

Elevated Risk Profile of Women in Secondary Prevention of Coronary Artery Disease: A 6-Year Survey of 117,913 Patients

Rona Reibis, M.D.,¹ Kurt Bestehorn, M.D.,^{2,3} David Pittrow, M.D.,² Christina Jannowitz, DVet Med,³ Karl Wegscheider, Ph.D.,⁴ and Heinz Völler, M.D., FESC¹

Abstract

Background and aims: The prognosis of female patients after acute coronary syndrome (ACS) has been shown to be inferior to that of male patients. Little is known about gender differences during the secondary prevention phase.

Methods: After ACS, 117,913 patients (30.7% female) were enrolled in two large-scale German registries from 2000 to 2005 during phase II cardiac rehabilitation (CR). Demographic parameters, reperfusion strategies, cardiovascular risk factors, exercise capacity, and medication use at admission and discharge were assessed. Temporary changes (trends) and gender-specific differences were determined.

Results: Compared to 2000, patients in 2005 were significantly older (females: 66.4 vs. 68.0 years; males: 62.3 vs. 63.3 years; $p = 0.001$) and had a higher body mass index (BMI) (females: 27.7 vs. 28.6 kg/m²; males: 27.6 vs. 28.1 kg/m², in 2000 and 2005, respectively, $p < 0.001$). Target blood pressure <140/90 mm Hg at discharge was obtained in a smaller proportion of women than men (81.0 vs. 83.0%, $p < 0.001$). Low-density lipoprotein cholesterol (LDL-C) levels at discharge were significantly higher in female patients (95.0 vs. 93.2 mg/dL, $p < 0.001$); 80.9% of female vs. 83.8% of male patients achieved a target fasting glucose <126 mg/dL during the CR ($p < 0.001$). Large between-center variability was noted for age, total cholesterol at entry, and exercise capacity at entry and discharge.

Conclusions: Although control of cardiovascular risk factors has improved in both genders, over a recent 6-year period, female patients compared with males were less likely to achieve target values for blood pressure, fasting glucose, and lipid values in the early period after acute coronary events.

Introduction

IN RECENT DECADES, the percentage of female patients suffering from coronary artery disease (CAD) has increased continuously. Compared with male patients, women with CAD have a worse prognosis in the early phase after acute cardiovascular events,^{1,2} which may be related to older age at the time of myocardial infarction (MI) and more complex comorbidities, such as diabetes, renal failure, and arterial hypertension.^{3,4} Additionally, higher periprocedural bleeding rates,⁵ underuse of GP IIb/IIIa receptor blockers,⁶ and a lower rate of revascularization⁷ have been reported.

Although much research on gender differences has been performed during the acute phase of CAD, little is known

about sex disparity during the secondary prevention phase, including inpatient cardiac rehabilitation (CR).⁸⁻¹¹ Under routine clinical practice conditions, the extent to which female patients receive optimal preventive care, including treatment of blood pressure (BP), of blood glucose, and of atherogenic dyslipidemia, according to guideline-based treatment goals has not been investigated in larger populations.

The purpose of our study was to describe and analyze potential sex differences in patient characteristics, risk factors, cardiac medication, and target level attainment at entry and discharge of CR programs in Germany. We compared female with male patients, who were referred to an inpatient CR program after ACS or coronary artery bypass grafting (CABG) and included statistical analysis of changes over time

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¹Department of Cardiology, Klinik am See, Rehabilitation Center of Cardiovascular Disease, Ruedersdorf/Berlin, Germany.

²Institute for Clinical Pharmacology, Public Health Association Saxony, Dresden, Germany.

³MSD Sharp & Dohme GmbH, Munich-Haar, Germany.

⁴University Medical Center Hamburg-Eppendorf, Hamburg, Germany.

in the individual centers as well as changes between centers over time.

Patients and Methods

Study population

From 2000 to 2005, investigators conducted a national survey throughout Germany, which consecutively included patients after an acute coronary event, including unstable angina, STEMI, and NSTEMI. Data used in this study were extracted from two consecutive large-scale German registries: Registry of Guideline-based Therapy (ROG), including 76,683 inpatients from 103 centers between 2000 and the end of 2002, which were suitable for a pooled analysis with the TROL dataset, and Transparency Registry to Objectify Guideline-Oriented Risk Factor Management (TROL), comprising the documentation of 41,300 inpatients from 116 CR centers between 2003 and the end of 2005, which additionally focused parameters of glucometric metabolism to the baseline protocol of 2000–2002. As 48 centers contributed to both registries, a total of 117,983 patients (35% from TROL, 65% from ROG) from 171 centers were analyzed. These patients were distributed over observation years as follows: 17,786 (15.1%) in 2000, 29,538 (25.0%) in 2001, 29,359 (24.9%) in 2002, 18,247 (15.5%) in 2003, 10,967 (9.3%) in 2004, and 12,086 (10.2%) in 2005.

