PAPERS AND SHORT REPORTS

Economic consequences of postinfarction prophylaxis with β blockers: cost effectiveness of metoprolol

GUNNAR OLSSON, LARS-ÅKE LEVIN, NINA REHNQVIST

Abstract

Treatment with certain β adrenoceptor blocking agents after myocardial infarction reduces mortality and the incidence of reinfarction. Data from a randomised placebo controlled study of the β_1 selective blocker metoprolol given as secondary prophylaxis were therefore analysed for the possible cost effectiveness of extending this treatment to the general population of patients with myocardial infarction.

Metoprolol 100 mg twice daily and matching placebo were given to 154 and 147 patients, respectively, for three years. During this period drug costs for the β blocker, digitalis, and diuretics were analysed as well as costs of readmission for cardiac problems and indirect costs arising from sick leave or early retirement. Active treatment with metoprolol significantly reduced costs of readmission as well as indirect costs. The net effect per patient over the three years was a reduction of roughly kr 19 000 (£1930).

These results suggest that β blocker treatment given as secondary prophylaxis after myocardial infarction is highly cost effective.

Introduction

Ischaemic heart disease is the most common cause of death in the Western World. In Sweden some 40 000 patients every year suffer an acute myocardial infarction. Since mortality and morbidity are high after myocardial infarction substantial resources have been spent on improving the prognosis of these patients.[1] Among interventions studied to date only stopping smoking[2] and treatment with certain β blockers have been shown to be effective.[3-6] Trying to change smoking habits in patients with infarction is now established, but the value of prophylactic treatment with long term β blockade in unselected patients remains controversial.[7] Geoffrey Rose stated in 1982 that the cost of preventing one death in the Norwegian timolol study[3] was equivalent to the cost of roughly 24 patient years of treatment.[8] Long term postinfarction treatment with β blockers must therefore be evaluated not only in relation to mortality and morbidity but also in relation to the quality of life achieved and the economic consequences. The effects of long term secondary prophylaxis with metoprolol on mortality, morbidity, and the quality of life have been reported.[6,9]

The economic consequences of chronic postinfarction treatment with β blockers have not been fully reviewed. Given present economic restrictions doubts have been raised against general prophylactic treatment for fears that this might increase overall health care costs. True cost effective treatments, however, reduce the need for other health care resources and so reduce total resource expenditure. Economic costs examined in this context must therefore include not only direct health care costs but also indirect costs, such as loss of production as a result of sick leave and early retirement. This study aimed at analysing the economic consequences of prophylactic treatment with a β blocker after an acute myocardial infarction in patients aged under 70.

Patients and methods

The analysis was based on data from the Stockholm metoprolol study, a randomised, double blind placebo controlled postinfarction study of metoprolol. The study has been fully described.[6] In brief, between May 1976 and December 1980, 301 patients aged under 70 were included in the study. The study population consisted of 66% of all patients in this age group surviving a myocardial infarction and living in the hospital catchment area. To be included patients had to be in sinus rhythm, without complete bundle branch block, and without contraindication to β blockade. Patients were randomised to double blind treatment with metoprolol 100 mg twice daily or matching placebo. Treatment was started one to two weeks after the acute onset of illness. The patients initially received half a tablet three times daily for three days and thereafter one tablet twice daily.

The patients were examined by a physician at our outpatient clinic after one, three, six, 12, 18, 24, 30, and 36 months and by a specially trained

Department of Medicine, Karolinska Institutet, Danderyd Hospital, S-182 88 Danderyd, Sweden
GUNNAR OLSSON, MD, associate professor
NINA REHNQVIST, MD, associate professor

Centre for Medical Technology Assessment, University of Linköping, Sweden
LARS-ÅKE LEVIN, BA, research assistant

Correspondence to: Dr Olsson.

research nurse afer nine, 15, 21, 27, and 33 months. If adverse symptoms developed possibly related to the study treatment the dose was halved. If symptoms persisted treatment was withdrawn without breaking the code. Patients with angina pectoris were primarily treated with non-β adrenergic blocking antianginal agents. If this was insufficient the patients were withdrawn blindly and given active β adrenoceptor blockade. Patients were referred for coronary artery bypass surgery if unresponsive to optimal medical treatment including β adrenergic blocking agents. Otherwise patients were treated according to standard routines. The individual study codes were not broken until all patients had been followed up for three years.

