Sex related differences in short and long term prognosis after acute myocardial infarction: 10 year follow up of 3073 patients in database of first Danish verapamil infarction trial

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Abstract

Objective—To re-examine the prevailing hypothesis that women fare worse than men after acute myocardial infarction.

Design—10 year follow up of all patients with confirmed acute myocardial infarction registered in the database of the Danish verapamil infarction trial in 1979–81.

Setting—16 coronary care units, covering a fifth of the total Danish population.

Patients—3073 consecutive patients with acute myocardial infarction, 738 (24%) women and 2335 (76%) men.

Main outcome measures—Early mortality (before day 15). For patients alive on day 15: mortality, cause of death, admission with recurrent infarction, and mortality after reinfarction.

Results—Early mortality increased significantly with age ($P<0.0001$) but was not significantly related to sex, with a 15 day mortality of 17% in women and 16% in men. Adjustment for age and sex simultaneously revealed a significant interaction ($P=0.02$) between these variables, with a greater increase with age in early mortality for men than for women (early mortality was equal for the two sexes at age 64 years). Ten year mortality in patients alive on day 15 was 58.8%. The overall age adjusted hazard ratio (95% confidence interval) for women versus men was 0.90 (0.80 to 1.01); 0.90 (0.78 to 1.04) for 10 year reinfarction (48.8%); and 0.98 (0.82 to 1.16) for 10 year mortality after reinfarction (82.3%). No difference in cause of death was found between the sexes. With a follow up of up to 10 years for patients alive on day 15 mortality, rate of reinfarction, and mortality after reinfarction increased with increasing age ($P<0.0001$).

Conclusion—Sex by itself is not a risk factor after acute myocardial infarction.

Introduction

The prevailing view regarding prognosis after acute myocardial infarction is that women fare worse than men,^{1–6} despite conflicting results regarding this subject before^{1–4} 7–16 as well as after⁵ 6 17–24 the thrombolytic era. Some investigators indicate that higher age and worse baseline variables explain at least part of the excess mortality in women,⁵ 8 10 11 15–17 24 whereas others regard sex as an independent prognostic factor.^{1–3} 6 20 21

There are relatively few large scale studies with more than 2500 patients with acute myocardial infarction, and these have studied mortality only in hospital and up to one year,³ 4 6 17 20 except for one retrospective study with a 12 year follow up.¹⁶

To clarify the nature of the prognosis in the two sexes after acute myocardial infarction we conducted a retrospective analysis of a prospective 10 year follow up

study with 3073 consecutive patients with acute myocardial infarction. We compared the sexes regarding mortality before day 15 and, for patients alive on day 15, mortality, reinfarction rate, and mortality after reinfarction up to 10 years. The causes of death in the sexes were also compared.

Patients and methods

From 1 June 1979 to 15 August 1981, 6631 patients under 76 years of age were consecutively admitted with suspicion of myocardial infarction to one of 16 coronary care units participating in the first Danish verapamil infarction trial.²⁵ The catchment population was about one million—that is, a fifth of the Danish population. In the present study we included 3073 patients with acute myocardial infarction at their first admission to a coronary care unit during the study period (fig 1). A diagnosis of acute myocardial infarction required that the patient was admitted with chest pain compatible with infarction; had electrocardiographic changes with development of Q waves, bundle branch block, or ST segment elevation or depression of at least 0.1 mV lasting for at least 24 hours; and increased activity of cardiac enzymes (lactate dehydrogenase, aspartate transaminase, or total creatinine kinase) to above 50% over upper normal limits.²⁵ 26 Of the patients with definite infarction 1401 were included in the verapamil trial

Fig 1—Numbers of patients registered because of suspicion of myocardial infarction distributed by confirmed and not confirmed acute myocardial infarction; patients with confirmed acute myocardial infarction are distributed by sex and thereafter by surviving or not surviving first 15 days after acute myocardial infarction

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Table 1—Causes of death during 10 year follow up of patients alive on day 15 after acute myocardial infarction. Figures are numbers (percentage) of subjects

Variable	No of patients	No of deaths	Causes of death			
			Acute myocardial infarction	Other cardiac deaths	Non-cardiac deaths	Unknown
Women	612	373	203 (54)	112 (30)	43 (12)	15 (4)
Men	1974	1158	651 (56)	325 (28)	114 (10)	68 (6)
Total	2586	1531	854 (56)	437 (29)	157 (10)	83 (5)

and randomised to 6 months' treatment with verapamil or placebo, whereas the 1672 remaining patients with definite infarction were excluded from that trial for various reasons, mainly because of congestive heart failure, hypotension, or bradycardia.²⁵

Follow up—Follow up time for mortality and reinfarction was about 10 years and up to 10 years with respect to mortality after reinfarction, as follow up related to this end point started at the time of reinfarction. Information on death was obtained from the National Person Registration Office on 1 October 1990. The causes of death were registered from the death certificates and classified as new infarction (*International Classification of Diseases*, eighth revision, code 410), other cardiac death (codes 411-4 and 427-9) and other causes, respectively. Information on admissions with recurrent infarction (code 410) was obtained from the Central County Patient Registry.

