Eur J Epidemiol (2014) 29:899–909
DOI 10.1007/s10654-014-9964-6

CARDIOVASCULAR DISEASE

Mortality after first myocardial infarction in diabetic and non-diabetic people between 1985 and 2009. The MONICA/KORA registry

Andrea Icks · Heiner Claessen · Inge Kirchberger · Margit Heier · Annette Peters · Ines Trentinaglia · Guido Giani · Wolfgang von Scheidt · Christa Meisinger

Received: 27 March 2013 / Accepted: 23 October 2014 / Published online: 1 November 2014
© Springer Science+Business Media Dordrecht 2014

Abstract The aim of the study was to analyse mortality after a first myocardial infarction (MI) and its trends in people with diabetes compared to those without diabetes in Southern Germany, 1985–2009. Using data of the population-based MONICA/KORA Myocardial Infarction Registry, we ascertained all patients with a first fatal or non-fatal MI between 1985 and 2009 (n = 16,478, age 25–74 years, 71 % male, 29 % with diabetes). The impact of diabetes and calendar time on mortality was examined using multiple logistic and Cox regression. Survival improved with calendar time: The crude cumulative 5-year survival was 26.9 and 46.3 % among diabetic and non-diabetic individuals (both sexes combined) with a first MI in the years 1985–1989, and 53.6 and 66.6 % among those with a first MI in the years 2005–2009. This significant decrease of mortality was confirmed in multivariate analyses. The proportion of fatal first MIs was significantly higher in diabetic compared to non-diabetic patients [adjusted odds ratio (OR) 1.26; 95 % confidence interval 1.17–1.36]. This association persisted in a similar manner between both sexes with no consistent change of OR over calendar time in which first MIs have been observed. Likewise, multiple adjusted risk of death after a non-fatal first MI was significantly higher among both diabetic men and women [hazard ratio (HR) 1.64; 1.47–1.82, 1.83; 1.55–2.14] with constant HR over calendar time. During the past 25 years, survival has improved in both diabetic and non-diabetic patients with incident MI in a similar manner. However, mortality after a first MI remained significantly higher in the diabetic population, particularly in women.

Keywords First myocardial infarction · Diabetic and non-diabetic population · Mortality trend · MONICA registry

Andrea Icks and Heiner Claessen have contributed equally to this work.

A. Icks (✉) · H. Claessen (✉) · G. Giani
Institute of Biometrics and Epidemiology, German Diabetes Centre, Leibniz-Centre for Diabetes Research, Heinrich-Heine-University, Düsseldorf, Germany
e-mail: andrea.icks@ddz.uni-duesseldorf.de

H. Claessen
e-mail: heiner.claessen@ddz.uni-duesseldorf.de

A. Icks
Department of Public Health, Medical Faculty, Heinrich-Heine University Düsseldorf, Düsseldorf, Germany

I. Kirchberger · M. Heier · A. Peters · I. Trentinaglia · C. Meisinger
Institute of Epidemiology II, Helmholtz Zentrum München, German Research Center for Environmental Health (GmbH), Neuherberg, Germany

I. Kirchberger · M. Heier · C. Meisinger
MONICA/KORA Myocardial Infarction Registry, Central Hospital of Augsburg, Augsburg, Germany

A. Peters
Munich Heart Alliance, Munich, Germany

W. von Scheidt
Department of Internal Medicine I - Cardiology, Central Hospital of Augsburg, Augsburg, Germany

Abbreviations

KORA	Cooperative Health Research in the Region of Augsburg
MI	Myocardial infarction
MONICA	Monitoring trends and determinants on cardiovascular diseases

Introduction

The risk of a first myocardial infarction (MI) is higher for patients with diabetes compared to those without diabetes [1, 2]. In addition, the risk of death after a first MI has been observed to be increased in people with diabetes compared to those without diabetes, which was particularly true in a period of between 28 days and 5 years. [3–5]. However, little is known about the long-term mortality after a first MI in the diabetic population compared to that in the non-diabetic population, and possible time trends. National surveys in Sweden and Finland have shown that one-year survival after a first MI has improved substantially, both in patients with and without diabetes, with no decrease in the mortality gap [5, 6]. The excess mortality among diabetic patients was found to be particularly pronounced among the female population [3, 6, 7]. To the best of our knowledge, there is only one population-based study which investigated mortality over more than a decade (18 years) between 1989 and 2006, including pre-hospital deaths in 25–64-year-old patients with diabetes compared to those without diabetes [8]. This Swedish study found a 1.56-fold increased mortality rate after a first MI in men with diabetes, and an even 1.97-fold increased mortality rate after a first MI in women with diabetes compared to their counterparts without diabetes. Survival has improved during the observation period; however, the impact of diabetes has not diminished [8]. The question is whether the Swedish data can be transferred to other countries. For instance, when comparing the trend of MI incidences in Sweden and Germany, different figures have been observed [1, 2]. In Sweden, the incidence of MI decreased between 1989 and 2000 in non-diabetic men, whereas a decline in the incidence of MI was seen neither in non-diabetic women, nor in male or female diabetic individuals. In Germany, the incidence of MI in women with diabetes decreased between 1985 and 2006 in line with the pattern in women and men without diabetes, whereas in men with diabetes, the incidence was found to remain stable or even increase since the mid-1980s. Compared to Germany, the relative risks of a first MI in diabetics compared to non-diabetics were higher in Sweden (relative risks about 6 (Germany) and 8 (Sweden) for men, and about 8 (Germany) and 15 (Sweden) for women, respectively), which might be explained since in Sweden only 35–64-year-old individuals were included. Hence, referring to Germans from a population-based register with fatal and non-fatal first MIs, the objective of our study was to investigate short and long-term mortality in diabetes compared to non-diabetic subjects and its trends. We were able to include people aged 25–74 years, assess also pre-hospital coronary deaths, and had an overview of individuals aged up to 26 years.

