
P. Abrahamsson, A. Rosengren and M. Dellborg
Department of Medicine, Sahlgrenska University Hospital/Östra, Göteborg, Sweden

Aims A more aggressive approach to unstable coronary syndromes has developed over the last decade. We set out to examine the long-term outcome among patients with acute coronary syndromes with respect to period of admission since 1988.

Methods 3918 patients with unstable angina or a non-Q wave myocardial infarction who were admitted to the coronary care unit at Östra Hospital in the period 1988–1997 were included. Standardized criteria were used to define a non-Q wave myocardial infarction and included fulfilment of the following: (1) typical enzyme changes (serial serum aspartate aminotransferase above 0.7 μkat·l⁻¹, serial creatine kinase above 3.3 μkat·l⁻¹ or serial creatine kinase MB subunit mass concentration above 15 μg·l⁻¹), and at least one of the following: (2) chest pain, shock, syncope or pulmonary oedema suggestive of a myocardial infarction, (3) development of electrocardiographic changes with serial ST-T changes without Q waves. The standardized criteria for unstable angina pectoris were fulfilment of at least one of the following: (1) a clear worsening of a previous stable pattern of angina pectoris, (2) chest pain at rest or minimal effort with transient ST-segment elevation or depression on electrocardiogram or elevation of cardiac enzymes not reaching the criteria for myocardial infarction. Information on vital status and cause of death after discharge was collected from the national cause-specific mortality register.

Results Two-year mortality decreased from 30% in 1988 to 19% in 1995 (relative risk per year 0.94 (0.90–0.97), 95% confidence interval). The improvement was consistent regardless of differences in age, prior myocardial infarction, diabetes mellitus, hypertension, development of non-Q wave myocardial infarction, treatment with heparin or thrombolytics or performance of acute coronary angiograms. The cumulative survival at 10 years was 53% in the unstable angina group and 36% in the non-Q wave myocardial infarction group (P<0.0001).

Conclusion Against a background of a more aggressive approach to acute coronary syndromes a decrease in long-term mortality is seen between 1988 and 1995.

Key Words: Unstable angina pectoris, acute myocardial infarction, prognosis.

Introduction

The acute coronary syndromes represent a wide spectrum of conditions from worsening of a previously stable pattern of angina pectoris to acute myocardial infarction. These conditions probably share a similar pathogenic pattern i.e. the disruption of an unstable coronary atherosclerotic plaque leading to the formation of a thrombus that will partially or totally occlude the vessel[1–3]. From previous reports we have learned that patients with unstable angina suffer a 1-year mortality of 2%–18% and have a 7%–21% risk for developing a myocardial infarction within 1 year[4–6]. Results from long-term follow up are scarce but in one study at least a comparatively favourable prognosis was reported (76% survivors after 7 years)[7].

Therapy in acute coronary syndromes has changed over the last decade. In the 1980s aspirin and oral beta-blockers were introduced. During the 1990s heparin, and later on low molecular forms of heparin came into use. Acute coronary interventions are increasingly being used and recently the GP IIb/IIIa blockers have come into clinical use. The aim of the present study was to assess the long-term outcome since 1988 for patients with acute coronary syndromes against a background of changed therapeutic strategies.
Methods

Östra Hospital is a University Hospital with 900 beds of which 174 are in the Department of Medicine. The catchment area of the hospital is the northern and eastern part of Gothenburg, with a population of 250,000. The coronary care unit currently has eight beds (six before 1991). All beds have an electrocardiographic monitoring system. There is a step down unit connected to the coronary care unit. Patients seen in the emergency room with chest pain of suspected cardiac origin, are transferred to the coronary care unit. Patients may also be admitted to the coronary care unit directly from the ambulance if there is a strong suspicion of ongoing myocardial ischaemia during transport. However, this option was not present until 1988 and only in the daytime until 1991. If the chest pain is presumed to be non-cardiac or if there is only a weak suspicion of cardiac disease, the patient is transferred from the emergency room to an observation unit with monitored beds. In case of recurrent pain, arrhythmia, heart failure or elevation of cardiac enzymes the patient will be transferred to the CCU. There are no age limits for admittance to the CCU.

