I. MEDIZINISCHE KLINIK UND POLIKLINIK

DER TECHNISCHEN UNIVERSITÄT MÜNCHEN

KLINIKUM RECHTS DER ISAR

(DIREKTOR: UNIV.-PROF. DR. A. SCHÖMIG)

Have Women with Coronary Artery Disease a Higher Risk than Men after Coronary Stenting?

Julinda Mehilli

Vollständiger Abdruck der von der Fakultät für Medizin der

Technischen Universität München zur Erlangung des akademischen Grades eines

Doktors der Medizin

genehmigten Dissertation.

Vorsitzender: Univ.-Prof. Dr. D. Neumeier

Prüfer der Dissertation:

1. Univ.-Prof. Dr. A. Schömig
2. apl. Prof. Dr. M. P. Gawaz

Die Dissertation wurde am 10. 04. 2002 bei der Technischen Universität München eingereicht und durch die Fakultät für Medizin am 17. 07. 2002 angenommen.

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1. Abbreviations

CAD	coronary artery disease
PTCA	percutaneous transluminal coronary angioplasty
CABG	coronary artery bypass graft
HDL	high-density lipoprotein cholesterol
INR	international normalized ratio
PTT	partial-thromboplastin time
AHA/ACC	American Heart Association/American College of Cardiology
TIMI flow	Thrombolysis in Myocardial Infarction flow
DS	diameter stenosis
MLD	minimal lumen diameter
RD	reference diameter
RAO	right anterior oblique
LV	left ventricle
CK	creatinin kinase
CK-MB	creatinin kinase MB isoenzyme
HR	hazard ratio
CI	confidence interval
CART	classification and regression tree
OR	odds ratio

2. BACKGROUND

2.1. Epidemiology

Historically, coronary artery disease has been considered as a disease predominantly affecting men. One of the reasons leading to this assumption is the difference in lifetime risk of developing CAD between men and women. At any given age, the prevalence of CAD is greater in men than in women [Castelli 1988; Wenger et al. 1993]. On the other hand, the prevalence of CAD among both men and women is highly dependent on environmental and life style factors. This is highlighted by the fact that women in countries with high prevalence of CAD have greater CAD rates than men in countries with low CAD prevalence.

Despite major advances in the management of CAD, it remains the leading cause of morbidity and mortality in both men and women in most industrialized nations. In addition, several recent reports have concluded that women with CAD have a worse prognosis than men with this disease [Fiebach et al. 1990; White et al. 1993; Becker et al. 1994; Stone et al. 1996; Malacrida et al. 1998; Hochman et al. 1999; Vaccarino et al. 1999; Roger et al. 2000]. Between 1981 and 1993, there has been a prominent decline of age-standardized CAD mortality rates for both men and women in Western world. But within this favorable trend, the decline in mortality rates in the United States, the United Kingdom and Sweden has been far greater for men than for women [Peltonen et al. 2000; AHA 2002]. CAD is a major cause of disability for women as well; Reports from The Framingham Disability Study demonstrate an age-depended increase in disability rate among women with clinical manifestation of CAD ranging from 36% to 55% [Pinsky et al. 1990].

A number of reasons have been described as likely explanations for the observed differences in clinical outcome in women with CAD [Healy 1991; Mark 2000].

2.2. Cardiovascular risk factors

On average, women develop heart disease some 6 to 10 years later than men. The mechanisms underlying this late onset still remain unexplained. A widely held explanation is the higher high-density lipoprotein cholesterol level in women. In fact, this is an androgen effect, not an estrogen one. Up to puberty, young men and women have similar HDL cholesterol levels. At puberty, concurrent with the rise in endogenous testosteron levels, the LDL cholesterol level increase and the HDL cholesterol levels decline in young men to adult levels [Kirkland et al. 1987].

To date research has overwhelmingly focused on the role of estrogen. Effects on LDL and HDL cholesterol levels, reduction of homocysteine levels, enhanced fibrinolysis, antioxidant properties and improved endothelial function are accepted as possible mechanisms of the cardioprotective effect of estrogens. The very low incidence of CAD before the age of menopause and the increased incidence of it after the age of menopause in women has been considered as an evidence of the estrogen protection. Actually, there is no evidence for an increase in the year-on-year rate of increase in CAD around the age of menopause. Additionally, natural menopause is not associated with an increased risk for CAD, when corrected for age and smoking status [Colditz et al. 1987].

Recently, the substantial evidence in favor of the protective effects of estrogen in women is being called into question by many clinical trials. Hormone replacement therapy is associated with an early excess of adverse cardiovascular events, such as death, myocardial infarction and stroke, when used for secondary prevention [Hulley et al. 1998; Viscoli et al. 2001]. These findings might be attributed to the undesirable prothrombotic effects of estrogen potentially caused by increase of some coagulation and inflammatory markers, such as factor VII, prothrombin fragments 1+2 and activated protein C resistance. These data provide evidence against the estrogen protection hypothesis, making more difficult the explanation of delayed onset of CAD in women.

In the published literature, there is a strong and constant evidence of gender differences in risk profile at the time of presentation with CAD. Women with CAD are more frequently presented with diabetes, arterial hypertension and hypercholesterolemia. Diabetes mellitus is a far more powerful coronary risk factor for women than men and is associated with a less favorable outcome of clinical coronary events in women. Female diabetics with myocardial infarction have a double risk of reinfarction and a fourfold greater likelihood of developing heart failure [Liao et al. 1993; Miettinen et al. 1998].

Smoking as well, is an important risk factor for both men and women. A number of studies demonstrate that smoking is a stronger risk factor for myocardial infarction in middle-aged women than in men . Moreover, the harmful effect on reduction of HDL cholesterol level is more pronounced in female smokers than in male one’s [Njolstad et al. 1996; Cullen et al. 1998].

2.3. Clinical Status at presentation

Stable or unstable angina pectoris are the predominant presentations of CAD in women, in contrast with myocardial infarction or sudden coronary death as the most frequent clinical presentations for men [Lerner and Kannel 1986; Hochman et al. 1999]. According to the data from the Coronary Artery Surgery Study Registry many women with angina pectoris-like chest pain have no significant atherosclerotic obstructions of their coronary vessels; the incidence was 50% in women against 17% in men [Kennedy et al. 1982; Thomas and Braus 1998]. Moreover, women often present with atypical symptoms, particularly abdominal, neck and shoulder pain. Painless dyspnoe and extreme fatigue are the most frequent symptoms of old diabetic women. Because women have a lower prevalence of CAD at any given age, a lower prevalence of multivessel coronary obstructions and left main disease, the non-invasive tests have a slightly lower sensitivity and specificity for women compared with men. These findings highlight the fact that clinical history and non-invasive tests have some limitations in providing an adequate diagnosis of CAD in women.

Nowadays, invasive cardiac procedures are the standard approach in daily practice for the diagnosis of CAD. A certain sex-bias in the use of cardiac procedures has frequently [Ayanian and Epstein 1991; Steingart et al. 1991; Kostis et al. 1994; Maynard et al. 1996; Stone et al. 1996] but not consistently [Krumholz et al. 1992; Mark et al. 1994] been reported.

2.4. “Yentl Syndrome”

The underuse of invasive cardiac procedures among women has been related to the „Yentl syndrome“ [Healy 1991]. Yentl, the 19th-century heroine of Isaac Bashevis Singer’s short story, had to disguise herself as a man to attend school and study the Talmud. Being “just like a man”, seems to be a price women have to pay for equality.

