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Effects of metoprolol vs verapamil in patients with stable angina pectoris

The Angina Prognosis Study in Stockholm (APSIS)

N. Rehnqvist, P. Hjemdahl*, E. Billing, I. Björkander, S. V. Eriksson, L. Forslund, C. Held, P. Näsman† and N. H. Wallén*

*Karolinska Institutet, Department of Internal Medicine, Danderyd Hospital, Danderyd, Sweden, *Department of Clinical Pharmacology, Karolinska Hospital, Stockholm, Sweden, and †Royal Institute of Technology, Stockholm, Sweden*

Objective To study long-term treatment effects of metoprolol or verapamil on combined cardiovascular end points and psychological variables in patients with stable angina pectoris.

Design Randomized, double-blind, double-dummy trial.

Patients The study included 809 patients under 70 years of age with stable angina pectoris. The mean age of the patients was 59 ± 7 years and 31% were women. Exclusion criteria were myocardial infarction within the previous 3 years and contraindications to beta-blockers and calcium antagonists. The patients were followed between 6 and 75 months (median 3·4 years and a total of 2887 patient years).

Intervention The patients were treated with either metoprolol (Seloken ZOC 200 mg o.d.) or verapamil (Isoptin Retard 240 b.i.d.). Acetylsalicylic acid, ACE inhibitors, lipid lowering drugs and long acting nitrates were allowed in the study.

End points Death, non-fatal cardiovascular events including acute myocardial infarction, incapacitating or unstable angina, cerebrovascular or peripheral vascular events. Psychological variables reflecting quality of life i.e. psychosomatic symptoms, sleep disturbances and an evaluation of overall life satisfaction.

Results Combined cardiovascular events did not differ and occurred in 30·8% and 29·3% of metoprolol and verapamil treated patients respectively. Total mortality in metoprolol and verapamil treated patients was 5·4 and 6·2%, respectively. Cardiovascular mortality was 4·7% in both groups. Non-fatal cardiovascular events occurred in 26·1 and 24·3% of metoprolol and verapamil-treated patients, respectively. Psychosomatic symptoms and sleep disturbances were significantly improved in both treatment groups. The magnitudes of change were small and did not differ between treatments. Life satisfaction did not change on either drug. Withdrawals due to side effects occurred in 11·1 and 14·6%, respectively.

Conclusion This long term study indicates that both drugs are well tolerated and that no difference was shown on the effect on mortality, cardiovascular end points and measures of quality of life.
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Key Words: Angina pectoris, metoprolol, verapamil, prognosis.

Introduction

Stable angina pectoris is a well defined clinical condition with a variable prognosis. The risk of cardiovascular events is increased but little is known about how drug treatment influences the prognosis of such patients[1–4]. The Swedish Angina Pectoris Aspirin Trial (SAPAT)[5] and a substudy in the Physicians Health Study[6] have shown that acetylsalicylic acid has protective qualities and the recent Atenolol Silent Ischemia Study (ASIST) showed that atenolol reduced the number of clinical events due to ischaemia in patients with silent ischaemia[7]. However, whether anti-ischaemic drug treatment influences the long-term prognosis of patients with stable angina pectoris has not been studied previously.

Several beta-blockers have been shown to increase survival in post-infarction patients[8]. For

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Correspondence: Assoc. Prof. Nina Rehnqvist, FESC, FACC, Department of Internal Medicine, Danderyd Hospital, S-182 88 Danderyd, Sweden.

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example, cardioprotective effects of metoprolol have been demonstrated in a large 3-month study[9] and a smaller 3-year study[10], but treatment with calcium antagonists after myocardial infarction has not always been shown to be effective[11]. The dihydropyridine, nifedipine, tends to have adverse effects, while verapamil has been shown to have neutral or positive effects. Early studies with verapamil indicated gains in some and losses in other subgroups[12]. However, the Second Danish Verapamil Infarction Trial (DAVIT II), in which therapy was instituted during the second week after infarction, showed beneficial effects both in patients without heart failure and in the group as a whole[13]. It has also been suggested that verapamil reduces the restenosis rate after coronary angioplasty in patients with stable angina[14]. Such effects have not been demonstrated with beta-blockers. Both beta-blockers and calcium antagonists have been shown to influence the atherosclerotic process favourably in cholesterol fed animals[15,16].

We chose to compare the effects of two established anti-ischaemic drugs, metoprolol and verapamil on the prognosis of patients with stable angina. The study was not placebo-controlled, as too many patients would have had to have been withdrawn from a placebo group to receive open-label anti-ischaemic therapy with a beta-blocker or calcium antagonist during long-term follow-up.