Since 1984 information on all admissions to the coronary care unit and the step down unit has been collected in a standardized manner with respect to previous history, symptoms and signs, prescribed treatment, diagnoses and vital status at discharge, and stored in a computerized database. Information is collected by the coronary care unit nurses during the hospital stay, and checked afterwards by specially assigned assistants. One physician is responsible for checking and analysing the database. This database now contains more than 21,000 records.

The present study was performed retrospectively. 3918 patients who were admitted to the coronary care unit at Östra Hospital in the period 1988–1997 with a diagnosis of non-Q wave myocardial infarction or unstable angina according to the standardized criteria were included. All patients were followed until death or 31 December 1997, and 3203 patients could be followed for at least 2 years. The patients were only included once, i.e. readmission during the investigation period was not considered a new case. Information on previous history, treatment and date and cause for in-hospital deaths was collected from the coronary care unit database. The criteria used to define a non-Q wave myocardial infarction included fulfilment of the following: (1) typical enzyme changes (serial serum-aspartate-aminotransferase above 0.7 µkat l⁻¹, serial creatine kinase above 3.3 µkat l⁻¹ or serial creatine-kinase Mb subunit mass concentration above 15 µg l⁻¹), and at least one of the following: (2) chest pain, shock, syncope or pulmonary oedema suggestive of a myocardial infarction, (3) development of electrocardiographic changes with serial ST-T changes without Q waves. The standardized criteria for unstable angina pectoris were fulfillment of at least one of the following: (1) a clear worsening of a previous stable pattern of angina pectoris, (2) chest pain at rest or minimal effort with transient ST-segment elevation or depression on the electrocardiogram, or elevation of cardiac enzymes not reaching the criteria for myocardial infarction. The diagnoses unstable angina pectoris and non-Q wave myocardial infarction were set at discharge. History of prior myocardial infarction, angina pectoris, diabetes and hypertension was defined as a doctor’s diagnosis of these conditions. Information on vital status and cause of death after discharge was collected from the national cause-specific mortality register.

Statistics

For statistical analyses we used the SPSS software. The impact of year of admission on 2-year mortality was assessed by logistic regression and included the 3203 patients who could be followed for at least 2 years. The Cox backward conditional model performed multivariate analysis of indicators of risk for death including treatment and year of admission and comprised all 3918 patients included until 31 December 1997. The Kaplan-Meier survival function was used and subgroups were compared by the log rank test.

Results

A total of 3918 patients with unstable angina pectoris or a non-Q wave myocardial infarction — 2612 men and 1306 women — 2419 with a non-Q wave myocardial infarction and 1499 with unstable angina pectoris, admitted to the coronary care unit during 1988–1997 were included in the study. The average age on admission was 69 years (SD=11 years).

Baseline characteristics with respect to age and sex distribution, prevalence of myocardial infarction, diabetes, hypertension and smoking were similar for patients admitted 1988–1995 (Table 1). With time, therapy was intensified in terms of use of heparin, intravenous beta-blockade and intravenous nitroglycerin. Acute coronary angiograms were increasingly being performed. The number of acute non-Q wave myocardial infarctions decreased as the number of patients with unstable angina pectoris increased between 1988 and 1995.

Patients who were admitted between 1993 and 1995 had a better 2-year survival than patients admitted between 1988 and 1990 (cumulative survival 80% vs 74%, P=0.001, Fig. 1).

Two-year mortality decreased from 30% in 1988 to 19% in 1995 (RR 0.94 (0.90–0.97) per year, 95% confidence interval) (Table 2). The presence of improvement was consistent in all age groups and was not influenced by prior myocardial infarction, diabetes, or hypertension, or whether the final diagnosis was myocardial infarction or unstable angina pectoris. Improvement was not quite significant among women (RR 0.94
(0.89–1.003), 95% confidence interval). Among patients who were smokers no improvement was found. When compared multivariately, the period of acute coronary care played an independent role in long-term mortality (Table 3). Furthermore, the use of heparin, thrombolitics and acute coronary angiogram were independently associated with improved outcome. Smoking, diabetes, prior myocardial infarction, increasing age and male sex were associated with a worse long-term outcome.

