

## Comparison of atenolol with propranolol in the treatment of angina pectoris with special reference to once daily administration of atenolol

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**SUMMARY** Fourteen patients with angina pectoris completed a double blind trial of atenolol 25 mg, 50 mg, and 100 mg twice daily and propranolol 80 mg thrice daily. In comparison with placebo, all active treatments significantly reduced anginal attacks, consumption of glyceryl trinitrate, resting and exercise heart rate, resting and exercise systolic blood pressure, and significantly prolonged exercise time. There was no significant difference between the effects of propranolol and atenolol.

Nine patients completed a further trial comparing atenolol given once or twice daily. Both regimens were effective and there was no significant difference between the reductions in anginal attacks, glyceryl trinitrate consumption, systolic blood pressure, or heart rate. Twenty-four-hour ambulatory electrocardiograms showed that atenolol consistently reduced heart rate throughout the 24-hour period whether given once or twice daily.

Atenolol is a potent antianginal agent which, in most patients, is likely to be effective once daily.

The use of adrenergic beta-receptor antagonists is well established in the treatment of patients with angina pectoris. In general there should be little effective difference between individual agents provided optimum peak exercise heart rate reduction is achieved in each 24-hour period (Jackson *et al.*, 1975b). The possession of intrinsic sympathomimetic activity (ISA) by a beta-blocking agent may, however, be a disadvantage because of a reduced effect on exercise heart rate (Caruthers *et al.*, 1976). In contrast, cardioselective properties may be advantageous to the small number of patients in whom non-selective agents such as propranolol predispose to bronchospasm (Stephen, 1966).

Atenolol is a cardioselective beta-blocking agent without intrinsic sympathomimetic activity (Åström, 1975), which has been shown in volunteers to produce blockade of exercise-induced tachycardia for at least 24 hours after single oral doses (Harry, 1977). The objectives of the present investigations were to compare the effects in patients with stable angina pectoris of graded doses of atenolol with those of a standard effective dose of propranolol (Jackson *et al.*,

1975a). This comparative study was randomised and double blind. In addition, using 24-hour ambulant electrocardiographic monitoring techniques a double blind comparison was also made between optimum doses of atenolol administered once and twice daily.

### Patients and methods

#### SELECTION OF PATIENTS

Patients with exercise-induced angina were selected. They were excluded if the angina was associated with anaemia (haemoglobin < 13 g/dl), valvar heart disease, cardiac failure, obstructive airways disease, cardiac infarction in the previous 3 months, hypertension (fifth-point resting diastolic pressure over 100 mmHg), diabetes, or thyroid disease. In all patients the angina had been stable for more than 3 months and all showed electrocardiographic abnormalities either at rest or on exertion, but no evidence of conduction defects. Chest x-ray pictures were normal. No other drugs were used except for glyceryl trinitrate. All patients were clearly informed of the nature of the study and all gave written consent without inducement (Ormrod, 1968). Fourteen patients aged 43 to 57 (mean 53) years entered the study; 12 were men and 2 were women.

## Dosage and regimen

### (i) DOUBLE BLIND COMPARISON OF ATENOLOL WITH PROPRANOLOL

Each patient received placebo on a single-blind basis for 4 weeks. They were then allocated to 4 fully randomised monthly treatment periods—atenolol 25 mg twice daily; atenolol 50 mg twice daily; atenolol 100 mg twice daily; and propranolol 80 mg thrice daily. All the preparations were in identical tablets, each dose being 2 tablets. The tablets were taken at 8 am, 2 pm, and 8 pm. For each time a separate tablet container was provided, and each patient was instructed on the importance of taking the correct tablets at the appropriate time. This enabled us to provide a 2 pm placebo dose for the atenolol periods making them indistinguishable from the thrice daily propranolol. Each drug course was checked by counting the trial tablets and glyceryl trinitrate tablets; blood and urine levels were not estimated. Glyceryl trinitrate was supplied in bottles of 100 tablets and replenished monthly.

