Prognostic implications of results from exercise testing in patients with chronic stable angina pectoris treated with metoprolol or verapamil

A report from The Angina Prognosis Study In Stockholm (APSIS)

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Aims To evaluate the prognostic implications of results from exercise testing, and of antianginal treatment among patients with chronic stable angina pectoris.

Material and Methods Out of 809 patients in the Angina Prognosis Study In Stockholm (APSIS), 731 (511 men) performed evaluable exercise tests before and after 1 month on double-blind treatment with metoprolol or verapamil. During a median follow-up of 40 months, 32 patients suffered a cardiovascular death and 29 a non-fatal myocardial infarction.

Results Prognostic implications of results from exercise tests were assessed in a multivariate Cox model which included sex, previous myocardial infarction, hypertension and diabetes mellitus. Maximal ST-segment depression, especially if ≥ 2 mm and occurring after exercise, as well as exercise duration independently predicted cardiovascular death. Similar results were obtained for the combined end-point of cardiovascular death + myocardial infarction. Among patients with a positive exercise test at baseline, verapamil reduced the maximal ST-depression more markedly than metoprolol (P<0.01). However, when the treatment given and treatment effects on ST-segment depression were added to the Cox model, no impact on prognosis could be detected for either cardiovascular death alone or combined with myocardial infarction. Anginal pain carried no prognostic information.

Conclusion Marked ST-segment depression during and after exercise, and a low exercise capacity independently predicted an adverse outcome in patients with stable angina pectoris, whereas anginal symptoms had no predictive value. Short-term treatment effects on ischaemia did not seem to influence prognosis. Post-exercise ischaemia should be examined carefully when evaluating patients with stable angina pectoris.

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Key Words: Angina pectoris, exercise testing, ischaemia, prognosis.

See page 875 for the Editorial comment on this article

Introduction

A major objective when treating patients suffering from angina pectoris is to identify those who have a high risk for an adverse outcome. There is thus a need for simple, yet accurate prognostic tools to identify patients who should be considered for prompt coronary angiography and invasive treatment. One possibility is to use the exercise tolerance test, which may provide both diagnostic and prognostic information[1-2]. This test has been used extensively for risk assessments after myocardial infarction[3,4], after stabilization of unstable angina[5,6] and in chronic stable angina pectoris[7-9]. However, there are, to our knowledge, few studies linking results from exercise tests to prognosis among patients with stable angina pectoris.
Several exercise test variables, such as different measures of myocardial ischaemia \[10,13\], maximal work-load \[12,13\] and chest pain \[14,15\] have been found to carry prognostic information in different patient groups. McNee et al. \[9\] showed that exercise duration and ST-segment responses predicted survival among 1170 medically treated patients, who underwent treadmill exercise test and coronary angiography. Weiner et al. \[9\] found that exercise-induced ST-segment depression combined with a low exercise capacity indicated a high risk for subsequent fatal outcome in 3833 medically treated patients from the CASS registry. However, Morris et al. \[17\] found no prognostic importance of exercise induced ischaemia in a study on 588 male patients. Different scoring systems have also been employed. For example, Mark et al. \[16\] found that a score based on exercise duration, ST-segment depression and chest pain was strongly related to prognosis.

Thus, exercise testing may provide valuable prognostic information, but there are still diverging opinions regarding which exercise test variable is most closely related to prognosis. Furthermore, previous studies have not evaluated if different types of antianginal treatment, e.g. beta-blockade vs calcium antagonist treatment, might influence the prognostic information afforded by exercise testing. It was therefore of interest to investigate these issues in the Angina Prognosis Study In Stockholm (APSIS), which is a prospective, randomized single-centre trial involving double-blind treatment of patients with chronic stable angina pectoris with verapamil or metoprolol. The design and main results of the study have been presented \[19\]. The patients were carefully managed by one medical team, and followed regularly for a long period of time (2445 patient years in this report); no patient was lost to follow-up. We examine results from exercise testing before and after short-term treatment with either metoprolol or verapamil in relation to prognosis, in order to examine possible influences of the treatment given on prognosis. The end-points analysed were cardiovascular death and the combined end-point of cardiovascular death and non-fatal myocardial infarction (cardiovascular death + myocardial infarction). We did not evaluate the risk of future revascularization, as results from the exercise tests most likely affected the decision to perform a coronary intervention.

