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Long-term mortality after first Acute Myocardial Infarction in the light of changing therapeutic guidelines and diagnostic criteria between 1995 and 2003: Analysis of the MONICA/KORA Coronary Event Registry, Augsburg, Southern Germany

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To my mother

and

in commemoration of my father.

Contents

List of abbreviations

ACC	-	American College of Cardiology
ACE-inhibitors	-	Angiotensin-converting enzyme inhibitors
AMI	-	acute myocardial infarction
BMI	-	body mass index
CABG	-	coronary artery bypass grafting
CER	-	coronary event registry
CHD	-	coronary heart disease
CI	-	confidence interval
CKMB	-	creatine kinase myocardial band
ECG	-	electrocardiogram
ESC	-	European Society of Cardiology
HR	-	hazard ratio
ICD	-	international classification of disease
KORA	-	Cooperative Health Research in the region of Augsburg
LDL	-	low density lipoprotein
MONICA	-	MONitoring of trends and determinants in CArdiovascular disease
PCI	-	percutaneous coronary intervention
PYRS	-	person years

1. Introduction

1.1 General introduction

Coronary heart disease is the leading cause of death world wide. 3.4 million women and 3.8 million men die each year from Coronary Heart Disease (CHD). Major risk factors are high blood pressure, high blood cholesterol, smoking, physical inactivity, unhealthy diet, diabetes, advancing age, male sex and genetic disposition (Niccoli, Iacoviello et al. 2001; Yusuf, Reddy et al. 2001; Yusuf, Reddy et al. 2001). A decline in death rates from CHD over the past decades has been reported for North America and many western European countries. Improved prevention, diagnosis and treatment are thought to be responsible for this decrease (Rosamond, Folsom et al. 2001; Fox, Evans et al. 2004; Unal, Critchley et al. 2004; Fox, Steg et al. 2007). The present study examines the effect of new treatment strategies for **A**cute **M**yocardial **I**nfarction (AMI) on long-term survival after a first AMI from the KORA Coronary Event Registry (WHO-MONICA Project/KORA-Initiative) (Lowel, Lewis et al. 1991) in the region of Augsburg, Southern Germany.

1.2 Background

1.2.1 Definition and symptoms of **A**cute **M**yocardial **I**nfarction

AMI usually develops on the basis of atherosclerosis in the coronary arteries. Inflammation leads to the rupture of atherosclerotic plaques, a process that causes stenosis of the coronary arteries which supply the heart muscle with

the oxygen that it needs to work properly. Depending on the degree of stenosis, the reduced blood flow may cause conditions from angina pectoris without damage of the myocardium to acute myocardial infarction with myocardial necrosis or even sudden cardiac death. AMI is defined as necrosis of myocardial tissue due to reduced or missing blood flow in the coronary arteries which leads to oxygen deficiency in the heart muscle.
Patients with AMI present with symptoms like long lasting thoracic pain (angina pectoris) which is not relieved through rest or the application of nitro-glycerine, ventricular arrhythmia, feelings of fear and feebleness and vegetative symptoms like shortness of breath, nausea, sweating, vomiting and others. Blood pressure is often low, but high or normal pressure is possible as well. About one third of the patients show symptoms of a left ventricular insufficiency.

1.2.2 Diagnostic criteria

Until recently medical doctors used differing definitions of myocardial infarction depending on whether their emphasis was on clinical, electrocardiographic, biochemical or pathologic characteristics of AMI. Neither the ECG nor the clinical history has the sensitivity or specificity to diagnose all myocardial infarctions correctly (White 2008). The WHO MONICA (MONitoring trends and determinants of CArdiovascular disease) definition of acute myocardial infarction was based on typical symptoms (e.g. chest pain), electrocardiographic changes corresponding to myocardial necrosis and elevation of serum enzymes, especially CKMB (creatine kinase myocardial band). The combination of two out of these three characteristics led to the

diagnosis “AMI” until new diagnostic criteria were established. In the year 2000 the European Society of Cardiology (ESC) and the American College of Cardiology (ACC) published a consensus document for the redefinition of myocardial infarction (The Joint European Society of Cardiology/ American College of Cardiology Committee 2000).

With the introduction of cardiac troponins T and I as indicators of myocardial necrosis the sensitivity and specificity of serologic biomarkers increased, because troponins are specific for myocardial tissue and even microscopic necrotic lesions in the myocardium lead to the detection of increased troponin levels in the serum. More precise imaging techniques also facilitate the discovery of microscopic areas of myocardial necrosis. As a consequence the consensus conference proposed that “any amount of myocardial necrosis caused by ischemia should be labelled as an infarct” (The Joint European Society of Cardiology/ American College of Cardiology Committee 2000). The new definition of myocardial infarction was published by the conference in the year 2000 and is cited here:

“Either one of the following criteria satisfies the diagnosis for an acute, evolving or recent MI:

1. Typical rise and gradual fall (troponin) or more rapid rise and fall (CKMB) of biochemical markers of myocardial necrosis with at least one of the following:

a) ischemic symptoms;

b) development of pathologic Q waves on the ECG;

c) ECG changes indicative of ischemia (ST segment elevation or depression); or

d) coronary artery intervention (e.g., coronary angioplasty).

2. Pathologic findings of an acute MI.”

The modification of the definition of AMI was expected to lead to an increase in the identification of cases of AMI due to the higher sensitivity and to the reduction of missed cases due to the increased specificity.
The introduction of the new definition of AMI in the clinical routine poses a problem for epidemiologic research and Coronary Event Registries in principle though. A change in definition causes incomparability of data from before the change with data afterwards. The Coronary Event Registry (CER) Augsburg continued to use the WHO-MONICA criteria of AMI definition to secure the comparability throughout the years. In the year 2001 the CER started to document the troponin values, but troponin was not included in the algorithm to derive the AMI cases. The influence of the new definition on the CER cannot completely be avoided, because clinicians started to use the new definition of AMI, which eventually led to change in the composition of the patient population presented for selection to the registry. The influence of these changes is one topic of the present work.

1.2.3 Treatment of AMI

The Task Force on the Management of Acute Myocardial Infarction of the European Society of Cardiology published their report in the year 2002 with new recommendations for the treatment of AMI (The Task Force on the Management of Acute Myocardial Infarction of the European Society of Cardiology, Van de Werf et al. 2003). Three phases of treatment with three different aims have to be considered. In the first phase of the acute event the relief of pain, breathlessness and anxiety are predominantly warranted. Intravenous opioids, the application of oxygen and eventually β-blockers or

nitrates and tranquillizers are given to reach this primary goal. The second phase consists in the restoration of coronary flow and myocardial tissue reperfusion either still in the pre-hospital or in the early in-hospital setting under the condition that no contraindications exist. Mechanical or pharmacological reperfusion can be distinguished. Percutaneous coronary intervention (PCI) with or without stent implantation is the mechanical reperfusion treatment and must be divided into primary PCI, PCI combined with pharmacological reperfusion and “rescue PCI” when pharmacological reperfusion failed. Coronary artery bypass surgery is rarely needed in the acute phase of myocardial infarction, but may be performed if PCI is contraindicated or failed to achieve reperfusion or caused another occlusion during catheterization. Fibrinolytic reperfusion treatment is performed with activators of fibrinolysis like streptokinase and tissue plasminogen activator or anistreplase. A short time to treatment is required for all types of reperfusion to obtain the lowest possible mortality and re-infarction rate.

The third phase of treatment comprises the secondary prevention to avoid re-infarction and death. Apart from changes in life style like cessation of smoking, moderate physical activity, healthy diet and optimal control of blood sugar in diabetic patients, pharmacological treatment is necessary. Clinical trials have shown that anticoagulants and antiplatelet medication, like low-dose aspirin, and β-blockers are effective in preventing re-infarction and death. Antipatelets and anticoagulants prevent the formation of new blood clots which could lead to renewed occlusion of the coronary arteries. β-blockers help to control blood pressure in hypertensive patients. In addition to these established medications Angiotensin-converting enzyme inhibitors (ACE-inhibitors) and lipid lowering agents, especially statins are now recommended as secondary prevention

treatment. ACE-inhibitors are known to reduce remodelling processes of the heart, which could lead to an expansion of the infarction scar and to the hypertrophy and dilatation of the left ventricle (Herold 2007). Lipid-lowering agents should be prescribed if the total cholesterol level is greater than 190 mg/dl and/or the Low-Density-Lipoprotein (LDL) cholesterol level is greater than 115 mg/dl (The Task Force on the Management of Acute Myocardial Infarction of the European Society of Cardiology, Van de Werf et al. 2003). The treatment of AMI has changed considerably during the last decades. Before the publication of the new treatment recommendations the application of PCI was done in cardiologic centres and pharmacological fribrinolysis played a more significant role in the treatment of AMI patients. With the establishment of the effectiveness of PCI treatment it became obvious that the more widespread use of the method was warranted and the acquirement of knowledge, practice and facilities in more hospitals was successfully promoted.

1.2 Aims of the present study

The change of diagnostic criteria of AMI led to an increase of AMI diagnoses (White 2008) on the clinical level. The registry continued to use the WHO criteria for myocardial infarction and classified the additionally diagnosed AMIs either as definite or possible AMI. It is hypothesized that the composition of the two categories has changed in respect of the number of cases and the type of infarction. Therefore the present study describes how the change of diagnostic criteria in the clinical setting affects the numbers and types of registered events over the course of the years 1995 through 2003 at the CER Augsburg.

The application of invasive and pharmacological treatments over the years is documented in the CER. The changes in treatments of patients with AMI and the implementation of the new treatment recommendations will be assessed. The main question of interest though is to examine the long-term mortality and re-infarction rate over time in the light of the changed diagnostic criteria and therapeutic guidelines. Therefore the mortality and re-infarction rates will be compared between patients who were registered between 1995 and 1999 and patients who were registered between 2000 and 2003 with a first myocardial infarction.