Statistical analysis—Survival was calculated according to the Kaplan-Meier method and survival expressed as percentages with 95% confidence intervals. Comparison of event rates in the sexes from day 15 and up to 10 years was done after adjustment for age with the Cox regression model. Mortality and reinfarction curves for the sexes were constructed from the estimated Cox model by using the three ages representing the quartiles. Proportions regarding death before day 15 and causes of death were compared by means of the χ^2 test. The influence of age and sex and the simultaneous influence of the two on mortality before day 15 was analysed with logistic regression analysis. Linearity of age in the Cox regression model as well as in the logistic regression model was checked as described by Thomsen, with three breakpoints for a piecewise linear age function at the 1st, 2nd, and 3rd quartiles of the age distribution.²⁷ The proportional hazard assumption for age and sex was checked by drawing the cumulative hazard as a function of time for different age groups and for the sexes.

Results

No significant difference was found in mortality before day 15 between the sexes. When age and sex were accounted for simultaneously by logistic regression, sex was not in itself associated with short term mortality, but there was an interaction between age and sex, such that the relation between age and short term mortality differed significantly ($P=0.02$) between the sexes. For younger women short term mortality was higher than for younger men as opposed to older women and men. The two sexes had equal short term mortality at age 64 years. No interaction between sex and age was found with respect to long term mortality, reinfarction rate, or mortality after reinfarction. Ten year mortality in patients alive on day 15 was 58.8% (56.9% to 60.8%) with an age adjusted hazard ratio for women versus men of 0.90 (0.80 to 1.01) (figs 2 (top), and 3). The figures for 10 year reinfarction rate were 48.8% (46.6% to 51.0%) and 0.90 (0.78 to 1.04) (figs 2 (middle), and 3); and for 10 year mortality after reinfarction 82.3% (79.3% to 85.3%) and 0.98 (0.82 to 1.16) (figs 2 (bottom), and 3). With a follow up of up to 10 years for

patients alive on day 15 after acute myocardial infarction, mortality, reinfarction rate, and mortality after reinfarction increased with increasing age ($P<0.0001$) (fig 2). No difference in cause of death was found between the sexes (table 1). Women experiencing infarction were older than men (median (range) age 66 (34-78) v 62 (22-81) years; $P<0.0001$).

Age was found to fit the statistical models well as a linear variable. The proportional assumption fitted well for age and sex with respect to long term mortality, reinfarction rate, and mortality after reinfarction.

Discussion

This study indicates that short and long term prognosis after acute myocardial infarction does not differ between the sexes. Our study describes the prognosis after acute myocardial infarction, reflecting natural history as registration of our patients took place at the beginning of the '80s, when treatment of patients with acute myocardial infarction in Denmark was conservative compared with the present treatment of such patients.^{28 29} The worse prognosis for women found in later studies may therefore reflect a less vigorous treatment in women.⁵ We included all patients

Fig 2—Ten year event curves for patients alive on day 15 after acute myocardial infarction constructed from estimated Cox regression models, showing both sexes at three age quartiles. Top—survival; middle—reinfarction rate; bottom—survival after reinfarction

under 76 years of age with acute myocardial infarction, over a period of 26.5 months from 16 coronary care units throughout Denmark, covering a fifth of the total population. Thus, the study population was homogeneous and representative for patients with acute myocardial infarction in the whole community.²⁵ This is in contrast with other studies with a more heterogeneous population,³ a more elective selection process,^{2, 17} or a single hospital or single city catchment population.^{11, 15, 30, 31}

The proportion of women in our study (24%) was similar to that in other studies.^{10, 15} The fact that women with acute myocardial infarction tend to be older than men^{3, 8, 17} is supported by our data. We found that women with acute myocardial infarction are on average four years older than men with acute myocardial infarction. Some investigators suggest that the protecting role of premenopausal oestrogen against ischaemic heart disease explains the later manifestation of acute myocardial infarction in women,³² whereas others regard differences in lifestyle, including smoking habits, to play an important part.³³

Several studies have examined prognosis in the total population and found an excess mortality among women.^{18, 19, 34} Some corrected for the influence of age afterwards, giving conflicting results with respect to sex as an independent prognostic factor.^{2-3, 8, 15, 17, 30, 31} Our data are presented after adjustment for age. Our overall in-hospital and long term mortality and reinfarction rate agree well with results from other studies carried out before thrombolysis was common.^{13, 15, 35}

For both sexes we found no difference in short as well as long term mortality after acute myocardial infarction. Short term mortality increased faster with age in men than in women, however, making the relation between age and short term mortality different in the sexes but not with sex as a prognostic factor in itself. This finding may in part explain the conflicting results regarding the influence of sex on short term mortality in some studies.^{2, 5, 17}

