Zusammenfassung

Schlüsselwörter
MONICA/KORA-Herzinfarktregister Augsburg · plötzlicher Herz- tod · kardiologische Akutversorgung · Epidemiologie · zeitliche Trends

Abstract
The population-based MONICA/KORA registry of acute myocardial infarction (AMI) for the study population of Augsburg was established in 1984. The major task was the description of time trends of AMI morbidity, ischaemic heart disease (IHD) mortality per 100,000 population and their underlying determinants. Results of 18 years of registration are presented stratified by gender and discussed from a public health point of view. From 1985 through 2002 a total number of 17,884 cases of AMI and IHD deaths (12,798 male; 5,086 female cases; age 25 – 74 years) were registered and validated according to MONICA rules. In the course of time, IHD mortality per 100,000 population decreased from 280 to 168 in men and from 88 to 54 in women; AMI morbidity decreased from 542 to 404 in men, and from 171 to 122 AMI in women. The important decrease of IHD mortality was mainly explained by a decline of recurrent events and a reduction of 28-day case fatality (men from 52 % to 42 %, women from 52 % to 44 %) as result of an intensified invasive reperfusion therapy and evidence-based drug medication. The presented results show positive developments, but underscore the necessity for increased primary prevention.

Key words
MONICA Coronary Event Register Augsburg · sudden cardiac death · acute cardiological care · epidemiology · time trends
Background

Since the beginnings of the 1980s, population-based registries of acute myocardial infarction (AMI) and coronary deaths for the 35 to 64 year old inhabitants were established as part of the WHO MONICA (multinational monitoring of trends and determinants in cardiovascular disease) project [1]. Registries from 21 countries and 38 study regions have contributed to testing the MONICA hypotheses [2]. The aim of the MONICA registries was a ten year long observation of the age and sex-specific rates of acute coronary events (AMI attacks and CHD deaths) per 100,000 population and of the 28-day case-fatality (CF) per 100 coronary events [3]. At least two population-representative cardiovascular risk factor surveys were conducted at the beginning and at the end of the 10-year MONICA study period (1984/85 to 1994/95). Ten-years time trends of risk factor prevalences were opposed to time trends of the AMI rates to quantify the impact of changes in risk factor profile on AMI occurrence within each study population.

Right from the start, the MONICA Augsburg registry was planned with four additional special features:

(1) It was broadened to the 25 to 74 year old population for a better representation of the AMI rates especially in the female population [4]. In Germany, only 10% of all coronary deaths among women (men 25%) occurred before the age of 65 in the year 1985; up to the 75th year of age, the percentage of coronary deaths increased to 28% in women and to 58% in men.

(2) The Augsburg registry works on the basis of a written patient consent (response > 95%) which allows a re-identification of each registered person with a primarily non-fatal MI. Therefore the possibility of a life-long follow-up for long-term survival analyses is given [5].

(3) In cases of a CHD death, the last treating physicians and/or coroners are questioned promptly through a written questionnaire for the cardiovascular history including drug medication and circumstances of death (e.g. seen alive by a physician, place of death) [6].

(4) Diabetes mellitus was added to the risk factor profile of the register cases for a better explanation of differences in 28-day case-fatality and survival [7].

After the 10-years MONICA period from (1984/95), the Augsburg AMI registration was continued as part of the KORA (Cooperative Health Research of the Region of Augsburg) research program. Since 2000, the register is partly financed by the German Ministry of Health and Social Security (BMGS) and is used as a data base for the German National Health Report [8]. In addition to the core questions of the Augsburg registry further register-based studies were implemented in cooperation with gsf-internal and -external partners:

(1) the register-based KORA Family Heart Study on genetic determinants of an AMI was conducted in 1996/97 in cooperation with the University of Regensburg.

(2) Since 1999, the GSF-working group of air pollution health effects had focused their research on registered AMI patients to study air pollution effects on cardiovascular health. The environmental studies were co-financed by financial support from US [9] and from the European Union (see www.gsf.de/KORA).

(3) As a cooperation with the Medical School of Hannover, the medical care data of the Augsburg AMI registry from the years 1985 to 2001 were made available for an international comparison in the frame of the Technological Change in Health Care (TECH) Research Network [10].