**Discussion**

The main finding in the present study was that long-term prognosis measured as 2-year survival in patients with unstable coronary artery disease i.e. unstable angina pectoris or non-Q wave myocardial infarction improved between 1988 and 1995.

The explanation for the improvement is not fully clear. Over the period the use of heparin, mostly
fractionated, increased (Table 1). The beneficial effect of heparin, low molecular or fractionated, in unstable coronary syndromes is well documented from earlier studies[8-11], but this could not fully explain the improved prognosis over the investigated period. In a multivariate analysis, use of heparin was associated with better outcome, but the impact of the period of coronary care was independent of the use of heparin.

Acute phase coronary angiograms were more frequently performed over the period. There are no available data regarding the frequency of coronary interventions during follow-up, but an acute phase coronary angiogram indicated the need for a revascularization procedure. The results from prior studies, regarding early coronary interventions in unstable coronary syndromes, vary from a harmful or neutral effect to an

Table 2  Two-year mortality, n (%), after an episode of unstable angina pectoris or non-Q wave myocardial infarction for 3203 patients admitted 1988–1995

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Total n (%)</td>
<td>137 (30)</td>
<td>95 (25)</td>
<td>76 (22)</td>
<td>86 (22)</td>
<td>118 (28)</td>
<td>96 (23)</td>
<td>78 (19)</td>
<td>70 (19)</td>
<td>0.94 (0.90–0.97)</td>
</tr>
<tr>
<td>Age &lt;65 years</td>
<td>21 (14)</td>
<td>11 (8.5)</td>
<td>11 (8.5)</td>
<td>13 (9.7)</td>
<td>10 (8.5)</td>
<td>7 (5.3)</td>
<td>7 (4.8)</td>
<td>9 (6.8)</td>
<td>0.87 (0.79–0.96)</td>
</tr>
<tr>
<td>65–75 years</td>
<td>46 (27)</td>
<td>29 (22)</td>
<td>26 (20)</td>
<td>23 (19)</td>
<td>35 (24)</td>
<td>24 (18)</td>
<td>22 (18)</td>
<td>19 (17)</td>
<td>0.94 (0.88–0.998)</td>
</tr>
<tr>
<td>≥75 years</td>
<td>70 (47)</td>
<td>55 (46)</td>
<td>38 (42)</td>
<td>50 (40)</td>
<td>73 (44)</td>
<td>65 (43)</td>
<td>49 (34)</td>
<td>34 (29)</td>
<td>0.92 (0.87–0.97)</td>
</tr>
<tr>
<td>Sex Male</td>
<td>93 (29)</td>
<td>66 (25)</td>
<td>56 (22)</td>
<td>55 (22)</td>
<td>71 (25)</td>
<td>62 (22)</td>
<td>46 (18)</td>
<td>48 (19)</td>
<td>0.93 (0.89–0.97)</td>
</tr>
<tr>
<td>Female</td>
<td>44 (31)</td>
<td>29 (25)</td>
<td>20 (21)</td>
<td>31 (23)</td>