2. Material and methods

2.1 Study population and study design

The Coronary Event Registry (CER) Augsburg was founded in 1984 in the context of the WHO MONICA studies to assess the incidence of myocardial infarctions in southern Germany. Since then the Coronary Event Registry has aimed to register every case of non-fatal myocardial infarction and fatal coronary death (WHO MONICA Project Principal Investigators 1988; Lowel, Lewis et al. 1991). The MONICA project ended in 1995, but the CER was continued as part of the KORA (Cooperative Health Research in the Region of Augsburg) initiative. The CER is located in the main hospital of Augsburg (Augsburg Central Hospital) and registers persons with myocardial infarction who are between 25 and 74 years old and are residents of the city of Augsburg or the two adjacent counties of “Aichach/Friedberg” and “Augsburg”.

In the year 2000 approximately 200 000 men and 202 000 women between 25 and 74 years were living in the study area.

All cases of AMI that occurred over the study period were followed up with respect to survival until 31st of December 2005. Recurring AMI events were linked to the individual. The present study is conducted as a cohort study with AMI as index event and mortality as well as re-infarction as outcome.

2.2 Case finding and data collection

To ascertain recording of subjects surviving the index event for at least 24 hours, trained nurses from the CER routinely checked the admission books from emergency room, intensive care unit and cardiac wards in the Hospital of Augsburg on a daily basis for coronary events. Physicians on cardiac wards in the eight other hospitals in the study area were called by phone at least once a week and asked for hospitalized AMI cases under their care. A list of suspected coronary event cases was created by the nurses and replaced by a list of confirmed cases when the treating physicians were contacted and confirmed the diagnosis. The final decision on the AMI diagnosis for the CER was not based on the clinical diagnosis but an algorithm that combined the information gathered from different sources (see 2.3). Patients with a clinically confirmed diagnosis of AMI were asked to participate in the Coronary Event Registry. In case of their informed consent a standardized interview was conducted by a trained nurse three or four days after the acute event. Questions were asked about their socio-demographic characteristics, the acute event, their family history, their medical history, medication and coronary risk factors. Information on diagnostic measures, treatment and medication

during hospitalization was derived through a concluding hospital chart review by means of a standardized protocol. All data were fed into the computer including the ICD codes of discharge diagnoses.

2.3 Case definition of the index event

All non-fatal *definite* incident cases of myocardial infarction, which were registered between 1995 and 2003 in the CER were included (index event) in the study presented here. The definition of non-fatal was based on a 28 day survival criterion. Incident cases are subjects that have not had a previous AMI. The three MONICA diagnostic criteria are acute chest pain, which lasts for more than twenty minutes and is resistant to treatment with nitrates, elevated heart muscle specific enzymes (either creatinine phosphokinase or aspartate aminotransferase or lactate dehydrogenase) to more than twice the upper limit of normal enzyme levels and typical ECG changes. AMIs were divided into four different categories. A *definite* case of AMI existed, if ECG changes showed transmural infarction or if ECG changes were typical for posterior or anterior infarction, typical symptoms (any pain or pressure, tightness or burning sensation in the chest with a duration of more than 20 minutes) were reported and enzymes showed double elevation, or if ECG was missing, but symptoms were typical and enzymes were doubled. A case of AMI was considered as *possible* AMI if typical symptoms were reported, ECG changes showed anterior or posterior infarction or ECG was missing and the enzymes were unspecific, normal, doubtful, not complete or had not been determined. The other two categories are ischemic AMI and insufficient data, which both were excluded from the analysis.

2.4 Definitions and formation of variables

Age was calculated as age in years at the time of the event and grouped in ten year classes (25 to 34, 35 to 44, 45 to 54, 55 to 64 and 65 to 74 years). Registration ended with the 75th birthday of a person.

The area of residence was divided into “urban” for persons who live in Augsburg city and “rural” for persons who live in either county Aichach/Friedberg or Augsburg.

In the interview patients reported about the type of school they visited and the highest degree they obtained. Education time was calculated with this information and categorized into 12 or more years or less than 12 years.

Marital status and cohabitation status were assessed and dichotomized into married or not married and living alone or not living alone.

Knowledge on preexisting illnesses was based on the information given by the patient during the interview or medical records. Angina, hypercholesterinaemia, hypertension, stroke and diabetes were therefore categorized into unknown, yes (the illness was diagnosed before hospitalization) or no (neither the physician nor the patient was aware of a preexisting condition).

The body mass index was calculated from information in the medical records and was dichotomized into ≥30 kg/m² and <30 kg/m².

Smoking status was also available from the interview as never smoker, ex-smoker and current smoker.

Medication at discharge as well as invasive treatment was derived from the medical records and was classified as present or absent for each patient. The

included groups of medications in the present study were antiplatelets, β-blockers, statins and ACE-inhibitors. PCI without stent, PCI with stent implantation, Coronary Artery Bypass Grafting (CABG) and pharmacological lysis were considered as invasive treatments.

2.5 Exposure of interest

Treatment of AMI changed considerably with the implementation of new therapeutic guidelines in the year 2000. At the same time diagnostic criteria were altered. To examine whether these changes influenced the survival after AMI the study sample was divided into two groups depending on the year in which a person had his/her first AMI either from 1st January 1995 to 31st December 1999 or from 1st January 2000 to 31st December 2003. To assess whether this division represented changes in mortality and re-infarction rates well an additional analysis was done using PCI with stent or no stent as exposure of interest, because the treatment with stents was the major change of treatment following the new guidelines.

2.6 Follow-up of mortality

The registry received the death certificates with suspected underlying cardiac causes on a regular basis from the three local health departments. The registry team checked routinely whether any of the deceased are registered in the CER and if applicable updated the record by adding the date and cause (ICD codes) of death. Active mortality follow-ups were performed to supplement this source of information. An independent institution was

authorized to check the existing addresses of the patients with the local registration offices to update the information if patients had moved or died. The last mortality follow-up was started in December 2005 and lasted about 4 months. The data for the present study were censored at the 31st December 2005.

2.7 Follow up of re-infarction

Re-infarctions of persons who were between 25 and 74 years old and were admitted to one of the hospitals in the study region are included in the CER as a new case. Name and birth date were checked at the beginning of the admission procedure for already existing cases of the person. If a person has records on a first AMI in the registry the following cases of AMI will be marked as re-infarction (1, 2,…). The second endpoint besides mortality in the present study was the first re-infarction after the first acute event. All patients were censored at their 75th birthday, because the registry does not admit persons or cases over 75 years of age.

2.8 Statistical analysis

Sex-specific frequencies and age adjusted prevalences were calculated for all covariates. Logistic regression was used to compare the two time periods of first AMI (from 1st January 1995 to 31st December 1999=Study Period 1 and 1st January 2000 to 31st December 2003=Study Period 2) and the two treatment groups (PCI with stent and without stent) with regard to differing age adjusted prevalence of covariates in the respective sub-groups. The duration of follow-

up was derived from the difference between the date of first AMI and the date of death or the last follow-up information or the 31st December 2005. Crude sex-specific mortality and re-infarction rates were calculated per 1000 person years (pyrs) for one year, three years and the whole time of follow-up. Kaplan-Meier survival curves were created with the outcome death and re-infarction. The subsequent analyses were stratified by sex. The association between time periods of first AMI (Study Period 1 and 2) and mortality or re-infarction rate was examined using Cox proportional hazards models. The proportional hazards assumption for all factors used in the Cox models was checked plotting log (-log (event)) versus log of event times. None of the covariates seemed to violate the PH assumption. At first the crude association between time periods and mortality/re-infarction rate was calculated. In a second step the model was adjusted for age as a continuous variable. Subsequently the model adjusted for socio-demographic variables (area of residence, education time, marital status, cohabitation status, working), preexisting diseases (angina, stroke, hypertension, hyperlipidaemia, diabetes), BMI, smoking (never, ex, actual), discharge medication (β-blocker, ACE-inhibitors, antiplatelets, statins) and invasive medical treatment during hospitalization (lysis, PCI with stent, PCI without stent, CABG). The following model contained only variables which showed significant influence in one of the former models at the 10% level. Consecutively all covariates were excluded following the same method until every covariate included in the model had a significant effect on mortality/re-infarction rate at the 10% level. Significance tests were two tailed and p-values less than 0.05 were stated as statistically significant. All analyses were performed using the Statistical Analysis System (Version 9.1, SAS Institute Inc., Cary, NC).

3. Results

3.1 Derivation of the study sample

Due to the changes of diagnostic criteria for myocardial infarction on the clinical level and the suspected influence on the registration of cases, it was important to find relatively homogeneous groups of AMI cases which could be compared for their mortality and re-infarction rates. Figure 1 shows that the percentage of persons who survived the first 28 days rose from between 50 and 60% in the year 1995 to 70% in the years 2001 to 2003 when including all incident MI cases 1995 to 2003 of all four diagnostic categories.

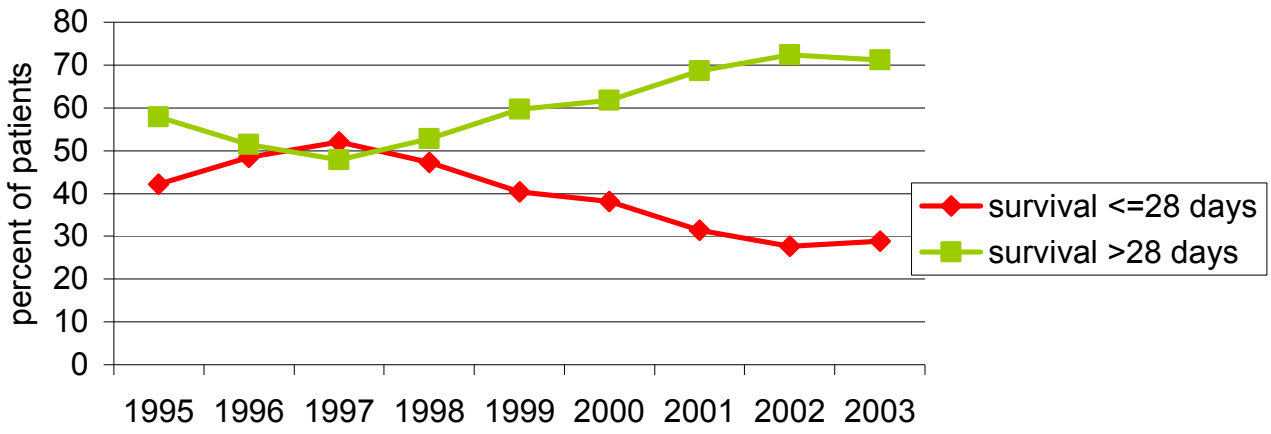


Figure 1: 28-day survival of patients with first AMI (index event) per year

Only cases with *possible* or *definite* AMI by sex are shown in figure 2 and 3.