The main aims of the Angina Prognosis Study in Stockholm (APSIS) were to: (1) evaluate whether there are differences in the effect of treatment between metoprolol and verapamil with respect of cardiovascular end points and/or psychological variables reflecting quality of life during long term follow-up, (2) describe the history, clinical findings and prognosis in patients with stable angina pectoris.

Methods

Patients with a clinical diagnosis of angina pectoris were referred to the heart research laboratory at Danderyd Hospital. At screening, clinical history and examination were undertaken. Angina pectoris was defined as pain or discomfort in the chest, as originally described by Heberden[17]. The symptoms had to be presented in a classical way, i.e. localized in the central part of the chest with or without radiation and elicited by physical or psychological stimuli. The symptoms had to be relieved gradually by rest or quickly by nitroglycerin. However, patients with angina at rest only were also included in the study. If the description of angina was atypical, complementary tests were undertaken. These included an exercise test, perfusion scintigraphy, radiological examinations and/or gastrointestinal investigations, as indicated.

Patients previously treated with either beta-blockers or calcium antagonists were put on minimal therapy during a run-in period of 14 days before the baseline examinations. The minimal therapy consisted of 25–50 mg metoprolol o.d. or 40 mg verapamil b.i.d., respectively. Complete withdrawal of beta-blockade or calcium antagonism was not undertaken due to the risk of severe deterioration or rebound phenomena[18]. Patients without such previous therapy continued on their basic treatment including organic nitrates.

The baseline investigations consisted of a psychological interview performed by specially trained nurses, an exercise test, a 24 h ambulatory ECG recording, an echocardiographic examination, ultrasonographic examinations of the carotid and femoral vessel and laboratory tests including lipoprotein analyses, haemostatic variables and catecholamine measurements. Double-blind treatment (double-dummy technique) with either metoprolol (Seloken ZOC, Astra Hässle AB, Mölndal, Sweden) or verapamil (Isoptin Retard, Knoll AG, Ludwigshafen, Germany) was then initiated. Full dose (200 mg metoprolol o.d. or 240 mg verapamil b.i.d.) was reached after 2 weeks, but it was possible to reduce the dose if side-effects occurred. The patients returned after 1 month for complete evaluation of the above variables to determine short-term effects of the drugs, and were thereafter followed between 6 and 75 months, at 6-monthly intervals. After 3 years, or at the end of the study the complete set of investigations was repeated in patients who had not been withdrawn from the study due to terminating end points or side effects.

Primary end points for follow-up were death, cardiovascular events and three psychological variables reflecting quality of life. The cardiovascular events constituting end points included acute myocardial infarction, incapacitating or unstable angina, cerebrovascular events (including transitory ischaemic attacks) or peripheral vascular events (threatening or overt gangrene, or surgery for aortic aneurysm). The diagnosis had to be hospital based and confirmed by the authors in all instances. Incapacitating angina was defined as symptoms which were insufficiently relieved by the study medication, complemented with long acting nitrates and severe enough to compromise ordinary life and indicate revascularization. The psychological variables included an inventory of psychosomatic symptoms defined by the Cornell Medical Index (scoring range 39–195)[19], an evaluation of sleep disturbances (scoring range 9–36)[20] and an estimate of life satisfaction on a visual analogue scale (range 0–120 mm)[21]. The extremes of the visual analogue scale were 'the last 3 years have been a very unhappy and bad period of my life' and 'a very happy and good period of my life', respectively.

Patients

Eight hundred and nine patients (248 women) under the age of 70 were included in the study. Inclusion was based on a clinical history of stable angina pectoris as described above. Exclusion criteria were contraindications to the study drugs, myocardial infarction within the last 3 years, unstable angina or anticipated need

for revascularization within one month. Furthermore, the presence of other severe disorders, alcohol abuse suspected non-compliance non-compensated heart failure, or significant valvular disease constituted exclusion criteria.

Statistical analysis

The calculation of sample size was based on the assumption that 14% of the patients with the inferior treatment and 10% in the better group would develop a fatal or non-fatal cardiovascular end point yearly. With an accumulated incidence of 35%, a type I error of 0·05 (two-tailed), and a type II error of 0·2, the requirement for randomized patients was calculated to be 800 and the total follow-up time 2400 patient years.