### (ii) DOUBLE BLIND COMPARISON OF ATENOLOL ONCE DAILY WITH ATENOLOL TWICE DAILY ADMINISTRATION

Of the original 14 patients, 9 entered and completed this additional study. The optimum individual dose of atenolol was based on the results of the graded comparison of atenolol with propranolol previously described. In a double blind randomised crossover design patients received either once or twice daily atenolol for one month at each level. The morning and evening tablets were stored in separate containers so that when once daily atenolol was being given at 8 am an identical placebo was given at 8 pm, thereby maintaining the double blind nature of the study. The total daily dosage of atenolol was the same for each patient, thus a patient receiving 200 mg once daily would receive 100 mg twice daily. All the preparations were identical tablets, each dose being two tablets. Each drug course was checked by counting the trial tablets and tablets of glyceryl trinitrate.

### PLACEBO MEDICATION PERIODS

The initial design of the present study included a randomised double blind placebo period. However, new evidence published at the time this trial started indicated that the rapid withdrawal of beta-blocking agents might exacerbate angina pectoris and induce myocardial infarction (Diaz *et al.*, 1973; Nellen, 1973; Slome, 1973; Miller *et al.*, 1975). A double blind placebo period was not, therefore, felt to be ethically justified and it was omitted from the present trial. All comparisons of active drug and

placebo periods are, therefore, between a single blind placebo run-in period and randomised double blind active treatment periods. The efficacy of each active beta-blocking agent may, therefore, be exaggerated when compared with placebo because of a beneficial natural history change. This would not, however, detract in any way from the randomised double blind comparison of graded doses of atenolol with a known effective dose of propranolol (Jackson *et al.*, 1975a).

## Assessment

The patients were seen at fortnightly intervals. At each visit the anginal attack rate and consumption of glyceryl trinitrate were assessed from simple record cards. Glyceryl trinitrate was used only for pain and not prophylactically. Only the records of the second two weeks of each monthly period were compared to avoid carry-over effects (Jackson *et al.*, 1975a). In addition, at each attendance, the supine heart rate was estimated from the electrocardiogram, a standard sphygmomanometer was used for blood pressure recordings, and a full clinical examination was carried out. Any side effects were noted.

In the atenolol versus propranolol study at the end of each 4-week period the patient was weighed and exercised. In the fourth week of the once daily and twice daily atenolol trial the patient underwent 24-hour ambulatory tape recording of his electrocardiogram (Avionics tape recorder system) to allow heart rate to be determined hourly throughout the 24 hours and also minimum and maximum heart rates to be determined and compared with events in the patient's record card. At the end of the study patients were asked directly which month's treatment they preferred.

## Exercise test

In 9 patients a step and wall bar test was used, the methodology of which has been described in detail elsewhere (Jackson *et al.*, 1975a). Five patients were exercised upright using a bicycle ergometer. This was calibrated in kpm/min and was pedalled steadily at about 60 rpm (range 45 to 75). The load was increased by 150 kpm/min every 3 minutes until angina occurred. The initial work load was chosen so that each patient experienced angina during the second level (3 to 6 minutes) of exercise.

All data are combined and expressed as exercise time in seconds. Patients were exercised until they experienced the onset of anginal pain or were too breathless to continue. Radiotelemetry with the electrode in the V5 position was used to record resting and exercise heart rates from the electro-

Table 1 Mean ( $\pm$  SE of mean) anginal attack rate and glyceryl trinitrate consumption (number of tablets) in each treatment period

	Placebo	Atenolol 25 mg twice daily	Atenolol 50 mg twice daily	Atenolol 100 mg twice daily	Propranolol 80 mg thrice daily
Anginal attacks in last 2 weeks	35 $\pm$ 12	25 $\pm$ 9	17 $\pm$ 5	18 $\pm$ 4	14 $\pm$ 4
Glyceryl trinitrate consumption in last 2 weeks	22 $\pm$ 11	16 $\pm$ 9	7 $\pm$ 3	9 $\pm$ 3	4 $\pm$ 2

cardiogram. Depression of the ST segment was measured during and after peak exercise. A downward-sloping depression of at least 1 mm persisting for 0.08 s or longer in at least 5 consecutive beats was considered indicative of ischaemia.

## Results

For brevity we have summarised our results as mean values with the standard error (SE) of the mean. Tables of more detailed data are available from D.J. Statistical analysis is based on the Wilcoxon Signed Rank Sum Test and Student's *t* test.