The study by Greenland *et al* with data from the database of the secondary prevention reinfarction Israeli nifedipine study, which in design resembles ours, found a worse prognosis in women even after correction for higher age.³ Their finding was supported by Tofler *et al*.² An important difference from our study, however, is that the patients in those studies were selected from more heterogeneous populations than ours,²⁵ thus Tofler *et al* found that black women particularly had a worse prognosis.²

Our study of over 700 women and over 2300 men shows that women experiencing acute myocardial infarction tend to be older than men and that early mortality, 10 year mortality, reinfarction rate, mortality after reinfarction, or cause of death do not differ between the sexes. In conclusion, this study indicates that sex itself is not an indicator of risk after acute myocardial infarction.

Fig 3—Age adjusted relative risk (95% confidence interval) for women versus men for mortality, reinfarction, and mortality after reinfarction, respectively. Follow up was up to 10 years for patients alive on day 15 after acute myocardial infarction

Key messages

- After acute myocardial infarction women and men have similar short term mortality
- Women and men have similar mortality at 10 year follow up
- Causes of death are not different between the sexes
- Women and men have similar reinfarction rates and similar subsequent mortality
- The prevailing view regarding sex as an independent prognostic factor after acute myocardial infarction may be due to present differences in treatment of women and men, selection bias, and the interpretation of the role of age differences

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Efficacy of a small single dose of oral dexamethasone for outpatient croup: a double blind placebo controlled clinical trial

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Abstract

Objective—To assess the efficacy of a single dose of oral dexamethasone 0.15 mg/kg in children with mild croup not admitted to hospital.

Design—Double blind, randomised, placebo controlled clinical trial.

Setting—The emergency department of a tertiary paediatric hospital.

Subjects—100 children aged 4-122 months presenting with mild croup.

Intervention—A single oral dose of dexamethasone 0.15 mg/kg or placebo.

Main outcome measure—Return to medical care with ongoing croup.

Results—Baseline characteristics of the two treatment groups were similar. Eight children (all from the placebo group) returned to medical care with ongoing croup, one being admitted. There was no reported difference in duration of croup symptoms, duration of viral symptoms, or rate of return to medical care for other reasons.

Conclusion—Oral dexamethasone in a dose of 0.15 mg/kg is effective in reducing return to medical care with ongoing croup in children with mild croup.

Introduction

Croup (acute laryngotracheobronchitis) is one of the more common childhood respiratory illnesses. Children with moderate to severe airway obstruction are traditionally admitted to hospital for observation. Corticosteroids are now often used for children hospitalised with croup, though the role of steroids for children with less severe illness who are not admitted to hospital has not been studied in depth. A survey of 112 paediatricians and family practitioners from the United States showed that 104 used steroids in children hospitalised with croup, though only 48 used steroids "always." By contrast, four used steroids "always" for outpatients whereas 36 "never" used them.¹ Only one study has looked for benefit from steroids in children not hospitalised with croup.² The small numbers in that study suggested but could not show conclusively that steroids were of benefit in preventing reattendance with croup.

A recent study from this hospital showed that both nebulised budesonide and oral dexamethasone (0.6 mg/kg) were more effective than placebo in reducing the duration of hospitalisation, croup scores, and need for nebulised adrenaline more than one hour after hospital admission.³ We subsequently showed that a smaller dose of dexamethasone (0.15 mg/kg) was as effective as 0.3 or 0.6 mg/kg.⁴

Because of the obvious benefits of steroids in children admitted to hospital with croup we proposed that steroids might also benefit children with croup who attend hospital emergency departments but are not admitted. Historically, 1800 to 2000 cases of croup present to our emergency department every year. Three quarters of these children are not admitted, though 10-15% subsequently present to medical care with ongoing croup. We hypothesised that a single oral dose of dexamethasone 0.15 mg/kg would be of benefit to children with milder croup who were not admitted to hospital.

Patients and methods

Children older than 3 months with no other acute or chronic medical problem were eligible for the study if they presented to the emergency department with a diagnosis of croup not severe enough to warrant admission. Croup was defined as the acute onset of inspiratory stridor, chest wall retractions, barking cough, and hoarseness. Generally only children with croup who have stridor and chest wall retractions at rest are admitted to our hospital, those with milder illness being discharged home at the discretion of medical staff. Children were excluded if their families did not have a telephone or had limited English; if they had received steroids of any description in the preceding week; or if they had a pre-existing upper airway condition, a history of prolonged stridor, or a clinical picture suggesting a diagnosis other than croup. Informed written consent was obtained from parents and the study approved by the hospital's ethics committee.

After enrolment the parents completed a questionnaire asking about current and past episodes of croup. Croup score (see box), pulse rate, and respiratory rate at presentation were recorded together with arterial oxygen saturation from a finger probe in room air by

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