Even when women present with typical angina, they are less likely to be referred for coronary angiography and coronary artery bypass graft surgery than men. Only when a women had an infarction, she was as likely as a men to undergo cardiac catheterization and revascularization [Healy 1991]. A comparable referral to coronary angiography for both men and women, has also been reported in case of abnormal results of exercise thallium testing [Lauer et al. 1996].

Additionally, data from United States and United Kingdom, report the same referral rate to myocardial revascularization after performing cardiac catheterization for both genders [Sullivan et al. 1994; Weintraub et al. 1996]. Studies that demonstrate no sex differences in the use of invasive cardiac procedures have mostly incorporated selected centers and nonacute settings.

Thus, most of the available literature reports a bias in the use of invasive diagnostic and interventional procedures in favor of men. Probably, the most likely explanations for the observed sex-based variations in invasive cardiac procedure use are the more advanced age in women, more comorbidity and, most importantly, a less favorable outcome of female patients treated with either CABG surgery [Fisher et al. 1982; O'Connor et al. 1993; Rahimtoola et al. 1993] or percutaneous transluminal coronary angioplasty [Kelsey et al. 1993; Bell et al. 1995; Malenka et al. 1996].

2.5. Myocardial revascularization

Registry data demonstrate a higher mortality and complication rate after percutaneous balloon angioplasty and CABG surgery in women even after correction for age, history of congestive heart failure, diabetes, and multivessel disease [Kelsey et al. 1993]. A smaller body size with smaller coronary arteries, more diffuse disease, increased coronary calcification and vessel tortuosity in women may contribute to a higher incidence of coronary dissection, abrupt vessel closure and overall vascular complications after PTCA. In addition, women are twice as likely as men to have severe concomitant disease and twice as likely to be considered inoperable or at high cardiac surgical risk. More frequent depression, delayed resumption of preoperative activities save for household tasks have been described for women after CABG surgery [King et al. 2000].

Today, coronary stenting has become the mainstay of catheter-based interventions in patients with CAD [Topol 1998]. Stenting has drastically reduced the incidence of large persistent dissections with threatening occlusion after balloon angioplasty, leading to a decline in the early complications rate of percutaneous intervention. On the other hand, coronary stent implantation carries the risk of thrombotic complications. Particularly, among high-risk subsets such as women who have small coronary arteries, the incidence of subacute stent thrombosis was higher and they (women) needed a more aggressive anticoagulation regime [Karrillon et al. 1996]. On the other hand, women are more prone to develop bleeding complications, which leads to a restricted indication for percutaneous coronary interventions in female patients [Van de Werf et al. 2001].

Introduction and use of antiplatelet therapy instead of former anticoagulation as maintenance therapy after coronary stenting, optimization of technical equipment as well as improved operational skills, have drastically changed the outcome after this procedure [Schömig et al. 1996; Topol et al. 1999]. In addition, stenting has improved the outcome of various subsets of patients compared with conventional PTCA [Fischman et al. 1994; Serruys et al. 1994; Savage et al. 1997; Versaci et al. 1997; Erbel et al. 1998]. It has also attenuated the negative prognostic role of known risk factors such as diabetes [Van Belle et al. 1997]. The large experience gained so far with coronary stenting may actually enable a comprehensive assessment of sex-related differences in the risk profile and outcome, and of the potential benefit that women may have obtained from this newer treatment strategy. Although there is a plethora of information on different aspects of CABG surgery and PTCA in women, the lack of similar data relative to stenting as the most common percutaneous intervention markedly limits our ability to choose the most appropriate form of therapy in female patients with CAD.

3. Purpose of the study

Purpose of this study is to examine whether there are sex-based differences in the early and late outcome as well as the prognostic factors in patients undergoing coronary stent placement.

4. Methods

4.1. Study population

In the period between May 1992 through December 1998, 6532 patients (23.7% women, 76.3% men) with symptomatic coronary artery disease underwent a percutaneous coronary intervention at the Deutsches Herzzentrum and 1. Medizinische Klinik der Technischen Universität, Munich. Of these, 1218 patients (25.0% women, 75.0% men) underwent conventional PTCA alone and were not eligible for this analysis focused on coronary stenting. An additional number of 1050 patients (23.1% women, 76.9% men) underwent stenting in the setting of acute myocardial infarction and were excluded from this study. Thus, the study population consisted of 4264 consecutive patients, 1001 women (23.5%) and 3263 men (76.5%), with stable or unstable angina pectoris treated with coronary stenting. All patients gave written informed consent before the intervention.

4.2. Stenting placement technique

In the initial period of this study , stent was mostly used as a “bailout” device following angioplasty coronary dissection with progressive lumen narrowing or abrupt vessel closure. Since 1994, elective stent placement was the preferred coronary intervention in both institutions (also dictated from ongoing randomized studies at this time). In all the patients we used the standard stent placement technique, that means stenting after balloon angioplasty. Conventional rapid-exchange balloon catheters were used for angioplasty. A commercially available stent delivery system was used in nearly 40 % of the cases. The stent was otherwise hand-crimped onto the angioplasty balloon. The balloon-stent assembly was advanced through 7 Fr guiding catheters appropriately selected to offer a sufficient backup support. To ensure exact positioning despite the low radiographic opacity of the Palmaz-Schatz, Jomed and Inflow ID stents, balloon catheters with radiopaque markers at both ends were used. The balloons were chosen slightly oversized. Nevertheless, the stent was frequently further dilated by an additional balloon inflation(s). The arterial sheath was removed when the partial-thromboplastin time fell below 60 seconds. Manual compression of the groin was carried out as long as necessary for local hemostasis, followed by pressure bandage [Schömig et al. 1994].

4.3. Adjunct pharmacological therapy

During these 5 years of experience with stenting, intravenous injection of 500 mg aspirin during intervention and oral administration of 100 mg aspirin twice daily, indefinitely, was the standard practice in both institutions.

In the initial phase, the standard medication for the intervention included an initial intra-arterial dose of 15 000 UI heparin and an additional 5000 UI for procedures longer than 1 hour. A continuous heparin infusion, adjusted to achieve a partial-thromboplastin time of 100 seconds, was started in all patients after application of pressure bandage. For patients treated with anticoagulant agents, heparin infusion was continued for 7 to 10 days until a stable level of oral anticoagulation was achieved (an international normalized ratio between 3.5 and 4.5 for prothrombin time). Therapy with phenprocoumon (Marcumar) was initiated on the day of the intervention and was given for 6 to 8 weeks. After September 1995, the standard regimen consisted of heparin infusion for only 12 hours after intervention and ticlopidine 250 mg twice daily for 4 weeks [Schömig et al. 1994; Schömig et al. 1996]. Also, during the last 3 and a half years of the study period, patients considered at higher risk for stent thrombosis (large residual dissections, thrombus at the stent site) received glucoprotein IIb/IIIa inhibitors (abciximab). Abciximab was given as a bolus of 0.25 mg/Kg of body weight followed by a continuous infusion of 0.125 µg/Kg/minute (up to maximal dose of 10 µg/minute) for 12 hours [Topol et al. 1999].

4.4. Qualitative angiographic evaluation

Lesion complexity was defined according to the AHA/ACC Task Force modified criteria on lesion morphology [Ellis et al. 1990; Kastrati et al. 1999]. Briefly, a number of lesion characteristics such as location, length (“shoulder-to-shoulder” extent of atherosclerotic narrowing), proximal vessel tortuosity, angulations, calcification, major side branch involvement, presence of thrombus and total occlusions were used to classify the lesions according to a four-scale score, A, B1, B2 and C; lesions of type B2 or C were considered complex.