## Methods

### Patients

Altogether 1276 patients with a presumed diagnosis of stable angina pectoris were referred from the Danderyd Hospital or from primary care in the catchment area to the Heart Research Laboratory at the Danderyd Hospital. Based on medical history and physical examination by a cardiologist, 809 patients (248 women) were considered to have stable angina pectoris and were included. In this report we analyse the results from exercise testing in 731 patients (220 women). The study was approved by the Ethics Committee of the Karolinska Institute, and all participants gave their informed consent before entering the study.

In order to avoid rebound phenomena or severe deterioration, patients already on beta-blockers or calcium antagonists received minimal doses of metoprolol (25–50 mg daily) or verapamil (40 mg twice daily) during a 2 week run-in period. Thus 55% of the patients were on low dose metoprolol (daily mean dose 48 mg) and 15% on low dose verapamil at the time of baseline investigations.

Inclusion criteria were: age <70 years, and a history of chronic stable angina pectoris according to the description by Heberden \[19\]. The chest pain could present itself as either effort induced or at rest, but not unstable angina \[20\]. Angina of the mixed form was also included. Episodes of chest pain or discomfort should persist for longer than a few seconds, but less than 15 min. Sublingual nitrates, when used, should provide prompt relief. When in doubt whether the symptoms were of cardiac origin or not, additional examinations (perfusion scintigraphy, radiological and/or gastrointestinal investigations) were performed in order to exclude non-cardiac chest pain. A positive exercise test was not a prerequisite for inclusion, but could be used for diagnostic purposes in patients with atypical histories.

Exclusion criteria were: myocardial infarction within the last 3 years (beta-blockade was considered to be indicated in such patients); anticipated need for revascularization within 1 month after inclusion; significant valvular disease or severe congestive heart failure; other severe diseases; contraindications to either study drug (metoprolol or verapamil); and risk of poor compliance (e.g. suspected alcohol abuse).

After baseline investigations, patients were randomized to treatment with metoprolol (Seloken ZOC) or verapamil (Isoptin SR). The starting dose was 100 mg and the target dose 200 mg once daily for metoprolol. For verapamil the corresponding doses were 120 mg and 240 mg twice daily. If there were problems with tolerance, it was possible to reduce the doses. Half of the patients in both groups were on target dose at the end of the study \[18\].

### Exercise tolerance testing

A symptom-limited exercise test was performed on an electrically braked cycle ergometer, with a starting load of 30 W and 10 W increments every minute. Exercise ECGs were registered on a Siemens-Elema Sicard 440/440S with an on-line ECG (leads I, II, V5), or a Mingograph 740 (both from Siemens-Elema, Solna, Sweden). The Sicard was attached to a Siemens Nixdorf computer, which produced averaged ECG complexes at 60 s intervals. From the Mingograph, on-line paper print-outs of six chest leads were produced continuously at 25 mm s\(^{-1}\) paper speed, and every minute a 12 lead
ECG at 50 mm s⁻¹ paper speed was registered. ECG print-outs were surveyed both automatically and manually, and analysed for ST-segment depressions. Significant ischaemia was defined as an ST-segment depression of at least 1 mm, horizontal or downsloping, 80 ms from the J-point in at least two adjacent leads.