The effect of treatment in relation to death and cardiovascular end points were analysed on an intention-to-treat basis. Life table curves according to Kaplan-Meier were calculated[22]. The curves were compared using log-rank tests and Cox regression analysis. The effects of the two different treatments were also compared at the end of the study. Treatment effects on the psychological variables were analysed in surviving patients who completed the trial on drugs. Group differences in continuous variables were assessed by two-tailed t-tests. Paired within-group comparisons were performed with Student's t-test. Discrete variables were compared by the Chi-square test with Yates' continuity correction[23]. Coefficients of skewness and kurtosis were used to test deviations from a normal distribution. Means and standard deviations are given, unless otherwise stated.

The study was approved by the Ethics Committee of the Karolinska Institutet.

Results

Demographic data and the previous medical history of the patients are given in Table 1. The total follow-up time was 2887 patients years (median follow-up time 3·4 years). During follow-up, 47 patients died, 22 (5·4%) in the metoprolol group and 25 (6·2%) in the verapamil group ($P=0·63$). The mode of death did not differ between the two treatment groups; 19 cardiovascular deaths (4·7%) occurred in both groups (Table 2). Non-fatal cardiovascular events occurred in 106 patients in the metoprolol group and 98 patients in the verapamil group, respectively ($P=0·56$). The types of cardiovascular events were similar in the two treatment groups (Table 2). Fatal and non-fatal cardiovascular events were evenly distributed over the follow-up time, as indicated by Figs 1 and 2.

At the end of the study the odds ratio and 95% confidence interval of metoprolol treatment compared to verapamil was 0·87 (0·48–1·56) for mortality and 1·03 (0·84–1·30) for the combined events. Using the Cox regression model, which takes the time course into account, the corresponding figures were 0·94 (0·53–1·67) and 1·22 (0·95–1·52), respectively. The post hoc calculated power to detect a a 30% difference

Table 1 Baseline characteristics

	Metoprolol (n=406)	Verapamil (n=403)
Age (years)	59 ± 7	59 ± 7
Women (%)	27	34*
Previous history (%)		
Previous AMI	16	16
Congestive heart failure	6	7
Hypertension	28	26
Previous cerebrovascular event	5	4
Previous CABG or PTCA	5	7
Intermittent claudication	4	2
Diabetes mellitus	8	9
Therapy at baseline (%)		
Acetylsalicylic acid	39	38
Long-acting nitrates	49	53
Beta-blockers	56	54
Calcium antagonists	14	16
Smoking habits (%)		
Smokers	22	22
Ex-smokers	50	36**
Non-smokers	28	42**
Median duration of angina (interquartiles, years)	2 (0;5·5)	2 (0;5·6)
Angina class (%)		
I	27	25
II	68	69
III	5	6

Mean ± SD. *$P<0·05$, **$P<0·001$.
CABG=coronary artery bypass grafting.
PTCA=percutaneous transluminal coronary angioplasty.
AMI=acute myocardial infarction.
Angina class according to NYHA.

Table 2 Deaths and non-fatal cardiovascular events

	Metoprolol (n=406)	Verapamil (n=403)
Deaths	22 (5·4%)	25 (6 2%)
Cardiovascular		
SD	5	6
AMI	12	11
Vascular	2	2
Malignancy	3	6
Non-fatal cardiovascular events	106 (26·1%)	98 (24·3%)
AMI	17	14
CABG	46	39
PTCA	12	5
Angiography without revascularization	17	20
Other unstable angina	0	5
CVD	11	13
PVD	3	2

SD=sudden death within 2 h.
Vascular deaths=1 pulmonary embolus and 3 cerebrovascular deaths.
CVD=cerebrovascular disease.
PVD=peripheral vascular disease (aortic aneurysm or gangrene).
Other abbreviations as in Table 1

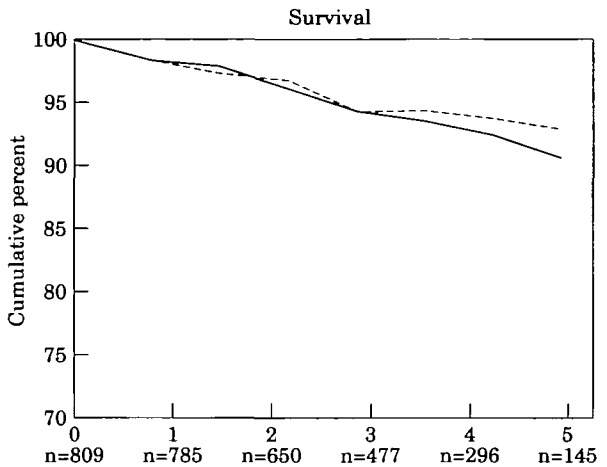

Figure 1 **Cumulative percentage survival in metoprolol (– – – –) and verapamil (———) treated patients. The curves were not extended beyond 5 years as few patients were followed thereafter.**