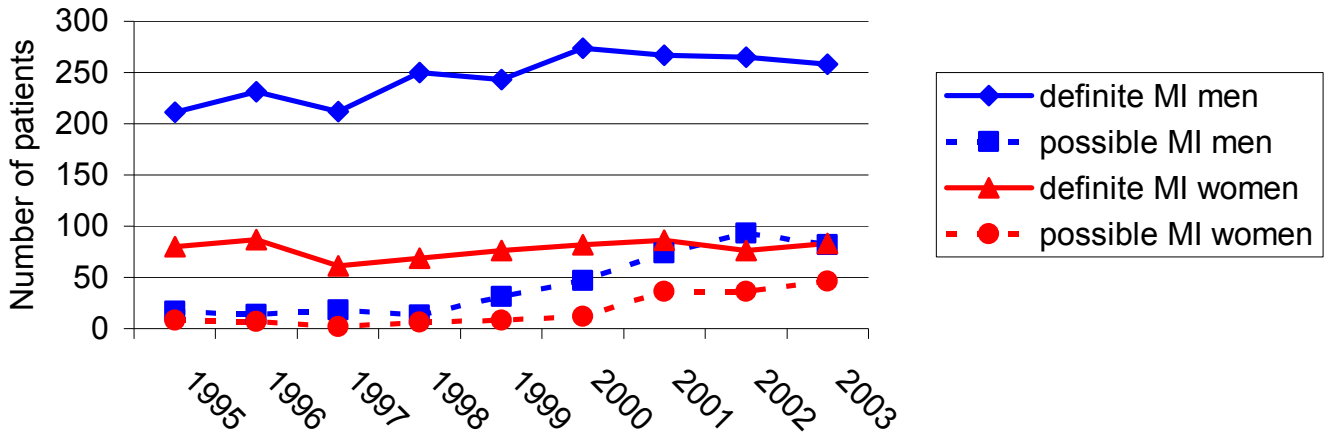


Figure 2: 28-day survivors of definite or possible first AMI per year

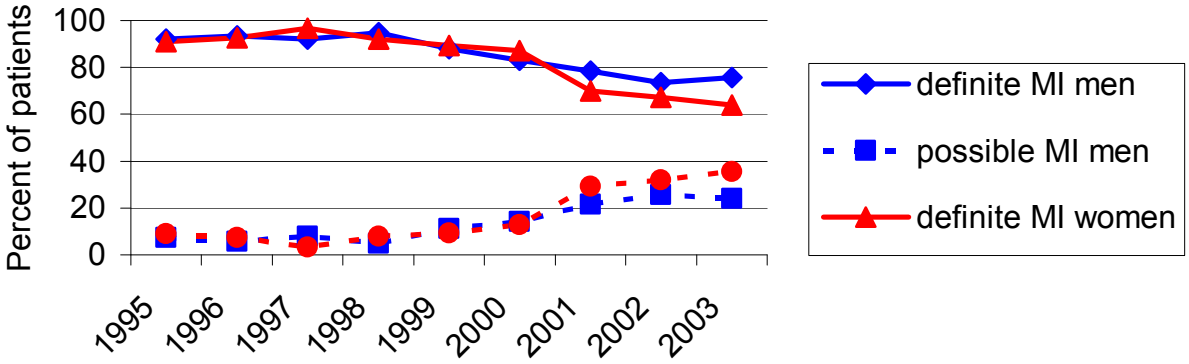
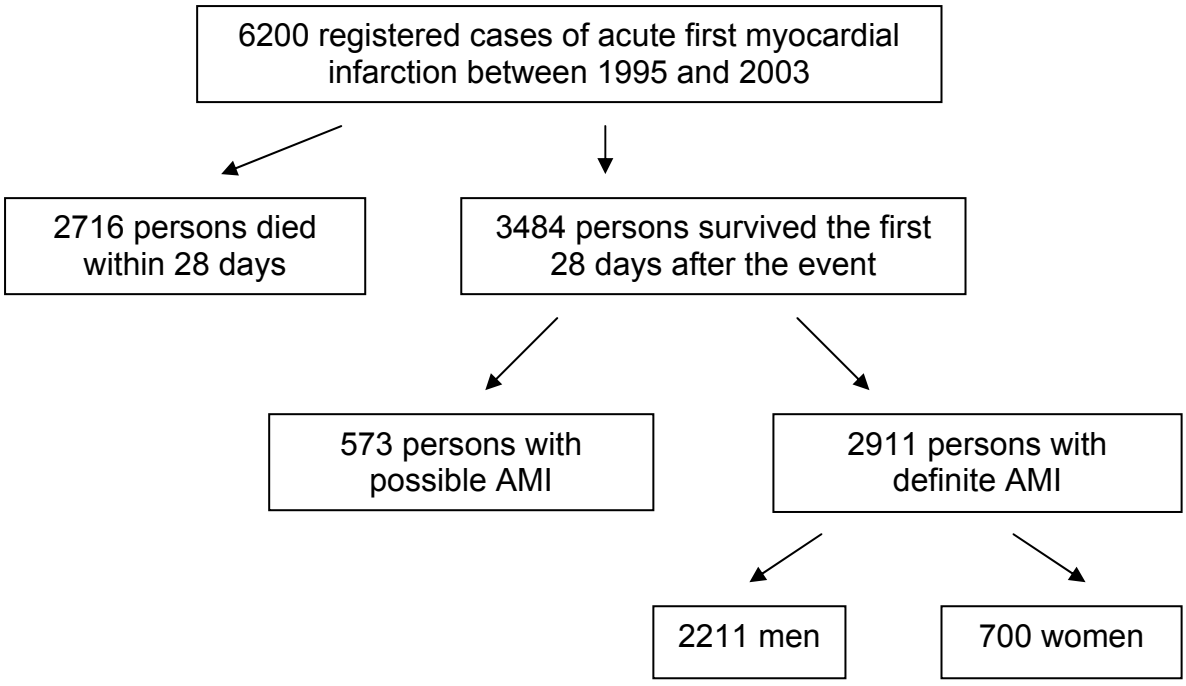


Figure 3: Distribution of definite and possible AMI in 28-day survivors

Figure 2 confirms the increase of the absolute number of cases during the examined study period. More men with *definite* AMI survived the first 28 days after infarction, but also the number of women and men with *possible* AMI rose from 8 and 17 in the year 1995 to 46 and 82 respectively in the year 2003.

Accordingly the frequency distribution of AMI cases of the years 2000 and 2003 differs from the distribution of cases between the years 1995 and 1999 in that the percentage of *possible* AMIs has risen to around thirty percent for both sexes (Figure 3). The increase of *possible* AMI cases was probably due to the change of diagnostic criteria and led to the conclusion that a comparison of the two study periods would become difficult if the inhomogeneous group of *possible* AMIs was kept in the analysis. *Possible* AMIs were therefore excluded from analyses. The remaining study sample comprised 2911 persons with *definite* AMI, 700 of them were women and 2211 were men (figure 4).

Figure 4: Flowchart on the derivation of the study sample



3.2 Description of the study sample

In crude analyses the absolute number of AMI increased with age for both sexes. Up to the age of 64 years the number of cases in men was 3 times the

number of cases in women. This discrepancy is somewhat reduced in the 65 to 74 year olds (figure 5).

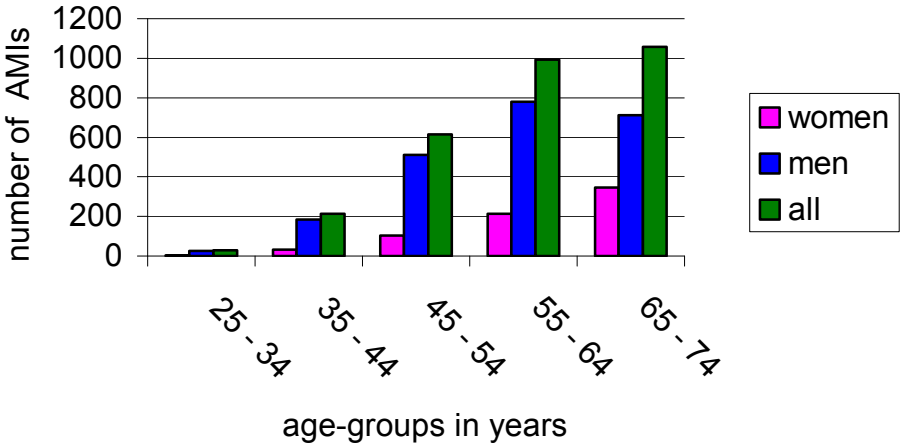


Figure 5: Number of incident definite AMI's by age and sex between 1995 and 2003 in Augsburg Germany

In this oldest age-group 50% of the AMIs among women occurred, whereas AMIs in men were more evenly distributed between 45 and 74 years of age (figure 6).

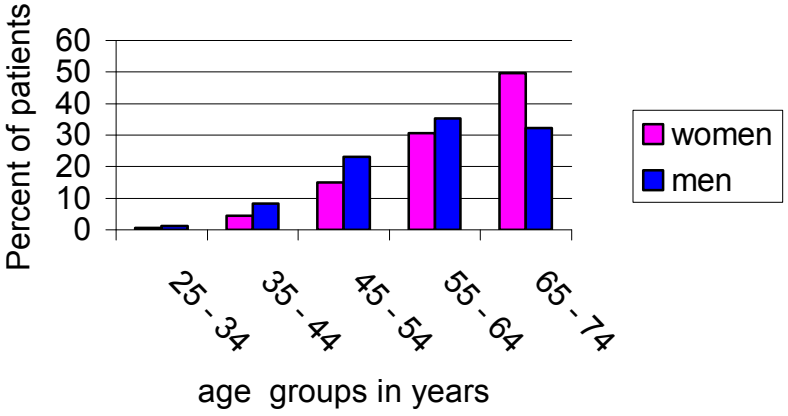


Figure 6: Age distribution for women and men

The frequency distribution of socio-demographic characteristics, pre-existing diseases and cardiovascular risk factors in men and women by study period are shown in table 1 and 2.