The inclusion criteria were age ≥ 18 years, first acute cardiac event (including acute coronary syndrome [ACS] and CABG) that was the indication for inpatient CR, and patient's written informed consent prior to inclusion in the study. The only exclusion criterion was refusal of patients to participate in the registry. Participation in a further investigational drug or device study was not an exclusion criterion; hence, a representative study population has been acquired. All patients took part in a multimodal inpatient CR program for a mean of 23 days. The proportion of patients who disagreed after information was 2.8%. As many as 97.2% of screened patients could be included in the registry.

In Germany, the vast majority of patients at high cardiac risk and, in particular, after an ACS or after CABG surgery, are entitled to undergo in-hospital rehabilitation therapy of 3–4 weeks' duration, which is performed in specialized institutions. Patients are continuously hospitalized and attend a variety of rehabilitation sessions (e.g., cardiovascular training, dietary and lifestyle counseling, psychological interventions, and also regular diagnostic and therapeutic follow-up). The rehabilitation programs are supervised by cardiologists, supported by nurses and other specialist staff (e.g., dietitians, physiotherapists) highly experienced in the field. All patients who were referred to CR in these centers and met the inclusion criteria were asked to participate in this survey and were registered in a center logbook for monitoring. An independent audit with source verification was periodically conducted in 20% of all participating centers to evaluate the correctness of data collection. There were no indications of implausibilities regarding the collected data.

Variables

The following patient characteristics were recorded on a regular basis from 2000 until the end of 2005:

1. Demographics: age, gender, body mass index (BMI)
2. Systolic and diastolic BP at entry and discharge

3. Laboratory parameters at entry and discharge: total cholesterol (mg/dL), low-density lipoprotein cholesterol (LDL-C) (mg/dL), high-density lipoprotein cholesterol (HDL-C) (mg/dL), triglycerides (mg/dL), fasting blood glucose (mg/dL)
4. Bicycle exercise capacity (Watts)
5. Pharmacological treatment at discharge: statins, acetylic salicylic acid (ASA), beta-blockers, and ACE inhibitors/angiotensin receptor blockers (ACE-I/ARB)

The registries used a single protocol and a standardized case report form for all participating centers. Laboratory tests were performed by the local laboratories at the individual rehabilitation centers (which are obliged to take part in quality control measures at regular intervals).

Statistical analysis

All repeated cross-sectional analyses were conducted with mixed models with three hierarchy levels (3-level mixed model) for continuous target variables to assess the influence of the factors "rehabilitation center" and "individual patient." For each variable, the initial analysis started with the full model, which contained random as well as fixed effects. Random effects included year-independent differences between rehabilitation centers (top hierarchy level), differences between registry years within the rehabilitation centers (mean hierarchy level), and differences between individual patients (residual error, on the bottom hierarchy level). Fixed effects comprised registry years, individual group variables, interaction between registry years and individual group variables, and all for the individual target variables relevant control variables (age categorized in five classes, BMI in three classes), including mutual interactions between gender and age or BMI, respectively. In the next step, nonsignificant variables were removed from the full model in a stepwise procedure, until for the respective variable, only significant covariates remained. The factors "registry year," "group," and "registry year*group interaction" were always kept in the model.

Three test procedures were performed: (1) test on general trend to assess the presence or absence of (group-independent) changes over time (test trend), (2) test on time-independent level differences between groups (related to the fixed effect group) (test level), and (3) test on parallelity of time trends to assess whether direction or effect size related to the fixed effect "group*registry year" difference (test parallelity). Cluster effects, if present, are summarized by intraclass correlation coefficients (ICC). Two types of ICC were calculated to quantify (1) changes between centers (within registry years, ICC level) or (2) changes between registry years (within centers, ICC trend). ICC $\leq 5\%$ were considered to be small, 5%–10% moderate, and $\geq 10\%$ large.

Results

Demographic parameters

The proportion of females in total was 30.7%. At the present time (in 2005), the mean age of female patients referred to CR in Germany is 68 years, and that of men is 63 years. The mean age of males and females at entry in CR has steadily increased since 2001. This trend is significantly stronger in females (females: 66.4 ± 0.5 vs. 68.0 ± 0.5 years; males: 62.3 ± 0.5 vs. 63.3 ± 0.5 years, $p = 0.001$). Between centers, mean age varied

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considerably (ICC 22%), whereas within centers, differences over the years were substantially smaller, albeit significant.

Risk factors at baseline

Body mass index. BMI increased over the registry years. This effect was more pronounced in females compared with males (females in 2000, 27.7 ± 0.1 vs. in 2005, 28.6 ± 0.1 kg/m²; males in 2000, 27.6 ± 0.1 vs. in 2005; 28.1 ± 0.1 kg/m², $p < 0.001$), with small differences between centers (ICC 4%).