Methods

Study population and data assessment

We used data from the MONICA/KORA myocardial infarction registry in Augsburg, Germany, to identify patients with fatal or nonfatal first MI. The population-based Augsburg Coronary Event Registry was implemented in October 1984 as part of the WHO MONICA (Monitoring trends and determinants on cardiovascular diseases) project [9–11]. Since 1996 the registry has been carried out within the framework of KORA (Cooperative Health Research in the Region of Augsburg). Methods of case finding, diagnostic classification of events and data quality control have been described elsewhere [9, 10]. In short, KORA continuously registers all cases of deaths due to coronary heart disease (CHD) and non-fatal first MI of the 25–74-year-old study population in the city of Augsburg (about 250,000 inhabitants) and the two adjacent regions Augsburg and Aichach-Friedberg (about 350,000 inhabitants) [12]. During the study period of 1985–2006, the population increased by 19.2 %, mainly in the years following the re-unification between Eastern and Western Germany in 1990. Pre-hospital CHD deaths and CHD deaths within 24 h after admission to a hospital (termed as fatal first MI in the present study) are identified through the regional health offices by checking all death certificate diagnoses where CHD is suspected to be the main cause of death. In addition, a written questionnaire is routinely sent to the last treating physician and to the coroner to enquire about disease history, risk factors, prior medication, and circumstances of death (mean response 85 %). Data sources for hospitalized patients include eight hospitals within the study region and two hospitals in the adjacent areas. Up to 31 December 2000, diagnostic criteria for a non-fatal MI were considered according to the WHO-based MONICA-protocol [9]. Since 1 January 2001, all patients with clinical MI diagnoses according to European Society of Cardiology (ESC) and American College of Cardiology (ACC) criteria including troponin assays for diagnosis were also registered [13]. The clinical diagnosis of first MI was validated and categorized according to MONICA criteria [9]. The diagnostic criteria used for the present analysis were

acute chest pain lasting 20 min or longer, not relieved by rest or nitrates, electrocardiographic changes suggestive of an evolving MI (Q waves, non-Q waves in up to four electrocardiograms), and a subsequent increase in the concentration of at least one of three cardiac enzymes (creatinine phosphokinase, aspartate aminotransferase, and lactate dehydrogenase) to more than twice the normal upper limit. For reasons of comparability over the whole time frame, documented troponin values that have been collected since 2001 were not considered for the epidemiologic MI diagnosis. According to MONICA diagnostic criteria, patients with a fatal first MI are defined as those who die pre-hospital or in-hospital within 24 h due to CHD. Patients surviving for at least 24 h (termed as non-fatal first MI in the present study) were interviewed during their hospital stay using a standardised questionnaire, and further data, e.g. from clinical documentation, were gathered in a concluding chart review. Assessment includes demographic data, data on cardiovascular risk factors, medical history, co-morbidities, education, as well as diabetes status (definition see below).

For the present study, we included all patients with a first MI between January 1, 1985 and December 31, 2009 (n = 16,784).

In all non-fatal first MI patients, vital status was ascertained by the registration offices in the study region. These patients were monitored for 26 years or until death occurred, or until the last date of registration (if they moved away from the region), whichever came first (median follow-up 7.2 years).

We had to exclude 306 individuals (1.8 %) since the diabetes status was unknown, thus resulting in a study population of 16,478 patients.

Covariates

The following variables were included: physician diagnosed known diabetes, assessed by chart review (99.7 % of the cases) or by self-report in the personal interview (0.3 %) (yes/no), age (at time of first MI), sex, date of first MI, date of last registration, vital status (dead/alive), and, in case of death, the exact date of death obtained through the local health department. For all patients with a non-fatal first MI, we included further a medical history of hypertension, angina pectoris and stroke, smoking status (i.e. non-smoker, former smoker and current smoker) and highest degree of education (i.e. elementary school, secondary school, A-levels, university, other degree) as proxy measure for socioeconomic status (SES).

Statistical analysis

All analyses were performed for the total population of patients with first MI as well as stratified for sex. A description of the study population was made. Fisher's exact test was used for group comparisons and for testing trends of baseline characteristics.

We assessed crude survival in the whole population by means of Kaplan–Meier estimates, stratified for diabetes.

Multiple logistic regression models were performed to assess the association between diabetes status and the probability of fatal first MI. Results were expressed as odds ratios (OR) and 95 % confidence intervals (CIs). All models were fitted as crude models and stepwise adjusted for age, sex (female vs. male) and calendar period of first MI (1985–1989, 1990–1994, 1995–1999, 2000–2004 and 2005–2009).

To examine the association between diabetes status and mortality among patients with a non-fatal first MI, hazard ratios (HR) with 95 % CI were computed by applying Cox proportional hazards models. The appropriateness of the proportional hazards assumption was visualized using log–log survival plots. If the assumption is fulfilled, the curves should be parallel. Furthermore, we tested the proportional hazards assumption using the test proposed by Grambsch and Therneau [14].

In Cox regression we additionally allowed the HRs to vary between several intervals into which the time until death was classified (28 days and 1, 5, 10 and 15 years) [15]. This was necessary with regard to the subgroup of patients with non-fatal MIs in order to find out whether the HRs for comparing diabetic and non-diabetic subjects were modified by the time between the non-fatal first MI and death. We chose the time intervals in line with previous studies and on the basis of clinical experience. Estimated HRs with 95 % CIs were presented from crude and multivariable analyses.

In addition to age, sex and calendar period of first MI, the multivariable Cox models were further adjusted stepwise for cardiovascular comorbidity (i.e. history of angina pectoris, hypertension or stroke; yes vs. no), smoking status (current or ex-smoking vs. never smoking), and degree of education (all higher levels vs. elementary school).

To analyze the time trends of survival, we fitted Kaplan–Meier curves stratified by calendar time period. Furthermore, we estimated multivariable ORs and HRs comparing individuals with a first MI occurring during the time periods 1990–1994, 1995–1999, 2000–2004 and 2005–2009 with those first diagnosed in the years 1985–1989. In order to investigate whether the calendar time period affects the association between diabetic and non-diabetic individuals we performed all models stratified by calendar time period. In addition, we tested for significance including interaction terms between diabetes and calendar time period.

All analyses were performed using the Statistical Analysis Systems SAS (SAS for Windows 7, Release 9.2, SAS Institute Inc. Cary, NC, USA).

The study was approved by the local ethic authorities and conducted according to the principles of good epidemiological practice [16]. All the patients gave written informed consents.

Results

Baseline characteristics of the study population

The description of the patients with a first MI is presented in Table 1. Of the 16,478 patients with a first MI between 1985 and 2009, 71.2 % were male, and 28.8 % were known to have diabetes mellitus; there was a higher proportion of diabetic patients among the female patients than among the male patients (35.3 vs. 26.2 %, p value Fisher exact test: $p < 0.001$). The majority of first MIs occurred among individuals over 60 years of age. Mean ages were higher in women compared to men, and in diabetic compared to non-diabetic individuals. The number of patients with a first MI increased markedly among male diabetic patients during the study period, the highest proportion of cases being in the period 2000–2004. In contrast, there was no increase among all the other groups. With 6,057 fatal first MIs more than one-third of all patients died before reaching the hospital or during the first day after admission. Patients with a fatal first MI were on average 4 years older compared to patients with a non-fatal first MI. Among patients with a non-fatal first MI the proportion of diagnosed hypertension, angina pectoris and stroke was high with substantially higher proportions among diabetic patients ($p < 0.001$ respectively). More than one-third of patients with non-fatal MI reported to be current smokers. In contrast to the comorbidities, the proportion of current smokers was lower among diabetic subjects compared to their non-diabetic counterparts, which was particularly true for the female population ($p < 0.001$ respectively). Twelve per cent of all non-diabetic patients had A-levels or a university degree, while this proportion was almost 10 % among diabetic patients with a particularly low percentage among the female patients.

