Angiographic patterns of in-stent restenosis in men and women

Daniela Trabattoni, Franco Fabbiocchi, Piero Montorsi, Giuseppe Calligaris, Stefano Galli, Paolo Ravagnani, Stefano De Martini, Giovanni Teruzzi, Antonio L. Bartorelli

Institute of Cardiology, University of Milan, Centro Cardiologico "Monzino", IRCCS, Milan, Italy

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Background. **The angiographic classification of in-stent restenosis (ISR) has been described. However, no comparative analysis of the morphologic ISR patterns between sexes has been performed. We sought to assess the ISR rate and the morphology of the different ISR patterns in the two genders.**

Methods. **The study population comprised 487 patients (231 male, 256 female) who underwent systematic angiographic follow-up 6 months after coronary stent implantation.**

Results. **The angiographic patterns of ISR were defined as: a) focal (length ≤ 10 mm), b) diffuse (length > 10 mm and within the stent margins), c) proliferative (length > 10 mm extending beyond the stent margins), and d) totally occlusive. Angiographic ISR had a significantly higher incidence in women as compared to men (35.9 vs 29.4%, p = 0.04). In addition, angiographic analysis showed that, although all ISR patterns were present in both sexes, more males had focal ISR (59.7 vs 28.2%, p < 0.001). Conversely, females showed a higher incidence of diffuse ISR (71.8 vs 40.3%, p < 0.001), including intrastent, proliferative and occlusive patterns. The only predictors of a specific ISR pattern were diabetes mellitus and hypertension for diffuse ISR in both sexes.**

Conclusions. **Females seem to be at higher risk of angiographic restenosis and higher levels of ISR class after coronary stent implantation. These findings may be prognostically important and should be considered for the appropriate use of newer revascularization strategies.**

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Address:

Dr.ssa Daniela Trabattoni

Istituto di Cardiologia
Università degli Studi
Centro Cardiologico
"Monzino", IRCCS
Via Parea, 4
20138 Milano
E-mail:
daniela.trabattoni@
cardiologicomonzino.it

The excellent clinical and angiographic results achieved with stent implantation have led to an exponential growth in the use of this breakthrough technology during percutaneous coronary interventions. In-stent restenosis (ISR) is the major limitation of stenting and has become a significant clinical problem. Its rate, although not well defined, ranges between 10 and 58% depending on the patient subset and lesion characteristics[1-4]. Prior studies have shown that neointimal tissue proliferation within and adjacent to the stent is the primary mechanism for ISR[5-7]. The angiographic classification of ISR according to the geographic distribution of intimal hyperplasia within the stent and along the stent edges has been reported[8]. However, a systematic analysis of the morphologic ISR patterns in males compared to females has not been performed. Thus, the purpose of this study was 2-fold: 1) to assess the rate of ISR between males and females, and 2) to evaluate whether there is any difference in the ISR pattern between sexes.

Methods

Patient population. Between January 1999 and January 2000, 771 consecutive patients underwent coronary stent implantation at the Centro Cardiologico "Monzino" in Milan, Italy. A retrospective analysis was performed for 487 of them who had been submitted to systematic angiographic follow-up. Patients lost to the 6-month angiographic follow-up or patients who refused repeat angiography (total n = 221; 99 male, 122 female) and those in whom quantitative coronary angiographic analysis was not feasible due to technical problems (total n = 63; 55 male, 8 female) were excluded from the present analysis.

The risk factors considered for coronary artery disease were diabetes mellitus (when medically treated), hypertension, smoking, hypercholesterolemia (total cholesterol > 220 mg/dl), and family history.

Follow-up. Six-month clinical and angiographic follow-up was performed, allowing precise recording of major late clinical events: death, Q and non-Q wave myocardial infarction, recurrence of angina, and target lesion revascularization by percutaneous coronary intervention or elective coronary artery bypass grafting (CABG).