The patients were urged to report chest pain immediately, as well as in increases in its severity, as assessed by the 10-degree modified Borg scale. The exercise test was stopped when patients were unable to continue due to chest pain, general and/or leg muscle fatigue or dyspnoea. For safety reasons, the responsible cardiologist could also stop the test if there was a fall in systolic blood pressure (≥20 mmHg in one measurement or ≥10 mmHg in two consecutive measurements), a severe ST-segment depression (4–5 mm in at least three leads), or a severe ventricular arrhythmia. The following parameters were registered: exercise duration (s); time to onset of chest pain (s); time to 1 mm ST-segment depression (s); maximal ST-segment depression (mm) both during exercise and at rest 2 min after exercise. Patients on treatment with cardiac glycosides or with left bundle branch block were excluded from analyses, leaving 731 patients with evaluable exercise tests.

Follow-up and definition of end-points

The patients returned for a complete examination after 1 month of double-blind treatment, and were seen at 6-month intervals thereafter. Follow-up varied from 6 to 75 months (median 40 months). End-points in the APSIS study were total and cardiovascular death, and non-fatal cardiovascular events. The present report focuses on cardiovascular death and cardiovascular death + myocardial infarction. Cardiovascular death was defined as death from acute myocardial infarction, sudden death (within 2 h of onset of symptoms) or death from other vascular causes (e.g. fatal cerebrovascular disease, pulmonary embolii). The criteria for myocardial infarction were typical symptoms, a significant rise in cardiac enzymes and/or development of new Q-waves on the ECG. Patients with a newly developed significant Q-wave without concomitant hospitalization were also classified as having had a myocardial infarction.

Statistical analysis

Statistical comparisons of continuous variables were made by non-parametric tests (Mann-Whitney U and Wilcoxon). Variables in contingency tables were compared by the Chi-square test. In addition, descriptive statistics and graphical methods were employed to characterize the data. Analyses were carried out using Statistica software package version 5.1 (Stat Soft, Tulsa, OK, U.S.A.). A P value less than 0·05 was considered significant.

To investigate associations between exercise test variables and events, univariate Cox regression analysis and log-rank statistics were performed. Follow-up times until cardiovascular death, non-fatal myocardial infarction or end of study were used. However, since the proportional risk changes considerably after revascularization, patients were censored at the actual dates of such procedures. In a second step exercise variables that showed relationships to events were further evaluated with adjustments for the following known risk factors: sex, previous myocardial infarction, hypertension and diabetes mellitus. Since the number of events was relatively small, we had to limit the number of co-variates in the Cox model. The analyses showed that smoking did not add much to the prognostic importance of the model when used together with the other co-variates. Therefore smoking was not used. The ST-segment depression during or 2 min after exercise, as well as exercise duration were analysed as continuous variables in the multivariate model. In order to analyse treatment effects on maximal ST-segment depression during exercise, we divided the patients into the following three groups: (1) no ST-segment depression either at baseline or at the 1 month follow-up, (2) ST-segment depression which did not change or increased (i.e. non-responders), and (3) reduced ST-segment depression on treatment (i.e. responders).

Data are presented for all patients and for men separately. The event rate for women was very low, thus not allowing meaningful statistical comparisons. All analyses were performed according to the principle of intention-to-treat.

Results

During follow-up, 32 patients (29 men) suffered a cardiovascular death and 29 (24 men) a myocardial infarction. In addition, 91 patients were revascularized, 35 had unstable or worsening angina, 21 suffered a cerebrovascular event, and five had other vascular events. Nine patients died of cancer. Thus there were 509 (335 men) event-free patients.

Exercise variables in patients with different outcomes

Patient characteristics known to influence risk and exercise test results at baseline are shown in Table 1. Patients suffering cardiovascular death had a shorter exercise duration (P<0·01), and a lower maximal heart rate during exercise (P<0·001) than patients without this event. They reported chest pain and showed significant ST-segment depression earlier (P<0·05 for both). Maximal ST-segment depression did not differ, but ST-segment depression at rest 2 min after exercise was significantly greater among patients suffering cardiovascular death (P<0·01). For patients suffering a non-fatal...
myocardial infarction, only maximal heart rate during exercise differed \((P<0.01)\).