Survival in the whole observation period

The crude survival rates of a first MI event in the whole observation period are shown in Table 2.

The proportion of patients surviving the first day after first MI (non-fatal first MI) ranged between 52.0 % (95 % CI 49.6–54.4) and 67.8 % (66.8–68.8) with the lowest number among the female population with diabetes and highest proportion among non-diabetic male individuals. This pattern was also observed with regard to all longer observation periods.

After 25 years, the crude cumulative survival was 7.8 % (95 % CI 4.3–11.3) and 3.7 % (1.5–6.0) in diabetic men and women, as well as 16.2 (14.1–18.4) and 10.2 % (6.6–13.8) in their non-diabetic counterparts, respectively.

Fatal first MIs in the whole observation period

As presented in Table 3, a positive association between diabetes and probability of a fatal first MI could be observed in a multivariable analysis after adjustment for age, sex and year of first MI with an odds ratio of 1.26 (95 % CI 1.17–1.36). The results were almost identical among both sexes (OR males: 1.27; 1.17–1.39; females: 1.23; 1.08–1.39). A positive association with fatal first MI in multivariable analyses was also found for age (OR for 1 year difference in the age groups compared; 95 % CI 1.05; 1.05–1.05) and sex (OR female vs. male: 1.17; 1.09–1.26).

Mortality in patients with non-fatal first MI in the whole observation period

As shown in Table 4, a strong relationship between diabetes and mortality could be seen among patients with a non-fatal first MI. This association weakened by some extent after adjustment for age, whereas further adjustment for sex and calendar period of first MI did not alter the results. This relationship persisted even after further adjustment for cardiovascular diseases (angina pectoris, hypertension, stroke), smoking status, and higher degree of education (HR: 95 % CI 1.68; 1.54–1.84; female: 1.83; 1.55–2.14; male: 1.64; 1.47–1.82).

Furthermore, Table 4 shows HRs comparing diabetic to non-diabetic patients, stratified by intervals in which the time from first MI to death was classified. In both men and women no significant differences between the HRs were found (p-values of test of Grambsch and Therneau: $p = 0.66$ and 0.65, respectively). Mortality risks were significantly higher in the population with diabetes compared to that without diabetes for all follow-up time intervals up to 15 years after adjustment for age, sex, year of first MI, angina pectoris, hypertension, stroke and smoking status. After further adjustment for highest degree of education, the relative risk decreased for the first 28 days substantially (HR 0.89; 0.52–1.55) but remained significantly increased for all time intervals between 28 days and 15 years with nearly constant values between 1.7 and 2.0. After 15 years of follow-up, the relative risk decreased again (HR 1.20; 0.87–1.66). This pattern could be observed for both sexes with somewhat higher relative risks among the female population after 1 year of follow-up.

Table 1 Description of the study population: patients with first fatal and non-fatal myocardial infarction 1985–2009, KORA population

Total cohort (n = 16,478)	Total		Male		Female	
	Diabetes (n = 4,746)	No diabetes (n = 11,732)	Diabetes (n = 3,075)	No diabetes (n = 8,664)	Diabetes (n = 1,671)	No diabetes (n = 3,068)
Mean age at first MI (SD)	64.4 (8.0)	60.9 (9.8)	63.2 (8.3)	59.8 (9.9)	66.7 (6.8)	64.0 (8.9)
Event in calendar period (n)						
1985–1989	774	2,349	430	1,755	344	594
1990–1994	868	2,379	520	1,690	348	689
1995–1999	932	2,334	594	1,707	338	627
2000–2004	1,131	2,427	794	1,838	337	589
2005–2009	1,041	2,243	737	1,674	304	569
Patients with fatal first MI (n = 6,057)	Diabetes (n = 2,012)	No Diabetes (n = 4,045)	Diabetes (n = 1,210)	No Diabetes (n = 2,791)	Diabetes (n = 802)	No Diabetes (n = 1,254)
Mean age at first MI (SD)	66.3 (6.8)	63.7 (9.2)	65.3 (7.1)	62.7 (9.4)	67.9 (6.0)	65.9 (8.2)
Event in calendar period (n)						
1985–1989	387	943	195	651	192	292
1990–1994	481	969	278	635	203	334
1995–1999	490	972	290	658	200	314
2000–2004	382	696	255	513	127	183
2005–2009	272	465	192	334	80	131
Patients with non-fatal first MI (n = 10,421)	Diabetes (n = 2,734)	No diabetes (n = 7,687)	Diabetes (n = 1,865)	No diabetes (n = 5,873)	Diabetes (n = 869)	No diabetes (n = 1,814)
Mean age at first MI (SD)	63.0 (8.5)	59.5 (9.8)	61.8 (8.7)	58.5 (9.8)	65.5 (7.4)	62.7 (9.1)
Event in calendar period (n)						
1985–1989	387	1406	235	1,104	152	302
1990–1994	387	1,410	242	1,055	145	355
1995–1999	442	1,362	304	1,049	138	313
2000–2004	749	1,731	539	1,325	210	406
2005–2009	769	1,778	545	1,340	224	438
Hypertension (n)[a]	2,124	4,579	1,402	3,345	722	1,234
Angina pectoris (n)[a]	595	1,354	377	973	218	381
Stroke (n)[a]	235	338	148	243	87	95
Smoking status (n)[a]						
Current smoker	745	3,184	586	2,581	159	603
Former smoker	762	1,868	668	1,657	94	211
Non-smoker	867	2,050	406	1,238	461	812
Highest degree of education (n)[a]						
Elementary school	1,448	4,226	988	3,207	460	1,019
Secondary school	236	852	169	636	67	216
A levels	40	173	33	141	7	32
University	144	533	134	507	10	26
Other degree	5	18	3	11	2	7

[a] Information available only for persons with non-fatal first MI, values missing regarding hypertension (n = 34), angina pectoris (n = 66), stroke (n = 589), smoking status (n = 945), highest degree of education (n = 2,746)

Time trend of fatal first MIs

The crude survival rates of a first MI event stratified by calendar time period are shown in Table 2 and Fig. 1. The proportion of fatal first MIs remained nearly constant until 2000 and decreased markedly thereafter, which was true both for males and females as well as diabetic and non-diabetic subjects. This pattern was confirmed in the