The degree of coronary anterograde perfusion distal to a stenosis before and after intervention was evaluated according to the Thrombolysis in Myocardial Infarction flow criteria [TIMI Study Group 1985]. A rapid anterograde filling of the terminal coronary artery segment through a lesion presents the higher degree of coronary perfusion, TIMI flow 3; whereas TIMI flow 0 or 1 presents absence or minimal persistence of perfusion. A total occlusion was considered chronic if it was more than 3 months old (chest pain history or previous coronary angiography). Restenotic lesions were in most of the cases restenosis after balloon angioplasty.

Left ventricular function was assessed qualitatively on the basis of biplane angiograms using a 7 segment division.

4.5. Quantitative angiographic evaluation

Quantitative analysis was performed off-line using Cardiovascular Measurements System (CMS Medis Medical Imaging Systems, Nuenen, Netherlands), a computerized automated edge-detection algorithm quantitative angiographic system. Images from 35 mm cinefilm or optical disk in the DICOM file format were digitized into 512 x 512 x 8 bit pixel matrix using 256 different gray values. The angiographic runs submitted were reviewed and single frames representing the “worst-view” projections at baseline, during and immediately after stent implantation, at the end of the procedure and at follow-up are selected. For estimation of absolute coronary dimensions, the angiographic catheter was used for calibration of the image. The coronary segment including the target lesion was through two-point user-defined path line identified. Finally, the system performed the automatic arterial edge detection using a 50% weighted threshold between the first and second derivative extremes and contour detection using a minimal cost matrix. The better contour detection by complex lesions was reached with additional use of the gradient field transform algorithm. After visual confirmation of the tracing by the operator, the measurements were displayed (FIGURE 1).

The parameters obtained were minimal lumen diameter (the absolutely minimal vessel diameter within the index lesion), reference diameter (estimation of vessel size prior to the occurrence of an obstruction), diameter stenosis [DS = (1 – MLD/RD)* 100], lesion length (distance between the proximal and distal end of lesion) and diameter of the maximally inflated balloon during stent placement.

Quantitative left ventricular analysis was performed using manual tracing of the left ventricular outlines from end-diastolic and end-systolic frames (in RAO 30 degree projection). Both outlines were used to calculate the global ejection fraction. In only 3017 patients (71%) left ventricular ejection fraction was available and was also reported.

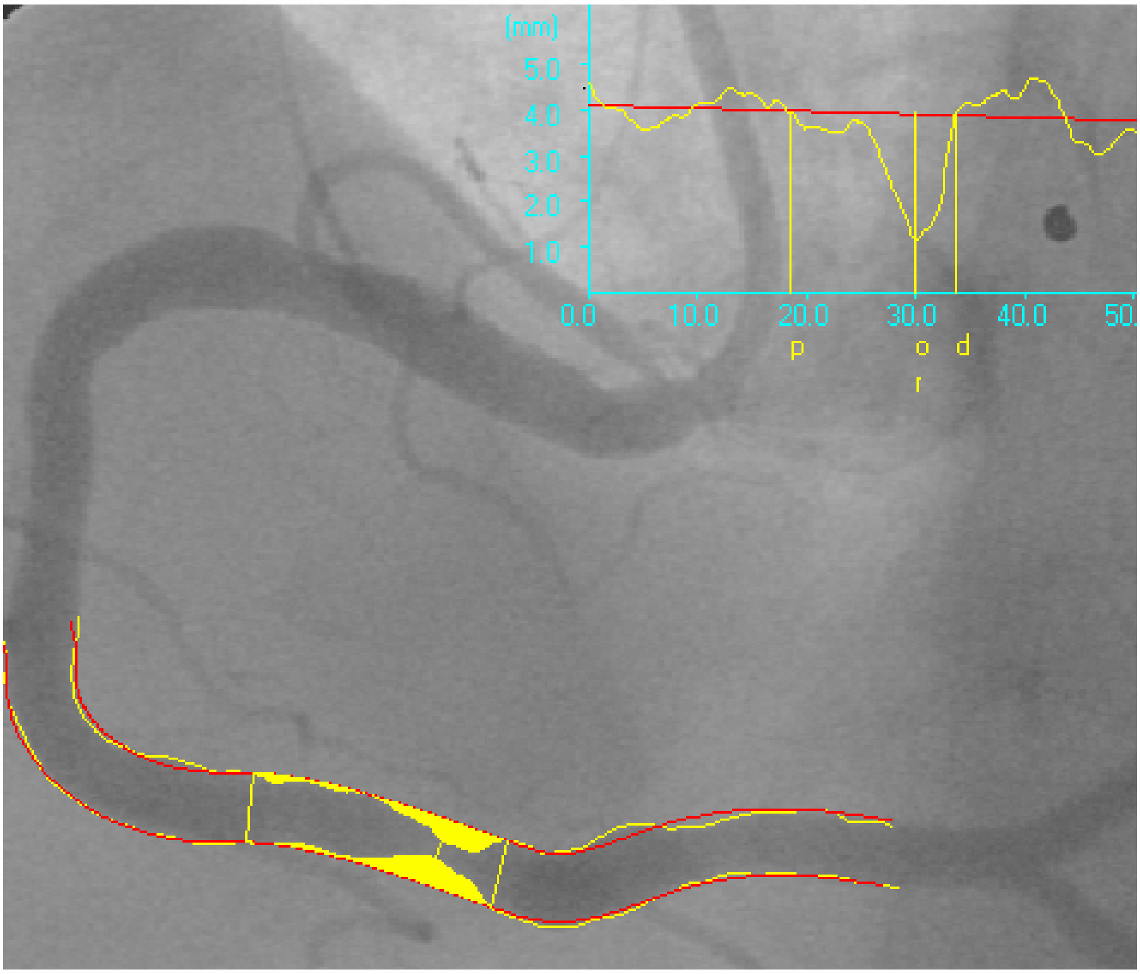
FIGURE 1. QUANTITATIVE CORONARY ANGIOGRAPHY

Picture presenting a quantitative coronary angiography measurement using CMS MEDIS System. The target lesion is allocated to the right coronary artery.

“o” indicates obstruction representing MLD;

“r” indicates interpolated reference diameter presenting the vessel size;

“p” and “d” indicate proximal and distal edge of the stenosis.



4.6. Definitions

Current smoking was considered any cigarette smoking in the prior 6 months. Hypercholesterolemia was defined as a documented cholesterol plasma level of more than 240 mg/dl. Information about the presence of diabetes derived from the past medical history of the patients, if they were on insulin or oral hypoglycemic agents medication, or on the basis of elevated levels (>140 mg/dl) of fasting, non-stressed blood glucose on at least two separate occasions during the hospital stay corresponding to the index intervention.

The diagnosis of unstable angina at presentation was based on a history of crescendo angina, angina pectoris at rest or with minimal exertion or angina pectoris of new onset (within 1 month) in the absence of clear-cut electrocardiographic and cardiac enzyme changes diagnostic of an acute myocardial infarction [Rutherford et al. 1988].

Procedural success was assessed by angiography. The procedure was considered successful when stent placement was associated with a residual stenosis of less than 30% and TIMI flow grade of 2 or more [TIMI Study Group 1985].

The diagnosis of reduced left ventricular function required the presence of hypokinesia in at least 2 segments in qualitative LV function analysis.

Binary restenosis was defined as a diameter stenosis ≥ 50% in the target lesion at the control angiography.