Table 1: Socio-demographic characteristics of the study sample

Sociodemographic characteristics	Women				Men				all
	Study period				Study period				
	≤31dec99		>31dec99		≤31dec99		>31dec99		
	N	%	N	%	N	%	N	%	N
Employment status									
unknown	57	15.3	17	5.2	100	8.7	40	3.8	214
no	259	69.4	248	75.8	543	47.3	545	51.2	1595
yes	57	15.3	62	19.0	504	43.9	479	45.0	1102
Years of education									
unknown	75	20.1	70	21.4	197	17.2	204	19.2	546
≥12 years	17	4.6	10	3.1	143	12.5	119	11.2	289
< 12 years	281	75.3	247	75.5	807	70.4	741	69.6	2076
Nationality									
unknown	.	.	.	.	2	0.2	1	0.1	3
other	18	4.8	15	4.6	101	8.8	107	10.1	241
german	355	95.2	312	95.4	1044	91.0	956	89.8	2667
Area of residence									
rural	170	45.6	164	50.2	598	52.1	578	54.3	1510
urban	203	54.4	163	49.8	549	47.9	486	45.7	1401
Marital status									
unknown	17	4.6	7	2.1	20	1.7	12	1.1	56
not married	133	35.7	130	39.8	192	16.7	208	19.5	663
married	223	59.8	190	58.1	935	81.5	844	79.3	2192
Living alone									
unknown	18	4.8	29	8.9	34	3.0	54	5.1	135
no	264	70.8	213	65.1	1012	88.2	898	84.4	2387
yes	91	24.4	85	26.0	101	8.8	112	10.5	389
All	373	100.0	327	100.0	1147	100.0	1064	100.0	2911

Table 2: Frequency distribution of pre-existing diseases and risk factors

Diseases and risk factors	Women				Men				all
	Study period				Study period				
	≤31dec99		>31dec99		≤31dec99		>31dec99		
	N	%	N	%	N	%	N	%	N
Angina									
unknown	1	0.3	.	.	5	0.4	2	0.2	8
no	323	86.6	278	85.0	1002	87.4	937	88.1	2540
yes	49	13.1	49	15.0	140	12.2	125	11.7	363
Stroke									
unknown	7	1.9	39	11.9	17	1.5	134	12.6	197
no	346	92.8	259	79.2	1099	95.8	877	82.4	2581
yes	20	5.4	29	8.9	31	2.7	53	5.0	133
Diabetes									
unknown	1	0.3	.	.	3	0.3	.	.	4
no	268	71.8	230	70.3	901	78.6	771	72.5	2170
yes	104	27.9	97	29.7	243	21.2	293	27.5	737
Hypertension									
unknown	1	0.3	.	.	2	0.2	3	0.3	6
no	126	33.8	69	21.1	508	44.3	345	32.4	1048
yes	246	66.0	258	78.9	637	55.5	716	67.3	1857
Hyperlipidemia									
unknown	6	1.6	3	0.9	19	1.7	11	1.0	39
no	129	34.6	74	22.6	367	32.0	234	22.0	804
yes	238	63.8	250	76.5	761	66.3	819	77.0	2068
BMI (kg/m^2)									
unknown	19	5.1	11	3.4	38	3.3	33	3.1	101
BMI<25	131	35.1	116	35.5	359	31.3	304	28.6	910
25≥BMI<30	152	40.8	119	36.4	561	48.9	521	49.0	1353
BMI≥ 30	71	19.0	81	24.8	189	16.5	206	19.4	547
Smoking									
unknown	18	4.8	31	9.5	21	1.8	60	5.6	130
current smoker	129	34.6	102	31.2	505	44.0	410	38.5	1146
ex-smoker	42	11.3	46	14.1	332	28.9	340	32.0	760
never smoker	184	49.3	148	45.3	289	25.2	254	23.9	875
All	373	100.0	327	100.0	1147	100.0	1064	100.0	2911

Several of the examined parameters showed differences between the compared study periods in women and men. During the years 2000 to the

2003 more subjects were identified to have had a stroke before hospitalization or to suffer from hypertension, hyperlipidemia or diabetes. The number of actual smokers decreased slightly in the same period of time. To assess whether these differences were significant, age adjusted prevalences in both groups were calculated and compared by using logistic regression. For easier comparison BMI was grouped into two categories for the following calculations. Women and men showed the same tendency of changes in the frequency distribution and age adjusted prevalence is presented for both sexes together.

Table 3: Age adjusted prevalence of socio-demographic characteristics, pre-existing diseases and cardiovascular risk factors

Variable	Study period						
	≤31dec99			>31dec99			
	Prevalence	95%-C.I.		Prevalence	95%-C.I.		*p-value
Men	76.3	74.1	78.4	77.5	75.2	79.7	0.4451
Urban	49.5	47.0	52.0	46.7	44.0	49.3	0.1278
Education time≥ 12 years	12.6	10.8	14.5	11.4	9.6	13.4	0.3632
Married	78.1	75.9	80.1	75.4	73.0	77.6	0.084
Living alone	13	11.4	14.8	14.9	13.1	17.0	0.1419
Working	36.3	32.9	39.8	38	34.5	41.7	0.491
Angina	11.9	10.3	13.6	11.8	10.2	13.6	0.9705
Hypertension	58.7	56.1	61.2	71.1	68.6	73.5	<.0001
Hyperlipidemia	66.9	64.5	69.3	77.8	75.6	80.0	<.0001
Stroke	3	2.2	3.9	5.9	4.6	7.4	<.0001
Diabetes	22.4	20.4	24.6	27.5	25.2	29.9	0.0017
BMI ≥ 30 kg/m^2	17.7	15.8	19.7	21.3	19.2	23.5	0.017
Never smoker	29.9	27.5	32.4	28.9	26.4	31.6	0.5775
Ex-smoker	24.7	22.5	27.0	29.2	26.8	31.8	0.0075
Current smoker	42.3	39.5	45.0	37.9	35.1	40.8	0.0311

*p-value derived through logistic regression by comparing the two study periods regarding the age adjusted prevalences of each variable

The differences seen in the crude frequency distributions were confirmed by comparison of the study periods through logistic regression as shown in table 3. Significantly more persons reported stroke, hypertension, hyperlipidemia or diabetes in Study period 2 compared to Study period 1. The prevalence of persons with a BMI above 30 kg/m^2 had increased significantly. Fewer patients were actual smokers, and more had given up smoking in the past.

3.3 Description of treatment

The changes of the treatment guidelines for myocardial infarction are reflected by the actual clinical practice. Figures 7 and 8 show the development of discharge medication and invasive treatment during hospitalization in the course of years.

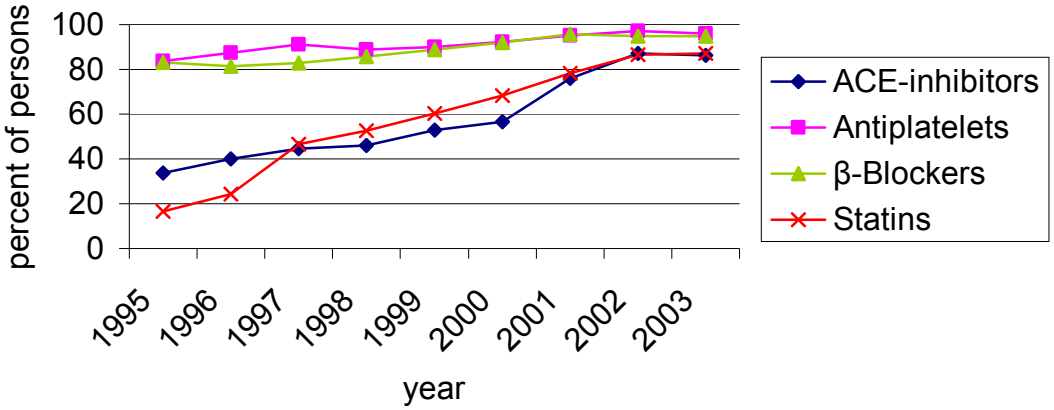


Figure 7: Discharge medication by year of event

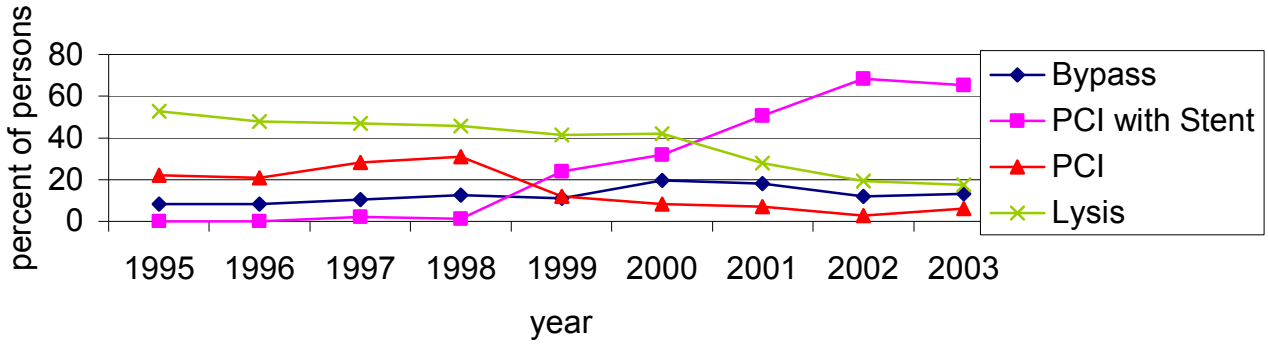


Figure 8: Invasive treatment by year of event

ACE-inhibitors as well as statins show a steady increase over the years. In the years 2002 and 2003 over 80% of patients in the study sample received a prescription for both medications at discharge from the hospital compared to less than 40% in 1995. The implementation of the PCI with stent started in the year 1999 and continued until 2002 and 2003 where it seems to have reached a peak with over 60% of patients being provided with such a therapy. With the rise of the stent therapies like lysis and PCIs without stent have been used less and less frequently. These changes are reflected in table 4 that compares treatment prevalences of Study period 1 and Study period 2.