Blood pressure. Mean systolic BP at the beginning of rehabilitation decreased significantly for both genders (in women as well as in men, from 135 mm Hg in 2000 to 131 mm Hg in 2005; trend level $p < 0.001$) over the years. Among centers, differences were moderate (ICC 9%). In contrast, diastolic BP was significantly lower in women continuing over the observational period (females in 2000, 79.1 ± 0.5 , in 2005, 77.8 ± 0.5 mm Hg; males in 2000, 79.6 ± 0.5 , in 2005, 78.2 ± 0.2 mm Hg; test trend $p = 0.005$, test level $p < 0.001$).

Lipid profile. Mean lipid values decreased significantly over time (in women, total cholesterol 221 ± 3 mg/dL in 2000, 214 ± 3 mg/dL in 2005, $p = 0.011$, LDL-C 141 ± 2 mg/dL in 2000, 133 ± 2 mg/dL in 2005, $p = 0.011$). The trend was significant for all lipid fractions. With the exception of HDL-C (in females in 2005, 50.6 ± 0.6 mg/dL vs. males 43.8 ± 0.6 mg/dL, $p < 0.001$), all types of lipid levels were more favorable in males compared with females. Among centers, there were large differences in total cholesterol and LDL-C values (ICC 26%), as there were also within centers over time (ICC trend 9%), whereas differences in HDL-C and triglycerides were less pronounced.

Glucose. Over time, mean fasting blood glucose remained constant for men and women; nevertheless, mean values were significantly higher in females compared with males (in males in 2000, 106.1 ± 1 mg/dL, in 2005 105.8 ± 1.0 mg/dL vs. in females in 2000, 109 ± 1 mg/dL, in 2005 109.5 ± 1 mg/dL, test level females vs. males $p < 0.001$). Differences among centers were moderate (ICC 7%).

The main demographic and baseline variables as well as cardiovascular risk profile at admission are listed by gender and by registry year in Table 1.

Medication at discharge

The use of ACE-I/ARB increased significantly only in males, whereas prescriptions in female patients remained low (in females in 2000, 66.5%, in 2005, 65.7%; in males in 2000, 65.1%, in 2005, 74.5%; test level females vs. males $p < 0.001$). The prescription of beta-blockers significantly increased in both genders (in females, 73% in 2000 to 84% in 2005; in males, from 74% to 85%; test trend $p < 0.001$). There were large differences among centers (ICC 15%) and moderate differences within centers over time (ICC 6%) (Fig. 1).

The prescription of statins was, on a high level, largely unchanged over time, without gender effects. Differences among centers were moderate (ICC 10%), but within centers, they were large (ICC 15%). Compared with 2000, ASA prescription was reduced in 2001 but increased to maximum values in 2005 (79% in males and 76% in females, $p < 0.001$). There was substantial variability in prescriptions among

centers (ICC 18%). Once again, the prescription rate in females was lower than in men (in 2005 in females, 76.1% vs. 79.7% in males; test level $p < 0.001$).

Table 2 gives the results of the temporal trends of pharmacological treatment at discharge in consideration of gender and center differences.

Risk factors at discharge

Blood pressure. In both groups, mean systolic and diastolic BP at the end of rehabilitation did not change over time, with moderate differences among centers (ICC level for systolic BP, 6%; ICC level for diastolic BP, 8%). The proportion of female patients who met the target BP values of $< 140/90$ mm Hg at discharge was significantly lower than that of male patients (in 2005, 81.0 ± 1.4 vs. 83.0 ± 1.3 , $p < 0.001$) consistently over the registration period, with a high homogeneity between rehabilitation centers (ICC level 5.4%).

Lipid profile. Mean lipid values were substantially lower at the end of the observation period (in women total cholesterol fell from 174 mg/dL in 2000 to 168 mg/dL in 2005 (test trend $p < 0.001$), and LDL-C fell from 101 mg/dL to 95 mg/dL (test trend $p < 0.001$). The trend to improved values was significant for total cholesterol, LDL-C, and HDL-C values in both males and females. Nevertheless, for LDL-C levels, women showed significantly poorer control at discharge in comparison to men (95.0 vs. 93.2 mg/dL, $p < 0.001$). Differences in control rates between centers (ICC 5%) and differences over time within the centers (ICC 2%) were small.

Glucose. Fasting blood glucose values at discharge were essentially unchanged over the observation period, but values in females were consistently higher compared with males (in 2005, 105 ± 0.8 mg/dL vs. 104 ± 0.8 mg/dL, $p < 0.001$). The target value (< 126 mg/dL) was achieved by a higher proportion of males (in females in 2005, $80.9 \pm 1.1\%$ vs. in males in 2005, $83.8 \pm 1.0\%$; test level $p < 0.001$). Differences among centers were moderate for glucose values (ICC 9%), and small for control rates (ICC 5%) (Fig. 2). The temporal trends of risk factors and exercise capacity at discharge are listed by registry year and by gender in Table 3.