Death from any cause, myocardial infarction and target vessel revascularization were considered as adverse events. The diagnosis of acute myocardial infarction was established in the presence of at least 2 of the following criteria: clinical episode of prolonged chest pain, the appearance of one or more new pathologic Q waves on the electrocardiogram, and the rise in creatine kinase (or its MB isoenzyme) levels to at least twice the upper normal limit. Target vessel revascularization refers to all percutaneous interventions and coronary artery bypass graft surgery performed to the target lesion in the presence of angiographic restenosis and symptoms or signs of ischemia.

4.7. Endpoints of the study

The main endpoint of this analysis was the combined event rate of death and myocardial infarction at 30 days and at one year. An additional endpoint was the investigation of the impact of sex-based differences of prognostic factors on clinical and angiographic late outcome after coronary stenting.

4.8. Patients follow-up

4.8.1. Clinical laboratory evaluation

Blood samples were drawn every 8 hours for the first 24 hours after index procedure and daily afterwards for the determination of cardiac markers (CK, CK-MB) and blood cell counts (hemoglobin, hematocrit, platelet count, white blood cell count). Also hemostatic tests (PTT, prothrombin time or INR) were performed twice daily to monitor heparin and phenprocoumon therapy. Electrocardiograms were recorded daily. The femoral puncture site was routinely monitored to assess for local vascular complication, and duplex ultrasonography was performed the next day after the pressure bandage was removed.

4.8.2. Clinical monitoring

In the initial phase, a bed rest regiment was enforced for 72 hours after the procedure and the hospital stay was at least 10 days. After changing from anticoagulant to antiplatelet therapy , the hospital stay was reduced to 3 days or even less. After discharge follow-up protocol demanded a phone interview or office visit at 30 days, a clinical visit at 6 months and an additional phone interview or office visit at 1 year after the procedure. For patients reporting cardiac symptoms during the phone interview, at least one clinical and electrocardiographic check-up was performed at the outpatient clinic or by the referring physician. During the whole monitoring time, all information derived from eventual hospital readmission records or provided by the referring physician or by the outpatient clinic was entered into the computer database.

4.9. Statistical analysis

The results are expressed as mean±SD or as proportions (percentages). The differences between groups were assessed using chi-square test or Fisher's exact test for categorical data and t-test for continuous data. Survival analysis was made applying the Kaplan-Meier method. Differences in survival parameters were assessed for significance by means of the log-rank test. The unadjusted and adjusted risk associated with female gender was assessed using the hazard ratios and 95% confidence intervals derived from univariate and multivariate Cox regression models, respectively. Patient's sex together with clinical and angiographic factors that were significantly different between women and men in univariate analysis were entered into the multivariate Cox model to adjust for baseline differences. All variables were entered into the model in their original form without transformation. We also tested whether there was an interaction between sex and age by entering into this model the interaction term *gender age*. The HRs for continuous variables reflect the hazard for patients at the 75^{th} percentile of the distribution of the variable versus patients at the 25^{th} percentile. Stratification according to different risk subsets was made by classification and regression tree analysis [Mathsoft Inc 1999]. A disadvantage of this method is that it does not take into account a possible interplay of the risk factors entered into the model. For this reason the CART model included only the independent correlates of the outcome as determined by the multivariate Cox model described above. All analyses were performed using the S-Plus statistical package (Mathsoft, Inc., Seattle, WA). Statistical significance was accepted for all values of $P<0.05$.

5. RESULTS

5.1. Patients baseline characteristics

Tables 1 and 2 display the baseline clinical and lesion-related characteristics of the patients as well as the procedural data. There were significant sex-related differences, particularly regarding the clinical features. In comparison with men, women were more likely to have hypertension, diabetes and hypercholesterolemia but were less likely to be smokers. Conversely, a relatively smaller proportion of women than men had multivessel disease, reduced left ventricular function and a history of myocardial infarction or CABG surgery. In women compared with men, the lesions involved more often the left anterior descending coronary artery and were situated in vessel of smaller size. The procedural data were essentially similar with regard to balloon-to-vessel ratio, stent model implanted, total stented length and final diameter stenosis. Procedural success was achieved in 98.2% of both women and men. No differences were seen in relationship to antithrombotic therapy used during and after the procedure. The use of concomitant pharmacologic therapy was also comparable with a high proportion of patients taking angiotensin-converting enzyme inhibitors, beta-blockers and statins.

TABLE 1. BASELINE CLINICAL CHARACTERISTICS

Characteristic	Women (n=1001)	Men (n=3263)	P value
Age, mean (SD), years	69±10	63±11	<0.001
Arterial hypertension	755 (75)	2216 (68)	<0.001
Diabetes	273 (27)	623 (19)	<0.001
Current smoker	166 (17)	971 (30)	<0.001
Hypercholesterolemia	569 (57)	1528 (47)	<0.001
Unstable angina	398 (40)	1251 (38)	0.42
Previous myocardial infarction	326 (33)	1220 (37)	0.006
Previous bypass surgery	85 (9)	464 (14)	<0.001
Reduced left ventricular function	236 (24)	977 (30)	<0.001
LV ejection fraction, mean (SD), % *	59±13	57±14	<0.001
Multivessel disease	649 (65)	2487 (76)	<0.001
Peri- and postprocedural therapy			
- Abciximab	158 (16)	579 (18)	0.15
- Ticlopidine	854 (85)	2819 (86)	0.38
- ACE inhibitors	639 (64)	2011 (62)	0.21
- Beta-blockers	742 (74)	2391 (73)	0.59
- Statins	689 (69)	2278 (70)	0.55
- Nitrates	221 (22)	630 (19)	0.06
- Calcium antagonists	64 (6)	166 (5)	0.11

Data are presented as number (percentage) unless otherwise indicated.

ACE indicates angiotensin-converting enzyme.

*Available in 707 women and 2310 men.

TABLE 2. LESION AND PROCEDURAL CHARACTERISTICS

Characteristic	Women (n=1001)	Men (n=3263)	P value
Vessel			<0.001
Left main artery	28 (3)	67 (2)	
LAD	464 (46)	1291 (40)	
LCx	151 (15)	671 (21)	
RCA	317 (32)	984 (30)	
Bypass graft	41 (4)	250 (7)	
Complex lesions	712 (71)	2384 (73)	0.23
Chronic occlusions	77 (8)	272 (8)	0.52
Restenotic lesions	205 (21)	779 (24)	0.03
Number of stented lesions			0.12
1 lesion	777 (78)	2433 (75)	
2 lesions	183 (18)	637 (19)	
3 or more lesions	41 (4)	193 (6)	
Lesion length, mean (SD), mm	11.8±6.5	12.3±7.3	0.03
Vessel size, mean (SD), mm	2.98±0.50	3.06±0.54	<0.001
MLD before the procedure, mean (SD),mm	0.69±0.48	0.70±0.49	0.45
DS before the procedure, mean (SD), %	77.0±14.9	77.1±14.6	0.77
Maximal balloon pressure, mean (SD), atm	13.7±3.2	13.9±3.2	0.03
Balloon-to-vessel ratio, mean (SD), %	1.08±0.10	1.08±0.10	0.82
Stent type			0.65
- Palmaz-Schatz*	332 (33)	1047 (32)	
- Inflow†	268 (26)	820 (25)	
- MULTI-LINK‡	127 (13)	415 (13)	
- JOSTENT§	97 (10)	350 (11)	
- PURA-A#	98 (10)	319 (10)	
- NIR¶	54 (5)	215 (6)	
- other	25 (3)	97 (3)	
Total stented length, mean (SD), mm	19.8±13.4	20.6±13.3	0.10
Final MLD, mean (SD), mm	2.89±0.53	2.94±0.54	0.005
Final DS, mean (SD), mm	5.6±10.4	6.0±10.3	0.26

Data are presented as number (percentages) unless otherwise indicated. DS=diameter stenosis; LAD=left anterior descending coronary artery; LCx=left circumflex coronary artery; MLD=minimal lumen diameter; RCA=right coronary artery.
*Johnson&Johnson Interventional Systems, Warren, NJ;
†Inflow Dynamics, Munich, Germany;
‡Guidant, Advanced Cardiovascular Systems, Santa Clara, CA;
§JOMED International AB, Helsingborg, Sweden;
Devon Medical, Hamburg, Germany;

¶Scimed, Boston Scientific Europe, Verviers, Belgium.

