Genetic, clinical and experimental aspects of restenosis : a biomedical perspective

Monraats, P.S.

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Current PTCA practice and clinical outcomes in the Netherlands: the real world in the pre drug eluting stent era

Pascalle S. Monraats, Willem R.P. Agema, Aeilko H. Zwinderman, Rob bert J. de Winter, René A. Tio, Pieter A.F.M. Doevendans, Johannes Walten berger, Moniek P.M. de Maat, Rune R. Frants, Douwe E. Atsma, Arnoud van der Laarse, Ernst E. van der Wall, J. Wouter Jukema

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Abstract

Background

To document the practice of interventional cardiology and clinical restenosis rate, as well as the risk factors for clinical restenosis in an unselected population of patients in daily practice and to provide a perspective for the need of new devices such as drug-eluting stents.

Methods and results

A total of 3,177 consecutive patients, who underwent successful PTCA in the Netherlands, were included. Patients with acute myocardial infarction were ex cluded. The predefined endpoint of clinical restenosis was defined as cardiac death, myocardial infarction and revascularisation of the target vessel. Follow-up (9.6 months, IQR 3.9) was complete in 3,146 (99.3%) patients with a mean age of 62.1±10.7 years. Of them 896 (28.5%) were female, 459 (14.6%) had diabetes and 1,459 (46.4%) had multivessel disease. Most patients (2,105, 66.9%) were treated for stable angina. Of all patients 819 (26.0%) were treated for multiple lesions, 2,340 (74.4%) underwent stenting and 820 (26.1%) received glycoprotein IIb/IIIa inhibitors. All stented patients received life-long aspirin and ticlopidin/ clopidogrel during at least 1 month after the procedure. Target vessel revasculari sation during follow-up by either CABG or PTCA was necessary in 304 patients (9.7%). Thirty-three (1.1%) patients died of cardiac disease and 22 (0.7%) patients suffered from MI attributable to the originally treated vessel. Overall a need for revascularisation, cardiac death or MI occurred in 346 patients (11.0%), at 9 and 12 months these event-rates were 10.2 and 12.0%, respectively. Diabetes, hyper tension, peripheral vessel disease, multivessel disease and treatment of type C le sions prevailed as independent risk factors for clinical restenosis. Longer stents and smaller minimal stent diameter were risk factors for in-stent stenosis.

Conclusion

In this unselected series of consecutive patients treated for stable and unstable angina in everyday clinical practice in the pre-drug-eluting stent era clinical re stenosis after 9 and 12 months follow-up of the patients occurred in 10.2 and 12.0%, respectively. The risk varies from 8.3% to 17.6% depending on the num ber of risk factors. A proper selection of patients that benefit from new devices is warranted, since the vast majority is well treated with standard techniques and proper assignment of expensive new devices obviously is of importance for overall health care.

Introduction

Restenosis has been the main drawback to percutaneous transluminal coronary angioplasty (PTCA) since its introduction. Despite lowering the restenosis rate with the implantation of coronary stents, restenosis occurs approximately in 12-60% of the patients within 6 months after intervention, depending on the patients' and procedural characteristics.[1;2] The recently introduced drug-eluting stents give an additional reduction of the restenosis rate.[3] However, long-term follow up for most drug-eluting stents is still lacking and only selected populations were studied.

Identifying patients at increased risk for restenosis is important, because these patients might benefit from additional or alternative treatment such as the novel drug-eluting stents or other therapeutic modalities, such as coronary artery bypass surgery (CABG).[4] Thus far however, it has proven difficult to stratify patients with regard to risk for coronary restenosis.[5;6] Most of the standard risk factors for atherosclerosis have no relation with restenosis.[7] Only diabetes is consistently reported to be associated with restenosis.[8]

The aim of this study was to evaluate the incidence of clinical restenosis in an unselected sample of patients treated with contemporary intervention techniques in the pre-drug-eluting stent era and to develop a statistical model to identify patients with an increased risk of restenosis related clinical events in order to provide a clinically relevant perspective for the use of drug-eluting stents.