In the present paper selected sex-specific results of the MONICA/KORA registry based on the four time intervals, 1985/87, 1990/92, 1995/97, and 2000/02 are presented. The register-based CHD mortality is discussed in relation to the official mortality statistics of Germany. Time trends of AMI attack rates subdivided into incident and recurrent event rates per 100,000 population are shown. For hospitalized patients with incident AMI, time trends of the cardiovascular risk profile, and the acute reperfusion therapy are presented. Finally, time trends of the survival course after incident AMI including pre-hospital deaths are reported. Possible explanations of the observed trends are discussed from a public health point of view.

Material and methods

Case finding and data collection by the Augsburg registry

Clinically confirmed AMI cases (from 1985 to 1998 Q-wave and non-Q-wave AMI, since 1999 additionally ST-elevation and non-ST-elevation AMI) were identified during their hospitalization contacting the treating physicians located primarily in up to 20 and presently in 9 still existing hospitals within and surrounding the study region (Table 1).

The study region comprises the city of Augsburg and the two adjacent more rural districts of Augsburg and Aichach-Friedberg, all together with about 200,000 female and 200,000 male registered residents in the age group 25 to 74 years. All patients with a clinically confirmed AMI were asked for their willingness for life-long register participation. Afterwards they were interviewed about their own AMI and family history including drug medication, circumstances of the acute event and the pre-hospital supply. Medical care data during hospitalization were collected by hospital chart review. In WHO MONICA, clinically confirmed cases of non-fatal AMI (patients surviving the 28th-day) were categorized in definite AMI (MD1), possible AMI (MD2), successful resuscitation without signs of an definite or possible AMI (MD3), no AMI (MD4) using a defined algorithm. The MONICA-algorithm for epidemiological comparability comprises the three diagnostic criteria, acute symptoms (nitrate resistant chest pain lasting 20 minutes or longer), elevated heart muscle specific enzymes (GOT, CPK, CK-MB, and troponin documented since 2001), and ECG signs (Q waves, ST-elevation) [11]. The MONICA ECG-variable based on Minnesota coding of up to 4 ECGs was realized during the 10 years MONICA period. Additionally, the clinical ECG diagnosis (diagnostic finding in at least one ECG) was also documented since 1985 to date and has built the basis for long-term comparisons. It is of epidemiological relevance, that in
Regional Health departments:
- City of Augsburg, Hoher Weg 8, 86 152 Augsburg
  Leitende(r) Medizinaldirektor(in): Prof. Dr. Johannes Gostomzyk (1984 to 2002)
  Dr. Traude Lämmer, Dr. Claudia Schorr, Fr. Christine Brechisen
- Rural district of Augsburg, Prinzregentenplatz 4, 86150 Augsburg
  Leitender Medizinaldirektor: Dr. Helmut Hößl, Dr. Uta Warncke,
  Fr. Gabriele Bader
- Rural district of Aichach-Friedberg, Schlossplatz 5, 86 551 Aichach
  Leitende(r) Medizinaldirektor(in): Dr. Renate Deckart (1985 to 2004),
  Dr. Michael Hennig, Fr. Renate Klatz