### Prognostic evaluation of exercise variables — univariate analysis

Maximal ST-segment depression during exercise and ST-segment depression at rest 2 min after exercise were both related to a higher risk for cardiovascular death. In order to evaluate the prognostic importance of the magnitude of ischaemia during exercise, we divided the patients into the following three groups: (1) no significant ST-segment depression, (2) ST-segment depression of at least 1 mm, but less than 2 mm, and (3) ST-segment depression of 2 mm or more. Kaplan–Meier plots show that the main difference was between patients with maximal ST-depression during exercise of 2 mm or more and the others. This difference was, however, not significant for cardiovascular death (Fig. 1(a)), but there was a significant difference between patients with ST-segment depression \(\geq 2\) mm and those without significant ST-segment depression for the combined end-point of cardiovascular death + myocardial infarction (Fig. 1(b)); log-rank \(P=0.028\). Similar results were found among male patients (data not shown). When ST-segment depression 2 min after exercise was similarly analysed the relationships to cardiovascular death (Fig. 2(a)); log-rank \(P<0.0001\), and to cardiovascular death + myocardial infarction (Fig. 2(b)); log-rank \(P=0.001\) were highly significant. Similar results were obtained for male patients only (data not shown).

Since exercise capacity differs between men and women, we only analysed the prognostic importance of exercise duration in male patients. When dividing the male patients into tertiles with regard to exercise duration \((<9\ min,\ 9–13\ min\ and\ \geq 13\ min)\), males with the shortest exercise duration had the worst prognosis regarding cardiovascular death (Fig. 3(a)). Differences were significant between the lower and upper (log-rank \(P=0.001\), as well as between the lower and intermediate tertiles (log-rank \(P=0.004\). Similar results were obtained for cardiovascular death + myocardial infarction (log-rank \(P=0.008\ and \(P<0.001\) respectively).

The presence or absence of anginal symptoms had no prognostic impact whether there was simultaneous ST-segment depression or not (data not shown).

### Prognostic evaluation of exercise variables — multivariate analysis

To assess the independence of the prognostic information afforded by the exercise variables in univariate analyses, we employed a Cox regression model, which included sex, previous myocardial infarction, history of hypertension and diabetes mellitus, as described above. After adjustment for these variables, maximal ST-segment depression during exercise, ST-segment depression 2 min after exercise, and exercise duration all carried independent relationships to both cardiovascular and the combined end-point of cardiovascular death + myocardial infarction. This was true for all males only (data not shown).
Both drugs reduced exercise-induced signs of ischaemia. The effects of treatment with the two drugs among patients with significant ST-segment depression on exercise at baseline were different. We found that verapamil-treated patients had a slight but significantly greater reduction of maximal ST-segment depression compared to metoprolol treated patients (from $2.0 \pm 1.1$ to $1.4 \pm 1.2$ mm vs from $2.0 \pm 1.1$ to $1.7 \pm 1.2$ mm; $P<0.01$) (Fig. 4(a)). Patients without minimal doses of metoprolol or verapamil at baseline showed similar effects of the study drugs (Fig. 4(b)). Exercise duration increased significantly among verapamil-treated patients only (from 584 s to 602 s; $P<0.01$), but this finding must be interpreted cautiously as the metoprolol group had a longer exercise duration at baseline (from 601 s to 611 s; ns). The time until 1 mm ST-segment depression increased significantly in both groups, but the magnitude of changes was small (for metoprolol from a mean of
394 s to 438 s; \( P < 0.001 \) and for verapamil from 377 s to 407 s; \( P < 0.01 \). The time until occurrence of chest pain did not change with either treatment.

In order to assess the prognostic information of the treatment given and treatment effects, we employed the multivariate Cox model described above, with further variables describing treatment effects added (see ‘Statistics’). We limited the analyses to treatment effects on maximal ST-segment depression, as exercise duration, and time until 1 mm ST-segment depression differed little between the baseline and 1 month investigations. The analysis showed that neither the type of drug given nor the effect of treatment on ischaemia, regardless of the drug given, had any independent prognostic impact. In other words, the slightly more marked reductions of ischaemia by verapamil did not influence prognosis significantly. Not even an elimination of ST-segment depression 2 min post-exercise after 1 month’s treatment influenced the prognosis significantly.

