Aims To examine the impact of sex on restenosis in a large cohort of consecutive patients undergoing coronary stenting and systematic angiographic and clinical follow-up.

Methods and results The study includes a cohort of 4374 consecutive patients (1025 women and 3349 men), undergoing coronary stenting for stable or unstable angina. Follow-up angiography at 6 months was performed in 80% of patients. Clinical events were assessed for a period of 1 year after the procedure. Main end-points of the study were angiographic and clinical restenosis at follow-up. Compared to men, women were older, presented more often with diabetes, smaller vessel size and shorter lesions. Clinical restenosis (need for reintervention) was found in 14.8% of women and 17.5% of men (P=0.048). The incidence of angiographic restenosis was significantly lower in women than in men (28.9% vs 33.9%, respectively, P=0.01). After adjustment for other covariates, women presented a 23% reduction of the risk of restenosis: odds ratio 0.77 (95% confidence interval 0.63 to 0.93). While a small vessel size was a risk factor for restenosis in both sexes, the influence of diabetes on restenosis was mostly confined to women.

Conclusion Compared with men, women present a lower risk of restenosis after coronary stenting despite a more preponderant presence of two major risk factors for restenosis, diabetes and small vessel size. There are sex-based differences in predictive factors of restenosis with diabetes having a particularly strong impact in women.

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KEYWORDS
Coronary artery disease; Gender; Restenosis; Stents
Methods

Patient population

Between January 1996 and December 1999, 4374 consecutive patients, 1025 women and 3349 men, underwent coronary stenting for stable or unstable angina at Deutsches Herzzentrum and 1. Medizinische Klinik der Technischen Universität, Munich, Germany.

Stenting and adjunct pharmacological therapy

All coronary interventions were performed in a standard fashion as previously described. Antiplatelet therapy after stenting consisted of 100 mg aspirin given orally twice daily, indefinitely and 250 mg ticlopidine twice daily for 4 weeks. Patients considered at a higher risk for stent thrombosis (thrombus containing lesions, large residual dissections, compromised flow during the intervention) received abciximab perioperatively.

The procedure was considered successful in the presence of a residual stenosis of <30% and Thrombolysis in Myocardial Infarction (TIMI) flow grade of 2 or 3 after stent placement.

Angiographic evaluation

Type B2 and C lesions were considered complex lesions, according to the modified classification of the American Heart Association/American College of Cardiology. Digital angiograms recorded in the same projection prior to and after the procedure as well as at follow-up were analysed off-line with an automated edge detection system (CMS, Medis Medical Imaging Systems, Nuenen, Netherlands). The measurements of the vessel lumen and balloon diameter were performed after calibration on the basis of the contrast-filled nontapered catheter tip.

Follow-up and end-points of the study

All patients were scheduled to undergo repeat angiography at 6 months. Clinical follow-up included a phone interview at 30 days, a visit at hospital at 6 months and a new phone interview 1 year after the index procedure.

Primary end-point of this analysis was the incidence of angiographic restenosis defined as a diameter stenosis ≥50% at follow-up angiography. Secondary end-point was clinical restenosis defined as the need of target vessel revascularization (percutaneous transluminal coronary angioplasty [PTCA] or coronary artery bypass graft surgery [CABG]) due to symptoms or signs of ischaemia in the presence of angiographic restenosis. In addition, the occurrence of death and myocardial infarction was monitored. The diagnosis of myocardial infarction was established in the presence of at least two of the following criteria: clinical episode of prolonged chest pain, the appearance of 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 on two consecutive blood draws.

Statistical analysis

Continuous variables were summarized as mean±SD, categorical variables were displayed as counts or proportions (%). The comparisons between women and men were performed using the Student’s t-test for continuous variables and the χ2 or Fisher’s exact tests for categorical variables. Two prespecified subgroup analyses were also done focusing on diabetes and small vessel size. Both are known as strong risk factors for restenosis and are usually differently distributed among women and men. We used logistic regression to assess the independent effect of sex on angiographic restenosis while adjusting for potential confounders. All baseline clinical and angiographic characteristics were included in this model. We also checked for a possible interaction between diabetes and vessel size on one side and sex on the other, by entering the respective interaction terms into the multivariate model of restenosis. The variables that resulted to be independent predictors of restenosis from multivariate analysis were embedded in a classification and regression tree (CART) model. This analysis enabled the stratification of women and men in subsets carrying a different risk for restenosis.