### (i) ATENOLOL COMPARED WITH PROPRANOLOL

#### Anginal attack rate and consumption of glyceryl trinitrate

The attack rate and glyceryl trinitrate consumption for each period of treatment are shown in Table 1. Atenolol 25 mg b.i.d. ( $P < 0.05$ ), atenolol 50 mg b.i.d. ( $P < 0.01$ ), atenolol 100 mg b.i.d. ( $P < 0.01$ ), and propranolol ( $P < 0.01$ ) significantly reduced anginal attacks when compared with the placebo run-in period. The frequency of anginal attacks was lowest when the two higher doses of atenolol and propranolol were administered. There was no significant difference between the reduction of anginal attack rate achieved by propranolol and any of the three dose levels of atenolol.

#### Heart rate and blood pressure

Compared with placebo, all treatments significantly

reduced heart rate at rest and on exertion ( $P < 0.001$ ) and similarly reduced systolic blood pressure ( $P < 0.001$ ) (Table 2). There were no significant effects on diastolic blood pressure. Atenolol 100 mg twice daily and propranolol significantly reduced resting and exercise heart rate when compared with atenolol 25 mg twice daily ( $P < 0.05$ ). There were no other differences between the active treatment periods.

#### Exercise tests

The exercise time was prolonged by all active treatments when compared with placebo ( $P < 0.05$ ), but there was no difference between the individual randomised double blind active treatment periods. ST depression was significantly reduced by atenolol in doses of 50 mg b.i.d., 100 mg b.i.d. and propranolol when compared with placebo ( $P < 0.05$ ). Atenolol 25 mg b.i.d. was significantly less effective in this respect than the higher concentrations of atenolol or propranolol ( $P < 0.05$ ).

### (ii) ATENOLOL ONCE DAILY COMPARED WITH ATENOLOL TWICE DAILY

The total daily dose of atenolol was 200 mg in 7 patients and 100 mg in 2 patients.

#### Anginal attack rate and glyceryl trinitrate consumption

The total number of anginal attacks and tablets of glyceryl trinitrate consumed for the last two weeks of each month are shown in Table 3. Both once daily and twice daily atenolol significantly reduced anginal attacks ( $P < 0.01$ ) and glyceryl trinitrate consumption ( $P < 0.01$ ) when compared with

Table 2 Mean ( $\pm$  SE of mean) changes in heart rate and blood pressure at rest and on exertion

	Placebo	Atenolol 25 mg twice daily	Atenolol 50 mg twice daily	Atenolol 100 mg twice daily	Propranolol 80 mg thrice daily
Heart rate/min					
{ At rest	84 $\pm$ 5	65 $\pm$ 4	62 $\pm$ 4	60 $\pm$ 4	60 $\pm$ 4
{ On exertion	145 $\pm$ 5	112 $\pm$ 4	107 $\pm$ 5	101 $\pm$ 4	101 $\pm$ 2
Systolic blood pressure					
{ At rest	140 $\pm$ 5	116 $\pm$ 5	114 $\pm$ 3	116 $\pm$ 5	117 $\pm$ 6
{ On exertion	166 $\pm$ 5	132 $\pm$ 7	133 $\pm$ 4	133 $\pm$ 5	129 $\pm$ 5
Diastolic blood pressure					
{ At rest	77 $\pm$ 4	74 $\pm$ 6	70 $\pm$ 3	73 $\pm$ 3	73 $\pm$ 4
{ On exertion	78 $\pm$ 6	71 $\pm$ 5	76 $\pm$ 4	73 $\pm$ 3	80 $\pm$ 2
Exercise time (s)	104 $\pm$ 16	133 $\pm$ 24	128 $\pm$ 16	135 $\pm$ 25	132 $\pm$ 16
ST depression on exercise (mm)	1.4 $\pm$ 0.48	1.13 $\pm$ 0.40	0.57 $\pm$ 0.20	0.86 $\pm$ 0.21	0.89 $\pm$ 0.30

Table 3 Summary of clinical findings (mean  $\pm$  SE of mean)

	Placebo	Atenolol once daily	Atenolol twice daily
Anginal attacks in last 2 weeks	49 $\pm$ 16.6	22 $\pm$ 5.9	23 $\pm$ 6.2
Glyceryl trinitrate in last 2 weeks	28 $\pm$ 17	6.6 $\pm$ 2.8	8.4 $\pm$ 4.2
Systolic blood pressure (mmHg)	140 $\pm$ 5	116 $\pm$ 3.5	109 $\pm$ 3.1
Diastolic blood pressure (mmHg)	79 $\pm$ 3.5	71 $\pm$ 2.6	69 $\pm$ 2.0
Pulse rate (beats/min)	84 $\pm$ 5.4	62 $\pm$ 3.2	64 $\pm$ 3.8

placebo. There were no significant differences between once or twice daily atenolol with regard to attack rate but once daily atenolol was slightly more effective in reducing glyceryl trinitrate consumption ( $P < 0.05$ ). Seven patients could detect no difference between once daily or twice daily atenolol whereas 2 patients were subjectively worse on the once daily regimen.