Discussion

Present data demonstrate that women referred to CR were less likely to achieve adequate control of BP, lipid profile, and fasting blood glucose. They were considerably older than men, and they received inferior pharmacological treatment.

After ACS, comprehensive CR has an important prognostic impact on both genders.¹²⁻¹⁵ The period of CR is of high interest, as it immediately follows the acute hospital stay, and the treatment measures and targets at the end of CR set the basis for further management by the general physician. Multifactorial strategies, including risk factor management, exercise training, and psychosocial management for secondary prevention of CAD, have been recommended in recent guidelines.^{16,17} Clinical guidelines for evidence-based primary and secondary prevention of cardiovascular diseases in women have been published, including explicit recommendations for female patients in lifestyle change, pharmacological treatment, and target values for BP, glucose, and lipid profile.¹⁸ The majority of information available about the

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TABLE 1. TEMPORAL TRENDS OF BASELINE PARAMETERS (2000–2005)

Variable	Gender	2000	2001	2002	2003	2004	2005	ICC ^a level (%)	ICC trend (%)	Test trend ^b	Test level ^c	Test parallelity ^d
Age (years)	m	62.3 (0.5) ^e	62.1 (0.5)	62.4 (0.5)	62.5 (0.5)	62.5 (0.5)	63.3 (0.5)					
	f	66.4 (0.5)	65.6 (0.5)	65.9 (0.5)	66.5 (0.5)	67.2 (0.5)	68.0 (0.5)		22.1	0.001	<0.001	<0.001
BMI (kg/m ²)	m	27.6 (0.1)	27.7 (0.1)	28.0 (0.1)	27.8 (0.1)	28.1 (0.1)	28.1 (0.1)					
	f	27.7 (0.1)	28.0 (0.1)	28.2 (0.1)	28.0 (0.1)	28.5 (0.1)	28.6 (0.1)		4.1	<0.001	<0.001	0.019
Systolic BP (mm Hg)	m	134.7 (0.8)	135.9 (0.7)	135.0 (0.7)	132.7 (0.7)	132.5 (0.8)	131.1 (0.8)					
	f	135.5 (0.8)	136.1 (0.7)	134.3 (0.7)	132.7 (0.8)	132.8 (0.9)	131.9 (0.8)		9.8	<0.001	n.s.	0.016
Diastolic BP (mm Hg)	m	79.6 (0.5)	80.0 (0.4)	79.6 (0.4)	78.6 (0.4)	78.9 (0.5)	78.2 (0.4)					
	f	79.1 (0.5)	79.4 (0.4)	78.8 (0.4)	78.1 (0.4)	78.9 (0.5)	77.8 (0.5)		9.1	0.005	<0.001	n.s.
Total cholesterol (mg/dL)	m	209.7 (2.9)	212.4 (2.7)	207.8 (2.7)	209.1 (2.8)	210.3 (3.1)	201.0 (2.9)					
	f	221.0 (3.0)	223.1 (2.8)	219.8 (2.8)	218.6 (2.8)	222.4 (3.2)	214.2 (2.9)		25.8	0.011	<0.001	n.s.
LDL-C (mg/dL)	m	135.4 (2.5)	134.9 (2.3)	131.0 (2.3)	132.9 (2.3)	133.5 (2.6)	126.9 (2.4)					
	f	140.7 (2.5)	140.2 (2.3)	137.5 (2.3)	137.1 (2.4)	139.6 (2.6)	133.5 (2.4)		25.7	0.011	<0.001	n.s.
HDL cholesterol (mg/dL)	m	41.8 (0.6)	42.6 (0.5)	43.2 (0.5)	43.3 (0.5)	43.9 (0.6)	43.8 (0.6)					
	f	46.9 (0.6)	48.2 (0.5)	49.2 (0.5)	48.5 (0.6)	49.4 (0.6)	50.6 (0.6)		11.3	0.001	<0.001	<0.001
Triglycerides (mg/dL)	m	166.3 (2.5)	167.3 (2.2)	166.6 (2.2)	166.7 (2.3)	170.8 (2.7)	168.6 (2.4)					
	f	164.7 (2.6)	163.9 (2.3)	164.0 (2.3)	168.6 (2.4)	170.7 (2.9)	167.3 (2.6)		4.7	n.s.	0.048	0.009
Fasting glucose (mg/dL)	m	106.1 (1.1)	106.4 (1.0)	106.0 (1.0)	103.5 (1.0)	104.2 (1.1)	105.8 (1.0)					
	f	109.2 (1.1)	109.2 (1.0)	107.8 (1.0)	108.1 (1.0)	107.2 (1.2)	109.5 (1.1)		6.6	n.s.	<0.001	0.001
Exercise capacity (W)	m	82.9 (1.8)	86.5 (1.7)	85.3 (1.7)	86.2 (1.7)	86.3 (2.0)	84.6 (1.8)					
	f	63.8 (1.9)	64.6 (1.7)	62.9 (1.7)	63.8 (1.8)	62.2 (2.1)	61.3 (1.9)		20.8	n.s.	<0.001	<0.001

^aICC, intraclass correlation coefficient; ICC lev, intraclass correlation coefficient level; BMI, body mass index; BP, blood pressure; f, female; m, male; TC, triglycerides; W, Watts.