Results

Baseline and procedural characteristics

As expected, women and men presented marked differences in baseline clinical characteristics (Table 1).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Women (n=1025)a</th>
<th>Men (n=3349)a</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>69±10</td>
<td>64±11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Arterial hypertension, %</td>
<td>78</td>
<td>70</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>28</td>
<td>20</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>—Receiving insulin therapy, %</td>
<td>11</td>
<td>5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>—Receiving oral therapy, %</td>
<td>10</td>
<td>9</td>
<td>0.51</td>
</tr>
<tr>
<td>—Receiving only diet, %</td>
<td>7</td>
<td>6</td>
<td>0.05</td>
</tr>
<tr>
<td>Current smoker, %</td>
<td>22</td>
<td>44</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypercholesterolemia, %</td>
<td>62</td>
<td>54</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Unstable angina, %</td>
<td>38</td>
<td>33</td>
<td>0.007</td>
</tr>
<tr>
<td>Previous myocardial infarction, %</td>
<td>31</td>
<td>37</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Previous bypass surgery, %</td>
<td>10</td>
<td>15</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*aData are mean±SD or percentages.
Compared with men, women were nearly 5 years older and had a worse cardiovascular risk profile, but they were less likely to have a history of myocardial infarction or aorto-coronary bypass surgery. Notably, there was a significantly greater proportion of diabetics among women. There were also important angiographic differences between the groups (Table 2). Women were less likely to have multivessel disease and to undergo multivessel treatment, but more likely to have lesions located in the left anterior descending coronary artery. In particular, women had smaller vessels than men, but shorter lesions. During the procedure (Table 3), as expected on the basis of vessel size and lesion length, smaller balloons and shorter stents were employed in women. No differences were, however, observed regarding the stent type implanted and the frequency with which abciximab was used as an adjunct therapy. The procedure was completed with a success rate of 98.9% in both women and men.

Regarding drug medications given at discharge, there were no significant differences in the proportion of women and men receiving statins (75 vs 76%, respectively; \( P=0.28 \)), \( \beta \)-blockers (both 80%; \( P=0.57 \)), angiotensin-converting enzyme inhibitors (67 vs 69%, respectively; \( P=0.35 \)) or nitrates (20 vs 19%, respectively; \( P=0.24 \)). However, women received more often calcium antagonists than men (6 vs 4%, respectively; \( P=0.01 \)).
Early, 30-day clinical outcome

During the first 30 days after index procedure, 21 women (2.0%) and 33 men (1.0%) died ($P=0.007$), and 17 women (1.7%) and 31 men (0.9%) incurred myocardial infarction ($P=0.049$). Thus, the 30-day combined incidence of death or nonfatal myocardial infarction was 3.2% among women and 1.8% among men ($P=0.004$). Women also showed a trend to a higher risk of urgent target vessel revascularization during the same period (3.0% vs 2.2% in men, $P=0.14$).

Restenosis

The main analysis was focused on angiographic restenosis at follow-up. There was no significant difference in the proportion of women and men who underwent repeat angiography at 6 months after procedure (79% vs 80% in men, $P=0.48$). As displayed in Fig. 1, women presented a lower risk of restenosis after coronary stenting than men (28.9% vs 33.9% in men, $P=0.01$). In addition, a high-degree restenosis (diameter stenosis ≥70%) was found less frequently in women than in men (17.2% vs 21.1%, respectively, $P=0.02$).

We applied a multivariate regression model to correct for the possible influence on restenosis of confounding factors other than sex. All baseline clinical and angiographic characteristics (gender, age, hypertension, diabetes, hypercholesterolaemia, unstable angina, previous myocardial infarction, previous bypass surgery, left ventricular ejection fraction, multivessel disease, vessel treated, complex lesion, chronic occlusion, restenotic lesion, lesion length, vessel size and diameter stenosis) were included in this model. As shown in Fig. 2, women presented a 23% reduction of the risk of angiographic restenosis, adjusted odds ratio of 0.77 (95% confidence interval, 0.63–0.93). The multivariate analysis also identified diabetes ($P=0.045$), hypertension ($P=0.047$), small vessel size ($P=0.001$), and restenosis severity ($P<0.001$) as independent factors associated with an increased risk of restenosis after coronary stenting. In this model, the analysis of the interaction between diabetes and sex yielded a $P=0.05$, whereas vessel size did not interact significantly with sex.

