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COST-EFFECTIVENESS OF FELODIPINE-METOPROLOL (LOGIMAX®) AND ENALAPRIL IN THE TREATMENT OF HYPERTENSION

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ABSTRACT

We present results from a Swedish retrospective cost-effectiveness analysis of felodipine-metoprolol (Logimax®) and enalapril in hypertension. In the 8-week trial, the average reduction of diastolic blood pressure (DBP) and the share of patients reaching target DBP were both significantly greater in the felodipine-metoprolol group. Cost of treatment (costs of drugs and physician visits) was somewhat higher in the felodipine-metoprolol group. After 8 weeks, an extra 4.8 mmHg reduction and an additional 22% of patients reaching target DBP were achieved with felodipine-metoprolol at the extra cost of SEK 19 (Swedish kronor, $US 1=SEK 7.90). The incremental cost per mmHg reduction and per patient

reaching target DBP was calculated at SEK 4 and SEK 86, respectively. Average cost-effectiveness ratios showed that the costs per mmHg reduction and per patient reaching target DBP after 8 weeks were 40 and 34% lower in the felodipine-metoprolol group, respectively. In conclusion, felodipine-metoprolol is cost-effective in the treatment of hypertension.

INTRODUCTION

In recent years, healthcare services have come under rising pressure to increase their efficiency (1). In deciding on drug therapy, however, often only the cost side of the equation has been taken into consideration. Although the cost of drugs generally constitutes only a fraction of the total cost of treatment, the need for containing healthcare expenditures has led to a growing interest in cost-effectiveness analysis of drug therapies. One area of particularly intense activity has been hypertension. To date, however, mainly extensive modelling cost-effectiveness analyses have been carried out and published (2). This paper illustrates that it is possible to identify cost-effective drugs using a somewhat less exhaustive approach.

Results obtained from population surveys show that blood pressure frequently remains uncontrolled despite treatment (3,4). One reason for the failure to achieve blood pressure control may be that a majority of patients are receiving monotherapy in general practice. Approximately 50% of the patients recruited to the recently completed Hypertension Optimal Treatment (HOT) Study were being treated at the time of enrolment (5). Of these patients, 59% were receiving monotherapy. However, three-year interim data from the HOT Study showed that the need for combination therapy increased as the target blood pressure was lowered (6). Thus, there is evidence that blood pressure may be inadequately managed in general practice and that monotherapy may not be sufficient to achieve blood pressure control.

A higher reduction in blood pressure is to be expected with antihypertensive combination therapy, compared with monotherapy. However, combination therapy is also more costly, suggesting the importance of evaluating the health economic consequences of switching or adding antihypertensive drugs. The current paper presents the results of a cost-effectiveness analysis of the fixed combination felodipine and metoprolol (Logimax®), and enalapril monotherapy in the treatment of hypertension. The secondary aim of the paper is to illustrate the importance of evaluating both costs and efficacy of drugs in the treatment of hypertension.

MATERIALS

The cost-effectiveness of felodipine-metoprolol and enalapril was calculated using data from a Swedish 8-week double-blind randomized clinical trial, with the purpose of comparing the antihypertensive efficacy and tolerability of the drugs (7). The study enrolled 120 patients (47 men and 73 women) with primary hypertension, either treated or untreated. The inclusion criteria also stated that patients should be between 20 and 70 years of age (average age in the study was 55 years) and have an initial diastolic blood pressure (DBP) between 95 and 115 mmHg. Among the exclusion criteria were secondary hypertension; average supine systolic blood pressure >200 mmHg; myocardial infarction, stroke, coronary by-pass surgery or transient ischaemic attack within 6 months prior to the start of the study; cardiac failure. After a 4-week run-in phase on placebo, the patients were randomly assigned to either felodipine-metoprolol 5/50 mg o.d. (n=59), or enalapril 10 mg o.d. (n=61). A DBP above 90 mmHg 24 hours after taking medication was defined as being sub-optimal. If the target DBP ($\leq$90 mmHg) had not been reached after 4 weeks of treatment, the dose was doubled for a further 4 weeks. The numbers of patients who were subsequently prescribed the higher dosage are shown in Table 1.