Regional hospitals:
- Klinikum Augsburg, Stenglinstr. 2, 86 156 Augsburg
  Chief physicians:
  I. Med. Prof. Dr. H-Dietrich Bolte (1985 to 2000), Prof. Dr. Wolfgang von
  Scheidt, PD Dr. Bernhard Kuch
  II. Med. Prof. Dr. Günter Schlimok,
  Ill. Med. Prof. Dr. Helmut Messmann, Herzchirurgie Prof. Dr. Michael Beyer
  Inst. für Labormedizin Prof. Dr. Werner Ehrat
  Zentralapotheke: Dr. Christian Bannert
- Klinikum Haunstetten, Sauerbruchstr. 6, 86 179 Augsburg
  Chief physician Dr. Gerd Ziesing
- Krankenhaus Bobingen, Wertachstr. 55, 86 399 Bobingen
  Chief physician Dr. Reiner Hoffmann
- Krankenhaus Schwabmünchen, Weidenhartstr. 35, 86 830 Schwabmünchen
  Chief physician Dr. Peter Schmidt
- Kreiskrankenhaus Aichach, Krankenhausstr. 11, 86 551 Aichach
  Chief physician Dr. Walter Remplik
- Krankenhaus Friedberg, Hergottsruhrstr. 3, 86 316 Friedberg
  Chief physician Dr. Alexander Steibens
- Kreiskrankenhaus Kruinbach, Mindelheimerstr. 69, 86 381 Kruinbach
  Chief physician Dr. Hanns Peter Otter
- Krankenhaus Schrobenhausen, Högnaue Weg 5, 86 637 Schrobenhausen
  Chief physician Dr. Stefan Hüttl
- Kreiskrankenhaus Wertingen, Ebersbergstr. 36, 86 637 Wertingen
  Chief physician Dr. Wolf Kühl, OA Dr. Riemenschneider-Müller
- Ärztlicher Kreisverband (Head physician Dr. Kurt D. Reising)
  mit ca. 1 139 niedergelassenen Ärzten und 907 Krankenhausärzten

Table 1 Cooperating institutions of the MONICA/KORA registry (status Nov. 2004)

2000 the AMI diagnosis was clinically redefined as acute coronary syndrome (ACS) in which patients with symptomatically angina and laboratory signs of ischemia (troponin positive) without persistent ST-segment elevations in the ECG are included [12]. The Augsburg registry is able to use both definitions the old and the new one. For long-term comparisons – presented in this paper – the clinical ECG diagnosis and CPK/CK-MB values in combination with observed acute symptoms AMI are used as diagnostic criteria; all non-fatal cases with MD1, MD2, and MD3 were included.

For the registration of fatal cases, the following death certificate diagnoses (ICD 9) were suspected for an AMI or coronary death, if no other underlying cause of death was diagnosed: Hypertension (401 – 405), ischemic heart disease (410 – 414), other cardiovascular diseases (420 – 429), atherosclerosis (440 – 447), diabetes mellitus (250), dyslipidemia (272), obesity (278), cardiac symptoms (797 – 799). All these fatal cases were identified by weekly (city of Augsburg) or monthly (rural districts of Augsburg, and of Aichach-Friedberg) checking of all death certificates within the regional health departments and by sending a questionnaire to the last treating physician and/or coroner. The physician questionnaire asks for socio-demographic data, cardiovascular history, and circumstances of death. Using the information of the death certificate and the physician questionnaires the registrar team reaches a decision to include the case or not.

The MONICA diagnostic category of coronary deaths (MD1, MD2, MD9) is based on autopsy result (only 2.3 % of the deceased), acute symptoms, and a positive history of CHD (angina pectoris or previous MI or diagnosed coronary heart disease). Despite interviewing physicians, about 31.0 % of fatal cases before or within 24 hours after hospitalization (sudden cardiac deaths SCD) were unclassifiable. In fact, a coronary heart disease could not be confirmed or excluded, and there is no information for another cause of death [13]. In the WHO MONICA project those unclassifiable deaths (MD9) were included for calculation of the AMI rates of the population, as a coronary death is the most plausible cause of death as seen in autopsied deceased of some MONICA registries.

Long-term follow-up studies of 28-days-AMI survivors demanded information on the survival status and the date and the region of death for deceased subjects. Cause of death information came from the health departments of the Augsburg region.

Definitions

The age- and gender-specific AMI attack rate per 100,000 population includes all incident and recurrent cases of acute myocardial infarction (fatal and non-fatal) and all coronary deaths divided by the mid-year population of the respective calendar year.

The age- and gender-specific incidence rate per 100,000 population includes all incident cases of acute myocardial infarction (fatal and non-fatal) and all coronary deaths (first ever events) divided by the mid-year population of the respective calendar year(s).

The age- and gender-specific coronary deaths rate per 100,000 population includes all fatal cases of acute myocardial infarction and all coronary deaths (incident and recurrent) divided by the mid-year population of the respective calendar year.

