CARDIOVASCULAR MEDICINE

Favourable long term prognosis in stable angina pectoris: an extended follow up of the angina prognosis study in Stockholm (APSIS)

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Objective: To evaluate the long term prognosis of patients with stable angina pectoris.

Design: Registry based follow up (median 9.1 years) of patients participating in the APSIS (angina prognosis study in Stockholm), which was a double blind, single centre trial of antianginal drug treatment.

Patients: 809 patients (31% women) with stable angina pectoris < 70 (mean (SD) 59 (7) years at inclusion) and an age and sex matched reference population from the same catchment area.

Interventions: Double blind treatment with metoprolol or verapamil during 3.4 years (median), followed by referral for usual care with open treatment.

Main outcome measures: Cardiovascular (CV) death and non-fatal myocardial infarction (MI) in the APSIS cohort and total mortality in comparison with reference subjects.

Results: 123 patients died (41 MI, 36 other CV causes) and 72 had non-fatal MI. Mortality (19% v 6%, $p < 0.001$) and fatal MI (6.6% v 1.6%, $p < 0.001$) were increased among male compared with female patients. Diabetes, previous MI, hypertension, and male sex independently predicted CV mortality ($p < 0.001$). Diabetes greatly increased the risk in a small subgroup of female patients. Male patients had higher mortality than men in the reference population during the first three years (cumulative absolute difference 3.8%) but apparently not thereafter. Female patients had similar mortality to women in the reference population throughout the 9.1 years of observation.

Conclusions: Female patients with stable angina had similar mortality to matched female reference subjects but male patients had an increased risk. Diabetes, previous MI, hypertension, and male sex were strong risk factors for CV death or MI.

Stable angina pectoris is usually related to coronary atherosclerosis and is a symptomatic condition with a highly variable long term prognosis.¹ Patients with stable angina are regarded as having a poorer cardiovascular (CV) prognosis than that of the general population. However, the management of angina pectoris is constantly changing, and no recent study has directly compared the prognosis of such patients with that of an age and sex matched general population.

Results from relatively recent clinical trials suggest a good prognosis in stable angina pectoris. The SAPAT (Swedish low dose aspirin trial; 2035 patients, median follow up 4.2 years) reported a cardiac death rate of 0.9% a year.² The TIBET (total ischaemic burden European trial; 682 patients, two years) reported 1% cardiac deaths a year among patients with a positive exercise test.³ Our APSIS (angina prognosis study in Stockholm; 809 patients, 3.4 years) recorded a cardiac death rate of 1.2% a year.⁴ The more recent ACTION (a coronary disease trial investigating outcome with nifedipine gastrointestinal therapeutic system) had a CV mortality of 0.9% a year.⁵ Rates of non-fatal myocardial infarction (MI) ranged from 1.0% (APSIS) to 2.6% (TIBET) a year. The small differences in outcome probably reflect differences in inclusion and exclusion criteria and ages of the patients. Even if the overall prognosis is favourable, risk stratification is needed to identify patients who may require invasive intervention or more aggressive risk factor management.

APSIS was a randomised, double blind study of long term antianginal treatment with verapamil or metoprolol in patients with clinically diagnosed stable angina pectoris.⁴ After the study the patients were referred to their ordinary care facilities for continued care. Since outcomes were similar

in the two treatment groups,⁴ we recommended open treatment with the randomised drug. APSIS did not include a placebo group, since we considered it unethical and impossible to withhold treatment with a calcium antagonist or a β blocker during a long period of time from symptomatic patients. The results may therefore reflect similar protective effects of the two drugs (as seen with β blocker treatment after MI⁶⁻⁷) but also that neither drug influenced the prognosis.

We report an extended follow up of the APSIS participants based on registry data and the long term impact of prognostic indicators. We examined total and CV death and hospitalisation for non-fatal MI during the APSIS study and six years thereafter. Furthermore, we compared the mortality of APSIS patients with that of all matched people in a reference population from the same catchment area.