When we analyzed diabetics and nondiabetics separately, we found a difference in restenosis rates between women and men only among nondiabetics. In the subgroup of diabetics, the restenosis rate was 36.8% in women and 36.1% in men ($P=0.86$); in the subgroup of nondiabetics, the restenosis rate was 26.0% in women and 33.3% in men ($P<0.001$, Fig. 3A). When diabetic women were compared to diabetic men according to the type of treatment they received, the restenosis rates were: 41.3% vs 37.0%, respectively, for patients receiving insulin ($P=0.54$); 37.3% vs 40.3%, respectively, for patients receiving oral antidiabetic drugs ($P=0.64$); and 29.6% vs 28.4%, respectively, for patients receiving only diet ($P=0.86$). When we analyzed interventions in small vessels (<2.7 mm, the lower tertile limit) and those in bigger vessels separately, women had a lower restenosis rate than men irrespective of the vessel size, but the difference was more pronounced in small vessels. In the subgroup of patients with small vessel size, the restenosis rate was 36.6% in women and 45.2% in men ($P=0.01$); in the subgroup of patients with bigger vessel size, the restenosis rate was 24.5% in women and 28.6% in men ($P=0.07$, Fig. 3B).

We assessed which factors had a greater prognostic power for restenosis in women and men, separately. This was done by using the CART analysis, which identified several subsets with a different risk of restenosis both in women (Fig. 4A) and men (Fig. 4B). Although a small vessel size was the strongest predictor of restenosis in
both sexes, the factors that were found on the second level differed between women and men, with diabetes playing a relevant role only for women.

Clinical outcome at 1 year

At the end of the 1-year follow-up period, the excess risk of adverse events observed during the first month after intervention among women, was no longer present. One-year mortality was 5.2% among women and 4.5% among men ($P=0.36$). The combined incidence of death or non-fatal myocardial infarction was 7.2% in women and 6.0% in men ($P=0.14$). Moreover, the incidence of clinical restenosis (target vessel revascularization due to restenosis) was lower in women than in men (14.8% vs 17.5% respectively, $P=0.048$; Fig. 1). At follow-up contact, 15.4% of the women and 17.9% of the men presented anginal complaints ($P=0.06$, Fig. 1). Among eligible patients who did not undergo angiographic restudy, 1-year mortality was 10.0% in women and 12.3% in men ($P=0.41$) and target vessel revascularization rate was 1.7% in women and 3.7% in men ($P=0.18$).

All baseline characteristics (see above the model of restenosis) were entered into a Cox-regression model for mortality. After adjustment for these factors, the independent risk of death was significantly reduced among women as compared to men, hazard ratio of 0.55 (95% CI, 0.34–0.89), $P=0.02$. There was also a significant interaction between gender and diabetes ($P=0.009$) in determining 1-year mortality. This is graphically illustrated by Fig. 5. Diabetic women had a higher mortality than diabetic men (Fig. 5A), whereas no difference was seen between nondiabetic women and men (Fig. 5B).

Discussion

The analysis of this large population of 4374 unselected patients with systematic angiographic follow-up enabled us to investigate comprehensively sex-based differences in angiographic and clinical restenosis after coronary stenting. The principal and novel finding of this study is that women present a lower risk of restenosis after
coronary stenting despite a more preponderant presence of two major risk factors for this complication, diabetes and small vessel size. Considering the large use of stenting as the main percutaneous interventional approach in patients with coronary artery disease and the frequently described observation of underused invasive procedures in women, our finding may have important implications for the clinical practice.