^bTest trend, test on general trend to assess the presence or absence of (group independent) changes over time.

^cTest level, test on general; time-independent level differences between groups (related to the fixed effect group).

^dTest parallelity, test on parallelity of time trends to assess whether direction or effect size related to the fixed effect "group*registry year" differ.

^eValues are means (±standard deviation).

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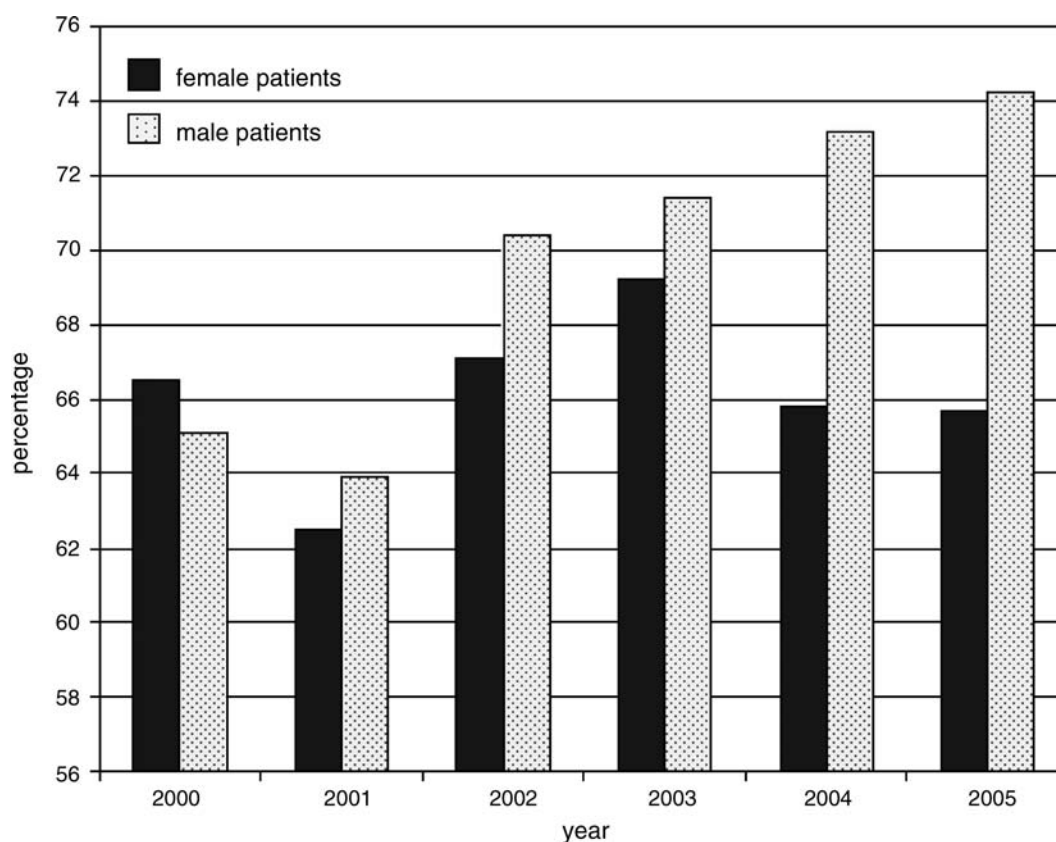


FIG. 1. Continuing undertreatment of women with ACE-I/ARB at admission to CR.

cardiovascular benefits has been derived from studies predominantly in men, despite the fact that the rehabilitation process seems to play an ascertainable role in improving quality of life, exercise tolerance, and optimization of risk factors in women as well¹⁹⁻²¹ when specific needs of women during CR are considered.²²⁻²⁴ Nevertheless, women are less likely to be enrolled in CR programs, especially after cardiac surgery.^{25,26} Furthermore, the continuous participation and completion rates of formal cardiac rehabilitation programs remain inferior compared with men.²⁷ Ades et al.²⁸ reported a disparity in referral to CR in older patients in favor of older men.