METHODS

Patients

Patients with a clinical history of angina pectoris were referred to the heart research laboratory at Danderyd Hospital. Referrals came either from general practitioners in the catchment area or from the department of medicine at Danderyd Hospital. At screening, a clinical history and a

Abbreviations: ACTION, a coronary disease trial investigating outcome with nifedipine gastrointestinal therapeutic system; APSIS, angina prognosis study in Stockholm; CCS, Canadian Cardiovascular Society; CV, cardiovascular; ICD-9, International classification of diseases, ninth revision; INVEST, international verapamil-trandolapril study; MI, myocardial infarction; RITA-2, second randomized intervention treatment of angina; SAPAT, Swedish low dose aspirin trial; TIBET, total ischaemic burden European trial

physical examination were undertaken. Of 1276 patients referred for evaluation, 809 (248 women) were enrolled in the APSIS study. The ethics committee of the Karolinska Institute approved the study, as well as this extended follow up, and all participants gave their informed consent before entering the study.

Inclusion criteria were age < 70 years and a history of chronic stable angina pectoris according to the description by Heberden.⁸ Chest pain was classified as effort induced angina, vasospastic angina,⁹ or angina of mixed form. Vasospastic angina was considered when symptoms were not related to exertion. Requirements were episodes of chest pain or discomfort lasting less than 15 minutes and sublingual nitrates, when used, providing prompt relief. When in doubt, additional examinations (perfusion scintigraphy and radiological or gastrointestinal investigations) were performed to confirm the diagnosis. A positive exercise test was not required for inclusion but was often used for diagnostic purposes. As part of the study protocol 99.6% of the patients underwent exercise testing, the results and prognostic implications of which have been reported.^{10–11} Only 14% of male and 11% of female patients had neither ST segment depression nor angina at the baseline exercise test. Signs of ischaemia or a previous manifestation of coronary artery disease (MI or revascularisation) were found in 69% of both male and female patients at baseline.

Exclusion criteria were MI within the past three years (β blockade was then considered to be indicated, based on a post-MI study⁷); anticipated need for revascularisation within one month; significant valve disease or severe congestive heart failure; other severe diseases; contraindications to either study drug; and risk of poor compliance (for example, suspected alcohol misuse).

After baseline investigations, patients were randomly assigned to treatment with metoprolol (Seloken ZOC, 100–200 mg once daily) or verapamil (Isoptin SR, 120–240 mg twice daily). During the double blind phase (first 3.4 years), drug treatment was withdrawn because of side effects in 11.1% and 14.6% of metoprolol and verapamil treated patients, respectively ($p = 0.13$).⁴ Acetylsalicylic acid was used by 39% of patients, angiotensin converting enzyme inhibitors by 6%, and lipid lowering drugs by 6% at baseline (1993 or earlier). After the study, the patients were referred for usual care with a recommendation to continue randomised treatment openly, since neither drug had a prognostic benefit compared with the other.

Age, sex, smoking habits, and histories of hypertension, diabetes mellitus, or previous percutaneous transluminal coronary angioplasty or coronary artery bypass grafting were registered at baseline. The protocol prespecified a clinical risk stratification based on type of angina and some well established risk indicators. Patients with vasospastic angina were classified as having low risk. Patients with effort induced or mixed angina were further classified according to presence of three indicators: age ≥ 60 years, ECG signs of multivessel disease during exercise testing,¹² and clinical signs of left ventricular dysfunction. Patients were classified as having low risk in the absence of these factors, intermediate risk with 1–2 factors, and high risk with all three factors.

Reference population

In Sweden there is a complete and up to date population registry that makes it possible to compare patient cohorts with the general population. The reference population was from the same catchment area—that is, a well defined area (population about 250 000) served by the Danderyd Hospital alone—to minimise mismatches of socioeconomic factors. Our reference population consisted of people from the

catchment area (about 65 000 people) who were matched to patients in the APSIS cohort regarding sex and age during each year of follow up.