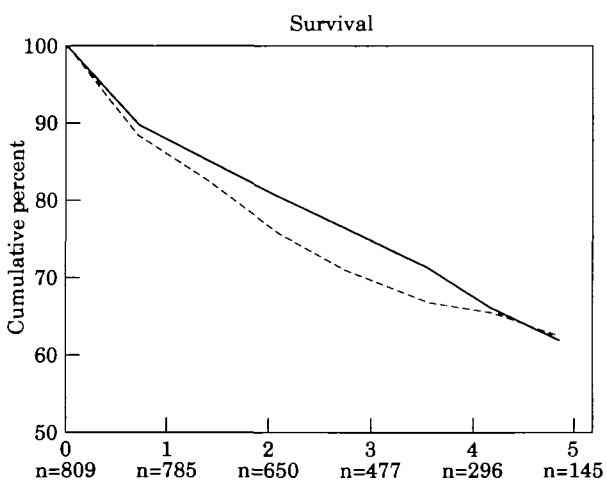

Figure 2 **Cumulative event free survival in metoprolol (– – – –) and verapamil (———) treated patients. The curves were not extended beyond 5 years as few patients were followed thereafter.**

between the two treatments was 0·8. At no point in time was there a significant difference between the treatments.

There were significantly more women and non-smokers in the verapamil group, which could reflect a slightly better prognosis. However, adjustments for sex and smoking in the Cox regression model did not significantly alter the results (Table 3).

The psychosomatic score and the estimate of sleep disturbances improved similarly and significantly in the two treatment groups, whereas overall life satisfaction did not change during follow-up (Table 4).

Withdrawal from drug treatment due to side effects occurred in 11·1 and 14·6% of metoprolol and verapamil treated patients, respectively (P=0·13). The

Table 3 Odds ratios (OR) of death, or death and non-fatal cardiovascular events (combined) for metoprolol compared to verapamil treatment. The figures refer both to the results at the end of the study and analyses based on the Cox regression model, which takes the time course into account

	OR (95% confidence interval)
Deaths	
End of the study results	0·87 (0·48–1·56)
Cox regression model	0·94 (0·53–1·67)
Cox regression model	
adjusted for sex	0·96 (0·54–1·70)
adjusted for smoking	0·96 (0·54–1·70)
Death and non-fatal cardiovascular events	
End of the study results	1·03 (0·84–1·30)
Cox regression model	1·22 (0·95–1·56)
Cox regression model	
adjusted for sex	1·23 (0·95–1·58)
adjusted for smoking	1·23 (0·95–1·58)

different side effects are summarized in Table 5. As expected, more verapamil treated patients were withdrawn due to gastrointestinal side effects (mainly constipation). Twenty metoprolol treated patients and 17 verapamil treated patients dropped out for other, mainly administrative, reasons (P=0·28). At the last visit 51% of the metoprolol treated patients were on full dose, 45% on half dose and 3% on quarter dose. The corresponding proportions were 49%, 48% and 2% in the verapamil group.

Discussion

Previous studies give variable estimates of the prognosis of patients with stable angina, with annual cardiovascular mortalities ranging from 2 to 10%[1,2,3,4,24]. Studies of patients after myocardial infarction clearly indicate that beta-blockers have been beneficial. The effects of verapamil were also found to be positive in post-infarction patients with angina pectoris but without congestive heart failure[8,25]. The APSIS study shows that there was a cardiovascular mortality rate of 1·3% per year on an intention-to-treat basis, and a non-fatal cardiovascular complication rate of 7·1% per year. When using the same primary end-points (all myocardial infarctions and sudden deaths) to compare the APSIS and SAPAT studies, our event rate was 2·3% per year and the corresponding figures for SAPAT were calculated as 1·9% with aspirin plus sotalol and 2·9% with sotalol treatment only[17]. The results of APSIS and SAPAT are similar although there are some differences between the two patient populations. SAPAT patients were slightly older, but that study included 52% women (with a better prognosis) and excluded patients with previous myocardial infarction. The proportion of patients taking aspirin increased in our study from 38% at inclusion to 51% at the end of the study. In the ASIST trial, which included patients with stable angina pectoris and few or no

Table 4 Psychological variables reflecting quality of life. The ranges of scales were 39–195 (psychosomatic symptoms), 0–120 (overall life satisfaction) and 9–36 (sleep disturbances) respectively