#### Heart rate and blood pressure

When compared with placebo both once daily and twice daily atenolol significantly lowered systolic blood pressure ( $P < 0.001$ ) and diastolic blood pressure ( $P < 0.05$ ) as well as heart rate ( $P < 0.001$ ) (Table 3). There was no significant difference between once or twice daily atenolol.

#### 24-hour ambulatory electrocardiograms

The 24-hour ambulatory tape recordings were

Table 4 24-hour ambulatory tape recordings (mean  $\pm$  SE of mean)

	Placebo	Atenolol once daily	Atenolol twice daily
Hourly heart rate (beats)	4505 $\pm$ 172	3761 $\pm$ 65	3630 $\pm$ 101
Maximum heart rate/min	124 $\pm$ 7.2	82 $\pm$ 6.0	89 $\pm$ 5.8
Minimum heart rate/min	63 $\pm$ 3.3	53 $\pm$ 3.5	53 $\pm$ 3.5

analysed to document heart rate by a trained technician who was unaware of which treatment the patient had been taking. The results are presented in Table 4 and show no significant difference on a group basis between once daily or twice daily atenolol. Further, both regimens significantly reduced the mean hourly heart rate for the whole 24 hours when compared with placebo ( $P < 0.001$ ) (Fig. 1). All patients were analysed individually as well (Fig. 2) and in 2 instances atenolol once daily produced significantly lower heart rates than twice daily ( $P < 0.001$  and  $P < 0.01$ ). Twenty-one episodes of pain occurred during tape recording. Though pain occurred at the maximal heart rate for the 24-hour period in some cases, in others it did not, and though a given heart rate produced pain in an individual on one occasion, it did not do so on others (Fig. 3).

#### SIDE EFFECTS AND TOXICITY STUDIES

Twice during the run-in period and at the end of each month of treatment the haemoglobin level,

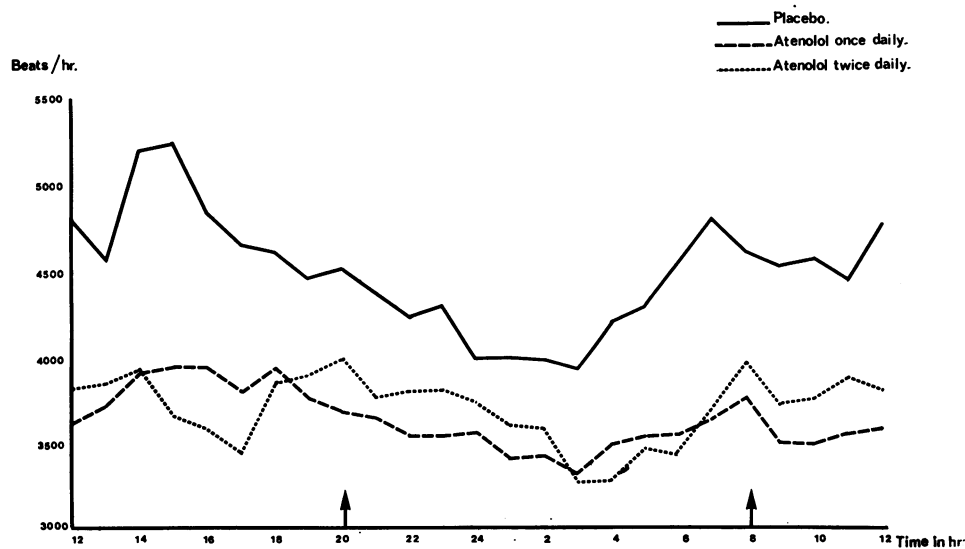


Fig. 1 Mean hourly heart rate for placebo and atenolol once or twice daily. Arrows indicate time tablets taken.