5.2. Early 30-day outcome

Table 3 indicates the number of patients with adverse events within the first 30 days after coronary artery stent placement. Compared with men, women had a significantly higher risk of death or nonfatal myocardial infarction during this period, unadjusted HR 1.70 (95% CI, 1.10-2.62). In multivariate analysis, female sex was a significant independent risk factor for adverse events, adjusted HR of 2.02 (95% CI, 1.27-3.19). The HRs for other independent risk factors were reduced left ventricular function, 1.77 (95% CI, 1.13-2.75); older age, 1.67 (95% CI, 1.09-2.56) for an age of 73 years (75th percentile) versus 57 years (25th percentile); and diabetes, 1.58 (95% CI, 1.00-2.56). Coronary vessel size did not correlate with the 30-day outcome as reflected by an HR of 1.00 (95% CI, 0.75-1.33) for a vessel size of 2.6 mm (25th percentile) versus 3.3 mm (75th percentile). However, there was a significant interaction (P=0.01) between sex and age as a result of a stronger association with age for 30-day outcome in men.

TABLE 3. ADVERSE EVENTS OBSERVED DURING THE 30 DAYS AFTER THE PROCEDURE

Adverse Events	Women (n=1001)	Men (n=3263)	P value
Death or nonfatal myocardial infarction	31 (3.1)	60 (1.8)	0.02
Death	17 (1.7)	28 (0.8)	0.02
Nonfatal myocardial infarction	14 (1.4)	32 (1.0)	0.34
Target vessel revascularization	32 (3.2)	73 (2.2)	0.09
Bypass surgery	9 (0.9)	22 (0.7)	0.46
Repeated balloon angioplasty	23 (2.3)	51 (1.5)	0.12
Any of the above events	49 (4.9)	102 (3.2)	0.008

Data are presented as number (percentage) of patients.

5.3. ONE-YEAR OUTCOME

The excess risk for death or nonfatal myocardial infarction among women generally declines during the first months after the intervention (FIGURE 2). At the end of the 1-year period, however, both women and men had a comparable cumulative incidence of this endpoint with 6.0% in women and 5.8% in men (P=0.77). The unadjusted HR associated with female sex was 1.04 (95% CI, 0.78-1.40).

In a multivariate model similar to that for the 30-day period, the adjusted HR for the endpoint of death or nonfatal myocardial infarction at 1 year was 1.06 (95% CI, 0.75-1.48) for women. The HRs for independent risk factors identified by this analysis were: age, HR of 2.07 (95% CI, 1.63-2.64) for an age of 73 years (75^{th} percentile) versus 57 years (25^{th} percentile); reduced left ventricular function, 1.73 (95% CI, 1.33-2.26); diabetes, 1.50 (95% CI, 1.14-1.98); and smoking habit, 1.42 (95% CI, 1.05-1.91). There was no significant interaction (P=0.18) between sex and age in this model.

To assess whether the risk stratification according to these factors was similar in women and men, we applied a CART analysis and identified subsets with a different 1-year risk for death or nonfatal myocardial infarction both in women (FIGURE 3) and men (Figure 4). Among female patients, the risk extremes yielded by this analysis were between 3.4% for non-diabetic women younger than 70 years and 16.7% for diabetic women 70 years or older who had reduced left ventricular function (FIGURE 3). Among male patients, the risk extremes were between 3.3% for patients younger than 70 years with normal left ventricular function and 13.7% for older patients with reduced left ventricular function (FIGURE 4). The following difference in the relevance of risk factors between women and men was observed: while diabetes followed by older age were the most important factors in female patients, the outcome of male patients was mostly influenced by an older age followed by a reduced left ventricular function.

The cumulative 1-year mortality was 4.0% in women and 4.1% in men (P=0.94). Regarding the risk of death at 1 year, female sex was associated with an unadjusted HR of 0.99 (95% CI, 0.69-1.40) and an adjusted HR of 0.78 (95% CI, 0.54-1.13). A distinctive risk pattern for women and men similar to that revealed above by the CART analysis was also evident for mortality. The major risk factor for death at 1 year was diabetes in women and older age in men. The risk increase that accompanied the presence of diabetes was 3.37 (95% CI, 1.80-6.33) in women and 1.59 (95% CI, 1.09-2.31) in men. The risk increase that accompanied the presence of older age (≥70 years) was 3.34 (95% CI, 2.36-4.71) in men and 2.61 (95% CI, 1.27-5.35) in women.

Subsequent revascularization procedures (either CABG surgery or PTCA) due to clinical and angiographic occurrence of restenosis were less frequently needed in women (14.5% in women vs. 17.5% in men, P=0.02). Among these reinterventions, the rate of CABG surgery was essentially the same (1.9% in women and 2.2% in men, P=0.52).

The observed angiographic restenosis rate also, showed only a trend toward reduced restenosis in women (30.7% in women and 33.3% in men, P=0.17). However, regarding the risk of developing restenosis at 1 year after index procedure, female sex was identified as a significantly protective factor in multivariate analysis, adjusted OR of 0.81 (95% CI, 0.67-0.98) (FIGURE 5). As expected, small vessel size, long lesions and presence of diabetes were associated with an increased risk for restenosis, with ORs ranging from 1.37 for diabetes to 2.21 for small vessel size.

FIGURE 2. CUMULATIVE INCIDENCE OF DEATH OR MI

Cumulative incidence of the composite endpoint of death and nonfatal myocardial infarction during 1 year after coronary stenting in women and men.