TABLE 1

Number of Patients Prescribed Low or High Dosage after Four Weeks, with Percentage of Patients Given in Parentheses (Data on File).

	Felodipine-metoprolol	Enalapril	p-value
Low dosage	35 (63)	23 (40)	$p<0.05$
High dosage	21 (37)	35 (60)	$p<0.05$
Total	56 (100)	58 (100)	

Three patients in the felodipine-metoprolol group and four in the enalapril group discontinued treatment, owing to side effects or other adverse events. (One of the patients in the enalapril group who discontinued the study drug continued to see the physician as scheduled and was therefore included in the analysis. The significance of the clinical results was not affected by this patient.)

The average DBP at randomisation, and the average reductions in DBP are presented in Table 2. The clinical efficacy improved only marginally in both groups between four and eight weeks.

METHODS

In a cost-effectiveness analysis of antihypertensive combination therapy and monotherapy, the extra cost of combination therapy is related to the extra healthcare benefits in order to calculate the cost for one additional unit of the outcome measure, e.g. mmHg reduction in blood pressure (8). In recent years, however, there has been a growing interest in the approach to evaluating the cost-

TABLE 2

Average DBP at Randomisation, Average Reductions in DBP, and Proportions of Patients Reaching Target DBP.

	Felodipine-Metoprolol	Enalapril	p-value
DBP at randomisation	100	101	p>0.10
Reduction in DBP (mmHg):			
- After 4 weeks	11.4	5.4	p<0.001
- After 8 weeks	12.0	7.2	p<0.001
Proportions of patients (%) reaching DBP ≤90 mmHg:			
- After 4 weeks[a]	63	40	p<0.05
- After 8 weeks	63	41	p<0.05

[a] Data on File.

effectiveness of drugs by also calculating average cost-effectiveness ratios (9-11). Although the incremental cost-effectiveness ratio is the most important parameter to present in a health economic evaluation, average ratios, too, provide decision-makers with useful information (e.g. a general view of the cost-effectiveness properties of all drugs available within a given area of indication).

The cost-effectiveness of felodipine-metoprolol and enalapril in the treatment of hypertension was investigated as follows: *(i)* the average and incremental cost per mmHg reduction in DBP after 4 and 8 weeks of treatment; and *(ii)* the average and incremental cost per patient achieving target DBP (<90 mmHg) after 4 and 8 weeks.

The cost-effectiveness analysis was carried out for Sweden, seen from the perspective of the third party payer. The total cost of treatment in the two patient

TABLE 3

Unit Prices Based on the Largest Package Sizes Available in Sweden (SEK, 1997 Prices).

Dosage	Felodipine-Metoprolol	Dosage	Enalapril[a]	Difference (%)
5/50 mg	7.62	10 mg	4.95	54
10/100 mg	15.24 (7.71[b])	20 mg	6.77	125 (14)

[a] Renitec® (MSD).
[b] The price of SEK 7.71 was obtained from The National Corporation of Swedish Pharmacies' price list.

groups was calculated by including the cost of drugs and the cost of physician appointments during the eight-week treatment period. The average cost of drugs after four and eight weeks of treatment was based on dosage information obtained from the clinical study and on Swedish 1997 prices (12). The unit prices employed in the evaluation are presented in Table 3. The figures are given in Swedish kronor; SEK; exchange rate July 1997 $US 1=SEK 7.90.

As the 10/100 mg dosage for felodipine-metoprolol is not currently available in Sweden, the price for this dosage was approximated by doubling the price of felodipine-metoprolol 5/50 mg. This tends to greatly overestimate the cost of treatment with felodipine-metoprolol, however, because doubling a specific dosage generally does not double the price (cf. enalapril, in which doubling the price for the 10 mg dosage results in overestimation by 46% of the price for 20 mg).

All the patients saw a physician at the beginning of treatment and after four weeks of treatment. A further follow-up visit after 8 weeks was deemed necessary

TABLE 4

Average Cost of Treatment after 4 and 8 Weeks (SEK, 1997 Prices).

Cost of treatment	Felodipine-Metoprolol	Enalapril	Difference (%)
0-4 weeks:			
Drugs	213	139	53
Physician appointments[a]	1576	1576	0
Total cost	**1789**	**1715**	**4**
0-8 weeks:			
Drugs	507	308	65
Physician appointments	1872[b]	2052[c]	-9
Total cost	**2379**	**2360**	**1**

[a)] Two physician appointments per patient.