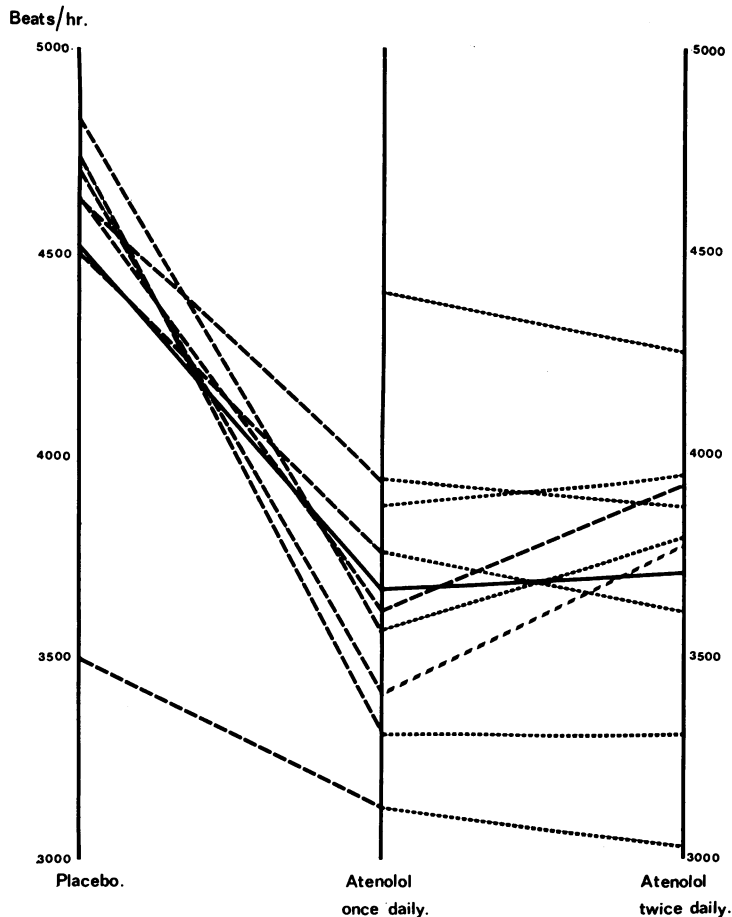


Fig. 2 Hourly heart rate reduction for individual patients.

erythrocyte sedimentation rate, results of liver function tests, urea and electrolytes, antinuclear factor titre, and appearances on urine microscopy were recorded. There were minor changes between treatments but none of significance compared with placebo. Twelve side effects were recorded in 5 patients. Headaches and malaise occurred in 2 patients on placebo, 2 on atenolol, and 2 on propranolol. Aching legs occurred in 2 patients on atenolol 50 mg twice daily, 1 on atenolol 25 mg twice daily, and 2 on propranolol. All were tolerated and were only mentioned after direct questioning.

### Discussion

The best means of assessing the degree of beta-blockade and in turn the potency and effectiveness of any new agent is by dose titrating the drug under study until there is optimum peak exercise heart rate

reduction (Jackson *et al.*, 1975b). Once this has been established a double-blind comparison with propranolol, the standard reference agent, is essential.

In this study, we have compared a dose titration of atenolol in a double blind randomised fashion with 80 mg thrice daily propranolol, which is generally held to be an effective dose (Jackson *et al.*, 1975a). The initial design of this study included a randomised double blind placebo period. However, the possibility of exaggeration of angina or precipitation of myocardial infarction after sudden withdrawal of beta-blockade now makes this type of trial unethical (Diaz *et al.*, 1973; Nellen, 1973; Slome, 1973; Alderman *et al.*, 1974; Miller *et al.*, 1975). Consequently, in our study all active agents were compared with each other and with the single blind placebo run-in period.

In comparing atenolol with propranolol all active agents significantly reduced the anginal attack rate and glyceryl trinitrate consumption. The two higher

