-years gain with surgery was predicted to fall to 7 per 100 patients. This is the equivalent of making about one person live an extra 10 years for every 100 operated. In some subsets there was a trend to a survival advantage with medical treatment when a statin was added.

Surgery had a greater impact on quality adjusted life-years than on life-years gained due to the more successful reduction in angina over the first 5 years (Fig. 3a). In this model the gain in quality-adjusted life-years (QALYs) attributed to the addition of a statin to medical therapy was due to the reduction in infarction. Although statins probably retard the progression of angina symptoms and reduce the need for surgery, which itself has an adverse, usually temporary, impact on the quality of life, these were not taken into account when adjusting for the impact of statins on the quality of life.

Overall, the impact of surgery on life-years gained or quality of life appeared low compared with the medical regime when statins were added (Fig. 3b).

Costs per life-year and per quality-adjusted life-year gained

Previous publications have suggested that treatments that cost <$20 000 per QALYs are highly cost-effective, though this would be considered a very generous budget in many industrialized countries. Treatments between $40 000 and $60 000 are considered borderline and above $60 000 per QALYs are considered expensive. Using these thresholds, CABG appears a relatively inexpensive option compared with standard medical therapy over 5 or 10 years (Tables 3a and b). Those groups with the greatest cost benefit were characterized by severity of angina and left ventricular dysfunction and both markers appeared better at determining cost-effectiveness than the coronary anatomy.

When surgery was compared with standard medical therapy with the addition of a statin, costs per QALYs for surgery rose dramatically (Tables 3c and d). As prognosis was equally good with or without surgery in those with mild angina, no advantage could be attributed to surgery at 10 years in this subgroup. Comparing standard medical therapy with medical therapy and additional simvastatin, the latter appeared highly cost-effective (<$20 000 per QALYs) in most subgroups and effective (<$40 000 per QALYs) in all.

Discussion

How much it is worth spending to gain a year of life is an arbitrary decision and may be set by the individual when the patient is paying the full cost. How much they are willing to pay will, of course, depend on how wealthy the individuals are and how high they perceive their own risk to be. Where a society is paying for the costs this will also depend on what the members of that society are willing to pay. Previous studies have suggested that surgery other than for severe angina or left main coronary disease is not very cost-effective.

As stated earlier, in the U.S.A. it has been suggested that treatments that cost <$20 000 per QALYs are highly cost-effective, though this would be considered a very generous budget in many other countries.
Table 3

<table>
<thead>
<tr>
<th>Costs per life-year gain over 5 years</th>
<th>Costs per life-year gain over 10 years</th>
<th>Costs per QALYs gain over 5 years</th>
<th>Costs per QALYs gain over 10 years</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Surgery vs medical+aspirin (U.S. $)</strong></td>
<td><strong>Surgery vs medical+aspirin + statin (U.S. $)</strong></td>
<td><strong>Medical+aspirin + statin vs medical+aspirin (U.S. $)</strong></td>
<td><strong>Medical+aspirin + statin vs medical+aspirin + simvastatin (U.S. $)</strong></td>
</tr>
<tr>
<td><strong>All cases</strong></td>
<td><strong>Mild angina</strong></td>
<td><strong>Severe angina</strong></td>
<td><strong>Three-vessel disease</strong></td>
</tr>
<tr>
<td>73 601</td>
<td>229 077</td>
<td>34 883</td>
<td>229 077</td>
</tr>
<tr>
<td>87 202</td>
<td>207 477</td>
<td>45 381</td>
<td>207 477</td>
</tr>
<tr>
<td>40 440</td>
<td>68 290</td>
<td>23 470</td>
<td>68 290</td>
</tr>
<tr>
<td>50 575</td>
<td>98 847</td>
<td>29 484</td>
<td>98 847</td>
</tr>
<tr>
<td>39 624</td>
<td>76 346</td>
<td>21 357</td>
<td>76 346</td>
</tr>
</tbody>
</table>

industrialized countries. Treatments between $40 000 and $60 000 are considered borderline and above $60 000 per QALYs are considered expensive. Based on cost-effectiveness result tables, in the U.K. and other European countries a cost of $7500 per QALYs would be considered cost-effective and costs >$15 000 expensive.