The outcome of women with coronary artery disease treated invasively has been the subject of intensive investigation in the last two decades. We have shown that there are differences in the temporal pattern of outcome between women and men after coronary stenting, a phenomenon that was also reported for plain balloon angioplasty. Although women had a greater risk during the first 30 days, at the end of the 1-year period their outcome was comparable to that of men. The results of the above study suggested an increased thrombotic risk in female patients, but the lack of angiographic data left open the question whether differences in the likelihood of restenosis were responsible for the subsequent equalization of outcome across the sexes. In fact, the present series also confirms the augmented risk of death among women during the first 30 days and the accompanying higher incidence of myocardial infarction during this period strongly supports
thrombotic mechanisms as an explanation for the higher early mortality of women. In addition, the present study provides the most likely explanation for the improved outcome of women after the first 30 days after stenting: women carry a lower risk of restenosis as compared to men.

Restenosis represents the main limitation of percutaneous coronary interventions including stenting. Although the exact mechanisms of lumen re-narrowing remain largely unknown, several clinical and lesion-related factors have been identified that are associated with an increased risk of restenosis. Diabetes certainly represents the most relevant clinical predictor of in-stent restenosis. Among the lesion-related factors, small vessel size is by far the most reliable herald of restenosis. In addition, longer lesions are also associated with augmented risk of restenosis. Considering the relative weight of the above factors in the prediction of restenosis, women might be expected to have a higher risk for restenosis than men. Contrary to the expectation, women had a lower incidence of in-stent restenosis in the present study.

We found an absolute difference in angiographic restenosis of five percentage points in favour of women, which represents a ~15% relative reduction in comparison with men. Considering the relative proportion of women and men in current series of coronary stent implantation, more than 3000 patients with follow-up angiography are required to prove the statistical significance of a difference of this magnitude. This may explain at least in part why the lower risk of restenosis for women did not emerge in previous smaller cohort of patients with routine angiographic follow-up. In the presence of several differences in baseline characteristics that may have opposing effects in restenosis, the independent impact of sex was assessed by means of multivariate analysis. Women demonstrated a 23% reduction of the adjusted risk for restenosis. Since this is the first report of a relationship between gender and restenosis, it is very challenging to try to offer an explanation. There is growing evidence about the protective role of estrogen not only in delaying atherosclerosis but also in attenuating the response of vessel wall to injury. Vascular endothelial and smooth muscle cells bind estrogen, but the number of functional estrogen receptors in atherosclerotic arteries is higher in women than in men. Estrogens reduce the rate of oxidative degradation of arterial wall nitric oxide, favour prostacyclin formation and diminish thromboxane A2 and endothelin-I synthesis; thus, they promote vasodilatation of diseased coronary arteries and may inhibit the inflammatory response to balloon-injury. Additionally, estrogen may prevent restenosis by acceleration of endothelial cell growth resulting in increased availability of nitric oxide and by altering cellular migration after coronary intervention. On the other hand, due to reduction of plasminogen activator inhibitor type-1 levels and increased plasmin activity, estrogen may increase expression of matrix metalloproteinease-9 and therefore, prevent the accumulation of extracellular matrix. Relative to these considerations, the lack of prospective information on hormone replacement therapy among female patients should be acknowledged as a limitation of the present study. However, recent findings from randomized studies show that postmenopausal hormone therapy should not be used to reduce risk for cardiovascular events in women with coronary artery disease.

Drug-eluting stents are emerging as a promising treatment approach for the prevention of restenosis. Due to the high costs connected with this therapy and still unknown long-term effects, a risk stratification of patients undergoing coronary stenting seems to be a logical strategy for identifying subsets of patients who can mostly benefit from drug-eluting stents in a cost-effective way. The findings of the present study provide a specific help in this regard. They support separate risk stratification for women and men, because the map of risk predictors is dependent on sex. The female subset with the highest risk of restenosis is defined by the presence of small vessel size and diabetes. The counterpart male subset is defined by the presence of small vessel size and systemic arterial hypertension.

An additional important finding of the present study is that the negative impact of diabetes on restenosis is confined to a great extent to women. This finding is new and certainly requires further specifically designed.
investigation able to provide confirmation and to clarify the mechanisms of this interaction. If we combine the present results with those of our previous study, it is clear that diabetes represents a particular risk factor in women for both early stent thrombosis and late in-stent restenosis. Studies are also needed in the future on our ability to attenuate this excess risk in diabetic women through a tight glycemic control. The present data support the concept that women with diabetes should become the target of optimized antithrombotic and antirestenotic strategies that may further improve the already favourable overall outcome of women after stenting.

References