Follow up and definition of end points

The main findings of the double blind study period have been described.⁴ This extended follow up is based on the Swedish cause of death registry, which gives complete data on death and its causes for all Swedish residents, and the Swedish national hospital discharge registry, which provides reliable data on hospitalisation for non-fatal MI.¹³ Complete registry data were available until 31 December 1999. Two cardiologists classified all end points according to a predefined protocol. Primary end points were CV death and non-fatal MI. The median follow up was 9.1 years (range 78–147 months). Comparisons with the general population were made only for total mortality.

CV death was defined as a primary cause of death coded as 402, 404, 410–414, and 420–429 (*International classification of diseases*, ninth revision (ICD-9)). Acute MI was considered to have occurred on the date of a hospital admission resulting in a discharge diagnosis of acute MI (ICD-9 code 410). For the composite end point of MI or CV death, the date of the first event was the time of the end point.

Statistical analysis

Discrete variables were compared by the χ^2 test with Yates's continuity correction. Group differences in continuous variables were assessed by two tailed t tests. Coefficients for skewness and kurtosis were used to test deviations from a normal distribution. If the underlying normality assumption was violated, a non-parametric method was used. Effects of randomised treatment were analysed on an intention to treat basis. Life table curves according to Kaplan-Meier were calculated and compared by using log rank tests. Cox regression analyses were used to identify predictive factors. Data were analysed with STATISTICA version 7.0 for PC (StatSoft, Tulsa, Oklahoma, USA). A probability value of $p < 0.05$ was considered significant.

Relative survival is defined as the observed survival among APSIS patients divided by the expected survival—that is, that of the reference population. An interval specific relative survival rate was calculated with SURV3.¹⁴ The Hakulinen cohort method¹⁵ was used to calculate cumulative, interval specific survival.

Table 1 Baseline characteristics of the two treatment groups in the APSIS (angina prognosis study in Stockholm)

	Metoprolol (n = 408)	Verapamil (n = 403)
Age (years)	59 (7)	59 (7)
Female sex	27%	34%*
Previous MI	16%	16%
Previous PTCA or CABG	5%	7%
Hypertension	28%	26%
Diabetes mellitus	8%	9%
Non-smokers	28%	42%*
Current smokers	22%	22%
Antianginal treatment at baseline		
Long acting nitrates	49%	53%
Calcium antagonists	14%	16%
β Blockers	56%	54%

Age is mean (SD).

* $p < 0.05$.

CABG, coronary artery bypass grafting; MI, myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty.

Table 2 Baseline characteristics of male and female patients in APSIS

	Men (n = 561)	Women (n = 248)
Age (years)	59 (7)	59 (7)
Previous MI	20%	7%***
Previous PTCA or CABG	7%	2%**
Hypertension	28%	25%
Diabetes mellitus	10%	6%
Non-smokers	27%	54%****
Current smokers	25%	15%***

p<0.01; *p<0.001; ****p<0.0001.

RESULTS

Table 1 presents demographic data and antianginal treatment at baseline for the two original treatment groups. According to the Canadian Cardiovascular Society (CCS) angina classification most patients had mild (25–27% in the two treatment groups) to moderate (68–69%) angina; 5–6% had CCS class III angina. Table 2 presents demographic data for male and female patients. Women were less prone to smoke and had a lower prevalence of previous MI. We do not have reliable data on changes in smoking habits and concomitant treatment during the follow up. For further details, see.⁴

During follow up for a median of 9.1 years, 77 patients (66 men) died of CV causes and 72 (60 men) had a non-fatal MI; 139 patients (121 men) either had a non-fatal MI or died of a CV cause. Forty one patients (5%) died of MI and 36 (4%) died of other CV causes; 30 (4%) died of cancer and 16 (2%) died of other causes. Death (19% v 6%, $p < 0.001$) and fatal MI (6.6% v 1.6%, $p < 0.001$) were more common among male than female patients. Figure 1 shows survival without CV death or MI of male and female patients.

Clinical stratification to high risk at baseline was associated with an increased risk of dying of a CV cause or having an MI ($p < 0.01$), whereas the type of angina was not (tables 3 and 4).

Diabetes mellitus was a strong risk factor among both men and women (tables 3 and 4, fig 2A). Interestingly, only 14 of 234 female patients without diabetes (6%) died of a CV cause or had an MI during the nine year follow up compared with four of 14 (29%) female patients with diabetes ($p < 0.05$).