<td>47 (35)</td>
<td>34 (25)</td>
<td>32 (21)</td>
<td>22 (18)</td>
<td>0.94 (0.89–1.003)</td>
</tr>
<tr>
<td>Prior MI No</td>
<td>64 (23)</td>
<td>56 (23)</td>
<td>35 (16)</td>
<td>45 (19)</td>
<td>53 (21)</td>
<td>46 (17)</td>
<td>46 (17)</td>
<td>46 (17)</td>
<td>0.95 (0.91–0.998)</td>
</tr>
<tr>
<td>Yes</td>
<td>73 (39)</td>
<td>39 (29)</td>
<td>41 (30)</td>
<td>41 (28)</td>
<td>65 (38)</td>
<td>50 (33)</td>
<td>32 (22)</td>
<td>24 (22)</td>
<td>0.93 (0.88–0.98)</td>
</tr>
<tr>
<td>Diabetes mellitus No</td>
<td>98 (25)</td>
<td>71 (23)</td>
<td>61 (21)</td>
<td>69 (21)</td>
<td>83 (24)</td>
<td>68 (19)</td>
<td>59 (17)</td>
<td>55 (18)</td>
<td>0.94 (0.90–0.98)</td>
</tr>
<tr>
<td>Yes</td>
<td>39 (51)</td>
<td>24 (34)</td>
<td>15 (25)</td>
<td>17 (35)</td>
<td>35 (46)</td>
<td>28 (43)</td>
<td>19 (28)</td>
<td>15 (23)</td>
<td>0.92 (0.85–0.99)</td>
</tr>
<tr>
<td>Hypertension No</td>
<td>77 (26)</td>
<td>56 (23)</td>
<td>51 (22)</td>
<td>51 (20)</td>
<td>68 (25)</td>
<td>65 (23)</td>
<td>46 (17)</td>
<td>49 (19)</td>
<td>0.95 (0.91–0.99)</td>
</tr>
<tr>
<td>Yes</td>
<td>60 (35)</td>
<td>39 (30)</td>
<td>25 (22)</td>
<td>35 (28)</td>
<td>50 (34)</td>
<td>31 (24)</td>
<td>32 (23)</td>
<td>21 (18)</td>
<td>0.92 (0.87–0.97)</td>
</tr>
<tr>
<td>Smoking No</td>
<td>100 (30)</td>
<td>86 (31)</td>
<td>63 (25)</td>
<td>70 (26)</td>
<td>89 (30)</td>
<td>77 (26)</td>
<td>57 (20)</td>
<td>48 (19)</td>
<td>0.92 (0.89–0.96)</td>
</tr>
<tr>
<td>Yes</td>
<td>37 (27)</td>
<td>9 (8.8)</td>
<td>13 (12)</td>
<td>14 (16)</td>
<td>29 (23)</td>
<td>19 (16)</td>
<td>21 (17)</td>
<td>22 (19)</td>
<td>0.99 (0.92–1.06)</td>
</tr>
<tr>
<td>NQWMI No</td>
<td>116 (36)</td>
<td>77 (30)</td>
<td>59 (30)</td>
<td>68 (28)</td>
<td>97 (34)</td>
<td>69 (27)</td>
<td>64 (27)</td>
<td>59 (28)</td>
<td>0.96 (0.92–0.996)</td>
</tr>
<tr>
<td>UAP</td>
<td>21 (15)</td>
<td>18 (14)</td>
<td>17 (11)</td>
<td>18 (13)</td>
<td>21 (15)</td>
<td>27 (16)</td>
<td>14 (8.1)</td>
<td>11 (6.8)</td>
<td>0.93 (0.86–0.97)</td>
</tr>
</tbody>
</table>

NQWMI=Non-Q wave myocardial infarction; UAP=Unstable angina pectoris.

Table 3  Probability of death in 1988 to 1997* after an episode of unstable angina pectoris or a non-Q wave myocardial infarction by year of admission, age, sex, prior myocardial infarction, diabetes mellitus, hypertension, smoking, non-Q wave myocardial infarction, nitroglycerin infusion, heparin treatment, thrombolytic therapy and acute coronary angiogram