Of 157 patients who were excluded from the study, 44 were rejected because of need for open β blockade and 23 patients were unwilling to take part in a long term follow up. There was therefore no absolute contraindication to β blockade in 80% of the study population.

Mortality and morbidity data were analysed according to the "intention to treat" principle—that is, according to the initial treatment randomised, independent of later changes. In the economic study data were analysed according to the actual costs attributed to the patients in the original randomisation group.

The analysis compares the costs and effects of conventional postinfarction treatment with or without the addition of metoprolol. Saved costs are therefore noted as a gain. Identified costs are divided into direct and indirect. Direct costs were estimated from drug consumption and costs of inpatient and outpatient care; indirect costs were approximated from the loss of productivity due to sick leave or early retirement as a result of the disease.

Drug costs—At each visit to the outpatient clinic treatment with metoprolol, digitalis, and diuretics was noted. Swedish market prices were used in estimating drug costs. Daily average doses of 0·25 mg digoxin and 60 mg frusemide were used in calculating costs for digitalis and diuretics. Consumption was estimated as average use—that is, those who were taking a drug at two consecutive visits were considered to have taken the drug for the entire period between the two visits. In those who changed medication between visits the change was deemed to have occurred halfway between the visits.

Readmission costs—Readmission to hospital for cardiovascular disorders (reinfarction, angina pectoris, heart failure, arrhythmias) during follow up was recorded. The analysis considered costs related to ischaemic heart disease alone. In the Swedish system of "socialised medicine" the estimated daily cost of inpatient care at the department of internal medicine is kr 1115 (£113 (exchange rate December 1986)).[10] In patients having coronary artery bypass surgery costs have been estimated as kr 65 000 (£6600) per operation plus kr 30 000 (£3050) for postoperative care (Sahlgren's Hospital, August 1984).

Outpatient clinic costs—The numbers of visits to the outpatient clinic were estimated from the fixed visits in the study. Survival of patients was considered. The cost of each appointment at the clinic was estimated as kr 370 (£37·50).[10]

Indirect costs—In a society with full employment the appearance of disease will reduce total productivity with a consequent reduction in average welfare status. To estimate costs of sick leave and early retirement due to cardiac disease an estimation of income from work and payroll taxes on labour was used. Yearly income was estimated as an average for the Swedish population with regard to age and sex.[11] As 28% of the patients on sick leave or who had taken early retirement in the placebo group were women, this proportion was also used in the calculation for the metoprolol group (20·8%) in order to counterbalance the slight difference in male to female ratios in the two groups. Social taxes on labour were estimated as 0·42 × income from work.

Table I lists the costs used in the calculations. All costs were adjusted to 1985 fixed prices at discount rates of 2·5% to 8·0%.

Statistical methods—The χ^2 and Fisher's exact tests were used in analysing differences between the two treatment groups with respect to complications and return to work. In the comparison of numbers of days spent in hospital an index for rehospitalisation was constructed. This was calculated as (number of patients in hospital)/(total number of surviving patients) for each day in the study. The Mann-Whitney U test was then used to compare the two treatment groups. All tests were two tailed. p Values of less than 0·05 were regarded as significant.

TABLE I—*Costs used in analysis*

		kr*
Metoprolol 200 mg daily/year		1085
Digoxin 0·25 mg daily/year		47
Frusemide 60 mg daily/year		182
Inpatient care at department of medicine/day		1115
Coronary artery bypass surgery/operation		65 000
Postoperative care		30 000
Outpatient clinic/visit		370
Mean yearly income†		
Men	Age 55-59	98 600
	Age 60-64	64 700
Women	Age 55-59	54 800
	Age 60-64	30 700

*Exchange rate December 1986 about kr 9·9=£1.
†Actual income calculated as income from work plus payroll tax, which equals 1·42 × income from work.