Figure 1 Kaplan-Meier plot illustrating the risk of cardiovascular (CV) death or non-fatal myocardial infarction (MI) among male and female patients with stable angina pectoris. Cox proportional hazard analysis showed a significantly increased risk among male compared with female patients ($p < 0.001$). The end of the double blind phase of the study (APSYS I (angina prognosis study in Stockholm) is indicated.

Table 3 Clinical characteristics of patients without versus with cardiovascular (CV) death

	No CV death (n = 732)	CV death (n = 77)
Age (years)	59 (7)	62 (6)***
Female sex	32%	14%***
Current smokers	21%	31%*
Hypertension	25%	47%**
Previous MI	14%	32%***
Previous revascularisation	5%	12%*
Hypertension	25%	47%***
Diabetes mellitus	7%	21%***
History of congestive heart failure	6%	12%*
Vasospastic angina	7%	5%
Effort induced angina	39%	39%
Mixed angina	53%	56%
Low risk stratification (n = 243)	31%	14%***
High risk stratification (n = 235)	27%	45%***

*p<0.05; **p<0.01; ***p<0.001.

Previous MI (fig 2B) and hypertension (fig 2C) were related to CV events also in the extended follow up phase. When age, sex, previous MI, hypertension, and diabetes mellitus were included in a multivariate Cox regression model, all of these risk markers were significantly ($p < 0.05$) and independently related to prognosis.

Treatment effects

During the double blind phase of APSIS outcomes were similar in the two treatment groups.⁴ Results did not change after extended follow up, as total mortality (14.1% v 16.3%), fatal MI (4.2% v 5.9%), and non-fatal MI (4.3 v 4.6%) were similar in the original verapamil and metoprolol treatment groups. There were slightly more women and non-smokers in the verapamil group (table 1), but adjustments for these factors did not significantly alter the results. Cancer deaths were evenly distributed between the two original treatment groups (15 in each).

Comparison with the reference population

Figure 3 shows Kaplan-Meier plots for men and women in APSIS and in the reference population. Compared with the reference subjects, male APSIS patients had a higher mortality, with a cumulative survival difference of 3.8% (92.7 v 96.5%) after three years of follow up; the survival curves for men were parallel thereafter. Female patients had similar annual mortality to the female reference population throughout the period of observation.

Table 4 Clinical characteristics of patients without versus with combined CV events (CV death or non-fatal MI)

	No CV event (n = 670)	CV event (n = 139) (CV death or non-fatal MI)
Age (years)	59 (8)	62 (6)***
Female sex	34%	13%***
Current smokers	20%	28%*
Previous MI	14%	28%***
Previous revascularisation	5%	11%*
History of hypertension	25%	38%***
Diabetes mellitus	7%	17%***
History of congestive heart failure	6%	10%
Vasospastic angina	7%	5%
Effort induced angina	38%	38%
Mixed angina	55%	57%
High risk stratification	27%	39%***

*p<0.05; **p<0.01; ***p<0.001.

Figure 2 Kaplan-Meier plots illustrating the influence of (A) diabetes mellitus, (B) previous MI, and (C) a history of hypertension on the risk of CV death or MI. All three risk indicators were significantly ($p < 0.001$) associated with an adverse outcome. Diabetes was the risk indicator providing the greatest separation between subgroups.

DISCUSSION

Our patients with stable angina pectoris, who had a median duration of angina of two years and a mean age of 59 years at baseline, had a good prognosis. Thus, the total mortality was 1.7% a year and CV mortality was 1% a year during nine years of follow up. Interestingly, female patients and reference subjects had similar mortality throughout the period of observation. However, the small subgroup of female patients with diabetes had a poor prognosis. Mortality was higher among male patients than among age matched men in a reference population from the same catchment area during the first three years after inclusion in APSIS. Thereafter, the survival curves were parallel. Increasing use of pharmacotherapy with statins, angiotensin converting enzyme inhibitors, and aspirin might have contributed to normalising the prognosis of our male patients after 1993, but we do not

Figure 3 Cumulative survival rates among male and female patients with stable angina pectoris (observed) and age matched male and female subjects in a reference population from the same catchment area (expected). Men had a poorer survival than women ($p < 0.001$). Male patients had a poorer survival than men in the reference population during the first three years of follow up but not thereafter. Female patients had similar mortality to women in the reference population throughout the period of observation.

have data on such treatment. The present results support the justification of managing the majority of patients with stable angina pectoris with a conservative strategy based on medical treatment.