Table 2 Crude survival according to event year, sex and presence of diabetes

Time from event	Men (n = 11,739)		Women (n = 4,739)	
	Diabetes Proportion surviving at end of interval (%) (95 % CI)	No diabetes Proportion surviving at end of interval (%) (95 % CI)	Diabetes Proportion surviving at end of interval (%) (95 % CI)	No diabetes Proportion surviving at end of interval (%) (95 % CI)
1 day[a]				
1985–1989	54.7 (49.9–59.4)	62.9 (60.6–65.2)	44.2 (38.9–49.4)	50.8 (46.8–54.9)
1990–1994	46.5 (42.3–50.8)	62.4 (60.1–64.7)	41.7 (36.5–46.8)	51.5 (47.8–55.3)
1995–1999	51.2 (47.2–55.2)	61.5 (59.1–63.8)	40.8 (35.6–46.1)	49.9 (46.0–53.8)
2000–2004	67.9 (64.6–71.1)	72.1 (70.0–74.1)	62.3 (57.1–67.5)	68.9 (65.2–72.7)
2005–2009	73.9 (70.8–77.1)	80.0 (78.1–82.0)	73.7 (68.7–78.6)	77.0 (73.5–80.4)
1985–2009	60.7 (58.9–62.4)	67.8 (66.8–68.8)	52.0 (49.6–54.4)	59.1 (57.4–60.9)
28 days				
1985–1989	48.4 (53.4–53.1)	58.6 (56.3–60.9)	35.8 (30.7–40.8)	46.8 (42.8–50.8)
1990–1994	42.7 (38.4–46.9)	58.9 (56.6–61.3)	35.3 (30.3–40.4)	47.8 (44.0–51.5)
1995–1999	46.5 (42.5–50.5)	57.6 (55.3–60.0)	34.3 (29.3–39.4)	46.9 (43.0–50.8)
2000–2004	61.3 (57.9–64.7)	68.3 (66.2–70.5)	55.8 (50.5–61.1)	64.5 (60.6–68.4)
2005–2009	68.2 (65.8–71.6)	75.5 (73.5–77.6)	64.8 (59.4–70.2)	71.9 (68.2–75.6)
1985–2009	55.2 (53.4–56.9)	63.8 (62.8–64.8)	44.7 (42.3–47.1)	55.1 (53.3–56.8)
1 year				
1985–1989	44.4 (39.7–49.1)	55.7 (53.3–58.0)	30.5 (25.7–35.4)	43.4 (39.4–47.4)
1990–1994	39.6 (35.4–43.8)	56.7 (54.3–59.0)	31.6 (26.7–36.5)	45.1 (41.4–48.9)
1995–1999	44.1 (40.1–48.1)	56.1 (53.7–58.4)	31.4 (26.4–36.3)	45.3 (41.4–49.2)
2000–2004	58.7 (55.2–62.1)	66.5 (64.3–68.6)	53.7 (48.4–59.0)	62.5 (58.6–66.4)
2005–2009	62.6 (59.8–66.2)	72.9 (70.7–75.1)	60.5 (54.9–66.2)	69.7 (65.8–73.5)
1985–2009	51.6 (49.9–53.4)	61.6 (60.5–62.6)	41.0 (38.7–43.4)	52.7 (50.9–54.5)
5 years				
1985–1989	31.6 (27.2–36.0)	49.0 (46.7–51.3)	21.2 (16.9–25.5)	38.6 (34.6–42.5)
1990–1994	30.9 (26.9–34.9)	50.9 (48.5–53.2)	23.0 (18.6–27.4)	38.0 (34.4–41.6)
1995–1999	37.7 (33.8–41.6)	51.9 (49.5–54.2)	25.4 (20.7–30.0)	42.1 (38.2–46.0)
2000–2004	51.2 (47.7–54.7)	61.8 (59.5–64.0)	45.1 (39.8–50.4)	58.9 (54.9–62.8)
2005–2009	55.7 (51.8–59.7)	67.9 (65.4–70.3)	50.2 (43.8–56.6)	63.4 (59.1–67.7)
1985–2009	43.1 (41.3–44.9)	56.2 (55.1–57.2)	32.4 (30.1–34.7)	47.5 (45.7–49.3)
10 years				
1985–1989	20.4 (16.6–24.2)	38.5 (36.2–40.8)	13.7 (10.0–17.3)	30.1 (26.4–33.8)
1990–1994	21.7 (18.2–25.3)	43.0 (40.7–45.4)	14.9 (11.2–18.7)	30.4 (27.0–33.9)
1995–1999	27.5 (23.9–31.1)	44.5 (42.1–46.8)	16.7 (12.7–20.7)	35.2 (31.5–39.5)
2000–2004	39.8 (35.8–43.7)	52.6 (49.9–55.3)	32.9 (27.0–38.8)	48.5 (43.6–53.4)
1985–2009	31.5 (29.6–33.4)	47.1 (45.9–48.2)	21.9 (19.6–24.1)	38.9 (37.0–40.8)
15 years				
1985–1989	13.8 (10.5–17.1)	28.9 (26.8–31.0)	5.8 (3.3–8.3)	21.7 (18.4–25.0)
1990–1994	12.2 (9.3–15.0)	33.4 (31.1–35.7)	7.5 (4.7–10.2)	23.4 (20.3–26.6)
1995–1999	20.4 (16.7–24.2)	35.4 (32.7–38.1)	7.4 (4.0–10.9)	29.2 (25.1–33.3)
1985–2009	20.6 (18.4–22.8)	36.5 (35.2–37.8)	10.2 (8.1–12.3)	29.9 (27.9–31.9)
20 years				
1985–1989	9.8 (7.0–12.7)	21.0 (19.1–22.9)	2.6 (0.9–4.3)	14.3 (11.5–17.2)
1990–1994	8.3 (5.7–10.9)	22.3 (19.9–24.7)	4.9 (2.0–7.7)	16.5 (13.2–19.8)
1985–2009	14.3 (11.9–16.7)	25.7 (24.2–27.1)	5.6 (3.4–7.8)	20.0 (17.6–22.3)
25 years				
1985–1989	5.2 (2.6–7.9)	13.2 (11.2–15.2)	1.7 (0.4–3.1)	7.4 (4.5–10.3)
1985–2009	7.8 (4.3–11.3)	16.2 (14.1–18.4)	3.7 (1.5–6.0)	10.2 (6.6–13.8)

[a] Proportion of fatal first MI

Table 3 Odds Ratios (OR) for the probability of fatal first MI in diabetic patients compared to non-diabetic patients—total and stratified by sex and/or time period representing the year of first MI, results of logistic regression