Classification of in-stent restenosis and angiographic analysis. Stent implantation

procedures and follow-up angiographies were performed with a high-resolution angiographic imaging system (Toshiba CASS-8000, Toshiba MS Inc., Tokyo, Japan). Two independent observers reviewed the angiograms off-line and used the classification proposed by Mehran et al.[8] to define ISR as follows:
a) "focal": lesions which are ≤ 10 mm in length and are positioned at the unscaffolded segment (i.e. the gap between adjacent stents), the body of the stent, the proximal or distal margin (but not both), or a combination of these sites (multifocal ISR);
b) "diffuse intrastent": lesions which are > 10 mm in length and are confined to the stent, without extending beyond the margins of the stent;
c) "diffuse proliferative": lesions which are > 10 mm in length and extend beyond the margin(s) of the stent;
d) "totally occlusive" ISR: lesions which have a TIMI flow grade 0.

All coronary angiograms (before and after stent implantation and at follow-up) were recorded after 0.2 mg intracoronary nitroglycerin administration to achieve maximal vasodilation. Two experienced operators not involved in the stenting procedure made the angiographic measurements. The end-diastolic cine frames of the coronary angiograms were quantitatively analyzed using a validated and automated edge-contour detection system (ARTREK, Quantim 2001, QCS Inc., ImageComm System Inc., Santa Clara, CA, USA) in a single "worst" view. Quantitative analysis of the follow-up angiograms was performed using matching views. The contrast-filled guiding catheter was used as a reference for calibration. Proximal and distal segments, considered to be without coronary artery disease and outside the stented segment, were selected and their diameters averaged. This average value was considered the normal reference vessel diameter and used to calculate the percent diameter stenosis. The minimal lumen diameter (MLD) was measured on the pre-intervention angiogram. Similar measurements were taken on the post-intervention angiogram and at angiographic follow-up. The acute gain (mm) was calculated as the improvement in lumen diameter immediately after stenting (post-procedure MLD minus pre-procedure MLD), the late loss (mm) as the decrease in MLD at follow-up (post-procedure MLD minus MLD at follow-up), the net gain (mm) as the difference between the acute gain and the late loss, and the loss index as the late loss divided by the acute gain. Angiographic restenosis was defined as a follow-up diameter stenosis > 50%.

Statistical analysis. Continuous data are expressed as means ± SD and compared using the Student's t-test. Qualitative data are presented as frequencies and/or percentages. Potential associations between qualitative parameters and restenosis among sexes were analyzed by cross-tabulations using the χ^2 test. P values were derived from two-sided tests. A statistical significance was established if the associated p value was ≤ 0.05. Logistic regression was used to evaluate the association between the probability of restenosis at 6-month follow-up and gender, by calculating the odds ratios and corresponding 95% confidence intervals using Proc Logistic in SAS (Cary, NC, USA). Adjustment of the coronary artery disease risk factors (age, smoking, family history, diabetes, hypertension, and hypercholesterolemia) was achieved by adding these variables to the model containing gender as the main independent variable. In addition, the severity of angina and the body mass index were included in some models. A linear regression analysis (ANOVA model) was repeated to evaluate the association between diffuse ISR and coronary risk factors both in women and men. Six-month restenosis was compared between focal and non-focal groups and for the ordinal grouping "focal < intrastent < proliferative < occlusive" using a χ^2 analysis for the trend between genders.

Results

Of the 487 patients enrolled in the study, 231 were male and 256 female. Their demographic and clinical characteristics are listed in table I. Both groups were matched for age (61 ± 10 years in males vs 62.5 ± 2 years in females, p = NS) and major cardiovascular risk factors, except for a higher prevalence of hypertension in females (51 vs 36.8%, p = 0.005). Unstable angina with more advanced symptomatic classes (II-III/b-c Braunwald classification) was more frequent in females (32 vs 15.3%, p < 0.001). Conversely, there was a significantly greater prevalence of prior acute myocardial infarction in males (12.6 vs 7%, p = 0.004). With regard to the baseline angiographic characteristics, no differences were observed in the number, type and lesion morphology of the diseased vessels. A smaller reference vessel diameter was present in females at baseline (2.97 ± 0.62 mm), although this difference did not reach statistical significance (3.24 ± 0.55 mm).