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unadjusted relative risk of death (95% confidence interval)</th>
<th>Adjusted relative risk of death (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute coronary angiogram (yes vs no)</td>
<td>0.25 (0.16–0.37)</td>
<td>0.47 (0.31–0.71)</td>
</tr>
<tr>
<td>Heparin (fractionated or unfractionated) (yes vs no)</td>
<td>0.58 (0.47–0.70)</td>
<td>0.72 (0.58–0.89)</td>
</tr>
<tr>
<td>Thrombolytic therapy (yes vs no)</td>
<td>0.65 (0.55–0.76)</td>
<td>0.81 (0.68–0.95)</td>
</tr>
<tr>
<td>Female sex (vs male)</td>
<td>1.19 (1.07–1.33)</td>
<td>0.88 (0.79–0.98)</td>
</tr>
<tr>
<td>Period of coronary care (per year 1988–1997)</td>
<td>0.96 (0.94–0.98)</td>
<td>0.97 (0.94–0.99)</td>
</tr>
<tr>
<td>History of hypertension (yes vs no)</td>
<td>1.24 (1.12–1.38)</td>
<td>1.07 (0.96–1.19)</td>
</tr>
<tr>
<td>Age (per year)</td>
<td>1.08 (1.05–1.12)</td>
<td>1.08 (1.05–1.09)</td>
</tr>
<tr>
<td>Smoking (yes vs no)</td>
<td>0.69 (0.61–0.78)</td>
<td>1.29 (1.14–1.47)</td>
</tr>
<tr>
<td>Prior myocardial infarction (yes vs no)</td>
<td>1.66 (1.45–1.85)</td>
<td>1.45 (1.31–1.61)</td>
</tr>
<tr>
<td>Diabetes mellitus (yes vs no)</td>
<td>1.82 (1.61–2.06)</td>
<td>1.74 (1.54–1.97)</td>
</tr>
<tr>
<td>Nitroglycerin infusion (yes vs no)</td>
<td>0.96 (0.86–0.97)</td>
<td></td>
</tr>
</tbody>
</table>

*In the Cox regression model patients 3918 patients admitted until 1997 were included.
impressive beneficial effect, as a result of early invasive strategies\cite{12-17}. It is possible that the increasing use of acute angiograms in the present study played a role in the improved long-term prognosis. However, again, it may only explain some of the improvement since the multivariate analysis showed that the period of coronary care as well as the acute coronary angiograms played an independent prognostic role.

Over the period 1988–1995 infarcts became less common and unstable angina more prevalent. The explanation is unclear but since the diagnoses were set at discharge it is possible that improving in-hospital treatment of unstable patients would, to a large extent, prevent development of a myocardial infarction. Thus, in-hospital course may have played a role in the change in distribution between unstable angina pectoris and non-Q wave myocardial infarction seen between 1988 and 1995. Nevertheless an improved long-term prognosis was found among unstable angina patients as well as among non-Q wave myocardial infarct patients.

About one third of the patients were women throughout the period. The magnitude of the decline in mortality among the women was about equal to that of the men but the trend did not quite reach statistical significance. Males on the other hand had a clear declining 2-year mortality, even though the multivariate analysis indicated that male gender was independently associated with worse outcome. Gender differences have been assessed previously over a shorter time frame. From a 6-week follow-up of unstable coronary syndromes it was reported that gender differences could be explained by co-morbidity and age\cite{19}. On the other hand men had significantly more three-vessel disease and a significantly lower ejection fraction, which could mimic the present results.

Approximately 30\% of the patients were smokers. Smoking was associated with higher mortality independent of age, gender, period of coronary care and other risk indicators. The prognosis among smokers seemed not to have improved during the investigated period. No firm conclusions can be drawn from a subgroup; however, one may speculate that the possibly beneficial changes in treatment seen over the period were not beneficial to a similar extent among smokers and non-smokers. In the FRISC trial, use of low molecular weight heparin seemed to have a lower influence on risk of death or myocardial infarction among smokers in the acute phase as well as long-term\cite{18}.

Lipid lowering among patients with elevated serum-cholesterol levels\cite{19–23} and aspirin are proven therapies for secondary prevention of coronary heart disease\cite{24–27}. During the investigated period 1988–1995 the use of aspirin and lipid lowering drugs, particularly statins, increased in the coronary care unit at Östra hospital but unfortunately detailed data on the use of these drugs are lacking. Increasing use of aspirin may have affected the long-term outcome with time in the present study.