[b,c)] An average of 2.375 and 2.604 physician appointments, respectively (based on the number of patients reaching target DBP after 4 weeks).

for those patients who had not reached the target DBP (<90 mmHg) after 4 weeks of treatment. This reflects Swedish clinical practice in the treatment of hypertension. The cost of an appointment with a physician for treatment of hypertension has been estimated at SEK 541 in 1988 prices (13). Adjusted by using the latest Swedish consumer price index (June 1997), a cost of SEK 788 per physician appointment was obtained.

RESULTS

Table 4 shows the average cost for the felodipine-metoprolol and enalapril groups after four and eight weeks of treatment. The cost of treatment is, on the whole, somewhat higher in the felodipine-metoprolol group.

TABLE 5

Average Cost of Treatment per mmHg Reduction in DBP, and per Patient Reaching Target DBP (SEK, 1997 Prices).

Cost of treatment	Felodipine-Metoprolol	Enalapril	Difference (%)
Per mmHg reduction:			
- After 4 weeks	157	318	-51
- After 8 weeks	198	328	-40
Per patient reaching target DBP:			
- After 4 weeks	2840	4288	-34
- After 8 weeks	3776	5756	-34

After 4 weeks, 21 out of 56 patients (37%) in the felodipine-metoprolol group and 35 out of 58 patients (60%) in the enalapril group had not yet reached target DBP (data on file). The average weighted cost of the extra physician appointment required at 8 weeks thus amounts to SEK 296 (21x788/56) in the felodipine-metoprolol group and SEK 476 (35x788/58) in the enalapril group.

When the total costs of treatment (Table 4) are combined with the reductions in DBP and the proportions of patients reaching target DBP after four and eight weeks of treatment (Table 2), the cost-effectiveness ratios reported in Table 5 are obtained.

As shown in Table 5, the average costs of treatment with felodipine-metoprolol are considerably lower than those with enalapril, both in terms of cost per mmHg reduction, and cost per patient reaching target DBP after four and eight weeks of treatment. The cost per mmHg reduction in DBP after 4 weeks in the felodipine-metoprolol group amounts, for example, to SEK 157, while the corresponding cost

in the enalapril group is twice as high. The cost per patient reaching target DBP after 4 weeks of treatment amounts to SEK 2840 in the felodipine-metoprolol group and SEK 4288 in the enalapril group.

It is worth noting that felodipine-metoprolol is also superior to enalapril in terms of cost-effectiveness after 8 weeks of treatment despite the fact that the price for the 10/100 mg dosage of felodipine-metoprolol is estimated at twice the price of felodipine-metoprolol 5/50 mg. If the price given for felodipine-metoprolol 10/100 mg in The National Corporation of Swedish Pharmacies' price list (SEK 756 for 98 tablets, i.e. SEK 7.71 per tablet, 1996 prices) is used, the weighted cost of drugs per patient in the felodipine-metoprolol group after 8 weeks amounts to SEK 428, compared with the previous figure of SEK 507 per patient (Table 4). With this latter cost estimate, it is found that felodipine-metoprolol dominates enalapril, i.e. treatment with felodipine-metoprolol implies both a superior efficacy and a lower average treatment cost (SEK 2300 versus SEK 2360 in the enalapril group).

In the incremental cost-effectiveness analysis of felodipine-metoprolol and enalapril, the incremental cost per mmHg reduction in DBP is estimated at SEK 4 (costs: SEK 2379-SEK 2360; divided by; efficacy: 12 mmHg-7.2 mmHg) after 8 weeks of treatment. The incremental cost per patient reaching the target DBP after 8 weeks is SEK 86 (costs: SEK 2379-SEK 2360; divided by; efficacy: 0.63-0.41). This means that the cost to have one more patient reaching the target DBP is SEK 86 (incremental cost-effectiveness ratio).