Table I. Demographic and clinical characteristics.

	Males (n=231)	Females (n=256)	p
Age (years)	60.9 ± 9.9	62.5 ± 2.1	NS
Hypertension	36.8	51	0.005
Smoking	48.1	31.7	0.005
Cholesterol	43.1	47.8	NS
Diabetes	12.8	11.4	NS
Angina			
Stable	72.1	61	< 0.001
Unstable	15.3	32	< 0.001
Prior AMI	12.6	6.9	0.004

With the exception of age, values are expressed as percentages. AMI = acute myocardial infarction.

Interventional procedure outcome. Second generation stents were deployed in all cases. The frequency of bailout stenting in females was more than double that in males (19.8 vs 7.2%, p < 0.001). This was due to the more frequent occurrence of high-grade flow-limiting dissections and abrupt vessel closure in females. No difference was observed between sexes in the number of stents implanted per vessel and per patient and in the average maximal inflation pressure used for stent post-dilation (Table II). The rate of procedural success was similar in the two sexes.

Clinical follow-up. During the follow-up period, 1.3% of females and no males (p = NS) had an acute myocardial infarction. Recurrence of angina and/or a positive stress test was observed in 17.5% of females and 20.7% of males (p = NS). Repeat revascularization procedures included coronary angioplasty in 11.8% of females and 10.3% of males (p = NS) and CABG in 3.9% of females and 2.1% of males (p = NS).

Quantitative angiographic results. The MLD increased from 0.73 ± 0.48 and 0.71 ± 0.5 mm before intervention to 2.72 ± 0.6 and 3.06 ± 0.6 mm after intervention, in females and males respectively (p = NS). At follow-up, the MLD similarly decreased to 1.75 ± 0.79 mm in females and to 2.15 ± 1.03 mm in males (p = NS). The loss index was almost the same in both sexes (0.54 ± 0.49 in females and 0.46 ± 0.49 in males, p = NS), whereas angiographic restenosis was significantly more frequent in females than in males (35.9 vs 29.4%, p = 0.04) (Tables III and IV). In addition, the angiographic analysis of the distribution of intimal hyperplasia showed that, although all ISR patterns were present in both sexes, there was a substantial difference in their frequency in males compared to females. "Focal" ISR was present in a significantly higher number of males (59.7 vs 28.2%, p < 0.001). Conversely, females showed a higher incidence of diffuse ISR (71.8 vs 40.3%, p < 0.001), including intrastent, proliferative and occlusive patterns, suggesting a more aggressive hyperplastic response (Table V). Linear regression analysis showed a strong correlation between diabetes and diffuse neointimal proliferation (p = 0.001) while only a trend toward a positive effect of hypertension on more severe ISR was observed (p = 0.069) in both females and males.

Discussion

In the present study, using systematic quantitative coronary angiography follow-up, we demonstrated that 1) angiographic ISR more frequently occurred in females, 2) all ISR patterns were present in the native coronary arteries of both sexes, 3) females showed more severe ISR classification (diffuse, proliferative, total occlusion), and 4) the only predictors of a specif-

Table II. Procedural characteristics.

	Males (n=231)	Females (n=256)	p
Lesion length (mm)	15.8 ± 8.0	15.7 ± 7.76	NS
No. stents/pt	1.25 ± 0.55	1.17 ± 0.42	NS
Multiple stenting (%)	13.9	16.7	NS
Max inflation pressure (atm)	14.9 ± 2.17	15.4 ± 2.31	NS
Reo-Pro use (%)	5.5	6.1	NS
Bailout stenting (%)	7.2	19.8	< 0.001
Procedural success (%)	98	95.9	NS

Values expressed as mean ± SD were compared using the Student's t-test whereas those expressed as percentages were compared using the χ^2 test.