It was not until the presentation of the results from the Scandinavian Simvastatin study in 1994 that the use of lipid lowering therapy was increased at the Östra hospital CCU\cite{20}. It is unlikely that increasing the use of statins after 1994 would have played a role in the declining 2-year mortality between 1988 and 1995.

Data from the Göteborg population studies showed a reduction in serum cholesterol levels and blood pressure in men between 1963 and 1990, resulting in declining risk for coronary heart disease\cite{23}. It is possible that the declining 2-year mortality seen in the present study was affected by similar changes in the risk-profile of our population.

Exact information on the post discharge use of oral beta-blockers is lacking. Even though there are no data indicating that oral beta-blockers were used differently throughout the period it is possible that therapeutic changes, with respect to oral beta-blockers, took place and helped to improve outcome.

It is unlikely that the declining 2-year mortality could be explained by changes in age profile, sex distribution or the presence of prior myocardial infarction, diabetes mellitus, hypertension or smoking. Age distribution varied little between 1988 and 1995, and a declining mortality was seen in all age categories. Even though there was no significant change in 2-year mortality among women and smokers, the percentage of women and smokers was unchanged throughout the investigation period and thus would not affect the overall positive trend. The prevalence of diabetes mellitus and hypertension was unchanged but the prevalence of prior myocardial infarction declined slightly. However, the 2-year prognosis improved over the period regardless of the presence of these conditions.

The mechanics of detecting myocardial ischaemia also probably improved over the investigated period. A better biochemical marker, Troponin-T, came into use and the technique of continuous ST-segment monitoring developed. It is possible that we were able to detect unstable coronary syndromes with less pronounced signs of ischaemia later in the period. Therefore it is possible that the later patients were at lower risk than the earlier ones, which may have biased outcome in a positive direction later in the period. However, among other factors, early reperfusion therapy improved our management of myocardial infarctions at least up to 1993\cite{29} possibly placing an increasing number of ST-elevation myocardial infarctions into the non-Q wave group. This theory is supported by the fact that 43\% of all infarct patients admitted to the CCU at Östra hospital in 1988 developed a Q wave compared to only 35\% in 1997. Therefore the investigated population may have been at increased risk later in the period, or better infarct care may have unbalanced the bias afforded to the improving diagnostic tools.

Independent of increasing use of heparin, acute phase coronary angiograms and an increasing proportion of unstable angina patients in the population, there was an improved prognosis from 1988 to 1997. The explanation for this improvement is not clear. A contribution from many factors such as therapeutic changes, more frequent use of invasive strategies, better diagnostic tools such as
outcome.

angioplasty and bypass surgery after discharge remains vital status and cause of death. The impact of coronary investigated population.

which may have played a role in the outcome of the change over the period, it is possible that there may have though the criteria for admission to the CCU did not CCU or the step down unit remains unclear. Even with unstable coronary syndromes treated outside the unit were included. The long-term course of patients hospital.

Eur Heart J, Vol. 21, issue 7, April 2000


do not influence outcome.

Conclusion

Two-year mortality among patients with unstable angina pectoris or non-Q wave myocardial infarction decreased between 1988 and 1995. Heparin during the acute phase, thrombolytics and early coronary angiogram were associated with an improved outcome, however, other factors have played a role in the improved long-term prognosis. The positive time trend was independent of the use of heparin, thrombolytics, acute phase angiogram, age and gender differences and prevalence of prior myocardial infarctions, hypertension and diabetes mellitus.

Limitations

The present study is a retrospective analysis of prospectively collected data from the CCU database at Ostra hospital. Only patients admitted to the CCU or the step down unit were included. The long-term course of patients with unstable coronary syndromes treated outside the CCU or the step down unit remains unclear. Even though the criteria for admission to the CCU did not change over the period, it is possible that there may have been minor changes in admission policy over the period which may have played a role in the outcome of the investigated population.

Information on post discharge course is limited to vital status and cause of death. The impact of coronary angioplasty and bypass surgery after discharge remains unclear. Post discharge medication is not known from our data.

References


Eur Heart J, Vol. 21, issue 7, April 2000