Results

The two treatment groups were well matched with respect to baseline characteristics (table II). Table III summarises the mortality and morbidity results, which are reported in detail elsewhere.[6]

TABLE II—*Baseline characteristics of the two treatment groups. Except where stated otherwise figures are numbers (percentages) of patients*

	Placebo (n=147)	Metoprolol (n=154)
Mean age (years) (SD)	59 (7)	60 (7)
Men	122 (83)	120 (78)
Smokers	88 (60)	82 (53)
Previous infarction	29 (20)	32 (21)
Mean LD_tmax (μkat/l) (SD)*	19·6 (13·7)	19·8 (14·0)
Non-transmural infarct	41 (28)	39 (25)
Infarct location:		
Anterior	75 (51)	68 (44)
Inferior	46 (31)	58 (38)
Uncertain	26 (18)	28 (18)
Heart size (ml/m²) (SD)	470 (88)	471 (89)
Complex arrhythmia	49 (33)	59 (38)
Treatment:		
Digitalis	35 (24)	35 (23)
Diuretics	70 (48)	65 (42)

*LD_tmax=Maximum value of thermostable fraction of lactate dehydrogenase.

TABLE III—*Mortality and morbidity during three year follow up of the two treatment groups. Figures are numbers (percentages) of patients*

	Placebo (n=147)	Metoprolol (n=154)	p Value
Total mortality	31 (21)	25 (16)	NS
Cardiac mortality	29 (20)	20 (13)	NS
Non-fatal reinfarction	31 (21)	18 (12)	<0·05
Readmission for:			
Angina pectoris	42 (29)	34 (22)	NS
Heart failure	10 (7)	5 (3)	NS
Arrhythmias	17 (12)	10 (6)	NS
Cerebrovascular events	11 (7)	3 (2)	<0·05
Coronary bypass surgery	9 (6)	3 (2)	0·058
Leg amputation	3 (2)	0	NS

DRUG COSTS

In 35 (24%) and 38 (25%) patients in the placebo and metoprolol groups, respectively, study treatment was discontinued during the three year period. After withdrawal of the treatment metoprolol was instituted openly in 11 and seven of these patients.[6] Table IV shows the costs of metoprolol treatment.

Use of digitalis and diuretics did not differ between the groups during follow up.[12] After 36 months 51 (35%) and 48 (31%) patients in the placebo and metoprolol groups, respectively, were treated with digitalis. Corresponding figures for diuretic treatment were 68 (46%) and 68 (44%). Table IV gives the costs of digitalis and diuretic treatment.

COSTS OF READMISSION

During follow up 42 placebo treated patients (29%) were admitted to hospital for angina pectoris, 10 (7%) for heart failure, and 17 (12%) for symptomatic arrhythmia. Corresponding figures in the metoprolol treated group were 34 (22%), 5 (3%), and 10 (6%) patients (table III). Thirty one (21%) and 18 (12%) patients in the placebo and metoprolol groups, respectively, were admitted to hospital because of a non-fatal reinfarction ($p<0·05$). The total numbers of days spent in the department of internal

medicine for cardiac disorders were 1032 in the placebo group and 638 in the metoprolol group ($p<0.01$). Table V shows the average number of days per patient spent in hospital during each year of follow up. Costs of inpatient care in the internal medicine ward are given in table IV.

TABLE IV—*Costs per patient over three years estimated at 5% discount rate. Values in parentheses are costs at discounts of 2·5% and 8%, respectively*

	kr*	
	Placebo	Metoprolol
Metoprolol	170 (180, 160)	2 000 (2 096, 1 895)
Digitalis + diuretics	310 (330, 300)	280 (300, 250)
Inpatient care, department of internal medicine†	7 320 (7 640, 6 970)	4 260 (4 410, 4 100)
Inpatient care, department of thoracic surgery	5 340 (5 560, 5 080)	1 710 (1 780, 1 630)
Outpatient clinic	3 980 (4 160, 3 780)	4 060 (4 250, 3 850)
Indirect cost	120 100 (124 780, 114 460)	106 300 (110 250, 101 900)
Total	137 220 (142 650, 130 750)	118 610 (123 086, 113 625)

*Exchange rate December 1986 about kr 9·9=£1.
†Includes costs attributed to cardiac disorders only.