Our patients were not screened by coronary angiography and a positive exercise test was not required for inclusion in APSIS, since our goal was to study the prognosis of patients with “clinical” angina pectoris. However, ischaemic heart disease was verified at baseline among 69% of both male and female patients, based on a history of MI or revascularisation, or ST segment depression during the exercise test. We treated our patients according to contemporary Swedish guidelines. Coronary angiography was performed on clinical grounds in 139 patients (17%), resulting in revascularisation of 102 patients (12%), during the double blind phase of the follow up—that is, until the end of 1993.⁴

We found a 3–4 times higher risk for major CV events among male than among female patients with similar ages. This is in agreement with the early Framingham report¹⁶ and more recent studies,^{17,18} and supports the contention that women with stable angina pectoris have a much better prognosis than men.¹ However, the event rate was greatly increased in a small subgroup of diabetic female patients in our study, in agreement with recent results for female patients with acute coronary events.¹⁹ Thus, identifying and treating diabetes appear important among female patients with CV disease. In the absence of diabetes, however, the CV mortality of female patients with stable angina pectoris is similar to that of the general population.

The 22 year follow up results from the Veterans Affairs cooperative study of coronary artery bypass surgery for stable angina showed that initial bypass surgery compared with medical treatment did not improve the survival of low risk patients and did not reduce the risk of MI.²⁰ Surgery conferred a survival benefit in high risk patients during the first decade but long term survival rates became comparable. The seven year follow up of the RITA-2 (second randomized intervention treatment of angina) study indicates that a conservative strategy based on medical treatment confers no disadvantage for patients with stable coronary artery disease compared with an invasive strategy based on percutaneous coronary intervention.²¹ Thus invasive procedures may be efficient in relieving anginal symptoms but do not improve prognosis unless the patient is at high risk.¹ A recent cohort study of 693 patients with stable coronary artery disease and a 4.6 year follow up also concluded that a conservative

strategy based on medical treatment resulted in few CV complications.²² The present results strengthen the view that many patients with stable angina pectoris are at low risk and that a conservative approach based on medical treatment is a viable alternative to more invasive strategies.

Even if the average patient with stable angina pectoris has a favourable prognosis, patients who are at increased risk of having CV complications need to be identified and should be further investigated by, for example, coronary angiography. We found that age, sex, diabetes mellitus, previous MI, and hypertension independently predicted an increased risk during the nine year follow up. Recently, we found that a fasting blood glucose concentration above 6.1 mmol/l (according to revised definitions of diabetes mellitus) carried a similarly increased risk as a diagnosis of diabetes at baseline.²³ Clinical stratification to a high risk group based on age, signs of multivessel disease on exercise ECGs, or clinical signs of heart failure at the baseline examination also predicted a worsened outcome. We have previously reported that signs of ischaemia on exercise¹¹ provided better prognostic information than did ambulatory ischaemia.²⁴ Low heart rate variability predicted a poorer outcome.²⁵ Measurements of apolipoproteins provided better prognostic information than those of blood lipids,²⁶ and disturbed fibrinolysis was associated with a poor prognosis.²⁷ Increased white blood cell counts were also predictive,²⁸ but this variable has no established cut off values and cannot be used in individual cases. Thus, detailed laboratory investigations provide further insight into the mechanisms of disease but are of less value in the individual case. Our findings indicate that high risk patients with stable angina pectoris may be easily identified on the basis of age, male sex, previous MI, diabetes mellitus, and hypertension. Thus, the routine clinical examination, including an exercise test that provides both diagnostic and prognostic information,¹⁻¹¹ will identify most patients in need of further investigation by coronary angiography.