Our results are of particular interest and extend the hitherto reported data, as the substantial numbers of included patients permit a reliable reflection of the practice of CR in Germany. This representative patient population supports the continuing discussion of gender bias in secondary prevention of CAD. In particular, the inadequate treatment of elevated blood glucose levels in women places them at high risk for progression of CAD. Our data have important implications for clinical practice because the poor prognosis for female diabetic patients, especially if elevated BP and atherogenic dyslipidemia coexist, is well documented.^{29,30}

TABLE 2. TEMPORAL TRENDS OF PHARMACOLOGICAL TREATMENT AT DISCHARGE (2000-2005)

Variable (%)	Gender	2000	2001	2002	2003	2004	2005	ICC ^a level (%)	ICC trend (%)	Test trend ^b	Test level ^c	Test parallelity ^d
BB	m	73.8 (1.9) ^e	69.3 (1.8)	73.1 (1.8)	82.5 (1.8)	80.5 (2.1)	84.9 (1.9)	14.7	6.0	<0.001	n.s.	n.s.
	f	73.3 (2.0)	67.4 (2.0)	72.2 (1.8)	82.8 (1.9)	79.6 (2.2)	84.0 (2.1)					
ACE-I/ARB	m	65.1 (2.0)	63.9 (1.8)	70.4 (1.8)	71.4 (1.9)	73.2 (2.2)	74.2 (2.0)	9.8	5.0	0.004	<0.001	<0.001
	f	66.5 (2.1)	62.5 (1.8)	67.1 (1.9)	69.2 (2.0)	65.8 (2.3)	65.7 (2.2)					
Statins	m	92.2 (1.6)	92.3 (1.4)	93.5 (1.4)	93.4 (1.5)	66.9 (1.7)	93.9 (1.5)	10.2	15.3	<0.001	n.s.	0.001
	f	93.1 (1.7)	92.1 (1.4)	92.8 (1.5)	93.4 (1.5)	64.6 (1.8)	92.7 (1.6)					
ASA	m	78.5 (2.2)	72.0 (2.0)	76.4 (2.0)	78.7 (2.0)	77.4 (2.4)	79.7 (2.1)	17.7	9.1	0.005	<0.001	0.012
	f	74.7 (2.2)	68.2 (2.0)	70.7 (2.0)	75.5 (2.1)	73.6 (2.4)	76.1 (2.2)					

^aICC, intraclass correlation coefficient; ICC level, intraclass correlation coefficient level; BB, beta-blockers; ACE-I, ACE inhibitors; ARB, angiotensin I receptor blocker; ASA, acetylsalicylic acid.
^bTest trend, test on general trend to assess the presence or absence of (group independent) changes over time.
^cTest level, test on general; time-independent level differences between groups (related to the fixed effect group).
^dTest parallelity, test on parallelity of time trends to assess whether direction or effect size related to the fixed effect "group*registry year" differ.
^eValues are means (±standard deviation).

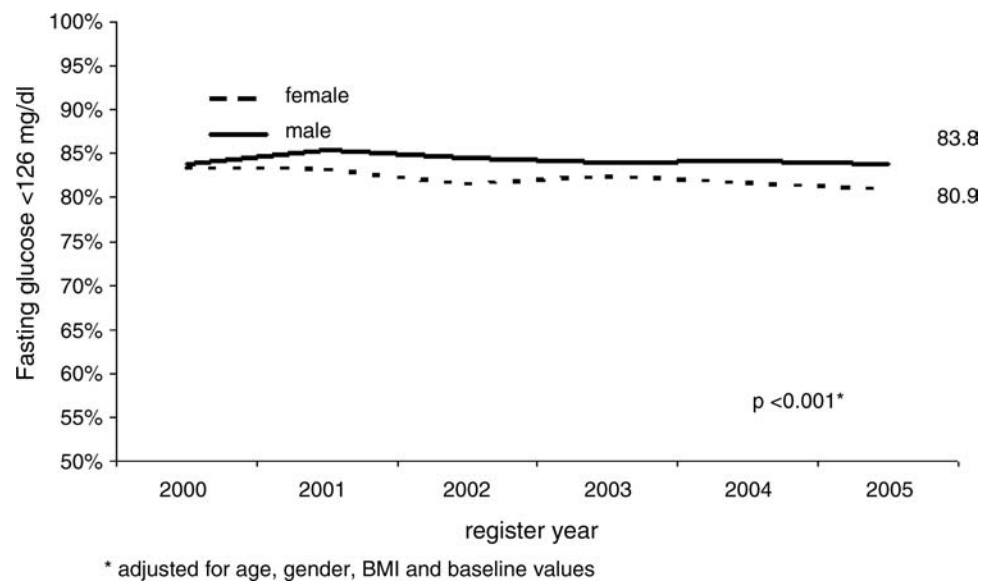


FIG. 2. Gender differences in fasting blood glucose <126 mg/dL at discharge from rehabilitation.

Blood pressure management

Although BP was significantly reduced during the observational period for both genders, target BP <140/90 mm Hg at discharge was reached in a somewhat smaller proportion of women compared to men (81.0 vs. 83.0%). Speculatively, reasons may include older age of women in CR with an elevated age-related stiffness of aorta³¹ in combination with sex-related differences in arterial size as well as the underuse of ACE-I/ARB. In accord with other investigators,^{32–35} we found that gender was an independent determinant of undertreatment with ACE-I/ARBs. Side effects of ACE-I/ARB in women are more common,³² which may be related to more prevalent hypotensive reactions as well as exacerbation of preexisting renal failure. There is a need for individualized strategies in pharmacotherapy of CAD, with consideration of LV and renal function, age, and comorbidity, especially in female patients.