Methods

Study design

The GENetic DEterminants of Restenosis project (GENDER) was designed as a prospective multicenter follow-up study to evaluate various gene polymorphisms in association with clinically important restenosis. Patients were eligible for inclusion if they were successfully treated for stable angina, non-ST elevation acute coronary syndromes or silent ischemia with PTCA. Patients treated for acute ST elevation myocardial infarction were excluded. All patients were treated in four of the thirteen-referral centers for interventional cardiology in the Netherlands (Academic Medical Center Amsterdam, Academic Hospital Groningen, Leiden University Medical Center and Academic Hospital Maastricht). The overall inclusion period lasted from March 1999 until June 2001, with inclusion intervals varying between the centers in order to include equal numbers of patients per

center. In total, 3,177 consecutive patients were included in this prospective multicenter cohort study.
The study protocol conforms to the Declaration of Helsinki and was approved by the ethics committees of each participating institution. Written informed consent was obtained from each participant before the PTCA procedure.

Angioplasty and stenting procedure

Balloon angioplasty and intracoronary stenting were performed with standard techniques using the radial or femoral approach. Before the procedure patients received 300 mg of aspirin and 7,500 IU of heparin. The use of intracoronary stents and additional medication, such as glycoprotein IIb/IIIa inhibitors was at the discretion of the operator. In case a stent was implanted, patients re ceived either ticlopidin or clopidigrel for at least one month following the pro cedure depending on local practice. In general routine re-angiography was not performed.

Follow-up and study endpoints

Patients were followed for at least nine months. They were either seen in the outpatient clinic of the center for interventional cardiology or contacted by tele phone. Primary endpoint of this analysis was the incidence of clinical restenosis, which is considered nowadays the most important endpoint by regulatory agen cies. Clinical restenosis was defined as death presumably from cardiac causes, myocardial infarction not attributable to another coronary artery than the tar get vessel, and target vessel revascularisation (TVR) either by repeat PTCA or CABG. An independent clinical events committee of experienced cardiologists (J.J. Schipperheyn, MD PhD; J.W. Viersma, MD PhD; D. Düren, MD PhD; J.Vainer, MD) adjudicated the clinical events. The committee members did not review patients treated in their own center.
Events occurring within one month were classified and analyzed separately, since these events are more likely attributable to sub-acute stent thrombosis or oc cluding dissections and not to restenosis. Data were collected with standardized case-report forms that were completed by the research coordinator at each site. Representatives from the data-coordinating center monitored the sites care fully.

Definitions

A PTCA procedure was considered successful if on visual inspection the luminal stenosis of at least one lesion was reduced to less than 50% of the luminal diam eter. Hypertension was defined as a blood pressure of either above 160 mmHg

systolic or 90 mmHg diastolic. Hypercholesterolemia was defined, as total cho lesterol concentrations of above 5 mmol/l. Current smokers were individuals who smoked within the month preceding the index intervention. Past smokers were those individuals who gave up smoking in the preceding year. Individuals who stopped smoking for more than one year were classified as non-smokers. A positive family history was noted if the patient had a first degree relative with history of coronary artery disease before the age of 60. Renal failure was defined as a serum creatinine concentration ≥150 µmol/l or patients treated with dialysis. Patients using anti-diabetic medication or insulin at study entry were considered to be diabetics. Patients with a history of surgical treatment for non-cardiac vas cular disease such as aortic aneurysm or bypass surgery of the peripheral arter ies were considered to have peripheral vessel disease. The preprocedural lesions were classified according to the modified American College of Cardiology and American Heart Association Task Force classification.[9]