	Crude OR (95 % CI)	Add age (95 % CI)	Add sex (95 % CI)	Add calendar period of first MI (95 % CI)
Strata				
Time periods				
1985–1989	1.49 (1.27–1.76)	1.26 (1.07–1.49)	1.21 (1.02–1.43)	
1990–1994	1.81 (1.55–2.12)	1.56 (1.33–1.84)	1.54 (1.31–1.81)	
1995–1999	1.55 (1.33–1.81)	1.31 (1.12–1.53)	1.29 (1.10–1.51)	
2000–2004	1.27 (1.09–1.48)	1.09 (0.93–1.27)	1.09 (0.93–1.27)	
2005–2009	1.35 (1.14–1.61)	1.21 (1.01–1.44)	1.21 (1.01–1.44)	
1985–2009 (total, n = 16,478)	1.40 (1.31–1.50)	1.20 (1.12–1.29)	1.19 (1.11–1.28)	1.26 (1.17–1.36)
Time periods (males)				
1985–1989	1.41 (1.14–1.74)	1.24 (1.00–1.55)	–	
1990–1994	1.91 (1.57–2.33)	1.64 (1.34–2.02)	–	
1995–1999	1.52 (1.26–1.84)	1.30 (1.07–1.58)	–	
2000–2004	1.22 (1.02–1.46)	1.06 (0.88–1.27)	–	
2005–2009	1.41 (1.15–1.73)	1.26 (1.02–1.55)	–	
1985–2009 (total, n = 11,739)	1.37 (1.25–1.49)	1.19 (1.09–1.29)	–	1.27 (1.17–1.39)
Time periods (females)				
1985–1989	1.31 (1.00–1.71)	1.19 (0.91–1.56)	–	
1990–1994	1.49 (1.15–1.93)	1.39 (1.07–1.81)	–	
1995–1999	1.45 (1.11–1.89)	1.27 (0.96–1.68)	–	
2000–2004	1.34 (1.01–1.78)	1.17 (0.88–1.56)	–	
2005–2009	1.19 (0.87–1.65)	1.10 (0.79–1.52)	–	
1985–2009 (total, n = 4,739)	1.34 (1.18–1.51)	1.20 (1.06–1.35)	–	1.23 (1.08–1.39)

multivariate analysis after adjustment for diabetes status, age and sex (OR and 95 % CI calendar time period of first MI in the years 1990–1994, 1995–1999, 2000–2004, 2005–2009 compared to 1985–1989: 1.08; 0.97–1.19, 1.07; 0.97–1.18, 0.57; 0.51–0.63, 0.38; 0.34–0.42) with consistent results in all relevant strata (data not shown). In contrast, no consistent change of the OR comparing diabetic and non-diabetic individuals regarding the probability of fatal MI during the calendar time period could be observed, as shown in Table 3. Although ORs varied significantly between the calendar year periods (p-values of interaction <0.05, data not shown), no consistent time trend could be observed. Again, results were similar for both sexes albeit among the female patients the significant association mostly disappeared due to low case numbers.

Time trend of mortality in patients with non-fatal first MI

As shown in Table 2 and Fig. 1, survival for longer observation time periods improved considerably throughout all calendar time strata of first MI events. This improvement was seen in both sexes among diabetic as well as non-diabetic individuals: Crude cumulative 5-year survival among diabetic and non-diabetic individuals with a first MI in the years 1985–1989 (both sexes combined) was 26.9 (95 % CI 23.7–30.0) and 46.3 % (44.3–48.3). These proportions increased substantially for those individuals with a first MI in the years 2005–2009 to 53.6 (50.1–57.0) and 66.6 % (64.5–68.8) respectively. Likewise, this pattern could be observed in a multivariate analysis for the total population after adjustment for diabetes status, age, sex, cardiovascular diseases, smoking status, and higher degree of education (HR and 95 % CI period of first MI in the years 1990–1994, 1995–1999, 2000–2004, 2005–2009 compared to 1985–1989: 0.88; 0.79–0.98, 0.69; 0.62–0.78, 0.48; 0.42–0.55, 0.51; 0.43–0.62) with consistent results in all relevant strata (data not shown). As shown in Table 4, no clear time trend in the relative risk between diabetic and non-diabetic individuals was found either in men or in women when models were classified by calendar time period of first MI occurrence. The association between diabetes and mortality remained significant for all calendar time periods with multiple adjusted HRs between 1.49; 1.20–1.86 (period 2000–2004) and 1.90; 1.61–2.25 (period 1990–1994). No significant

Table 4 Hazard ratio (HR) for mortality in diabetic patients compared to non-diabetic patients with a non-fatal first MI—total and stratified by sex and/or time period representing the year of first MI, results of Cox-regression