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Lipid management

Despite consistent benefits of lipid-lowering therapy a significant number of CAD patients do not reach treatment goals for lipoproteins.^{36–40} In this study, during the rehabilitation program, significant improvement in all lipid fractions was observed in both men and women. Nevertheless, control of lipids in females after CR was still suboptimal and differs markedly between the genders. Fewer women achieved target LDL-C levels at admission, as well as at discharge. Our data are concordant with earlier findings of Ansell et al.,³⁷ who reported a reduced treatment success in lipid management among women with coronary heart disease. In accord with other investigators,^{36,38} women in our study were more likely to be at the guideline-recommended goal for HDL-C. The proportions of both male and female patients treated with statins (with the exception of 2004) remained stable and at a comparably high level.

We could not confirm the reported gender bias in the prescription of statins.^{39–41} As the percentage of women receiving statins was comparable with that of men, alternative gender-

specific lipid-lowering strategies for LDL-C might be necessary.⁴² The reasons for the sex difference in the efficacy of statins remain to be elucidated.

Blood glucose management

In the given registry, patients demonstrated gender differences in achieving target values of fasting blood glucose. Prior studies^{43,44} documented suboptimal glucose regulation with a greater prognostic impact presumably in women with CAD than in men. In our data, age did not appear to contribute significantly to the higher glucose level of female patients. Although aging during the registry period, the percentage of women having a fasting glucose level >126 mg/dL remains constant. According to other investigators,^{45,46} despite having a higher BMI, women achieved a lower exercise load, which may serve both as an indicator of a more inactive lifestyle and a consequence of a greater disposition to hyperglycemia.

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Center variability

Independently of gender, there was a noticeable between-center variability in many of the baseline and follow-up parameters. The largest differences with an ICC of >20% between centers were documented for age, total cholesterol at entry, and exercise capacity both at entry and discharge. Moderate variability (ICCs 10%–20%) was seen for the use of beta-blockers, statins, and aspirin as well as for total cholesterol and LDL-C levels at discharge. Variability of this type should be considered if CAD treatment quality and gender biases are evaluated.

Strengths and limitations

Certain methodological aspects deserve attention. One limitation is that participation in the registries was voluntary and, thus, not without a selection bias. A further limitation of this registry was the lack of data on socioeconomic status (SES). It has been reported that SES is inversely associated with CAD mortality.^{47,48} Low education and income seem to

TABLE 3. TEMPORAL TRENDS OF RISK FACTORS AND EXERCISE CAPACITY AT DISCHARGE (2000–2005)

Variable	Gender	2000	2001	2002	2003	2004	2005	ICC ^a level (%)	ICC trend (%)	Test trend ^b	Test level ^c	Test parallelity ^d
Systolic BP (mmHg)	m	123.8 (0.4) ^e	124.2 (0.4)	124.0 (0.4)	122.9 (0.4)	123.1 (0.4)	123.0 (0.4)					
	f	123.2 (0.4)	123.9 (0.4)	123.6 (0.4)	123.2 (0.4)	123.8 (0.5)	123.3 (0.4)	6.1	2.0	n.s.	n.s.	0.006
Diastolic BP (mmHg)	m	74.6 (0.3)	74.7 (0.3)	74.2 (0.3)	74.0 (0.3)	74.3 (0.3)	73.9 (0.3)					
	f	74.3 (0.3)	74.5 (0.3)	74.2 (0.3)	74.1 (0.3)	74.4 (0.4)	73.8 (0.3)	8.1	3.7	n.s.	<0.001	<0.001
BP <140/90 (mmHg) (%)	m	80.6 (1.3)	80.2 (1.2)	80.8 (1.2)	82.0 (1.2)	82.1 (1.4)	83.0 (1.3)					
	f	79.3 (1.4)	78.4 (1.2)	80.0 (1.2)	79.4 (1.3)	79.9 (1.5)	81.0 (1.4)	5.4	2.8	n.s.	<0.001	n.s.
Total cholesterol (mg/dL)	m	168.7 (1.3)	169.2 (1.2)	168.1 (1.2)	167.5 (1.2)	164.6 (1.4)	161.7 (1.3)					
	f	173.9 (1.4)	174.6 (1.2)	174.8 (1.2)	173.6 (1.3)	171.1 (1.5)	168.2 (1.3)	11.6	3.9	<0.001	<0.001	n.s.
LDL-C (mg/dL)	m	99.7 (1.2)	98.7 (1.1)	98.9 (1.1)	98.0 (1.1)	95.2 (1.3)	93.2 (1.1)					
	f	101.3 (1.2)	100.8 (1.1)	101.4 (1.1)	100.3 (1.1)	97.2 (1.3)	95.0 (1.2)	11.6	5.4	<0.001	<0.001	n.s.
HDL-C (mg/dL)	m	42.6 (0.4)	42.9 (0.4)	43.7 (0.4)	43.9 (0.4)	43.9 (0.5)	44.6 (0.4)					
	f	45.7 (0.5)	46.2 (0.4)	47.8 (0.4)	47.3 (0.4)	47.5 (0.5)	49.2 (0.4)	9.3	4.1	<0.001	<0.001	<0.001
Triglycerides (mg/dL)	m	137.7 (1.2)	139.9 (1.1)	138.4 (1.1)	139.1 (1.1)	139.9 (1.3)	139.1 (1.2)					
	f	139.1 (1.4)	141.5 (1.2)	140.1 (1.2)	140.3 (1.2)	140.7 (1.5)	137.2 (1.4)	2.9	1.4	n.s.	0.009	n.s.
Fasting glucose (mg/dL)	m	104.2 (0.8)	103.4 (0.7)	103.8 (0.7)	104.3 (0.7)	103.6 (0.8)	104.0 (0.8)					
	f	105.3 (0.8)	105.3 (0.7)	105.8 (0.7)	105.4 (0.8)	104.7 (0.9)	105.4 (0.8)	8.9	3.2	n.s.	<0.001	n.s.
Glucose <126 mg/dL (%)	m	83.9 (1.0)	85.5 (0.9)	84.6 (0.9)	84.0 (0.9)	84.1 (1.1)	83.8 (1.0)					
	f	83.3 (1.1)	83.2 (1.0)	81.5 (1.0)	82.4 (1.0)	81.6 (1.2)	80.9 (1.1)	5.0	1.2	n.s.	<0.001	n.s.
Exercise capacity (W)	m	101.6 (1.4)	99.3 (1.3)	99.0 (1.3)	102.3 (1.4)	103.4 (1.6)	101.9 (1.4)					
	f	89.3 (1.5)	89.4 (1.4)	88.6 (1.4)	88.3 (1.4)	87.4 (1.6)	87.2 (1.5)	20.4	7.1	n.s.	<0.001	<0.001