Table 4: Age adjusted prevalence of treatment

Treatment	Study period						
	≤31dec99			>31dec99			
	Prevalence (%)	95%-C.I.		Prevalence (%)	95%-C.I.		*p-value
Lysis	46.8	44	49	26.8	25	29	<.0001
PCI with stent	5.5	4.5	6.8	54	51.4	56.6	<.0001
PCI w/o stent	22.2	20.1	24.4	6	4.8	7.3	<.0001
Bypass	10	8.6	11.6	15.7	13.9	17.7	<.0001
Antiplatelets	89.5	87.9	91.0	95.6	94.4	96.6	<.0001
β-Blockers	85.7	83.9	87.4	95	93.7	96.0	<.0001
Statins	40.6	38.1	43.1	80.6	78.4	82.6	<.0001
ACE-inhibitors	44.1	41.6	46.6	76.5	74.2	78.7	<.0001

*p-value derived through logistic regression by comparing the two study periods regarding the age adjusted prevalences of each treatment

3.4 Mortality

Follow up time overall was on average 5.6 years with a maximum of 10 years for those with their index event in 1995 and a minimum of 2 years for those entering the cohort in 2003. Given by this design the average follow up time was 7.4 years for those subjects who were entered in Study Period 1 and 3.8 years for subjects of Study Period 2. Crude mortality rates per 1000 person years were calculated for the total time, three years and one year of follow-up, assuming that mortality rates are more comparable within these time windows (Table 5). Mortality was higher for the group of the first study period regardless of the length of follow-up time and sex. Considering the maximum follow-up time, total mortality was much higher in Study period 1 compared to Study period 2 which is explained by the length of observation period. This is not true for women whose one and three year follow-up mortalities are much higher in the first cohort than in the second one whereas this difference is smaller when calculated for the total follow-up time. For all follow-up times the calculated mortality was higher in women than in men. Until the 31st December 2005 331 men and 133 women have died. 62 men died within the first year after their acute event, 141 deceased within the first three years after registration. 27 women did not survive the first year after onset of acute myocardial infarction and 58 died within the first three years after their event.

Table 5: Crude mortality in men and women for different times of follow-up

Follow-up time	Men	Study period ≤31dec99	>31dec99	all
	Number of persons	1147	1064	2211
1 year follow-up	**Number of deaths**	34	28	62
	Person years	1122.46	1038.6	2161.06
	Mortality*	30.29	26.96	28.69
3 years follow-up	**Number of deaths**	81	60	141
	Person years	3283.99	2927.77	6211.76
	Mortality*	24.67	20.49	22.7
total follow-up	**Number of deaths**	248	83	331
	Person years	8508.53	4033.08	12541.6
	Mortality*	29.15	20.58	26.39
Follow-up time	**Women**	**Study period ≤31dec99**	**>31dec99**	**all**
	Number of persons	373	327	700
1 year follow-up	**Number of deaths**	16	11	27
	Person years	359.26	316.13	675.39
	Mortality*	44.54	34.8	39.98
3 years follow-up	**Number of deaths**	37	21	58
	Person years	1048.11	888.17	1936.27
	Mortality*	35.3	23.64	29.95
total follow-up	**Number of deaths**	97	36	133
	Person years	2736.27	1209.38	3945.65
	Mortality*	35.45	29.77	33.71

* rates per 1000 person years

The Kaplan Meier survival curves for mortality in figures 9 and 10 show an almost identical survival for the two study periods in both sexes when adjusted for age. The p-values of the corresponding log-rank tests are 0.2693 for men and 0.9236 for women.

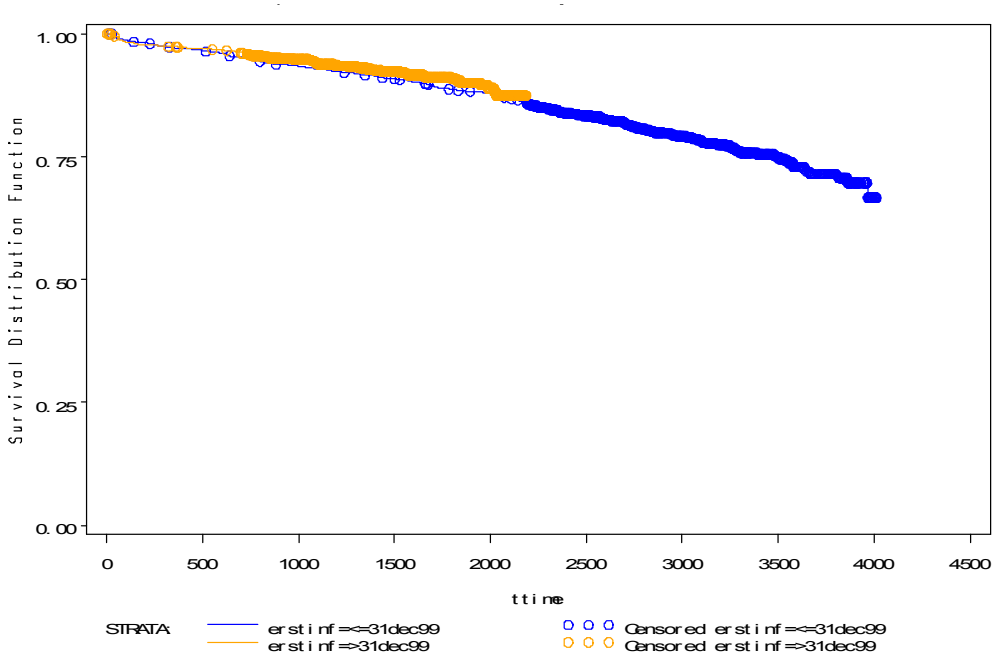


Figure 9: Kaplan Meier survival curve for mortality of men

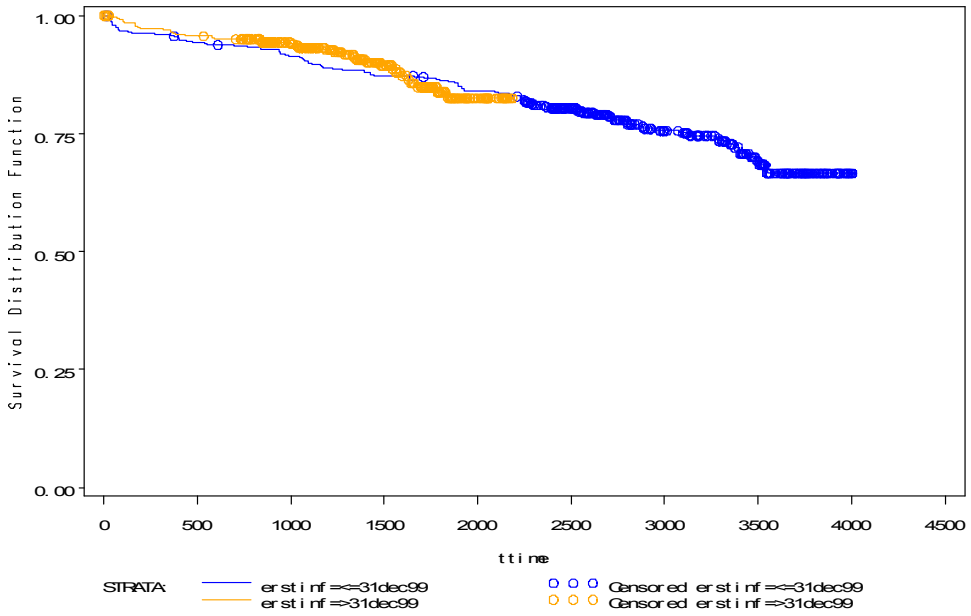


Figure 10: Kaplan Meier survival curve for mortality of women

Cox models were built to compare the mortalities of the two study periods through the total follow-up time. The hazard ratio (HR) in an unadjusted model for Study period 2 compared to Study period 1 is 0.86 (p-value= 0.270, 95% CI

0.65 to 1.13) for men and 0.98 (p-value= 0.924, 95% Confidence interval 0.64 to 1.50) in women (table 6). With adjustment for age (model 2) only slight changes of the HR can be seen. In the fully adjusted model (model 3) the HR for men is 0.78 (p-value= 0.211, 95% CI 0.52 to 1.16) and the tendency of a reduced risk of mortality is more pronounced than in the first two models. This tendency cannot be found for women for whom the HR for mortality in the fully adjusted model is 1.37 (p-value= 0.254, 95% CI 0.80 to 2.36) which is consistent with no improved survival for women, who had their first AMI after the 31st December 1999 (table 6).

Table 6: Gender specific mortality Hazard ratios and 95% C.I. for index event in Study Period 2 compared to Study Period 1

Mortality	Model	Hazard ratio	95% Confidence interval		p-value
Men	1	0.86	0.65	1.13	0.270
	2	0.83	0.63	1.10	0.189
	3*	0.78	0.52	1.16	0.211
Women	1	0.98	0.64	1.50	0.924
	2	0.94	0.62	1.45	0.793
	3**	1.37	0.80	2.36	0.254

* variables included age, angina pectoris, stroke, diabetes, education, working status, area of residence, ace-inhibitors, PCI, lysis, stent, bypass
** variables included age, stroke, diabetes, lysis, stent, β-blockers, statins, ace-inhibitors

3.5 Re-infarction rate

To evaluate the rates of re-infarction the same procedures were used as for the evaluation of mortality, but the follow-up times were censored in the case of death, at the 75th birthday, at the day of moving out of the study area or at the 31st December 2005. Crude re-infarction rates were calculated for one

year, three years and total time of follow-up and are presented in table 7. In total 123 men suffered a re-infarction within the time of follow-up. Re-infarction rates are similar for men in both periods of time when calculated for the full time and three years of follow-up. The re-infarction rates within the first year of follow-up are 17.48 for the first cohort and 25.77 for the second. 35 women were affected by a re-infarction during follow-up. The rates differ between the two periods of time for all follow-up times. The re-infarction rates are generally lower for women with first AMI after the 31st of December 1999 (table 7). But these differences are hardly seen in the according age adjusted Kaplan Meier survival curves for re-infarction (figures 11 and 12), the p-values of the corresponding log rank tests are 0.9117 for men and 0.0531 for women.