TABLE V—*Average number of days spent in department of internal medicine for cardiac disorders in each year of follow up in the two treatment groups*

	1st Year	2nd Year	3rd Year
Placebo group	3·03	2·40	1·48
Metoprolol group	2·79	0·59	0·58

Placebo group *v* metoprolol group: $p<0.01$.

During the three years of follow up nine patients in the placebo group (6%) had coronary artery bypass surgery compared with 3 (2%) in the metoprolol group ($p=0.058$). Table IV shows the costs of these operations.

Apart from the complications listed above, other atherosclerotic complications requiring hospitalisation occurred during the study, including cerebrovascular events (11 (7%) patients given placebo *v* 3 (2%) given metoprolol; $p<0.05$) and leg amputation for peripheral arterial insufficiency (3 (2%) patients in the placebo group). The costs of these complications are not included in the analysis. Table III summarises the morbidity data.

COSTS OF VISITS TO OUTPATIENT CLINIC

Since the patients were followed up in the outpatient clinic at prespecified intervals the frequency of visits did not differ between the two groups. The slightly higher cost of these visits in the metoprolol group (table IV) was related to improved survival.

INDIRECT COSTS

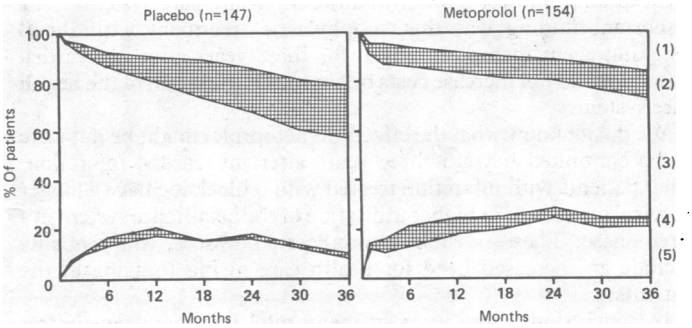
Information on return to work was not included in the database until the visit at nine months; hence all patients were considered to have been on sick leave during the first six months. Table VI shows the proportions of patients who returned to work or who were on sick leave or had taken early retirement. The decreasing proportions of patients in all categories in the two treatment groups is explained by the fact that anyone in Sweden may retire and receive a pension by the age of 65. The difference between the two groups with respect to return to work and sick leave or early retirement was significant ($p=0.011$). Table IV shows the economic consequences of loss of productivity as a result of sick leave and early retirement.

TABLE VI—*Numbers (percentages) of patients in the two treatment groups who returned and did not return to work*

Time in months	Placebo (n=147)		Metoprolol (n=154)	
	Returned	Did not return*	Returned	Did not return*
9	44 (30)	50 (34)	61 (40)	32 (21)
18	46 (31)	35 (24)	58 (38)	26 (17)
24	41 (28)	35 (24)	57 (37)	28 (18)
30	42 (29)	30 (20)	52 (34)	27 (18)
36	37 (25)	29 (20)	52 (34)	24 (16)

*Represents patients on sick leave or who had taken early retirement.

The figure shows the effects of treatment with respect to mortality, morbidity, side effects, and wellbeing. In the metoprolol group a reduced mortality, reduced morbidity, and increased proportion of patients in functional group I (New York Heart Association[13]) were observed. Details are given elsewhere.[9] In an overall comparison of the two groups these differences were significant ($p<0.05$).



Distribution of patients with respect to mortality and cardiovascular morbidity. (1) Death. (2) Patients with any atherosclerotic complication (non-fatal reinfarction, cerebrovascular event, coronary bypass surgery, leg amputation). (3) Patients in New York Heart Association functional groups II-IV without atherosclerotic complication. (4) Patients in functional group I with suspected side effects of study treatment. (5) Patients in functional group I without side effects of study treatment.