^aICC, intraclass correlation coefficient; ICC level, intraclass correlation coefficient level; BMI, body mass index; BP, blood pressure; f, female; m, male; TC, triglycerides; W, Watts.

^bTest trend, test on general trend to assess the presence or absence of (group independent) changes over time.

^cTest level, test on general; time-independent level differences between groups (related to the fixed effect group).

^dTest parallelity, test on parallelity of time trends to assess whether direction or effect size related to the fixed effect "group*registry year" differ.

^eValues are means (±standard deviation).

be significant factors contributing to a poorer prognosis and lower quality of life among patients with coronary heart disease.⁴⁹ The case report form of ROG and TROL was reduced to biochemical and anthropometric data as well as to the pharmacological treatment. No data can be reported for sociodemographic factors, smoking, nutritional or psychosocial counseling, or details of exercise training. We also lacked data on details of drug treatment (e.g., dosing and combination therapy). The possible influence of these factors on the observed data, therefore, cannot be ruled out. These facts should be considered when interpreting the results and would have been of interest in order to provide comprehensive insight into important aspects of CR. Among the strengths of our study are the large numbers of patients and centers in the database, thus being representative of the German rehabilitation setting and a national distribution of cardiovascular patients; the relatively long period of time covered; and the novel analytical approach that gives weight to the influence of rehabilitation programs.

Conclusions

The present analysis suggests that in a nationwide, large-scale population of 117,913 patients with CAD, both women and men received improved (compared with previous studies) but insufficient control of cardiovascular risk factors. In particular, female patients were less likely to achieve target values for BP, fasting blood glucose level, and atherogenic dyslipidemic profile than their male counterparts. In addition to optimal prehospital treatment and revascularization, the key to improving clinical outcomes of female CAD patients may lie in consistent secondary preventive care, including stringent control of conventional cardiovascular risk factors. Our data support the need for gender-based treatment algorithms of CAD.

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Disclosure Statement

K.B. and C.J. are employees of MSD. R.R. and H.V. have received travel expenses from MSD Sharp & Dohme GmbH and Essex Pharma GmbH. No competing financial interests exist for any authors.

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Address reprint requests to:

Rona K. Reibis, M.D.

Klinik am See

Department of Cardiology

Rehabilitation Center of Cardiovascular Disease

Seebad 84

D-15562 Ruedersdorf/Berlin

Germany

E-mail: rona.reibis@hotmail.de

AUTHOR QUERY FOR JWH-2008-1082-REIBIS_1P

AU1: Define GP IIb/IIIa.

AU2: Define STEMI & NSTEMI.

AU3: Rewrite sentence to clarify meaning.

AU4: update?

AU5: Define LV.

AU6: Rewrite to clarify meaning.

AU7: Ref. 21 is Correct?

AU8: Closing page for ref 24.

AU9: Closing page for ref 28.