Table 7: Crude re-infarction rates in men and women for different times of follow-up

Follow-up time	Men	Study period ≤31dec99	>31dec99	all
	Number of cases	1147	1064	2211
1 year follow-up	**Number of re-AMIs**	19	26	45
	Person years	1086.71	1009.01	2095.72
	Re-infarction rate*	17.48	25.77	21.47
3 years follow-up	**Number of re-AMIs**	39	35	74
	Person years	3068.08	2740.22	5808.3
	Re-infarction rate*	12.71	12.77	12.74
total follow-up	**Number of re-AMIs**	80	43	123
	Person years	7165.37	3675.24	10840.6
	Re-infarction rate*	11.16	11.7	11.35

Follow-up time	Women	Study period ≤31dec99	>31dec99	all
	Number of cases	373	327	700
1 year follow-up	**Number of re-AMIs**	8	1	9
	Person years	348.4	303.64	652.04
	Re-infarction rate*	22.96	3.29	13.8
3 years follow-up	**Number of re-AMIs**	17	5	22
	Person years	938.89	796.97	1735.86
	Re-infarction rate*	18.11	6.27	12.67
total follow-up	**Number of re-AMIs**	28	7	35
	Person years	2074.04	1034.54	3108.58
	Re-infarction rate*	13.5	6.77	11.26

* rates per 1000 person years

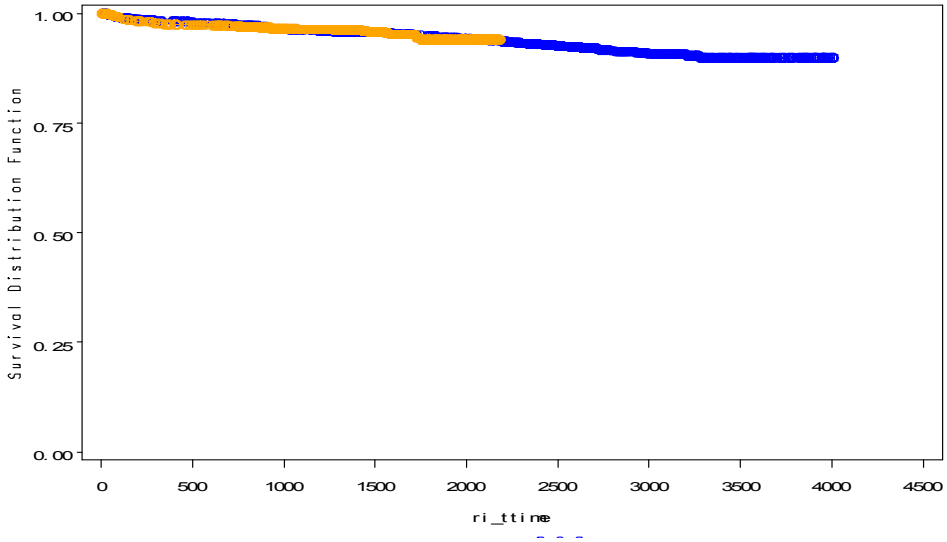


Figure 11: Kaplan Meier survival curve for re-infarction rate of men

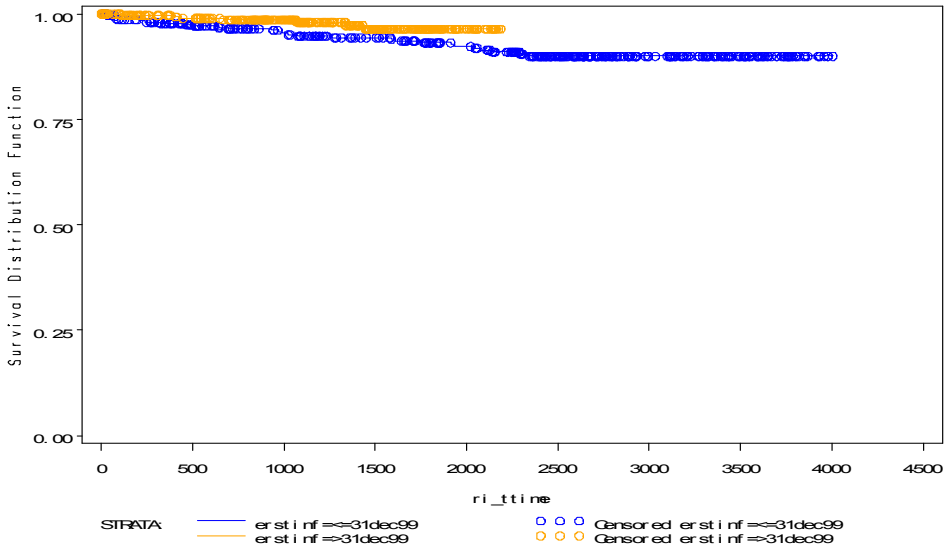


Figure 12: Kaplan Meier survival curve for re-infarction rate of women

These results are confirmed for men by the Cox Proportional Hazards models with a HR of 1.02 (p-value= 0.912, 95% CI 0.68 to 1.53) in the unadjusted model (model 1) and 0.91 (p-value= 0.679, 95% CI 0.57 to 1.44) in the fully adjusted model (model 3) (table 8). For women on the other hand the risk of re-infarction is more than halved after the 31st of December 1999 with HRs of

0.44 (p-value= 0.059, 95% CI 0.19 to 1.03) and 0.4 (p-value= 0.040, 95% CI 0.17 to 0.96) in the unadjusted and the fully adjusted model.

Table 8: Gender specific re-infarction rate Hazard ratios and 95% C.I. for index event (first AMI) in Study Period 2 compared to Study Period 1

Re-infarction rate	Model	Hazard ratio	95% Confidence interval		p-value
Men	1	1.02	0.68	1.53	0.912
	2	1.02	0.68	1.53	0.909
	3*	0.91	0.57	1.44	0.679
Women	1	0.44	0.19	1.03	0.059
	2	0.44	0.19	1.03	0.059
	3**	0.40	0.17	0.96	0.040

* variables included age, education, angina pectoris, PCI, bypass, ex-smoking
** variables included age, working status, hypertension

3.6 The association of survival with treatment

Age adjusted prevalence, mortality, re-infarction rate and the according cox models were calculated comparing two treatment groups, namely the patients without stent were compared with the patients who had received stents. The age adjusted prevalence differs significantly for the variables “men”, “living alone”, “working”, “angina pectoris”, “hypertension”, “hyperlipidemia”, “ex-smoker” and all treatments (Table 9).

Table 9: Age adjusted prevalence of socio-demographic characteristics, pre-existing diseases and cardiovascular risk factors in treatment group with and without stent

Variable	Treatment						
	No stent			Stent			
	Prevalence	95%-C.I.		Prevalence	95%-C.I.		*p-value
Men	75.3	73.4	77.2	80.6	77.8	83.2	0.0025
Urban	48.8	46.6	50.9	46.5	43.1	49.9	0.2669
Education time≥ 12 years	11.4	10	13.1	13.3	11	16	0.2035
Married	77.8	75.9	79.6	74.3	71.3	77.2	0.0478
Living alone	13.1	11.7	14.7	15.7	13.4	18.4	0.0753
Working	35.4	32.6	38.4	41.1	36.6	45.9	0.0399
Angina pectoris	12.8	11.4	14.3	9.5	7.7	11.7	0.0144
Hypertension	62	59.8	64.1	71.2	67.9	74.2	<.0001
Hyperlipidemia	69.4	67.3	71.4	79.2	76.3	81.8	<.0001
Stroke	4.2	3.4	5.3	4.3	3.1	6	0.9223
Diabetes	25.1	23.3	27	24.1	21.3	27.2	0.5792
BMI ≥ 30 kg/m^2	18.8	17.1	20.5	21	18.3	23.9	0.1768
Never smoker	30.3	28.2	32.5	27.5	24.3	30.8	0.154
Ex smoker	25.7	23.8	27.7	29.5	26.4	32.8	0.0452
Current smoker	40.6	38.3	43	39.1	35.5	42.9	0.5169
Lysis	41.5	39.4	43.6	26.7	23.8	29.8	<.0001
PCI w/o stent	20.4	18.7	22.2				
Bypass	17.1	15.6	18.8	1.7	1	2.8	<.0001
Antiplatelets	89.9	88.5	91.2	98.6	97.5	99.2	<.0001
β-Blockers	87.7	86.2	89.1	96.3	94.7	97.4	<.0001
Statins	49.7	47.5	51.8	84.8	82.1	87.1	<.0001
ACE-inhibitors	50.3	48.1	52.5	82.7	80	85.1	<.0001

*p-value derived through logistic regression by comparing the two treatment groups regarding the age adjusted prevalences of each treatment

The crude mortality is lower for men and women who were treated with PCI and stent compared to persons without this kind of treatment. During total follow-up 331 men and 133 women died of whom only 40 respectively 8 had received a stent. The difference of crude mortality was higher in women than in men.

Table 10: Crude mortality in men and women for different times of follow-up in the two treatment groups

Follow-up time	Men	Stent		
		no	yes	all
	Number of cases	1537	672	2209
1 year follow-up	**Number of deaths**	54	8	62
	Person years	1494.26	664.8	2159.06
	Mortality*	36.14	12.03	28.72
3 years follow-up	**Number of deaths**	112	29	141
	Person years	4338.15	1867.61	6205.76
	Mortality*	35.3	20.49	22.72
total follow-up	**Number of deaths**	291	40	331
	Person years	9928.91	2599.57	12528.48
	Mortality*	29.31	15.39	26.42

Follow-up time	Women	Stent		
		no	yes	all
	Number of cases	537	163	700
1 year follow-up	**Number of deaths**	25	2	27
	Person years	517.52	157.87	675.39
	Mortality*	48.31	12.67	39.98
3 years follow-up	**Number of deaths**	55	3	58
	Person years	1486.63	449.64	1936.27
	Mortality*	37	6.67	29.95
total follow-up	**Number of deaths**	125	8	133
	Person years	3317.58	628.07	3945.65
	Mortality*	37.68	12.74	33.71

*per 1000 person years

Table 11 summarises the hazard ratios from different cox models regarding the mortality in the group with and the group without stent. The hazard ratio in the fully adjusted model (model 3) for men is 0.66 with a p-value of 0.042 (95% C.I. 0.44 to 0.99) which represents a reduction in mortality of 34% for men who were treated with stent. This reduction is even higher for women, whose hazard ratio in the fully adjusted model (model 3) is 0.46 (p-

value=0.042; 95% C.I. 0.22 to 0.97) which corresponds to a reduction of mortality over 50% after the introduction of stents.