	Crude HR (95 % CI)	Add age (95 % CI)	Add sex (95 % CI)	Add calendar period of first MI (95 % CI)	Add angina[a], HT[a] and stroke (95 % CI)	Add smoking[b] (95 % CI)	Add education[c] (95 % CI)
Modelled with proportional hazards							
Strata							
Time periods							
1985–1989	1.95 (1.73–2.20)	1.57 (1.39–1.78)	1.61 (1.42–1.82)		1.56 (1.37–1.77)	1.57 (1.36–1.80)	1.62 (1.37–1.91)
1990–1994	2.02 (1.77–2.30)	1.69 (1.49–1.93)	1.70 (1.49–1.94)		1.68 (1.47–1.92)	1.80 (1.57–2.07)	1.90 (1.61–2.25)
1995–1999	2.06 (1.78–2.40)	1.85 (1.59–2.15)	1.85 (1.59–2.15)		1.82 (1.56–2.12)	1.82 (1.55–2.14)	1.81 (1.50–2.18)
2000–2004	1.84 (1.57–2.14)	1.57 (1.34–1.84)	1.57 (1.35–1.84)		1.52 (1.26–1.82)	1.54 (1.26–1.89)	1.49 (1.20–1.86)
2005–2009	1.82 (1.49–2.22)	1.58 (1.29–1.93)	1.58 (1.29–1.93)		1.62 (1.28–2.03)	1.52 (1.16–2.01)	1.54 (1.12–2.12)
1985–2009 (total, n = 10,421)	1.88 (1.76–2.00)	1.60 (1.50–1.70)	1.60 (1.50–1.71)	1.66 (1.56–1.77)	1.62 (1.52–1.74)	1.66 (1.55–1.79)	1.68 (1.54–1.84)
Time periods (males)							
1985–1989	1.74 (1.49–2.03)	1.56 (1.33–1.82)			1.49 (1.28–1.75)	1.58 (1.34–1.87)	1.78 (1.46–2.17)
1990–1994	1.94 (1.65–2.28)	1.63 (1.38–1.92)			1.59 (1.35–1.88)	1.73 (1.45–2.05)	1.94 (1.59–2.37)
1995–1999	1.78 (1.48–2.14)	1.55 (1.29–1.87)			1.54 (1.27–1.86)	1.55 (1.27–1.88)	1.52 (1.21–1.91)
2000–2004	1.76 (1.47–2.11)	1.49 (1.24–1.79)			1.38 (1.11–1.71)	1.40 (1.11–1.78)	1.29 (0.99–1.67)
2005–2009	1.77 (1.39–2.25)	1.54 (1.20–1.96)			1.62 (1.23–2.14)	1.51 (1.08–2.10)	1.62 (1.10–2.37)
1985–2009 (total, n = 7,738)	1.72 (1.59–1.86)	1.48 (1.36–1.60)		1.55 (1.43–1.68)	1.51 (1.38–1.64)	1.57 (1.44–1.72)	1.64 (1.47–1.82)
Time periods (females)							
1985–1989	2.27 (1.84–2.81)	1.72 (1.38–2.13)			1.75 (1.39–2.20)	1.56 (1.21–2.01)	1.40 (1.03–1.91)
1990–1994	2.01 (1.61–2.51)	1.83 (1.46–2.28)			1.84 (1.46–2.31)	1.94 (1.52–2.46)	1.76 (1.28–2.41)
1995–1999	2.76 (2.12–3.60)	2.77 (2.12–3.62)			2.65 (2.01–3.49)	2.73 (2.04–3.67)	2.83 (1.98–4.04)
2000–2004	2.04 (1.52–2.74)	1.84 (1.37–2.47)			1.90 (1.35–2.66)	1.99 (1.35–2.92)	2.27 (1.48–3.48)
2005–2009	1.84 (1.29–2.64)	1.67 (1.16–2.39)			1.67 (1.10–2.55)	1.68 (0.99–2.84)	1.58 (0.89–2.81)
1985–2009 (total, n = 2,683)	2.15 (1.92–2.42)	1.90 (1.69–2.13)		1.91 (1.71–2.15)	1.91 (1.69–2.16)	1.91 (1.67–2.18)	1.83 (1.55–2.14)
Modelled with time dependent hazards							
Total (n = 10,421)							
1–28 days	1.79 (1.55–2.07)	1.49 (1.29–1.72)	1.50 (1.29–1.73)	1.55 (1.34–1.80)	1.46 (1.23–1.73)	1.43 (1.15–1.77)	0.89 (0.52–1.55)
28 days–1 year	1.90 (1.56–2.32)	1.59 (1.30–1.94)	1.60 (1.31–1.95)	1.66 (1.36–2.03)	1.56 (1.26–1.92)	1.68 (1.33–2.11)	1.75 (1.34–2.28)
1–5 years	2.10 (1.84–2.39)	1.76 (1.54–2.01)	1.77 (1.55–2.02)	1.85 (1.62–2.12)	1.82 (1.59–2.09)	1.81 (1.56–2.09)	1.68 (1.43–1.98)
5–10 years	1.87 (1.64–2.13)	1.59 (1.40–1.82)	1.60 (1.40–1.82)	1.68 (1.48–1.92)	1.64 (1.43–1.88)	1.68 (1.46–1.93)	1.70 (1.46–1.99)
10–15 years	2.03 (1.71–2.40)	1.78 (1.50–2.11)	1.79 (1.51–2.12)	1.82 (1.53–2.15)	1.83 (1.54–2.17)	1.91 (1.61–2.28)	2.03 (1.68–2.46)
>15 years	1.25 (0.96–1.62)	1.11 (0.85–1.44)	1.11 (0.86–1.45)	1.11 (0.86–1.45)	1.17 (0.89–1.52)	1.17 (0.89–1.53)	1.20 (0.87–1.66)
Males (n = 7,738)							
1–28 days	1.57 (1.30–1.89)	1.31 (1.09–1.58)		1.38 (1.15–1.67)	1.28 (1.03–1.58)	1.30 (1.00–1.69)	0.98 (0.51–1.89)
28 days–1 year	1.86 (1.46–2.36)	1.56 (1.23–1.99)		1.64 (1.29–2.09)	1.57 (1.22–2.03)	1.75 (1.32–2.31)	1.85 (1.35–2.52)

Table 4 continued

	Crude HR (95 % CI)	Add age (95 % CI)	Add sex (95 % CI)	Add calendar period of first MI (95 % CI)	Add angina[a], HT[a] and stroke (95 % CI)	Add smoking[b] (95 % CI)	Add education[c] (95 % CI)
1–5 years	1.98 (1.69–2.33)	1.68 (1.43–1.98)		1.78 (1.52–2.10)	1.71 (1.44–2.02)	1.67 (1.40–1.99)	1.61 (1.33–1.95)
5–10 years	1.79 (1.53–2.10)	1.53 (1.31–1.80)		1.65 (1.40–1.93)	1.60 (1.36–1.88)	1.68 (1.42–1.99)	1.69 (1.41–2.03)
10–15 years	1.64 (1.32–2.03)	1.45 (1.17–1.81)		1.50 (1.21–1.86)	1.50 (1.21–1.87)	1.63 (1.30–2.03)	1.82 (1.43–2.31)
>15 years	1.18 (0.86–1.61)	1.09 (0.80–1.49)		1.09 (0.80–1.49)	1.13 (0.83–1.55)	1.12 (0.81–1.55)	1.21 (0.82–1.78)
Females (n = 2,683)							
1–28 days	2.12 (1.66–2.73)	1.84 (1.44–2.37)		1.86 (1.45–2.38)	1.79 (1.35–2.37)	1.69 (1.16–2.46)	0.69 (0.25–1.89)
28 days–1 year	1.91 (1.34–2.71)	1.66 (1.17–2.37)		1.69 (1.19–2.41)	1.50 (1.04–2.16)	1.48 (0.98–2.21)	1.50 (0.91–2.49)
1–5 years	2.26 (1.78–2.87)	1.98 (1.56–2.51)		2.02 (1.59–2.57)	2.09 (1.64–2.67)	2.17 (1.66–2.83)	1.85 (1.37–2.50)
5–10 years	1.97 (1.56–2.50)	1.77 (1.39–2.23)		1.79 (1.41–2.27)	1.76 (1.38–2.24)	1.68 (1.30–2.18)	1.79 (1.34–2.41)
10–15 years	3.00 (2.25–4.01)	2.77 (2.08–3.70)		2.74 (2.05–3.66)	2.83 (2.11–3.79)	2.77 (2.06–3.72)	2.63 (1.88–3.67)
>15 years	1.44 (0.88–2.35)	1.18 (0.72–1.93)		1.18 (0.72–1.92)	1.31 (0.79–2.17)	1.36 (0.81–2.29)	1.23 (0.67–2.25)

[a] 66 values missing regarding angina, 34 values missing regarding hypertension (HT)

[b] 589 values missing regarding apoplexy

[c] 945 values missing regarding smoking, 2,746 values missing regarding education

interaction between diabetes and calendar time periods was found, indicating that this relationship remained nearly constant over the whole follow-up (data not shown).