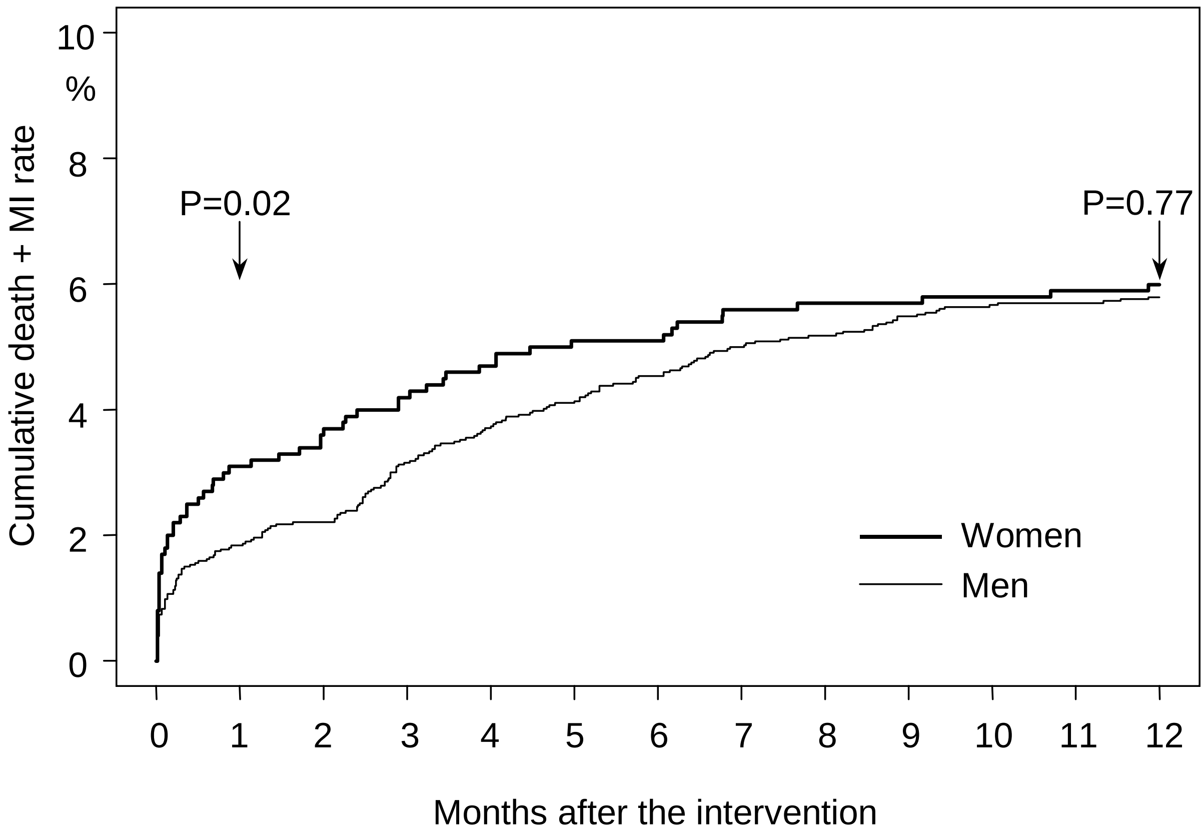


FIGURE 3. CART MODEL IN WOMEN

Graph presenting the CART model in women constructed with the independent risk factors for the composite endpoint of death or myocardial infarction. The area of each circle is proportional to the size of the subgroup relative to the total population of female study sample. The shaded area of each circle represents the percentage of patients with the composite endpoint in a given subgroup. Ratios represent the number of patients with events as the numerator and the total number of patients in the subgroup as the denominator. At each level, the CART analysis identifies the most relevant risk stratification factor.

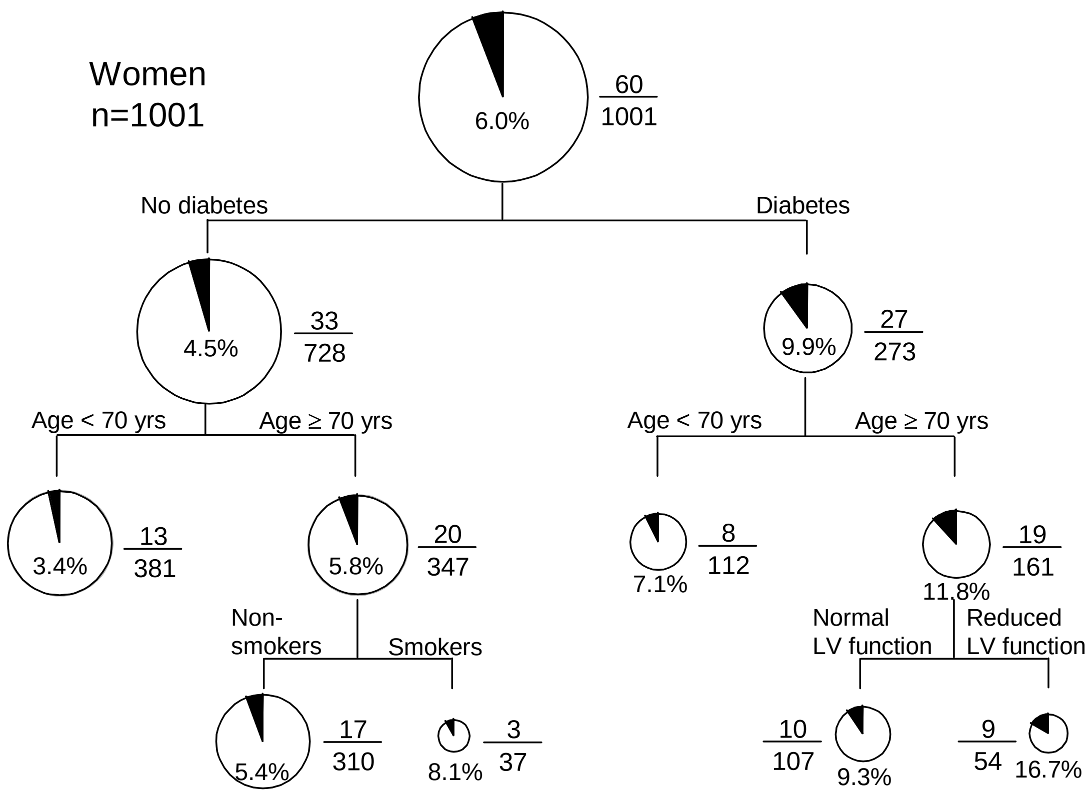


FIGURE 4. CART MODEL IN MEN

Graph presenting the CART model in men constructed with the independent risk factors for the composite endpoint of death or myocardial infarction. The area of each circle is proportional to the size of the subgroup relative to the total population of male study sample. The shaded area of each circle represents the percentage of patients with the composite endpoint in a given subgroup. Ratios represent the number of patients with events as the numerator and the total number of patients in the subgroup as the denominator. At each level, the CART analysis identifies the most relevant risk stratification factor.