The case fatality rate (in %) includes all fatal cases in the nominator divided by all fatal and non-fatal cases (denominator) within a defined time interval: total 28-day case fatality, pre-hospital case fatality, 24-hour case-fatality of hospitalized cases, 28-days case fatality of the 24 hour survivors were determined.

For comparisons by gender and/or over time the mean population rates (incidence, attack, and death rate) with 95% confidence intervals (CI) were age-standardized using the age-specific weights of the German population 2002. Mean case-fatality rates were age-standardized using the age-specific weights of all registered cases.

Patient characteristics (in %), e.g. cardiovascular risk factors, medication before and during hospitalization, and at discharge from hospital, diagnostic and therapeutic procedures during hospitalization, clinical complications, and survival status at the 28th day after onset of symptoms were available.

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For comparisons of patient characteristics mean percentages were age-adjusted by linear logistic regression models. Age-stratified Mantel-Haenszel odds ratios with 95% confidence intervals (CI) were calculated to test case fatality differences for significance. In general, a p-value less than 0.05 was considered as statistically significant.

**Results**

From 1985 to 2002 a total of 17,884 (men 12,798, women 5,086) cases of acute myocardial infarction including sudden cardiac death were registered. 9,886 of them (men 6,750, women 3,136) died within 28 days.

Fig. 1 shows the sex-specific CHD-mortality rate per 100,000 population by 5-years age groups from the German cause of death statistics in comparison to the registry based rates for 1985/87 and 2000/02. At all ages, the register based CHD mortality rates (1985/87 men 280, women 88; 2000/02 men 168, women 54) are slightly higher than the official CHD-mortality rates (1985: men 258, women 80; 2002: men 138, women 45). Therefore CHD mortality decrease was more pronounced in the official statistics (men 46%, women 44%) compared to the registry validated rates (men 40%; women 38%).

The MONICA/KORA registry based time trends of age-standardized AMI attack rates subdivided into rates of incident and recurrent AMI are presented by sex in Fig. 2 for four time intervals each including three years.

From 1985/87 to 2000/02, the total age-standardized AMI attack rate per 100,000 population decreased from 541 to 404 acute coronary events (–25%) in men. In women, an initial increase of the attack rate from 171 to 193 coronary events was observed with a subsequent decrease to 123 AMI cases in 2000/02. The age-standardized rate of first ever AMI of the male population decreased continuously from 377 to 299 in 1995/97 followed by a not yet significant re-increase to 313 incident cases in 2000/02. In the female population incidence rates increased from 135 (1985/87) to 149 cases in 1990/92, and subsequently decreased continuously to 100 incident cases per 100,000 population in 2002/0. In contrast, the rates of recurrent AMI cases per 100,000 population show a remarkably changing trend from 164 to 91 in men (–44%), and an increase from 36 to 44, followed by a decrease to 23 in women (overall decrease: –35%).

As shown in Table 2 the hospitalized patients with an incident AMI were characterized by high and mostly increasing proportions of hypertension, dyslipidemia, and diabetes mellitus. Against the background of the decreasing AMI morbidity, the decrease of a positive history of angina pectoris from 41 to 15% in men and from 52 to 18% in women with an acute coronary event has to be emphasized. Of further great importance is the falling proportion of never smokers among female AMI patients.

From 1985 to 2002 a tremendous increase of evidence-based drug medication (acetyl salicylic acid [ASA], beta-blockers, ACE inhibitors, lipid lowering drugs, especially statines, and throm-
At the beginning of the MONICA Project, thrombolytic drug treatment started at a low level of less than 10% in 1985/87 and increased to 47% in male and 39% in female AMI patients in 1995/97. After a timely delay, in 2000/02 about 50% of all incident AMI cases were provided with a PCI and most of them with a coronary stent; finally 25% of the male and 14% of the female cases needed a coronary artery bypass surgery. Therefore, the lower rate of reperfusion therapy in women (70%, 95% CI 65; 75) compared to men (79%, 95% CI 76; 81) resulted from a less often conducted ACVB surgery. For secondary prevention, in 2000/02 51% of men (95% CI 48; 55) and 56% of women after an incident AMI (95% CI 51; 62) received a concomitant treatment with ASA, beta-blockers, ACE-inhibitors and statins at discharge; three of the drug groups were prescribed to 35% (95% CI 32; 38) of male and 33% (95% CI 28; 38) of female survivors of an incident AMI (data not shown in a table). Actually, less then 10% of the cases were discharged with one or none of the designated cardiovascular drug groups; in 1985/87 about one third of the incident AMI survivors received none of the four drug groups (men 33%, 95% CI 29; 37; women 31%, 95% CI 25; 37). In contrast, cardiovascular drug medication before the incident AMI has remained suboptimal. In 2000/02 55% (95% CI 52; 58) of male and 45% (95% CI 40; 50) of female patients received none of the four CVD drug groups relevant for prevention of an incident AMI; only 8% of men and 11% of female patients were pre-treated with three or four of the drug groups.