Table III. Quantitative coronary angiographic analysis.

	Males (n=231)	Females (n=256)	p
Baseline RVD (mm)	3.12 ± 0.6	2.94 ± 0.62	0.089
Baseline MLD (mm)	0.71 ± 0.5	0.73 ± 0.48	NS
Post-PCI MLD (mm)	2.77 ± 0.6	2.56 ± 0.6	NS
6-month MLD (mm)	1.89 ± 0.73	1.64 ± 0.74	NS
Loss index	0.46 ± 0.49	0.54 ± 0.49	NS

MLD = minimal lumen diameter; PCI = percutaneous coronary intervention; RVD = reference vessel diameter.

Table IV. Odds ratios (OR) of restenosis after coronary stent implantation according to gender after adjustment for the angiographic characteristics and coronary heart disease risk factors.

Restenosis: yes/no Parameter in model	No.	OR female/male	95% CI§	p§§
Sex (female/male)	487	1.55	1.02-2.36	0.039
Sex, age, risk factors*, BMI	454	1.60	1.01-2.54	0.045
Sex, age, angiographic factors**	485	1.57	1.02-2.43	0.042
Sex, age, angiographic factors, risk factors, BMI	485	1.64	1.02-2.61	0.039

BMI = body mass index (kg/m^2); CI = confidence interval. * includes hypertension, diabetes, smoking, family history and hypercholesterolemia, coded as dichotomous variables and using the group lacking the risk factor for comparison; ** includes catheter size and pressure; § Wald χ^2 associated p value; §§ Wald χ^2 associated probability assessing the importance of the sex coefficient in the model.

Table V. Angiographic restenosis.

	Males (n=231)	Females (n=256)	p
Overall ISR (%)	29.4	35.9	0.04
Focal ISR (%)	59.7	28.2	< 0.001
Diffuse ISR (%)	40.3	71.8	< 0.001
Intrastent	26.8	34.8	
Proliferative	7.4	25	< 0.005
Occlusive	5.9	11.9	

ISR = in-stent restenosis.

ic ISR pattern were diabetes mellitus and hypertension for diffuse ISR in both sexes.

The role of the female gender as a potential risk factor for restenosis after percutaneous coronary interventions has been controversial. Initial studies failed to find any difference between sexes in the restenosis rate after coronary angioplasty[9]. Only a few studies using newer interventional devices have reported long-term angiographic results in a gender-specific manner, without showing different restenosis rates in females compared to males treated with coronary stent implantation, directional atherectomy and coronary stenting[10,11]. In contrast with these reports, more recent studies found a significantly higher restenosis rate among females following coronary stent implantation. A significantly higher incidence of restenosis was observed in females compared to males (34 vs 25%, p = 0.03) in a subgroup analysis of patients enrolled in the PAMI study who underwent stent implantation and 6-month angiographic follow-up[12] (Grines C.L., personal communication). A single-center retrospective analysis, including 1100 consecutive patients treated with stenting, found a 64% (p = 0.04) higher angiographic restenosis rate in female patients as compared to their male counterparts[13]. Similarly, *post-hoc* analysis of the recently completed TAXUS II trial showed a higher incidence of binary restenosis (26.3 vs 16.6%) and late loss (0.87 ± 0.46 vs 0.75 ± 0.47 mm) in females compared to males after bare metal stent implantation (Grube E., CRF Symposium, Chicago, 2003, unpublished data). In agreement with these studies, our 6-month angiographic follow-up showed an excess risk of angiographic restenosis in females, not associated with a higher rate of recurrent angina or an increased need of revascularization procedures, whether coronary angioplasty or CABG. Specifically, the rate of restenosis was 64% higher in female patients after taking into account age, body mass index and risk factor differences (odds ratio 1.64, 95% confidence interval 1.02-2.61). As already demonstrated in a recent analysis, gender differences in the reference vessel diameter may explain the increased restenosis risk in women[12]. Several studies have already shown that a small reference vessel diameter is a risk factor for angiographic restenosis. This is probably related to the fact that the absolute amount of neointima growth required for a greater than 50% reduction in lumen diameter is lower for a stent of smaller size[14-16]. Our study confirms that females undergoing coronary interventional procedures tend to have a smaller reference vessel diameter than males.