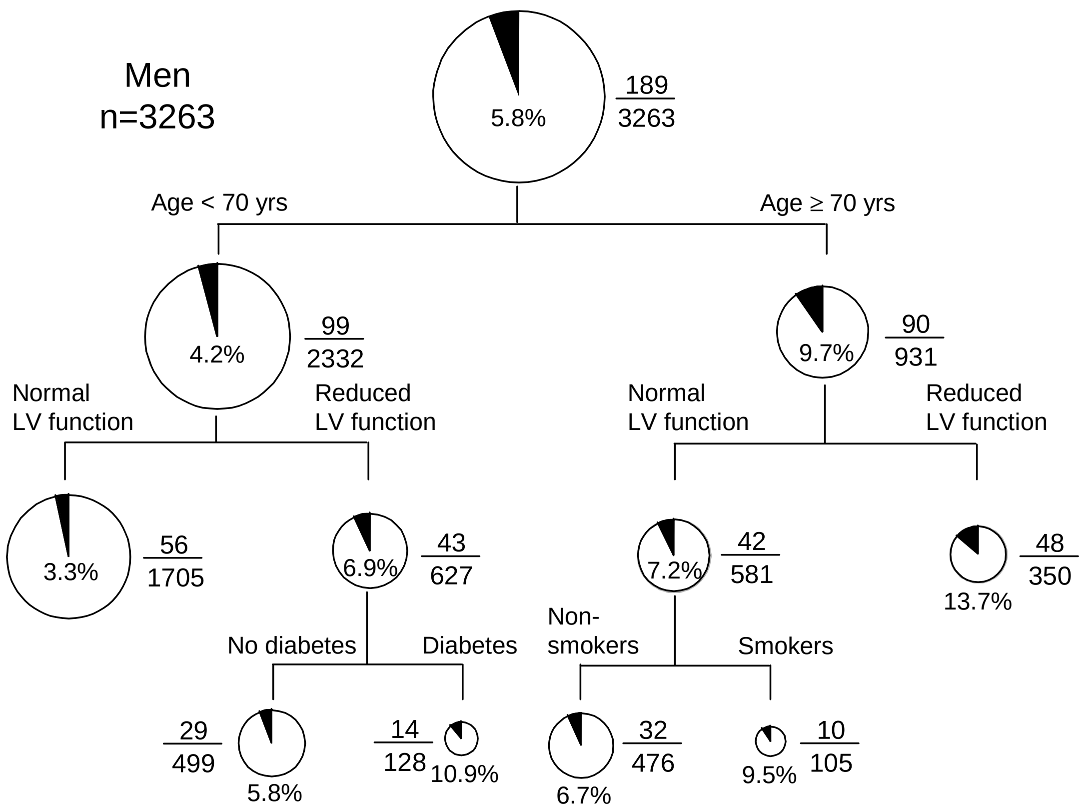
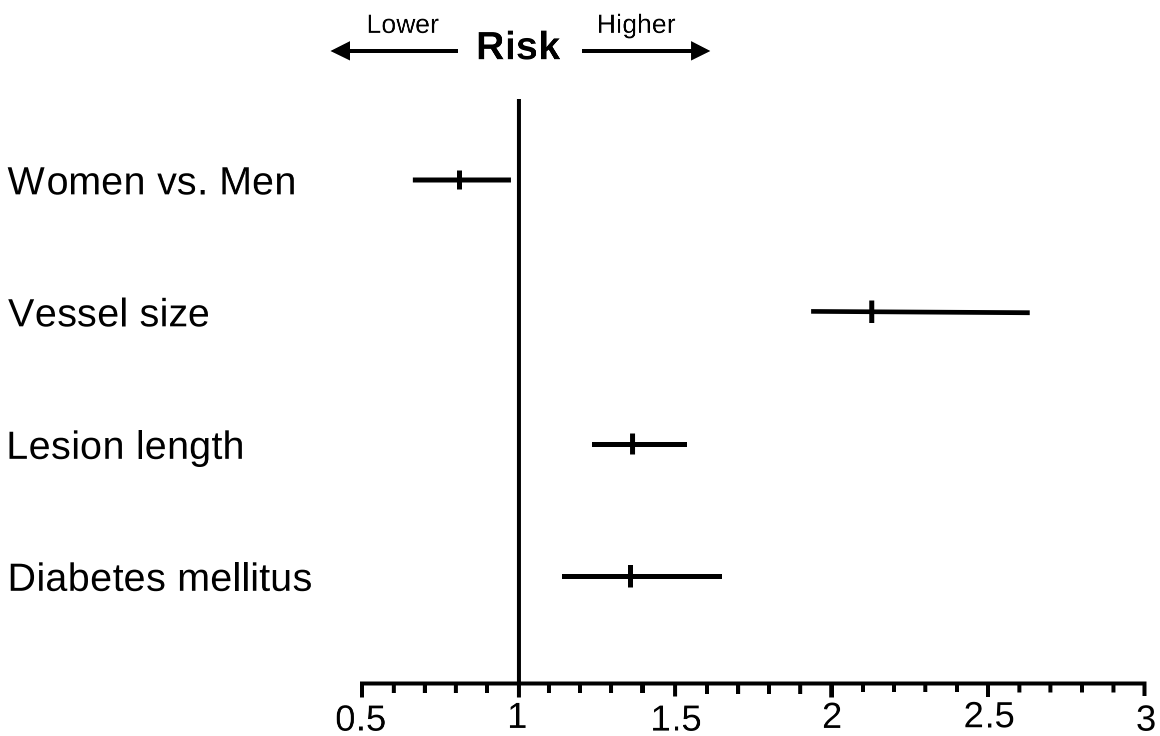


FIGURE 5. MULTIVARIATE LOGISTIC REGRESSION ANALYSIS

Graph presenting odds ratios and their 95% confidence intervals for significantly independent risk factors for development of angiographic restenosis as identified by multivariate logistic regression analysis.



6. COMMENT

The main finding of this study indicates that women are expected to have the same 1-year outcome as men after coronary artery stenting. Other findings of the study are that when compared with men, women currently undergoing coronary stent placement present substantial differences in baseline characteristics, in the temporal pattern of outcome, and in the relative value of the prognostic factors, all of which may have relevant implications in clinical practice.

6.1. Differences in baseline characteristics

We analyzed a consecutive series of patients with stable or unstable angina who underwent intracoronary stenting. The unselected nature of the population encompassed in this study is representative of the current practice of percutaneous coronary interventions and comparable to that of the series enrolled in the most recent randomized trials of coronary stenting [Topol et al. 1999].

There were pronounced differences in baseline characteristics between women and men. Except for having a lower prevalence of smoking, women presented with a higher prevalence of cardiovascular risk factors. Women generally develop CAD between 6-10 years later than men [Castelli 1988] as a result of the protective role of endogenous estrogen [Barrett-Connor and Bush 1991]. This explains the older age of female patients in our cohort and, as a consequence, the denser aggregation of risk factors among women. Yet, women showed less severe CAD considering the proportion of patients with multivessel disease, and they were less likely to have prior myocardial infarction and reduced left ventricular function. The reason for this apparent dissociation between prevalence of risk factors and severity of ischemic heart disease, which has also been described previously [Jayes et al. 1992] is not completely clear. In cohort studies of patients with percutaneous coronary interventions, this may reflect a sex-bias with women more likely to be denied the access to these procedures in the presence of a more advanced CAD. Differences between men and women in the initial presentation of CAD may be an alternative explanation. Framingham data have shown that women with CAD are more likely to present with angina pectoris initially whereas men first present with myocardial infarction [Lerner and Kannel 1986]. This may increase the chances of women to be percutaneously treated when left ventricular function is still preserved.

6.2. Differences in outcomes

During the early phase (30 days) after coronary stenting, women in our study experienced more adverse events than did men. In particular, the risk of death or myocardial infarction was significantly higher among women even after adjustment for baseline differences. Stent thrombosis accounts for most of the early complications after stenting [Schühlen et al. 1998]. Thus, women appear to be at higher risk for thrombotic complications. This finding is consistent with previous studies after PTCA, which have almost invariably shown the increased early hazard carried by women [Cowley et al. 1985; Kelsey et al. 1993; Weintraub et al. 1994; Bell et al. 1995; Malenka et al. 1996]. As with the findings of our study, other studies have also shown that the differences in conventional baseline characteristics may not sufficiently explain this risk increase. In a large series after PTCA, Malenka et al. [Malenka et al. 1996] found that the risk of in-hospital death remained elevated in women even after adjusting for case-mix.

Our data also show that, the excess risk observed in women gradually diminishes and, at the end of the 1-year follow-up period, both men and women have an essentially identical outcomes. A similar outcome pattern was also shown in the early PTCA registry of the National Heart, Lung and Blood Institute [Cowley et al. 1985]. In that Registry, although in-hospital mortality was significantly higher in women compared with men, the cumulative incidence at 18 months was virtually the same [Cowley et al. 1985]. However, the study reported on patients with a particularly low-risk profile who were treated in the early phase of PTCA, and therefore the findings may not be comparable with current practice. Subsequent reports have generally shown that the initial difference in mortality to the disadvantage of women is maintained for years after PTCA [Kelsey et al. 1993; Weintraub et al. 1994; Bell et al. 1995]. Our 1-year findings are in concert with the results of a more recent study which showed no sex-specific differences in outcome among patients treated with either PTCA or CABG surgery [Jacobs et al. 1998]. Thus, greater experience and advances in interventional cardiology and surgery may have improved the results of coronary interventions especially in female patients [Bell et al. 1993; Jacobs et al. 1997] and reduced the excess risk previously described for women.