Discussion

Before introducing a regimen for preventing disease possible advantages (reduction of illness and death) must be balanced against possible disadvantages (side effects of treatment, negative economic consequences). In a critical economic setting expensive prophylactic regimens cannot be adopted without thorough evaluation of cost effectiveness.

In this study a reduction in mortality and morbidity[6] as well as an improvement in the quality of life[9] were observed in the group treated with conventional postinfarction treatment plus long term metoprolol. The disadvantage of adding metoprolol was a slightly increased proportion of patients with suspected side effects of the trial preparation (figure).[9] Considering the influence of side effects on the quality of life will mainly concern patients without cardiac symptoms, since treatment of patients with symptoms may be regarded as conventional treatment resulting in relief of the total burden of symptoms.

In the analysis of the economic consequences of three years of postinfarction treatment with metoprolol the presumed cost of treatment resulted in a "gain" of kr 18 593 (£1888) per patient. In this evaluation both direct costs of treatment and indirect costs due to sick leave and early retirement were taken into account. Had costs of the other atherosclerotic complications, such as cerebrovascular events and leg amputation, also been taken into account the difference between the two groups would have been even larger.

Economic implications of side effects of metoprolol were evaluated only in severe cases—that is, in patients for whom readmission was necessary. Non-severe side effects were ignored, since giving a price in monetary terms of non-severe side effects entails making a series of assumptions. This does not mean that non-severe side effects are negligible, but rather that there is no reliable method by which to value them. Patient related costs—for example, transportation to hospital—were not included owing to lack of valid data. Nevertheless, even if costs of ordinary transportation to the outpatient clinic are assumed to have been slightly higher in the metoprolol group

these were probably outweighed by the more frequent admissions to the emergency room by ambulance in the placebo group. Thus excluding costs of non-severe side effects and transportation probably did not influence the overall result.

The most obvious economic gain with long term metoprolol was in the reduction of indirect costs. Direct costs (costs of readmission), however, were also lower in the metoprolol group compared with the placebo group. The difference between the two groups became most evident later in follow up.

As any evaluation of costs and benefits of a treatment requires many different assumptions, we performed a sensitivity analysis using various discount rates. At discount rates ranging between 2·5% and 8·0% metoprolol was associated with reduced overall costs. We did not set out to achieve exact costs for the two different treatment regimens, as the analysis needed to be based on several assumptions, and costs differ in different health care systems. The important finding was that prophylactic treatment with the β blocking agent metoprolol given for three years after myocardial infarction did not increase costs but reduced utilisation of the health care system.

We do not know what the effects of metoprolol might be if it were to be continued beyond three years after myocardial infarction. That patients with infarction treated with β blockade have a longer survival may result in higher utilisation of the health care system in a later phase. These possible future costs, however, will probably include an increased need for health care owing to aging of the patients.

In conclusion, three years of metoprolol treatment given after myocardial infarction improved the prognosis and reduced utilisation of the health care system. Postinfarction treatment with metoprolol therefore appears to be cost effective.