Discussion

Study findings and implications

Considering survival of individuals after first MI, both the probability of a fatal first MI as well as mortality in patients with non-fatal first MIs is significantly higher in the diabetic population compared to the non-diabetic population. This excess mortality is observed particularly in women. In both sexes, there is a tendency that the excess mortality due to diabetes decreases after 15 years. It may be that individuals with diabetes who survive the first years have less severe diabetes. Furthermore, individuals with MI may develop several comorbidities, so that the difference between individuals with and without diabetes diminishes. However, these estimates were quite imprecise due to low case numbers, since only earlier MI cases (years 1985–1994) could be followed in this time span where the survival rate was worse than in later periods.

During the past 25 years, survival after a first MI has improved continuously regarding first non-fatal MIs and since 2000 also with regard to fatal MIs. However, the excess risk with diabetes remained unchanged with respect to both outcomes. One may argue that no improvement has been seen. On the other hand, one may state that patients with diabetes experience the same improvement as patients without diabetes.

One has to consider that the definition of diabetes changed over the study period. Furthermore, due to higher awareness of undiagnosed diabetes and more screening activities, the proportion of people whose diabetes is diagnosed may have changed. Both aspects would probably lead to a larger but less severely diseased pool of persons with diabetes in later years, which is associated with an increased survival after first MI in the diabetic population. We previously performed an analysis covering the years 1985–2006 [2]. In the estimated non-diabetic population, we found a decrease of MI incidence of about 1.5–2.0 % per year. In the estimated population of diabetic women, there was a comparable decrease. In contrast, in the estimated population of diabetic men, the incidence of MI increased by about 1 % per year. Regarding the whole study period, the incidence of MI decreased by 34 and 27 % in the estimated population of non-diabetic men and women (RR 0.66; 0.59–0.74 and 0.73; 0.62–0.87 in men and women, respectively). In diabetic women, it decreased by 27 % (RR 0.73; 0.61–0.88), whereas in the estimated population of diabetic men, it increased by 25 % (RR 1.25;

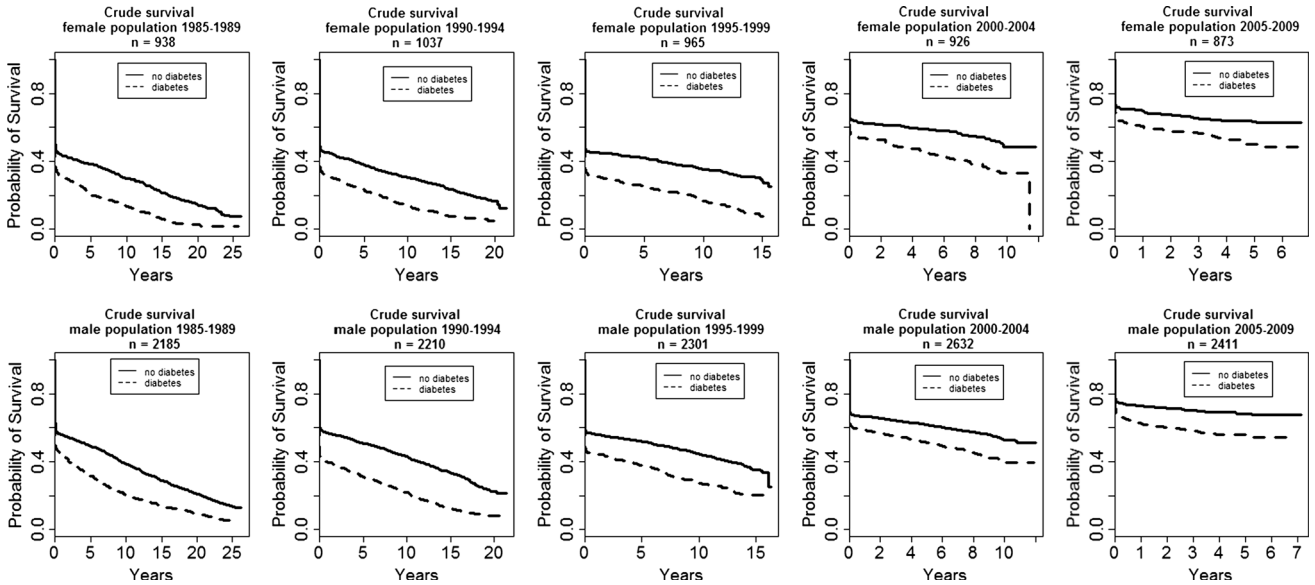

Fig. 1 Kaplan–Meier estimates of crude survival in diabetic patients compared to non-diabetic patients with first fatal and non-fatal MI

1.07–1.45) [2]. It is possible that these changes affect survival in patients with a first MI. However, we assume that a better survival is most probably due to an improved emergency system, a much higher rate of acute revascularisation after implementation of primary percutaneous coronary intervention (PCI) as therapy of choice, and advances in pharmacological treatment, as also concluded in other studies [8].

Comparison with other studies

Most studies are limited in various ways. Some are based on hospital data and thus do not include pre-hospital deaths [4, 7]. Others include several covariates, but cover only a short follow-up period [3, 13]. Winell et al. analysed acute coronary syndrome, without separating first MIs from other first acute coronary syndromes [6]. However, the study results are in line with our findings, with higher mortality after a first MI in diabetic patients compared to non-diabetic patients, in particular in women, and higher relative risks for the long-term follow-up.

In contrast to the study of Meisinger et al. [3], in which the same data source was used but with a shorter observation period, we found a significant increased relative risk of short-term mortality, which was also true not only for the first day but also for the 28 day period following a first MI including pre-hospital deaths (OR 1.34; 1.25–1.44). However, our findings that survival after a first MI improves among diabetic and non-diabetic individuals in the same manner compare well with previous studies stemming from Scandinavian registries [5, 6]. To the best of our knowledge there is only one population-based study which investigated mortality after a first MI in the diabetic and the non-diabetic population aged 25–64 years over more than a decade (1989–2006), and including pre-hospital deaths [8]. To be able to compare both studies, we performed our analyses for the age group 25–64 years and the same time period (1989–2006; n = 6,292). Furthermore, we classified only patients who died before reaching hospital as pre-hospital deaths, as Eliasson did. We found 19–24 % first MIs with pre-hospital death with the highest proportion among non-diabetic women, which is higher than in the Swedish study (10–17 % with the highest proportion among diabetic men). After exclusion of pre-hospital deaths, the long-term age-adjusted relative risk of death in diabetic compared to non-diabetic patients was somewhat lower than in the Swedish study (HR 1.6; 1.5–1.8 in Germany vs. 2.1; 1.9–2.4 in Sweden). Likewise, when including pre-hospital deaths, these estimates in Germany were lower than in Sweden (HR 1.3; 1.2–1.4 vs. 1.7; 1.5–1.8), which was true for both sexes. However, in both studies, mortality was significantly increased among diabetic patients, with higher differences in women. Furthermore, in both studies, a marked improvement in survival can be observed after the year 2000.