Figure 2  Kaplan–Meier plots illustrating the risk of cardiovascular death (a) or cardiovascular death + myocardial infarction (b) in relation to ST-segment depression at rest during 2 min after exercise among all patients. There was a significant difference between the three subgroups both for cardiovascular death and cardiovascular death + myocardial infarction (chi-square, \( P < 0.001 \) for both). Log rank statistics showed that the risk for cardiovascular death was increased in patients with ST-segment depression \( \geq 2 \) mm compared both to patients without significant ST-segment depression \( (P < 0.001) \) and to those having ST-segment depression between 1 and 2 mm \( (P = 0.009) \). The number of patients in each subgroup was: day 0: 458/204/59, day 1000: 268/100/22 and day 2000: 45/24/2 respectively. For cardiovascular death + myocardial infarction log rank statistics showed significant differences for patients with ST-segment depression \( \geq 2 \) mm compared to those with <1 mm \( (P = 0.001) \), and also for patients with ST-segment depression between 1 and 2 mm compared to those with <1 mm \( (P = 0.043) \). The number of patients in each subgroup was: day 0: 458/204/59, day 1000: 267/100/22 and day 2000: 45/24/2 respectively. ST-depression <1 mm = – – – ; ST-depression 1–2 mm = – – ; ST-depression \( \geq 2 \) mm = · · · .
Discussion

Our findings support the contention that results from exercise testing can provide important prognostic information, and help us to identify patients with a higher risk for adverse outcomes. The patients who died from cardiovascular causes differed from patients who survived regarding several exercise test variables. However, patients with a non-fatal myocardial infarction showed smaller differences. In multivariate analyses the maximal ST-segment depression during exercise, ST-segment depression 2 min after exercise and exercise capacity (in males) independently predicted cardiovascular death. Similar results were obtained for the combined end-point of cardiovascular death + myocardial infarction. Our results concerning ischaemia on exercise are in agreement with the results of two previous large studies\cite{8,16}, but the prognostic impact of post-exercise ischaemia has not been highlighted previously.

In our study, ST-segment depression of 2 mm or more occurring 2 min after exercise showed the closest relationship to cardiovascular death. ST-segment depression during recovery has been shown to relate to coronary events in apparently health individuals\cite{23} and analyses of ST-segment depression after exercise increases the diagnostic yield of the exercise test\cite{22}. Thus, ST-segment depression occurring after exercise appears to be a useful marker for severe ischaemia and indicates a high risk for cardiac events among patients with coronary artery disease. Conversely, absence of ischaemia on exercise indicated a favourable prognosis.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure3.png}
\caption{Kaplan–Meier plots illustrating the risk of cardiovascular death (a) or cardiovascular death + myocardial infarction (b) in relation to exercise capacity among male patients. There was a significant difference between the three subgroups both for cardiovascular death (chi-square $P=0.002$) and cardiovascular death + myocardial infarction (chi-square $P=0.001$). Log rank statistics showed significant differences for both the lowest and the intermediate tertiles compared to the highest tertile (cardiovascular death: $P=0.004$ and $P=0.001$ respectively and cardiovascular death + myocardial infarction: $P=0.008$ and $P=0.001$ respectively). The number of male patients in each subgroup was: day 0: 141/218/152, day 1000: 63/114/89 and day 2000: 12/22/20 respectively. Longest $\geq 13$ min = ---; Intermediate 9–12 min = - - -; Shortest <9 min = · · ·.}
\end{figure}
Patients with stable angina pectoris.

vascular death and non-fatal myocardial infarction in carries independent prognostic information for cardio-

Diabetes mellitus. Calculations concerning exercise duration have been performed on male patients only due to the sex related differences in exercise capacity.