One of the factors contributing to this later decline in the incidence of adverse events after coronary interventions in women, is the observed reduced long-term need for repeat reinterventions due to the presence of angiographic restenosis and ischemia. This finding has also been reported by others [Cowley et al. 1985].

Women with a higher prevalence of diabetes, smaller vessels and more complex lesions than men, represent a subset with a high theoretical risk for restenosis after coronary stenting [Elezi et al. 1998; Elezi et al. 1998]. On the contrary, we found a slightly lower binary restenosis rate in women compared with men. Multivariate analysis also identifies female sex as an independent protective factor against restenosis. We can only speculate about the possible mechanisms leading to this lower than expected neointimal hyperplasia in female patients. Estrogen anti-inflammatory effects, through slowing the rate of oxidative destruction of arterial wall nitric oxide, favoring prostacyclin formation and diminishing thromboxane A2 synthesis, may probably be responsible for the diminished inflammatory response to balloon-injury [Chen et al. 1996]. Additionally, a sex-specific influence of genetic factors can not be excluded. As an example, we reported previously that a genetic variant of platelet glycoprotein IIIa increases the risk of restenosis after stenting more in women than in men [Kastrati et al. 1999].

To our knowledge, this is the first report about the impact of sex on restenosis. Further investigation would be necessary to establish the role of sex on this process.

6.3. Differences in prognostic factors

Age, diabetes, left ventricular function and smoking were the independent correlates of 1-year outcome in the entire population analyzed in our study, but their prognostic strength presented a sex-based difference. Multivariate risk stratification methods such as CART analysis applied to men and women, separately, showed that older age was the major determinant of an adverse outcome in men whereas diabetes had the greatest prognostic value in women. The weaker age-dependence of outcome in women treated with coronary artery stenting may be relevant to the issue of the definition of treatment guidelines considering the older age with which women present with symptomatic CAD. To our knowledge, however, differences in the prognostic pattern after percutaneous coronary interventions have not been described previously and further studies are needed before trying to draw definitive implications.

6.4. Clinical implications

Our finding of a comparable 1-year outcome among women and men following coronary artery stenting does not justify a less aggressive treatment approach of CAD in women than in men, as observed in several previous studies [Ayanian and Epstein 1991; Steingart et al. 1991; Kostis et al. 1994; Maynard et al. 1996; Stone et al. 1996]. The greater hazard presented by women was only confined to the early post-stenting period. With the availability of new, effective antithrombotic drugs such as the glycoprotein IIb/IIIa inhibitors, there is a potential to reduce the early excess risk and improve the overall results of coronary interventions in women. This hope is further strengthened by considering the specific nature of prognostic factors in women. The postinterventional outcome in women depended primarily on relatively modifiable factors such as diabetes. Women with diabetes undergoing coronary stenting can especially benefit from a better control of glycemia. In addition, recent findings suggesting a more pronounced salutary effect of glycoprotein IIb/IIIa inhibition among patients with diabetes, who were treated with coronary stenting, [Marso et al. 1999] may open encouraging prospects for women with diabetes who undergo this procedure.

6.5. Limitations

The main limitation of this study is that it offers data only about coronary stenting in women. The inclusion of other revascularization techniques such as CABG surgery and PTCA is indispensable for the establishment of the optimal treatment strategy for women with CAD.

Moreover, the patients included in this study were referred for diagnostic coronary angiography by family physicians. This may be the source of another limitation of this study due to the possible referral bias that generally affects studies performed in tertiary medical centers. Referring physicians may use different, sex-specific, symptomatic and functional thresholds for referring patients for invasive diagnostic tests. In our study, we are unable to evaluate the magnitude of this potential bias which has been the focus of extensive work in the past [Ayanian and Epstein 1991; Steingart et al. 1991; Krumholz et al. 1992; Kostis et al. 1994; Mark et al. 1994; Maynard et al. 1996; Stone et al. 1996].

7. Conclusion

The results of this study indicate that the 1-year outcome for women with CAD undergoing coronary artery stenting is similar to that for male patients. Despite the similarity in outcome, there are several sex-specific differences in baseline characteristics, and clinical course after the intervention. In addition, differences in the relative weight of prognostic factors may aid in clinical decision making and help to further reduce the risk and improve the outcomes of coronary interventions in women.

8. ABSTRACT

Background. Women with coronary artery disease are believed that bear a higher risk for adverse outcomes than men after conventional coronary interventions. The increasing use of coronary stenting has improved the outcome of patients undergoing coronary interventions, but little is known about the nature of outcomes in men versus women after this procedure.

Objective. To examine whether there are sex-based differences in prognostic factors and in early and late outcomes among CAD patients undergoing coronary stent placement.

Patients and methods. This is an inception cohort study, which included a consecutive series of 4264 patient (1001 women and 3263 men) with symptomatic CAD who were treated with coronary stenting between May 1992 and December 1998, at two tertiary referral institutions in Munich, Germany. Patients who underwent stenting in the setting of acute myocardial infarction were excluded. The main endpoints of the study were the combined event rates of death and nonfatal myocardial infarction, assessed at 30 days and 1 year after stenting, compared by sex.

Results. Compared with men, women undergoing coronary stenting were significantly older (mean age, 69 vs. 63 years) and more likely to present with diabetes, arterial hypertension and hypercholesterolemia. Women had less extensive CAD, a less frequent history of myocardial infarction and better preserved left ventricular function than men. Women presented an excess risk of death or nonfatal myocardial infarction only during the early period after stenting: the 30-day combined event rate of death or myocardial infarction was 3.1% in women and 1.8%

in men (P=0.02) and the multivariate-adjusted hazard ratio for women was 2.02 (95% CI, 1.27-3.19). At 1 year, the outcome was similar for both women and men (combined event rate for women, 6.0%, and for men, 5.8% (P=0.77); multivariate-adjusted HR for women, 1.06 [95% CI, 0.75-1.48]).There was a sex difference in the prognostic value of baseline characteristics: the strongest prognostic factors were diabetes in women and age in men. Women also presented a reduced risk for restenosis (target vessel revascularization, 14.5% vs. 17.5% in men, P=0.02).

Conclusion. The results of this study indicate that the 1-year outcomes of women with CAD undergoing coronary artery stenting are similar to those of men. Despite the similarity in outcomes, there are several sex-specific differences in baseline characteristics, clinical course after the intervention, and relative weight of prognostic factors.

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9. ACKNOWLEDGMENTS

Mein Dank gilt Herrn Prof. A. Schömig und Herrn Prof. A. Kastrati für die Überlassung des Themas und für die anregenden Diskussionen während der Betreuung meiner Doktorarbeit.

Ganz besonderes danken möchte ich auch den Mitarbeitern der klinischen Forschungsabteilung der Kardiologie am Deutsches Herzzentrum, Frau Holle, Frau Rodriguez, Frau Hösl und Frau Koch für die gute Zusammenarbeit während der Datensammlung und Patientenbetreuung. Sie haben wesentlich zum Gelingen dieser Doktorarbeit beigetragen.

Allen Mitarbeitern des QCA Core Lab, Herr Redl, Frau Pinieck und Frau Kienmoser bin ich für die praktische Hilfe bei quantitativen angiographischen Auswertungen sehr dankbar. Das Klima war in der Arbeitsgruppe immer gut und die Arbeit während der Zeit hat mir in dieser Abteilung viel Freude gemacht.

Zuletzt danke ich auch ganz besonders die Schwestern des Herzkatheter am Deutschen Herzzentrum, besonders Frau Gleissl und Frau Pavlovic für die große Unterstützung und ihre praktische Hilfe bei Fertigstellung dieser Arbeit.