In Fig. 4 the survival structure of the registered incident cases is compared between the four time intervals. From 1985/87 to 1995/97, neither in men nor in women significant changes could be observed.

Compared to men, between 1985 and 1997 a higher percentage of female cases died before hospitalization, whereas no significant gender differences were observed in the percentage of in-hospital deaths. A statistically significant lower percentage of 28-day survivors were observed in women than in men (Mantel-Haenszel age-weighted odds ratio men to women: 1985/87 OR 1.52, 95% CI 1.24–1.86; 1990/92 OR 1.24, 95% CI 1.02 – 1.50; 1995/97 OR 1.74 95% CI 1.44 – 2.11). But in 2000/02, a significantly reduced percentage of pre-hospital (men 26%, women 27%) and early in-hospital (men and women 12%) deaths were seen in both, men and women. The percentage of 28-day-survivors increased to 57% in men and 56% in women, from now on without gender differences (OR 1.04; 95% CI 0.85; 1.27).

<table>
<thead>
<tr>
<th>Table 2</th>
<th>History of cardiovascular risk profile of 25 – 74 year old hospitalized patients (% and 95% Confidence Interval, age adjusted). MONICA/KORA Augsburg Registry of Acute Myocardial Infarction 1985/87, 1990/92, 1995/97, and 2000/02</th>
</tr>
</thead>
<tbody>
<tr>
<td>1985/87</td>
<td>1990/92</td>
</tr>
<tr>
<td>men</td>
<td>n = 834</td>
</tr>
<tr>
<td>employed</td>
<td>37 (35; 40)</td>
</tr>
<tr>
<td>cigarette smoking</td>
<td></td>
</tr>
<tr>
<td>present smokers</td>
<td>37 (34; 41)</td>
</tr>
<tr>
<td>never smokers</td>
<td>25 (22; 28)</td>
</tr>
<tr>
<td>hypertension</td>
<td>44 (40; 48)</td>
</tr>
<tr>
<td>angina pectoris</td>
<td>41 (37; 44)</td>
</tr>
<tr>
<td>dyslipidemia</td>
<td>36 (32; 39)</td>
</tr>
<tr>
<td>diabetes mellitus</td>
<td>19 (16; 22)</td>
</tr>
<tr>
<td>stroke</td>
<td>6 (4; 8)</td>
</tr>
<tr>
<td>women</td>
<td>n = 269</td>
</tr>
<tr>
<td>employed</td>
<td>21 (16; 26)</td>
</tr>
<tr>
<td>cigarette smoking</td>
<td></td>
</tr>
<tr>
<td>present smokers</td>
<td>23 (18; 28)</td>
</tr>
<tr>
<td>never smokers</td>
<td>58 (52; 64)</td>
</tr>
<tr>
<td>hypertension</td>
<td>66 (60; 72)</td>
</tr>
<tr>
<td>angina pectoris</td>
<td>52 (46; 58)</td>
</tr>
<tr>
<td>dyslipidemia</td>
<td>40 (34; 47)</td>
</tr>
<tr>
<td>diabetes mellitus</td>
<td>33 (27; 38)</td>
</tr>
<tr>
<td>stroke</td>
<td>8 (3; 10)</td>
</tr>
</tbody>
</table>