	Baseline	Last visit	P	Intra individual change	
Psychosomatic symptoms					
Metoprolol n=275	61·6 ± 16·4	60·5 ± 15·6	<0·05	− 1·1 ± 13·8	P=0·34
Verapamil n=282	64·0 ± 16·4	61·8 ± 16·6	<0·005	− 2 2 ± 12·9	
Overall 'life satisfaction'					
Metoprolol n=268	77·2 ± 28·1	75·2 ± 25·6	0·28	− 3·0 ± 30·1	P=0·85
Verapamil n=275	78·4 ± 29·2	75 9 ± 26·3	0·19	− 2·5 ± 31·1	
Sleep disturbances					
Metoprolol n=270	16·9 ± 5·3	16·2 ± 5·2	<0·01	− 0·7 ± 4·5	P=0·97
Verapamil n=275	17·3 ± 5·6	16·6 ± 5·5	<0·01	− 0·7 ± 4·3	

Table 5 Side effects necessitating withdrawal from study drug

Side effect	Metoprolol (n=406)		Verapamil (n=403)	
Gastrointestinal	10		22*	
Neurological	22		25	
Tiredness		6		9
Sleep disturbances		7		4
Sexual problems		5		4
Headache		3		4
Depression or anxiety		1		4
Cardiovascular	15		16	
Arrhythmia and/or heart failure		10		7
Peripheral vascular symptoms		2		5
Dizziness		3		4
Respiratory	3		2	
Other	4		4	
Total no. of side effects		54		69
Total no. of patients withdrawn		45		59†

*P=0·029.
†P=0·13.

symptoms but with a previous infarction rate of 37%, the annual cardiovascular complication rate (death, and various signs of aggravated myocardial ischaemia) was 11·2% in atenolol-treated patients, and as high as 25·3% in the placebo-treated patients[7]. The relative risk of atenolol treatment was thus 0·55 with a confidence interval of 0·22 to 1·33. Our corresponding figure was 8·4% per year. We can only speculate on what results might have been obtained in APSIS patients with placebo treatment.

TIBET and IMAGE are two other studies that have compared the effects of a calcium antagonist and a cardioselective beta-blocker in patients with stable angina pectoris. The TIBET study is comparable to ours in that 682 patients were followed for 2 years. They were treated with either atenolol, nifedipine or the two combined. The mean age was 60 years, 86% were men but only 7% had undergone a revascularization procedure. The number of patients with a previous myocardial infarction was higher, however (33%). The annual rate of primary endpoints did not differ between atenolol and nifedipine-treated patients (10% respectively) and is comparable to APSIS, 9% in both treatment groups[26]. In the IMAGE study, 290 patients were treated with either metoprolol or nifedipine for 6 weeks; half the patients continued on single therapy for another 6 weeks and half were given the combination. There was no difference in cardiovascular events during follow-up, but the total number was only 12[27]. These studies as well as APSIS showed that, in patients with stable angina pectoris, there was no difference in treatment effects measured as clinical outcome between a calcium antagonist and a cardioselective beta-blocker. Both the IMAGE and TIBET studies showed, however, that the clinical effect was better with combination therapy. In IMAGE, it could be shown that this effect was due mainly to the recruitment of responders among those not responding to single therapy and not to a true additive effect. Further studies may well identify subgroups of patients prone to be responders to either drug.

The present data indicate that there are no clinically important differences in the effects of treatment with metoprolol and verapamil on prognosis in patients with stable angina pectoris. The 95% confidence intervals of the odds ratios of treatment effect for mortality and non-fatal cardiovascular events combined was 0·84 to 1·30 at the end of the study. The power requirements set up for the study were fulfilled. Although the overall effects of metoprolol and verapamil were similar, this does not necessarily mean that the two drugs act on the same mechanisms or are equally effective in all types of patients with stable angina pectoris. Various mechanisms may be operational in different patient groups, and it would be desirable to identify such mechanisms and patients, in order to improve the individual patient's medical therapy. APSIS includes a wide range of substudies which may give some answers to these questions. Results regarding treatment effects and their relationship to prognosis will be presented concerning mechanistic variables, traditional risk factors and interim 'surrogate' end-points. For example,

differential treatment effects on platelet aggregatability were found in a subgroup of APSIS patients[28] but we do not yet know the prognostic relevance of changes in platelet function. Other haemostatic markers have been studied in the entire material.

The similar withdrawal rates in the two groups and the similar and favourable treatment effects on psychological variables are also interesting, since the general impression among cardiologists seems to have been that beta-blockers are less well tolerated than calcium antagonists.

In conclusion

There was no statistically significant difference in treatment effects of metoprolol and verapamil on mortality and non-fatal cardiovascular events, or psychological variables reflecting quality of life. Both drugs are well tolerated.

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