DISCUSSION

In this pharmaco-economic analysis, the fixed antihypertensive combination therapy felodipine-metoprolol was compared with enalapril monotherapy. It may

be argued that combinations of enalapril and, for example, a thiazide diuretic may have been more effective than enalapril alone and possibly also cost-effective. However, patient characteristics at the time of enrolment in the HOT Study suggest that a majority of patients in general practice are receiving monotherapy (5). There is also evidence that blood pressure may be inadequately managed in general practice and that monotherapy may not be sufficient to achieve target blood pressure (3,4,6). Thus, the pharmaco-economic evaluation of felodipine-metoprolol and enalapril may not only reflect general practice but also the measures necessary to achieve blood pressure control.

The proportion of patients reaching the target DBP (<90 mmHg) after 8 weeks of treatment was significantly higher in the felodipine-metoprolol group. These figures indicate short-term advantages for felodipine-metoprolol, as the lower effect of treatment with enalapril in all probability leads to increased consumption of healthcare resources after the initial 8 weeks. This increased consumption may, for example, take the form of additional physician appointments, either in connection with following up a change to (or addition of) other drugs, or a second increase in the dosage of enalapril to reach the target DBP. Furthermore, extra physician appointments may also be necessary owing to adverse events or side effects. In the clinical study, however, both drug therapies were equally well tolerated in that a similar share of patients reported adverse events in both treatment groups. From the patient's perspective it should also be noted that the need for switching or adding drugs is reduced. As the Swedish patient is paying for ambulatory drugs and physician visits out of his own pocket, treatment with the fixed combination felodipine-metoprolol (Logimax®) has a financial advantage.

Pharmaco-economic evaluations of drug therapies for chronic diseases, such as hypertension, should ideally reflect the long-term properties of the investigated therapies. Antihypertensive treatment may not only reduce mortality rates but also

the incidence of morbidity related to for example cardiovascular disease and stroke. The long-term properties of antihypertensive therapy are therefore most appropriately captured using "quality adjusted life-years" as the measure of effectiveness. It has been documented in a mortality study in patients at the Glasgow Blood Pressure Clinic (14) that at all ages, the influence of achieved DBP on mortality is great§1er than that of initial DBP. In that study, the greatest benefits in terms of reduced mortality rates were seen in those patients with the lowest achieved DBP on treatment (<90 mmHg). Therefore, the significantly higher proportion of patients reaching target DBP in the felodipine-metoprolol group (63% vs 41% in the enalapril group) may imply important long-term mortality and morbidity advantages for patients treated with felodipine-metoprolol.

Due to a shortage of long-term clinical data in the area of hypertension, computer simulations are often used to model the likely long-term cost-effectiveness properties of the drugs being investigated. The advantage of such simulations is, of course, that an estimate of the long-term cost-effectiveness is obtained. One disadvantage associated with the modelling approach is the frequent use of Framingham data (15), the relevance of which to other settings is questionable (16). Other criticism refers to the functional forms of the risk functions and the inadequacy of data for older patients (16). Furthermore, since modelling outcomes are based on numerous assumptions (e.g. the impact of a number of risk factors) these studies tend to be complex and might be difficult to interpret in general practice decision-making.

To date, the vast majority of pharmaco-economic evaluations have relied on efficacy data recorded in clinical studies. Clinical study results, however, may not always be readily transferable to general practice. For example, patient samples in clinical studies may not represent a random selection of patients encountered in general practice. Also, there may be poorer compliance with drug therapy and less

patient monitoring in general practice. In recent years, there has therefore been a growing interest in evaluating drugs using data from "real-life studies". In such studies, patients would be randomised to one of the drug therapies considered and then followed over a relevant treatment period as to clinical effect and utilisation of healthcare resources. Thus, "real-life studies" would provide the ultimate data for pharmaco-economic evaluation of antihypertensive treatment. To the best of our knowledge, such studies have not yet been carried out in the area of hypertension.

This paper illustrates, through a simple cost-effectiveness model, the importance of not allowing the price of drugs to be the major determining factor when choosing therapy. It is shown here that efficacy is the most important parameter in determining the cost-effectiveness of felodipine-metoprolol in comparison with enalapril, in that a significant difference in efficacy counterbalances the difference in price. The conclusion drawn from the current study is that felodipine-metoprolol is, at least in the short-term perspective, cost-effective in the treatment of high blood pressure.

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