The calculations were performed with the following co-variates: sex, previous myocardial infarction, hypertension and
disease.

Previous myocardial infarction. They found that a positive
effect on maximal ST-segment depression during exercise at
baseline and after 1 month of treatment with metoprolol or verapamil among patients with significant ST-depression at baseline. (a) All patients. (b) Patients without treatment with minimal doses of metoprolol or verapamil at baseline. Mean values and 95% confidence intervals for the mean. Mann-Whitney U and Wilcoxon matched pair tests. **P<0.01, ***P<0.001. ● =metoprolol-treated patients; ○ =verapamil-treated patients.

Exercise induced ST-segment depression was the single most important factor in the exercise score developed by Mark et al. Brunelli et al. studied 1083 patients with either symptoms suggesting myocardial ischaemia, documented myocardial ischaemia or a previous myocardial infarction. They found that a positive exercise test, defined as ST-segment depression, ST-segment elevation or typical anginal pain, predicted survival only in univariate analyses. Our results are in agreement with results from previous studies, and indicates that exercise-induced ST-segment depression carries independent prognostic information for cardiovascular death and non-fatal myocardial infarction in patients with stable angina pectoris.

Exercise duration, i.e. the maximal workload, independently predicted cardiovascular prognosis among male patients. Similar findings have been made previously in patients undergoing exercise testing and coronary angiography, patients with angiographically documented coronary artery disease, and male patients with a high prevalence of angiographic coronary disease. Exercise duration also had prognostic importance in the ACIP study. Thus, exercise capacity may be regarded as an established marker of prognosis in patients with stable coronary artery disease.

It is interesting to note that symptoms of angina pectoris carried no prognostic information, regardless of whether objective signs of ischaemia during exercise

### Table 2 Results of the Cox proportional hazard analysis regarding the risk of suffering a cardiovascular end-point.

<table>
<thead>
<tr>
<th>Prognostic factors</th>
<th>A. CV death</th>
<th>B. CV death+MI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds ratio (OR) 95% CI of OR</td>
<td>P-value</td>
</tr>
<tr>
<td>Maximal ST-segment depression</td>
<td>1.450 1.15–1.83 0.0018</td>
<td></td>
</tr>
<tr>
<td>Maximal ST-depression 1–2 mm</td>
<td>0.827 0.30–2.30 0.7199</td>
<td></td>
</tr>
<tr>
<td>Maximal ST-depression ≥2 mm</td>
<td>1.619 0.73–3.59 0.2360</td>
<td></td>
</tr>
<tr>
<td>ST-segment depression after exercise</td>
<td>1.850 1.43–2.39 0.0000</td>
<td></td>
</tr>
<tr>
<td>ST-depression 1–2 mm</td>
<td>1.902 0.63–3.59 0.3607</td>
<td></td>
</tr>
<tr>
<td>ST-depression ≥2 mm</td>
<td>5.180 2.12–12.67 0.0003</td>
<td></td>
</tr>
<tr>
<td>Exercise duration (male patients)</td>
<td>0.786 0.69–0.90 0.0006</td>
<td></td>
</tr>
<tr>
<td>Exercise duration 9–13 min</td>
<td>0.358 0.16–0.82 0.0152</td>
<td></td>
</tr>
<tr>
<td>Exercise duration ≥13 min</td>
<td>0.250 0.08–0.77 0.0160</td>
<td></td>
</tr>
</tbody>
</table>

CV=cardiovascular; MI=myocardial infarction; CI=confidence interval.
were present or not. These results are in agreement with previous results showing that patients with silent ischaemia during exercise had the same prognosis as patients with symptomatic ischaemia[26,27].