Table 11: Gender specific mortality Hazard ratios and 95% C.I. comparing the group with stent to the group without stent

Mortality	Model	Hazard ratio	95% Confidence interval		p-value
	1	0.60	0.43	0.84	0.003
men	2	0.65	0.47	0.92	0.015
	3*	0.66	0.44	0.99	0.042
	1	0.37	0.18	0.76	0.007
women	2	0.36	0.18	0.75	0.006
	3**	0.46	0.22	0.97	0.042

*variables included age, angina pectoris, stroke, diabetes, education, working status, area of residence, ace-inhibitors
** variables included age, stroke, diabetes, β-blockers, statins, ace-inhibitors

The crude re-infarction rate in men is higher for those who received stents. The rate is especially high within the first year of follow-up. The treatment has almost no effect on the re-infarction rate of women, where the total number of re-infarctions is 35 and therefore very low.

Table 12: Crude re-infarction rate in men and women for different times of follow-up in the two treatment groups

Follow-up time	Men	Stent		
		no	yes	all
	Number of cases	1537	672	2209
1 year follow-up	**Number of re-AMIs**	24	21	45
	Person years	1450.42	643.3	2093.72
	Re-infarction rate*	16.55	32.64	21.49
3 years follow-up	**Number of re-AMIs**	46	28	74
	Person years	4064.78	1737.53	5802.3
	Re-infarction rate*	11.32	16.11	12.75
total follow-up	**Number of re-AMIs**	92	31	123
	Person years	8463.25	2364.24	10827.48
	Re-infarction rate*	10.87	13.11	11.36

Follow-up time	Women	Stent		
		no	yes	all
	Number of cases	537	163	700
1 year follow-up	**Number of re-AMIs**	8	1	9
	Person years	499.25	152.79	652.04
	Re-infarction rate*	16.02	6.55	13.8
3 years follow-up	**Number of re-AMIs**	20	2	22
	Person years	1334.04	401.83	1735.86
	Re-infarction rate*	14.99	4.98	12.67
total follow-up	**Number of re-AMIs**	29	6	35
	Person years	2577.08	531.5	3108.58
	Re-infarction rate*	11.25	11.29	11.26

*per 1000 person years

The results from the crude re-infarction rates are confirmed by the according hazard ratios which are not significant in both sexes as can be seen in table 13.

Table 13: Gender specific re-infarction rate Hazard ratios and 95% C.I. comparing the two treatment groups

Re-infarction rate	Model	Hazard ratio	95% Confidence interval		p-value
Men	1	1.18	0.78	1.81	0.437
	2	1.21	0.79	1.85	0.378
	3*	1.15	0.73	1.84	0.545
Women	1	0.94	0.38	2.29	0.887
	2	0.94	0.38	2.29	0.888
	3**	0.91	0.36	2.25	0.832

*variables included age, education, ex-smoking, bypass
**variables included age, working status, hypertension

4. Discussion

4.1 Aims of the study

The two major endpoints of this study were long-term mortality and re-infarction rate in 28-day survivors after first myocardial infarction in the light of changing therapeutic guidelines and diagnostic criteria. Survival improved since the year 2000 when the new therapeutic guidelines were implemented, although the reduction in mortality was not significant. On the other hand the re-infarction rate remained unchanged for men when comparing Study Period 1 and 2 while for women it decreased after the year 2000, but the total number of 35 cases of re-infarction during the complete follow-up time is small and this result must therefore be treated with caution.

4.2 The role of changes in diagnostic criteria, risk factors and treatment

4.2.1 The role of changing diagnostic criteria

In the beginning of the study it was planned to include patients from the two categories "*definite*" and "*possible*" AMI into the analysis. But it was important

that the two groups of patients from Study Period 1 and 2 were as similar as possible concerning the severity of their AMI. The WHO-MONICA criteria for acute myocardial infarction are based on symptoms, changes in electrocardiograms and the concentrations of the cardiac enzymes CK, CK-MB, LDH and GOT. These criteria are still used in the algorithm to create the four diagnostic categories of AMI. Since the year 2000 the inclusion of raised Troponin concentration in the diagnostic criteria has been recommended as a more sensitive marker of cardiac muscle damage by the European Society of Cardiology and the American College of Cardiology. This led to an increase of clinically diagnosed cases of acute myocardial infarction, which were earlier treated as unstable angina pectoris (Koukkunen, Penttila et al. 2001; Pell, Simpson et al. 2003; Salomaa, Koukkunen et al. 2005; White 2008). Salomaa et al. found 83% more *definite* AMIs using the new definition compared to the WHO MONICA definition. They state that about one third of these additional cases of AMI were classified as *possible* AMIs by the WHO MONICA definition. Roger et al. reported not only an increase in diagnosed AMIs, but also found a change in the case mix of patients with AMI, who were older, more likely to be female with lower Killip class and more non-ST-elevation ECG (Roger, Killian et al. 2006). The CER in Augsburg using the WHO MONICA definition of AMI has registered more cases of *possible* AMI since the year 2000, as is shown in figure 2 and 3, which is probably due to the application of the new guidelines from the ACC and ESC by the CER (Kuch, Heier et al. 2008). This result led to the conclusion that the category of *possible* AMI from before the year 2000 differs from the same category since the year 2000 concerning the nature of AMIs and these cases were therefore excluded from the analysis. It is also possible that more cases of *definite* AMI

are identified through the application of the new diagnostic criteria by clinicians. These cases might be less severe, what would explain the increase of 28-day survivors with *definite* AMI.

4.2.2 Age-adjusted prevalence of cardio-vascular risk factors

The patients of Study Period 2 reported significantly more diabetes, high blood pressure, stroke, obesity and hyperlipidaemia. These results are in accordance with the international literature where the raising trend of these conditions due to changing dietary patterns and an increasingly sedentary lifestyle in the general population has been stated repeatedly (King, Aubert et al. 1998; Pradhan, Skerrett et al. 2002; Wilborn, Beckham et al. 2005; Pradhan 2007; Centers for Disease Control and Prevention [rev. 26 Mar 2007; cited 3 Dec 2007].). Long-term mortality in men and women with diabetes is significantly higher after a first AMI (Koek, Soedamah-Muthu et al. 2007). Evans et al. on the other hand found declining 10 year trends of blood pressure and serum cholesterol in the majority of the 38 populations of 21 countries of the WHO MONICA project (Kuulasmaa, Tunstall-Pedoe et al. 2000; Evans, Tolonen et al. 2001), but they confirmed the upwards trends in body mass index in both sexes. The proportion of smokers was lower in patients of Study Period 2 and the proportion of ex-smokers was accordingly significantly higher, a trend, which has also been reported by Evans et al. and Kuulasmaa et al. It is possible that the patients of the present study reflect the trends in the general population, but other explanations for the increase in prevalence of pre-existing illnesses are possible. Since the introduction of the new therapeutic guidelines more patients survived the first 28 days after their

first myocardial infarction which is in accordance to the current literature (Buch, Rasmussen et al. 2007; Fox, Steg et al. 2007) and it seems plausible that these patients are less healthy and owe their survival to the new treatment strategies. Another explanation is the risen awareness in the general population and doctors concerning cardio-vascular risk factors (Böhm M 2008). More patients received preclinical treatment of hypertension or diabetes and therefore report these conditions in the interview of the CER. The higher prevalence of pre-existing illnesses in patients of Study Period 2 is a possible reason for the non-significance of the hazard ratios for mortality, if the increase of illnesses is real and not generated through a higher rate of diagnosis.

4.2.3. The role of new treatment strategies

The prescription of antiplatelet medication, β-blockers, ACE-inhibitors and statins has risen continuously since 1995 to a level of over 95% for antiplatelet medication and β-blockers and of over 85% for ACE-inhibitors and statins. This trend has been seen by Goldberg et al. in 2007, who studied the use of single and combination medical drug therapy from patients included in the Global Registry of Acute Coronary Events (GRACE) between 2000 and 2005 (Goldberg, Spencer et al. 2007) and by Setoguchi et al. (Setoguchi, Glynn et al. 2008), whereas Hasdai et al. stated in 2002 that acute coronary syndrome (ACS) patients are often treated according to routine and not to the current practice guidelines (Hasdai, Behar et al. 2002), because they found lower levels of the respective discharge medications (Aspirin 88.5%, ACE-inhibitors 60.7%, β-blockers 76.1% and statins 54%) for patients with ST-elevation

myocardial infarction from 25 European countries. The level of PCI treatments in their population was 40.4% in the end of the year 2000 and the first half of 2001, whereas over 50% of the CER patients had received a stent in 2001 increasing to 65% in the year 2003. The implementation of the new treatment strategies seems to have worked well in the participating hospitals in Augsburg. The prompt enactment of the practice guidelines is probably partly due to the fact that the Augsburg Central Clinic, where around 85% of the patients were treated, is one of the teaching hospitals of the University of Munich with angiography, PCI and heart surgery facilities.