Fig. 3 Time trends in reperfusion therapy (PCI = Percutaneous Coronary interventions, CABS = Coronary artery bypass surgery) after incident acute myocardial infarction by sex (age-standardized using the weights of the total registered cases) in percent. MONICA/KORA Augsburg Registry of Acute Myocardial Infarction 1985/87, 1990/92, 1995/97, and 2000/02.
In Germany, the decrease of CHD mortality and AMI morbidity among the middle-aged population observed during the 10-year WHO MONICA period continued to date. Similar trends were also reported from many other industrialized countries within and outside Europe [14–18]. Morbidity of recurrent AMI decreased to a higher extent as the rates of incident AMI, because more effort was observed concerning intensified drug treatment for secondary prevention after AMI than in treatment of high risk individuals before incident AMI among the Augsburg population. In the time period 2000/02, an increase of non-fatal AMI was observed in the Augsburg region. On the one hand this could be the result of the reported intensified and more effective acute coronary care, but on the other hand it could also be the result of the changed definition of AMI. As a consequence of the new definition, symptomatic patients with elevated concentrations of the heart-specific marker troponin, and without typical ECG changes (NSTEMI) are admitted to hospital at an earlier stage of the acute event [9]. Possibly, this fact could result in an improved prevention of recurrent AMI due to the aggressive invasive treatment during their first acute event, as recently also reported from France [19]. The still high risk profile of the patients with an incident AMI in combination with an ongoing low level of preventive drug medication before their incident event highlighted the great potentials of primary prevention.

On the other hand, the observed large increase of therapy with thrombolytic agents and other cardiovascular drug combinations was clearly associated with an increase of 28-day-survival of the hospitalized 24 hour survivors and a decrease of recurrent events per 100,000 population. The population-based Augsburg registry has shown, that – for the first time – the since 2000 implemented strategy of a very early coronary stenting was associated with a decrease of the 24 hour case-fatality, and therefore a 10%-point increase of 28-day survival; this high impact of declined early case-fatality on the overall CHD mortality of the population was also reported from the FINAMI study [20]. Presumably, a further decrease of recurrent event morbidity per population might be expected in the future. The strength of hospital-based registers is the standardized quality control of the implementation of evidence-based therapy for the welfare of the patients. However, only population-based registries including clinically confirmed AMI cases and validated CHD deaths inside and outside a hospital can quantify the public health consequences of intensified acute coronary care strategies.

**Future planning**

The population-based registration of AMI cases and CHD deaths in the study region of Augsburg will be continued, and long-term survival analyses will be performed with special regard to medical care effects.

Furthermore, studies of a possible inflammatory effect of air pollution on cardiovascular health will be continued and flanked by the measurement of special properties of ambient particles by the newly established GSF monitoring station located in the city of Augsburg.

Another still important challenge of the Augsburg registry is the identification of clinical outcomes among the MONICA/KORA cohort members as basis for the long-term prediction of AMI and diabetes mellitus in healthy individuals.

The GSF Institute of Health Economics and Health Care Management is testing the opportunity to get individual data on long-term health care utilization and expenditure (related as well as unrelated) of the registered AMI patients by contacting the relevant health security institutions, in order to explore the trends of costs and cost-effectiveness in health services delivered to these patients.

In the years 2005/06 a follow-up examination on sub-clinical outcomes in participants of the KORA-Family Heart Study from 1996/97 is planned, again in close cooperation with cardiologists of the University of Regensburg.

All together the Augsburg registry builds an important base for further cooperative investigations on positive or critical developments of the AMI risk in the population and for AMI survivors from the public health point of view.

**Acknowledgement**

The authors wish to thank all the participants of the MONICA/KORA registry during the 20 year long study time. We specifically would like to thank all our partner institutions (see Table 1) and to the registry team: Dorothea Lukitsch, Anita Schuler (management of the registration procedures), Gabriele Zimmermann, Christine Winter, Petra Heiland, Gabriele Orlik (patient interview and medical record reviewing), Walter Huss (data bank programming), Ursula Kaup (data handling and data analyses). Last but not least, we are thankful to Prof. Dr. med Ulrich Keil, PhD, the principal investigator of the WHO MONICA Augsburg project.
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The article refers specifically to the following contributions of this special issue of Das Gesundheitswesen: [21 –26].

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