This analysis of the cost-effectiveness of early CABG compared with initial standard medical therapy shows that, in unselected patients over 5 years, CABG is towards the upper limit of what can be considered cost-effective treatment both in terms of its effects on mortality (life-years gained) and morbidity (QALYs).

Few patients in the trials of surgical treatment were given long-term aspirin. Although there remains controversy about the benefits of aspirin in patients with stable coronary artery disease, there is reasonably strong evidence to support its routine use, at least among those with well preserved ventricular function. Using the data from the SAPAT study it appears that aspirin might have reduced mortality in the medical treatment arm and approximately doubled the cost of surgery per life-year gained. Addition of simvastatin, for which the evidence of a mortality benefit in patients with chronic stable coronary disease is much stronger than for aspirin, makes CABG surgery a very expensive option in terms of QALYs, while the predicted overall mortality would actually be lower in an aggressively medically-treated cohort than in the CABG group. Simvastatin not only reduced mortality but also improved the quality of life, hence the cost per QALYs of simvastatin, in terms of the U.S. healthcare system at least, is very cost-effective in this patient group.

Clinicians will point out that the clinical trials suggested that surgery was only worthwhile for some subgroups of patients, for example, those with three-vessel coronary or left main stem disease. Others will point out that the benefits of surgery are only really proven in patients with important left ventricular dysfunction. Other cardiologists might reserve CABG, as a procedure for improving prognosis, only for younger patients. Even more conservative cardiologists might suggest that the only good reason for revascularization is angina that has failed to respond to medical therapy to the patient's satisfaction pointing out that the prognostic benefits of surgery are dubious. Using data from the meta-analysis of surgery and data from the CASS registry (not shown here) we have explored the cost-effectiveness of surgery relative to medical management in these subgroups.
Patients with more severe angina, a logical group to target for revascularization in order to relieve symptoms, had a greater prognostic benefit from surgery than patients with mild angina. In terms of life-years gained and QALYs, a gain in this group appeared to benefit at reasonable cost, whether compared with standard medical therapy alone or medical therapy with a statin added. Severity of angina seemed a better determinant of the efficiency of surgery both in terms of life-years gained and quality-adjusted life-years than coronary anatomy. This has major implications for how patients with angina are managed. A strategy based on symptom relief requires fewer angiograms. This will save money not only by reducing the number of angiographic procedures, but also by preventing unnecessary coronary interventions for ‘cosmetic’ reasons in patients without symptoms. A trial to test this hypothesis is underway.

CABG surgery for patients with three-vessel disease is more cost-effective than for the general population with angina but remains a relatively expensive treatment when the benefits of aspirin and lipid-lowering therapy are added to medical therapy. It is likely that this analysis underestimates the true costs of adopting an anatomical approach to selecting patients for surgery, partly due to the additional costs of unnecessary angiograms, but also because it is quite likely that the prognosis of patients with triple-vessel disease and few symptoms is better than the prognosis of those with triple-vessel disease and severe angina. A symptom-guided strategy would have treated those patients with severe symptoms anyway. The cost-effectiveness of CABG relative to medical management is enhanced when patients below 65 years are excluded from analysis (CASS registry data); the medical prognosis of younger patients with angina is sufficiently good that surgery makes little difference. Operating on older patients with three-vessel disease makes more sense from the health-economic point of view even after adjustments for life expectancy.

Among patients with poor left ventricular function, surgery appears highly cost-effective compared with standard medical therapy. However, statins may also have their greatest impact on quality and quantity of life-years gained in this group. The majority of patients in the 4S study had a history of MI and it is likely that a substantial proportion had ventricular dysfunction, suggesting that the benefits of statins are retained in this group of patients. Surgery became a relatively expensive option compared with standard medical therapy and simvastatin in this subgroup.

In conclusion, the preferred options for each patient group in two different scenarios are shown in Tables 4a and b. In the first, purchasers are unwilling to pay more than $20,000 to gain an extra QALY, while in the second they are unwilling to pay more than $40,000. It should be noted that the conclusions are sensitive to the assumptions used to construct them and particularly to the duration of follow-up. The results are also sensitive to the value put on a quality-adjusted life-year or a non-adjusted life-year, a figure that will vary markedly between countries and the system under which healthcare is delivered. Changes in these assumptions can change the results quite dramatically. Accordingly, studies such as this should be used to stimulate further research and develop general policies for treatment rather than being used as rigid constraints on medical practice.

### References