CV outcomes did not differ between patients treated with verapamil and with metoprolol during the double blind phase of APSIS⁴ or during this extended follow up. Our findings agree with results from the INVEST (international verapamil-trandolapril study),²⁹ which compared verapamil with atenolol based treatment in 22 576 hypertensive patients with coronary artery disease (67% angina pectoris; 32% previous MI). A meta-analysis of 72 trials comparing calcium antagonists with β blockers in stable angina pectoris indicated similar outcomes with the two drug classes.³⁰ However, the mean duration of the studies in this meta-analysis was only eight weeks. A meta-analysis restricted to six larger trials reached a similar conclusion.¹ Thus, the choice between β blocker and calcium antagonist treatment may be guided by individual tolerability and the presence of other disease and co-treatment, rather than on expectations of prognostic benefits.

The possibility of an increased risk of cancer with calcium antagonist treatment has been debated,³¹ and a recent retrospective study implicated verapamil in this respect.³² However, we found similar incidences of fatal cancer among verapamil and metoprolol treated patients (15 cases in each group) after nine years of follow up.

Patients in APSIS were recruited by referral and selected by clinical examination that verified chest pain of presumed cardiac aetiology (that is, angina pectoris). Selecting patients with exercise tests or coronary angiograms might have yielded slightly different results due to exclusion of some patients with vasospastic or mixed angina. However, our results are generalisable to an ordinary patient population with stable angina pectoris in the same age range and without a recent MI. Such patients are common in everyday

practice, and our selection criteria may also be considered a strength of the study.

Epidemiological studies based on Rose questionnaires have suggested that the prognosis of patients with undiagnosed angina pectoris is worse than that of patients with a diagnosis.³³⁻³⁴ Thus, our data from patients with an established diagnosis should not be extrapolated to the general population.

In conclusion, this long term follow up shows a favourable prognosis of most patients with stable angina pectoris. Compared with registry data from the general population in the same catchment area, male but not female patients in APSIS had an increased mortality. The increased mortality among male patients was apparent during the first three years of observation. Easily identified risk markers, such as age, diabetes, previous MI, or hypertension, predicted an increased risk of dying of CV causes or having a non-fatal MI. Further prognostic information is provided by the routinely performed exercise test. Of note, female patients without diabetes had a very low risk of dying of CV causes or having an MI. Clinical risk stratification based on signs of multivessel disease, signs of heart failure, and age > 60 years also identified patients with an increased risk. Thus, diagnostic procedures aimed at invasive treatment may be restricted to patients at high risk or in need of revascularisation for symptomatic reasons, whereas a large proportion of patients with stable angina will do well with a conservative strategy based on medical treatment.

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IMAGES IN CARDIOLOGY

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False positive massive pulmonary embolus

A 9 year old male child with congenital bilateral superior vena cava (SVC), complete atrioventricular septal defect, double outlet right ventricle, right atrial isomerism, and pulmonary stenosis presented with symptoms of increasing shortness of breath and chest pain. Given that the patient's congenital heart disease is a risk factor for pulmonary embolism, a ventilation perfusion scintigram (V/Q scan) was performed. The initial V/Q scan (left panel) showed global reduction of perfusion of the right lung (posterior image), mismatched with ventilation. Although the appearances are compatible with massive central right pulmonary artery embolism, this clinically seemed surprising, as the patient was relatively asymptomatic. The injection site was noted to be in the left antecubital fossa.

Considering the patient's complex cardiac history, the V/Q examination was repeated 24 hours later. On this occasion the isotope was administered into a right antecubital fossa superficial vein. The repeat study (right panel) revealed a startling change in perfusion pattern with global reduction of perfusion of the left lung with a relatively normal right lung perfusion (posterior image).

Further examination of the patient's medical records revealed that this patient had undergone palliative venous surgery. The right SVC had been anastomosed to the right pulmonary artery and the left SVC into the left pulmonary artery. This case illustrates the importance of knowing the patient's full history before imaging, the technical details of the radiological examination, and the differential diagnosis of asymmetrical lung perfusion.

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