The discharge medication plays an important role in secondary prevention and is known to reduce mortality after a first AMI (Smith, Jackson et al. 2004; Setoguchi, Glynn et al. 2008). Primary PCI reduces the risk of non-fatal re-infarction, short-term and long-term mortality in randomized trials and large prospective studies (Keeley, Boura et al. 2003; Muhlestein, Anderson et al. 2005; Stenestrand, Lindback et al. 2006). These positive effects are not clearly confirmed by the present study when comparing the patients of the two study periods, because the trend for a reduced mortality is not significant for men and women and the hazard ratio for re-infarction stayed the same before and after the introduction of the new therapeutic guidelines. The mortality hazard ratio in patients with PCI and stent compared with other patients is significant for men and women after full adjustment for possible confounders. This difference in outcomes is difficult to explain, because before the year 2000 only few patients received PCI and stents so that the comparison of the two time periods should reflect this fact, but other factors seem to influence the mortality which was not adjusted for. Tables 3 and 9 show the age-adjusted prevalences of risk factors for the two study periods and for patients with and

without stent. The age-adjusted prevalence of diabetes is significantly higher in Study Period 2, but there is no significant difference in age-adjusted prevalence of diabetes between patients with or without stent. On the other hand significantly more patients, who received a stent, are still working, whereas the prevalence of working patients is similar in Study Period 1 and 2. History of diabetes and the working status were included in the Cox models and should not influence the results, but it becomes clear that patients with stent are probably healthier (healthy worker effect) and have therefore a better chance of survival. Buiatti et al state that physicians tend to select less severe cases of AMI for reperfusion treatment (Buiatti, Barchielli et al. 2003; Balzi, Barchielli et al. 2008) which would explain a better outcome for patients with stent in the presented study population. Nieuwlaat et al. found that patients with a previous PCI and long pre-hospital delay, who arrived in a hospital with PCI-facilities and did not participate in a clinical trial, were more likely to receive PCI-treatment. Although the present study confirms that physicians in the Augsburg hospitals adhere well to current practice guidelines, hospital culture may still influence the decision which treatment is used and therefore leads to an undeterminable selection of patients (Hasdai, Behar et al. 2002; Nieuwlaat, Lenzen et al. 2006).

4.3 Strengths and limitations

The present study is a population based epidemiologic cohort study addressing the changes in survival after myocardial infarction due to changes of therapeutic measures since the year 2000. It represents the conditions of a real life setting which differ from the conditions of a randomized controlled trial

in that selection bias is reduced. The decision whether a patient is treated with PCI and stent should be based on current guidelines, but individual judgement by the treating physician and hospital culture influence (Buiatti, Barchielli et al. 2003; Nieuwlaat, Lenzen et al. 2006) this decision and a certain degree of selection bias cannot completely be avoided. Patients have been recruited by the same means and nurses almost since the beginning of the CER. The internal validity of data has to be considered as very strong, because of the long existing routine of interviewing and record handling. Interviews are conducted shortly after the event (2 to 3 days after) to minimize recall bias concerning the event. The information on pre-existing illnesses which is also retrieved through the interview is confirmed through the medical records and information bias can be excluded in this respect.

One of the limitations of the study is that time to treatment has not been considered as a predicting risk factor for survival after myocardial infarction (de Labriolle, Pacouret et al. 2008). Information on drug compliance and eventual alteration of the discharge medication through the treating physician after discharge from the hospital was not available. The Cox models were calculated using the discharge medication, which will differ from the actual medication to a degree, which is unknown.

Finally it has to be stated that the results from this study cannot be generalized to other regions with a different hospital infrastructure, because the facilities at the Central Clinic Augsburg are better equipped to treat myocardial infarctions than many smaller hospitals in more rural areas. The generalizability is also reduced through the age limit which excludes patients to participate in the study after their 75th birthday. The effect of the new treatment strategies might differ for older patients in both directions. It is thinkable that they profit even

more from the new treatments and their mortality decreases, but because of more severe pre-existing illnesses the effect of new treatments could also be reduced. A separate study and analysis of this patient group is warranted because especially women are affected by myocardial infarction more in their later years.

4.4 Conclusions

In the present study a decreasing trend of mortality after first AMI was observed in 25 to 74 year old men and women between the years 1995 and 2005 albeit the reduction was not significant. The re-infarction rate after the index event remained stable in the same time period. Patients who received a PCI with stent showed significantly lower mortality during follow-up, but their re-infarction rate stayed unchanged when compared to patients without PCI and stent. Residual confounding could not be excluded completely and might be responsible for the differing results comparing time periods or treatment groups.

The new therapeutic guidelines have been successful implemented in the study hospitals with high rates of PCI with stent and prescription of the recommended discharge medication.

These findings confirm the current publications concerning the comparison of therapeutic measures in a real life setting and the realisation of the new therapeutic guidelines.

5. Summary

The introduction of new invasive therapies for acute myocardial infarction and new medication schemes for secondary prevention is thought to increase life expectancy in 28-day survivors of a first myocardial infarction. The present thesis examined mortality and re-infarction rate of those patients in the light of changed therapeutic guidelines.

Cases of 25 to 74 year old 28-day survivors of a first definite AMI based on MONICA criteria were identified in the Coronary Event Registry in Augsburg, Southern Germany, who had their index event between the 1st of January 1995 and the 31st of December 2003. Information on patients was gathered through personal interviews shortly after the event and the processing of medical records for relevant data. Mortality follow-up was done by registration of deaths which occurred until 31st of December 2005. Re-infarctions were registered in the CER if they were suffered before the 75th birthday of a patient and/or 31st of December 2005. Patients were divided into two groups depending on the year of the index event. Patients with AMI before the 31st of December 1999 belonged to Study period 1, patients who had their first AMI between the years 2000 and 2003 belonged to Study period 2. Mortality and re-infarction rates were calculated for 1 year, 3 years and total follow-up for both study periods and separately for men and women. Cox models were built to compare the rates of Study period 1 and 2 including possible confounding factors. Additionally the same calculations were performed comparing patients who received PCI with stent with all other patients.

Of the total number of registered cases 2911 persons with definite MI survived the first 28 days after the event. Crude mortality was higher in Study period 1

than in Study period 2 and higher for women than for men. Re-infarction rates remained stable for men during both study periods, but women from Study period 1 had a much higher re-infarction rate than women in Study period 2. The hazard ratios showed no significant differences for mortality and re-infarction in men. Hazard ratios of re-infarction in women were significantly reduced, but have to be treated with caution as the number of re-infarctions during Study period 2 was very small. Mortality hazard ratios in women were also not significant. When comparing patients with PCI and stent with all other patients the hazard ratios for mortality in men and women were significantly reduced. In contrast hazard ratios for re-infarctions were not significantly reduced.

The results confirm that stents reduce the mortality of patients who survived their first AMI for more than 28 days in a real life setting, but when comparing the time periods before and after the introduction of stent as a routine therapy with the implementation of new therapeutic guidelines the effect is not seen. Several reasons are probably responsible for this finding. The population of patients has changed with respect to their risk factors and new diagnostic criteria may have also contributed. Further studies are needed to illuminate these questions.

6. Zusammenfassung

Die Einführung neuer invasiver Therapien zur Behandlung des akuten Myokardinfarkts und neuer medikamentöser Therapieempfehlungen zur Verbesserung der sekundären Prävention sollten zu einer Verlängerung des Lebens von Patienten führen, die ihren ersten akuten Herzinfarkt mehr als 28 Tage überlebt haben. In der vorliegenden Arbeit wurde der Zusammenhang

zwischen Mortalität und Reinfarktrate dieser Patienten und den neueren Therapieverfahren untersucht.

Patienten, die zwischen 25 und 74 Jahre alt waren und die ersten 28 Tage nach ihrem ersten Herzinfarkt überlebt hatten, wurden im MONICA/KORA-Herzinfarktregister, Augsburg, identifiziert. Der Erstinfarkt musste zwischen dem 1. Januar 1995 und dem 31. Dezember 2003 statt gefunden haben. Durch persönliche Interviews kurz nach dem Ereignis und die Bearbeitung der Krankenakten wurden relevante Daten zu den Fällen erhoben. Todesfälle und Reinfarkte wurden kontinuierlich registriert. Als Ende der Folgebeobachtung wurde für die Mortalität der 31. Dezember 2005 festgelegt. Für die Berechnung der Reinfarktrate galt der 75. Geburtstag oder der 31. Dezember 2005 als Endpunkt. Die Patienten wurden in zwei Gruppen eingeteilt. Die erste Gruppe hatte ihren Erstinfarkt zwischen dem 1. Januar 1995 und dem 31. Dezember 1999 (Studiengruppe 1), in der zweiten Gruppe waren die Patienten, die zwischen dem 1. Januar 2000 und dem 31. Dezember 2003 ihren ersten akuten Herzinfarkt hatten (Studiengruppe 2). Mortalität und Reinfarktraten wurden für 1 Jahr, 3 Jahre und den gesamten Beobachtungszeitraum getrennt nach Studiengruppe und Geschlecht berechnet. Cox Modelle wurden erstellt um die Raten der Studiengruppen unter Einbeziehung möglicher Confounder zu vergleichen. Die gleichen Berechnungen wurden durchgeführt, um Patienten mit Stent- Behandlung mit Patienten ohne Stent-Behandlung zu vergleichen.

Von der Gesamtzahl der registrierten Patienten überlebten 2911 Personen mit definitivem Herzinfarkt die ersten 28 Tage nach dem Ereignis. Die Mortalität der Patienten in Studiengruppe 1 war höher als die Mortalität in Studiengruppe 2 und höher für Frauen als für Männer. Die Reinfarktraten waren für Männer in

beiden Gruppen statistisch nicht unterschiedlich, während die Frauen in der ersten Gruppe eine wesentlich höhere Reinfarktrate hatten als die Frauen der zweiten Gruppe. Die Hazard Ratios unterschieden sich bei den Männern weder für die Mortalität noch für die Reinfarktraten. Bei den Frauen waren die Hazard Ratios für Reinfarkte zwar signifkant, müssen aber mit Vorsicht behandelt werden, da die Anzahl der Reinfarkte im Zeitraum 2000-2003 sehr klein ist. Die Hazard Ratios für Mortalität waren bei den Frauen ebenfalls nicht signifikant. Bei dem Vergleich von Patienten mit und ohne Stent zeigte sich eine signifikante Reduktion der Mortalität bei Männern und Frauen, während sich die Reinfarktraten nicht signifikant veränderten.

Die vorliegenden Ergebnisse bestätigen, dass die Behandlung mit Stents die Mortalität bei Patienten, die den ersten Infarkt mindestens 28 Tage überlebt haben, unter klinischen Bedingungen reduziert. Der Vergleich der beiden Zeiträume vor der offiziellen Empfehlung zur Therapie mit Stent und nach der Einführung der neuen Therapierichtlinien zeigt keine Verbesserung. Die Gründe hierfür sind wahrscheinlich sehr komplex und können mit der Veränderung der diagnostischen Kriterien sowie der Veränderung der Patientenpopulation zu tun haben. Es werden weitere Studien benötigt, um diese Fragen beantworten zu können.

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