References

1 May GS, Eberlein KA, Furberg CD, Passamani ER, DeMets L. Secondary prevention after myocardial infarction: a review of longterm trials. *Prog Cardiovasc Dis* 1982;**24**:331-51.
2 Wilhelmsson C, Vedin JA, Elmfeldt D, Tibblin G, Wilhelmsen L. Smoking and myocardial infarction. *Lancet* 1975;i:415-20.
3 Norwegian Multicenter Study Group. Timolol-induced reduction in mortality and reinfarction in patients surviving acute myocardial infarction. *N Engl J Med* 1981;**304**:801-7.
4 Hjalmarson Å, Elmfeldt D, Herlitz J, *et al.* Effect on mortality of metoprolol in acute myocardial infarction. A double-blind randomised trial. *Lancet* 1981;ii:823-7.
5 Beta-blocker Heart Attack Trial Research Group. A randomized trial of propranolol in patients with acute myocardial infarction. I. Mortality results. *JAMA* 1982:247:1707-14.
6 Olsson G, Rehnqvist N, Sjögren A, Erhardt L, Lundman T. Longterm treatment with metoprolol after myocardial infarction: effect on 3 year mortality and morbidity. *JACC* 1985;5:1428-37.
7 Breckenridge A. Should every survivor of a heart attack be given a beta-blocker? Part II. Evidence from a clinical pharmacological standpoint. *Br Med J* 1982;**285**:37-9.
8 Rose G. Prophylaxis with beta-blockers and the community. *Br J Clin Pharmacol* 1982;**14**:45-8S.
9 Olsson G, Lubsen J, van Es G-A, Rehnqvist N. Quality of life after acute myocardial infarction: effects of chronic metoprolol treatment on mortality and morbidity. *Br Med J* 1986;**292**:1491-3.
10 Landstingsförbundet. *Kostnad per intagen vårddag och läkarbesök 1982.* Stockholm: Swedish Federation of County Councils, 1984.
11 Statistiska Centralbyrån (SCB). *Statistiska meddelanden Be20 SM 8501.* Stockholm: Statistics Sweden, 1985.
12 Olsson G, Rehnqvist N. Evaluation of anti-arrhythmic effect of metoprolol treatment after acute myocardial infarction: relationship between treatment responses and survival during a 3-year follow-up. *Eur Heart J* 1986;7:312-9.
13 Goldman L, Cook EF, Mitchell N, Flatley M, Sherman H, Cohn P. Pitfalls in the serial assessment of cardiac functional states: how a reduction of "ordinary" activity may reduce the apparent degree of cardiac compromise and give a misleading impression of improvement. *J Chronic Dis* 1982;35:763-71.

(Accepted 25 November 1986)

Type I (insulin dependent) diabetes: a disease of slow clinical onset?

ANNE C TARN, CLAIRE P SMITH, KATE M SPENCER, GIAN FRANCO BOTTAZZO, EDWIN A M GALE

Abstract

Type I (insulin dependent) diabetes is usually believed to present acutely and it is assumed that metabolic decompensation is sudden. In a prospective family study, however, 10 of 13 subjects developing the disease showed progressive or intermittent development of hyperglycaemia over many months and the others had non-specific symptoms over a long period. All were first degree relatives of a child with type I diabetes; 10 were siblings (aged 5-24) and three were parents (aged 45-58). All possessed HLA-DR4 or DR3, or both, and all but two had been positive for islet cell antibodies for six to 86 months before diagnosis. Ten had non-specific symptoms for two to 14 months before the onset of thirst and polyuria; one remained asymptomatic even when insulin became necessary. Six subjects had an oral glucose tolerance test before clinical onset, of whom five were diabetic by World Health Organisation criteria four, four, six, seven, and 21 months before insulin was needed. Nine showed random blood glucose concentrations above the 97·5th centile (6·3 mmol/l) six to 34 months (median 12) before diagnosis. Two others had a glucose tolerance test result compatible with diabetes but had not reached the stage of needing insulin.

Hyperglycaemia is often of insidious onset in type I diabetes, even in children and young adults. Diagnosis will inevitably be late if considered only when acute symptoms of thirst and polyuria develop.

Department of Diabetes and Immunogenetics, St Bartholomew's Hospital, London EC1A 7BE

ANNE C TARN, MRCP, research registrar
CLAIRE P SMITH, MRCP, research registrar
KATE M SPENCER, MRCP, senior registrar
EDWIN A M GALE, MRCP, consultant physician

Department of Immunology, Middlesex Hospital, London W1

GIAN FRANCO BOTTAZZO, MD, MRCP, reader in clinical immunology

Correspondence to: Dr Gale.

Introduction

Traditionally type I (insulin dependent) diabetes is thought to present acutely, especially in childhood. The most recent edition of a standard paediatric textbook states that "the onset of diabetes in childhood is always acute with thirst and polyuria as the presenting symptoms."[1] In practice the presentation of childhood diabetes may be more varied. A survey of 66 children showed that 19 (29%) had symptoms for less than two weeks, 18 (27%) had symptoms for two to four weeks, and 29 (44%) had symptoms for more than four weeks.[2]

More recent studies have shown that the onset of type I diabetes is preceded by a prodromal period, often extending over years,