Study limitations and strength

Several limitations have to be considered. Firstly, the study population is limited to patients aged 25–74 years. This is a larger age span than considered in other studies. However, a relevant number of first MIs occur in older ages only. Secondly, we have limited information about patients with pre-hospital death, and diabetes-specific information such

as HbA1c is not available over the whole study period. However, we were able to include a number of covariates for all patients with a non-fatal first MI. Thirdly, some bias may exist, e.g. patients without diabetes at baseline may have developed diabetes during the observation period, and patients with diabetes may be more likely to have a recurrent MI because first MIs were "silent MIs". However, this limitation is present in all observation studies.

The strengths of the study are the following: It is based on a standardised data assessment according to the MONICA protocol, which has remained stable since 1985. An important advantage is that we were able to include all first MIs in the study region, including pre-hospital CHD deaths. Furthermore, we observed a large number of cases over a long time span and could follow patients with non-fatal first MIs over a long period.

Conclusions

In conclusion, our population-based study covering a period of 25 years shows that survival has improved in both diabetic and non-diabetic patients in a similar manner. However, mortality after a first MI remained significantly increased in the diabetic population, in particular in women.

Acknowledgments The project was supported by a grant of the German Ministry of Health and the German Diabetes Foundation. The German Diabetes Centre is financed by the German Federal Ministry of Health and by the Northrhine-Westphalian Ministry of Science. The KORA research platform and the MONICA Augsburg studies were initiated and financed by the Helmholtz Zentrum München, German Research Centre for Environmental Health, which is funded by the German Federal Ministry of Education, Science, Research and Technology and by the State of Bavaria. Since the year 2000 the myocardial infarction data collection is co-financed by the German Federal Ministry of Health to provide population-based myocardial infarction morbidity data for the official German Health Report (see www.gbe-bund.de). We thank all members of the Helmholtz Zentrum München, Institute of Epidemiology and the field staff in Augsburg who were involved in the planning and conduction of the study. We wish to thank the local health departments and the private physicians of the study area as well as the clinicians of the hospitals involved for their support. Finally, we express our appreciation to all study participants.

Conflict of interest All authors declare that they have no conflict of interest.

References

1. Rautio A, Lundberg V, Messner T, Nasic S, Stegmayr B, Eliasson M. Favourable trends in the incidence and outcome of myocardial infarction in non-diabetic, but not in diabetic subjects: findings from the MONICA myocardial infarction registry in northern Sweden in 1989–2000. J Intern Med. 2005;258:369–77.
2. Icks A, Dickhaus T, Hörmann A, et al. Lower incidence of myocardial infarction in non-diabetic subjects and in diabetic women, but not in diabetic men, in the population aged 25 to 74 years. Findings from the MONICA/KORA myocardial infarction registry in Southern Germany, 1985–2006. Diabetologia. 2009;52:1836–41.
3. Meisinger C, Heier M, von Scheidt W, Kirchberger I, Hörmann A, Kuch B. Gender-specific short and long-term mortality in diabetic versus nondiabetic patients with incident acute myocardial infarction in the reperfusion era (the MONICA/KORA Myocardial Infarction Registry). Am J Cardiol. 2010;106:1680–4.
4. Koek HL, Soedamah-Muthu SS, Kardaun JW. Short and long-term mortality after acute myocardial infarction: comparison of patients with and without diabetes mellitus. Eur J Epidemiol. 2007;22:883–8.
5. Norhammar A, Lindback J, Ryden L, Wallentin L, Stenestrand U. Improved but still high short- and long-term mortality rates after myocardial infarction in patients with diabetes mellitus: a time-trend report from the Swedish Register of Information and Knowledge about Swedish Heart Intensive Care Admission. Heart. 2007;93:1577–83.
6. Winell KM, Paakkonen R, Pietila A, Niemi MK, Reunanen AR, Salomaa VV. Case fatality rates after first acute coronary syndrome in persons treated for type 2 diabetes show an improving trend. Diabetologia. 2009;53:472–80.
7. Crowley A, Menon V, Lessard D, et al. Sex differences in survival after acute myocardial infarction in patients with diabetes mellitus (Worcester Heart Attack Study). Am Heart J. 2003;146:824–31.
8. Eliasson M, Jansson JH, Lundblad D, Näslund U. The disparity between long-term survival in patients with and without diabetes following a first myocardial infarction did not change between 1989 and 2006: an analysis of 6,776 patients in the Northern Sweden MONICA Study. Diabetologia. 2011;54:2538–43.
9. Löwel H, Lewis M, Hörmann A, Keil U. Case finding, data quality aspects, and comparability of myocardial infarction registers. Results of a Southern German register study. J Clin Epidemiol. 1991;44:249–60.
10. WHO Monica Project Principal Investigators. The World Health Organisation MONICA Project (monitoring trends and determinants in cardiovascular disease): a major international collaboration. J Clin Epidemiol. 1988;41:105–14.
11. Tunstall-Pedoe H, Kuulasmaa K, Amouyel P, Arveiler D, Rajakangas AM, Pajak A. Myocardial infarction and coronary deaths in the World Health Organisation MONICA Project. Registration procedures, event rates, and case-fatality rates in 38 populations from 21 countries in four continents. Circulation. 1994;90:583–612.
12. Löwel H, Meisinger C, Heier M, Hörmann A. The population-based Acute Myocardial Infarction (AMI) Registry of the MONICA/KORA study region of Augsburg. Gesundheitswesen. 2005;67(Suppl 1):S31–7.
13. Meisinger C, Hörmann A, Heier M, Kuch B, Löwel H. Admission blood glucose and adverse outcomes in non-diabetic patients with myocardial infarction in the reperfusion era. Int J Cardiol. 2006;113:229–35.
14. Grambsch P, Therneau T. Proportional hazards tests and diagnostics based on weighted residuals. Biometrika. 1994;81:515–26.
15. Machin D, Cheung YB, Parmar MKB. Survival analysis: a practical approach. 2nd ed. Wiley: New York; 2005.
16. Work Group Epidemiological methods. Good practice analysis of secondary data: revision after detailed working-over (in German). Gesundheitswesen. 2008;70:54–60.