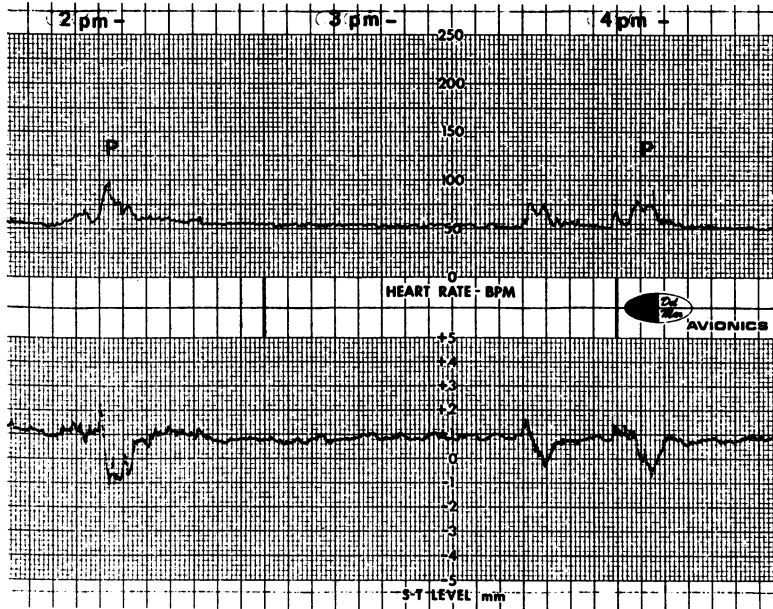


Fig. 3 Heart rate and ST segment trend recording. Pain occurred with an increase in heart rate on 2 occasions (P) but not with a similar increase on another. ST segment depression is clearly shown.

doses of atenolol and propranolol were more effective than atenolol 25 mg twice daily.

Adrenergic beta-receptor antagonists reduce myocardial oxygen consumption mainly by reducing heart rate and systolic blood pressure (Balcon, 1971). All active agents significantly ( $P < 0.001$ ) reduced resting and exercise heart rate and systolic blood pressure. Atenolol 100 mg twice daily produced a similar peak exercise heart rate reduction to propranolol 80 mg thrice daily and the two are probably equipotent in man. In addition, all drugs significantly prolonged exercise time to pain when compared with single blind placebo ( $P < 0.05$ ) but no differences emerged between active agents.

Our results, therefore, show that the beta-adrenoceptor blocking drug atenolol, in optimal dosage, is as effective as propranolol in reducing the attack rates and glyceryl trinitrate consumption in patients with angina pectoris. Further, the results show that there is no difference in these subjective measurements between atenolol given as a single daily dose or as a twice daily dose. The collection of subjective data is, however, dependent upon patients accurately recording attacks, etc. on their record cards for subsequent analysis, and, as such, even with good motivation on the part of the patient, must be subject to some error (Lawrie *et al.*, 1976). Usually an exercise tolerance test of some kind is carried out during each treatment period in an attempt to obtain an objective assessment of the drugs' antianginal activity. However, this suffers

from the disadvantages of being carried out in an artificial hospital setting, of recording only one small time period to represent the whole of the treatment period (usually one month), and of being an artificial form of exercise (Jackson *et al.*, 1975b).

We have attempted to overcome the problem of the hospital exercise test by obtaining an objective assessment of the heart rates from a group of patients during their normal daily lives. This has been made possible by the use of 24-hour ambulatory tape recordings of heart rate during treatment with placebo and active agents. The aim of this monitoring was to determine if patients have episodic heart rate increases, that is, sympathetic nerve activity and/or vagal withdrawal which may be related to anginal attacks, and if the heart rates are more stable when the patients are taking beta-blocking drugs. The results showed that atenolol, whether given once daily or twice daily, did reduce the overall hourly heart rate and that the mean maximum heart rate achieved during the 24-hour recording for the group was indeed lower than when the patients were on placebo (124 beats/min on placebo, 83 beats/min on atenolol once daily, and 89 beats/min on atenolol twice daily). If it is accepted that the heart rate reduction is important in achieving beneficial response when beta-blocking drugs are used to treat angina pectoris (Jackson *et al.*, 1975b), then this was achieved with atenolol. We feel that this type of objective ambulatory electrocardiographic recording is an important requirement in the assessment of beta-blocking drug therapy,

particularly when an agent under study is being administered only once per 24 hours.

Thus our study shows that atenolol is effective as an antianginal agent given once a day. However, 2 patients found on the once a day therapy that their symptoms were worse in the evenings. It is interesting to note that in contrast to the other 7 patients, these 2 worked hardest in the evening rather than during the day (one was a publican and the other a part-time mechanic). With these 2 patients in mind, we believe these results show that atenolol 100 mg can be initially prescribed once a day for patients with angina pectoris, perhaps increasing to 200 mg/day to obtain maximum benefit; occasionally patients may benefit from an additional dose in the evening. We believe this drug offers practical advantages to the working patient.

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