ISR may present in different morphologic patterns that can be described on an angiographic basis. The type of ISR classification relates both to the lesion length and to the geographic localization of the neointimal tissue within the stent body and the segments adjacent to the stent edges[8]. Our analysis showed that females showed a more severe ISR classification, suggesting that in females the vessel wall shows an intrinsic biological tendency for increased neointimal tissue accumulation after initial stent implantation. Although there is no clear explanation for this exaggerated vascular response, previous studies have hypothesized genetic factors in the pathogenesis of ISR. Increased C-reactive protein levels and polymorphism of the gene encoding for the angiotensin-converting enzyme have been found to correlate with diffuse ISR[17]. These data support the theory of intrinsic biological factors that determine the proliferative process, whose intensity may be related to genetic and gender-based differences. These gender differences in ISR class may have important clinical implications. The long-term outcome of percutaneous treatment (i.e. balloon, atherectomy or laser) for ISR is significantly modified by the pre-procedure patient characteristics (i.e. diabetes) and ISR pattern. With regard to our results, females seem to be a population at increased risk for more complex forms of ISR and may show higher recurrence rates after treatment with different interventional devices. Thus, they may benefit from the use of newer therapies that demonstrated a dramatic reduction in restenosis, such as drug-eluting stents[18-20], especially when other clinical or lesion risk factors for ISR are present.

Finally, our analysis showed the only predictors of a specific ISR pattern to be diabetes mellitus and hypertension for diffuse ISR in both sexes (Table VI). The

Table VI. Correlations between the angiographic patterns of in-stent restenosis and coronary heart disease risk factors in both females and males.

ANOVA model*	F	p
Regression	3.051	0.011**
Diffuse restenosis: yes/no	t	p
Parameter in model		
Hypertension	-1.8	0.069
Smoking	0.80	0.42
Hypercholesterolemia	-1.600	0.115
Diabetes	-3.528	0.001

* dependent variable: diffuse in-stent restenosis; ** includes hypertension, diabetes, smoking and hypercholesterolemia, coded as dichotomous variables and using the group lacking the risk factor for comparison.

correlation between diabetes and a diffuse ISR pattern is consistent with previous reports showing that diabetes is strongly associated with a more aggressive neointimal hyperplastic response and with increased target lesion revascularization after coronary stenting[21,22].

Study limitations. The first limitation of the present study is inherent to its retrospective nature. Moreover, we did not verify the accuracy of the angiographic classification by intravascular ultrasound. However, previous studies demonstrated an excellent correlation between the angiographic definition of ISR patterns and intravascular ultrasound assessment[8]. In addition, the high resolution of the angiography system used in this study allowed appropriate recognition of the ISR class even in the presence of minimal stent radio-opacity. Finally, angiographic follow-up was completed in 487 out of 771 (63%) of the treated patients. This may have caused an overestimation of the overall restenosis rate. However, it is unlikely that it may have significantly modified the difference observed between sexes in the restenosis rate and ISR class.

In conclusion, despite these limitations, the present study shows that females are at higher risk for angiographic restenosis and for a more severe ISR class after coronary stent implantation. Thus, female gender should be probably taken in account in decision-making with regard to the early and appropriate use of powerful but more expensive revascularization strategies, such as drug-eluting stents, that may significantly improve the cost-effectiveness profile of percutaneous coronary interventions.

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