Favourable effects of treatment with metoprolol or verapamil on prognosis have been demonstrated in placebo-controlled studies in post-myocardial infarction patients[28-29]. Studies have also demonstrated that treatment with metoprolol[30,31] or verapamil[31,32] reduces signs of ischaemia on exercise in patients with stable angina pectoris. However, it is not known if the anti-ischaemic effects of drug treatment influence the prognosis. In the APSIS study, treatment effects on signs of ischaemia and exercise duration were modest, but significant, and differed between the two drugs studied. Verapamil reduced exercise-induced ischaemia and increased exercise duration significantly more than metoprolol, whereas both drugs increased the mean time until 1 mm ST-segment depression by about 30–40 s. However, neither the treatment given (i.e. metoprolol or verapamil), nor the treatment effects on ischaemia, regardless of which drug was given, influenced the prognostic evaluation significantly.

Several studies have focused on the prognostic importance of ischaemia detected by ambulatory ECG. In the ASIST study[33], atenolol treatment was found to reduce the incidence of ischaemia detected by ambulatory ECG. In the increased exercise duration significantly more than metoprolol, whereas both drugs increased the mean time until 1 mm ST-segment depression by about 30–40 s. However, neither the treatment given (i.e. metoprolol or verapamil), nor the treatment effects on ischaemia, regardless of which drug was given, influenced the prognostic evaluation significantly.

Several studies have focused on the prognostic importance of ischaemia detected by ambulatory ECG. In the ASIST study[33], atenolol treatment was found to reduce events (mainly worsened angina), but no analysis regarding prognostic impact of baseline ischaemia was performed. In the TIBBS study[34], patients with two or more ischaemic events had an increased incidence of a combination of end-points, but results from the TIBET study contradicted this finding[35]. The latter study included exercise testing and an evaluation of the anti-ischaemic effects of treatment with nifedipine SR and/or atenolol[36]. However, the prognostic implications of exercise test results do not appear to have been analysed. In the ACIP study[25], patients should have arteriographically documented coronary disease amenable to revascularization, as well as signs of ischaemia on both the exercise test and the ambulatory ECG at the qualifying examination. End-points studied were death, myocardial infarction, percutaneous transluminal coronary angioplasty, coronary bypass surgery and ischaemic events requiring hospitalization. The ACIP investigators found that exercise duration and the number of ischaemic episodes on ambulatory ECG at baseline carried prognostic information in multivariate analysis. We have also analysed results from ambulatory ECG monitoring, and found that ambulatory signs of ischaemia had prognostic importance[37]. The differences in results may be related to differences in patient selection and in the end-points evaluated; the studies on prognostic importance of ambulatory ischaemia tend to have wider definitions of end-points than the end-points used by us.

Limitations

Our study patients were selected on clinical grounds. All had chest pain of presumed cardiac aetiology, i.e. stable angina pectoris, but we did not require invasive diagnostics or a positive exercise test. We made efforts not to include patients with non-cardiac chest pain, but despite these precautions some patients may have had other causes of chest pain. However, neither a positive exercise test nor a positive coronary angiogram might be considered as the gold standard for diagnosing myocardial ischaemia. Our aim was to study patients who were representative of an ordinary patient population, as seen in everyday practice, and we included two thirds of the patients referred for diagnostic evaluation in the study. Therefore, the generalizability of our results is good and our patient selection might equally well be considered a strength of the study.

Conclusion

Patients with stable angina pectoris and signs of marked myocardial ischaemia during or, especially after exercise, and patients with low exercise capacity have an increased risk for subsequent cardiovascular death or non-fatal myocardial infarction. Patients without ST-segment depression (n=234) were a low risk group, 15 cardiovascular deaths and non-fatal myocardial infarction vs 31 among patients with ST-segment depression ≥ 2 mm (n=281). Treatment effects on ST-segment depression, which were greater among verapamil treated patients, showed no independent relationship to prognosis. Thus, anti-ischaemic effects of drug treatment, as evaluated by exercise testing, were not found to be a major determinant of prognosis, even though the presence of ischaemia on exercise was clearly predictive.

Symptoms of angina pectoris on exercise carried no prognostic information.

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