Statistical methods

All data are expressed as mean ± standard deviation, unless stated otherwise. Time to first clinical event was compared between (sub) groups of patients with the log-rank test. Prognostic value of clinical and procedural variables was as sessed with Cox' proportional hazards model. We univariately evaluated all known clinical risk factors of restenosis and risk factors related to the PTCA procedure. The proportional hazards assumption of the model, and the assumed linear relation between the log-hazard and quantitative variables were checked graphically by inspection of the martingale residuals.[10] Age and univariate pre dictors of clinical restenosis or TVR with a p-value <0.1 were entered into a mul tivariable Cox' model. A backward selection algorithm was used to select inde pendent predictors. In case of multivessel PTCA the worst lesion characteristics were evaluated as factors in the univariate and multivariable model. In stented patients the total length of the stented segment and the minimal diameter of the stents were calculated per patient. A two-sided p-value of 0.05 or less was con sidered statistically significant in the univariate analysis and a two-sided p-value of 0.1 or less was considered statistically significant in the multivariable analysis. The predictive accuracy was quantified by calculating the percentage variance of the clinical restenosis rate and of TVR that is explained by the Cox' proportional hazards model; for this purpose we used Schemper's R2 measure, which uses a bootstrap method to validate the Cox' model.[11] Analyses were performed with SPSS for Windows version 10.0 and SAS version 8.

Results

Demographic and clinical characteristics

A total of 3,509 patients were eligible for the study, of them 3,177 patients were included in the study. Of the 3,509 eligible patients, 223 (6.4%) underwent an unsuccessful procedure or during the procedure the operator decided to refer the patient for alternative treatment options (CABG). 140 patients (4%) refused informed consent for DNA analysis and 5-10% of the patients, who were already included in the cohort, were readmitted for restenosis or PTCA of a lesion in another vessel. These individuals were not included a second time in the registry. Of the included 3,177 patients, 23 were lost to follow-up and 8 withdrew their consent after inclusion. Follow-up was complete in 3,146 patients (99.3%) with a median duration of 9.6 months (interquartile range 3.9). The baseline charac teristics of the study population are presented in Table 1. Most patients were men (2,250, 71.5%), 459 (14.6%) were diabetics, 1,272 (40.4%) had hypertension. Patients had a history of MI, PTCA or CABG in 1,264 (40.2%), 567 (18.0%), 383 (12.2%), respectively. Most patients (2,105, 66.9%) were treated for stable angina and 1,459 (46.4%) patients had multivessel disease. Only 1,706 (54.2%) of the patients used cholesterol-lowering therapy at the time of the procedure.

Lesion characteristics

A total of 4,112 lesions were treated in this population. Lesion characteristics are depicted in Table 2. Complex (type C) lesions were the target in 817 (26.0%) patients. In 819 (26.0%) patients more than one lesion was treated. The series in cluded procedures of restenotic lesions (210, 6.7%), total occlusions (435, 13.8%) and vein grafts (125, 4.0%).

Table 1. Demographic and clinical characteristics (N=3,146)

Age (years)	62.1 ± 10.7
BMI ($kg.m^{-2}$)	27.0 ± 3.9
Male sex	2,250 (71.5%)
Diabetes	459 (14.6%)
Hypercholesterolemia	1,911 (60.7%)
Hypertension	1,272 (40.4%)
Current smoker	769 (24.4%)
Stopped smoking within last year	413 (13.1%)
Family history of MI	1,117 (35.5%)
Previous MI	1,264 (40.2%)
Previous PTCA	567 (18.0%)
Previous CABG	383 (12.2%)
Stable angina	2,105 (66.9%)
Multivessel disease	1,459 (46.4%)
Renal failure	65 (2.1%)
Peripheral vessel disease	104 (3.3%)
Beta-blocker	2,466 (78.4%)
Calcium-antagonist	1,650 (52.4%)
Nitrates	1,799 (57.2%)
ACE-inhibitor	614 (19.5%)
AT-receptor antagonist	91 (2.9%)
Diuretics	338 (10.7%)
Lipid lowering medication	1,706 (54.2%)

BMI: body mass index, MI: myocardial infarction, ACE: angiotensin converting enzyme, AT: angiotensin II

Table 2. Lesion characteristics (N=3,146)

Number of lesions treated per patient	
1	2,327 (74.0%)
2	672 (21.4%)
3	147 (4.7%)
Worst residual stenosis	
< 20%	2,753 (87.5%)
20-50%	360 (11.4%)
Restenotic lesions	210 (6.7%)
Total occlusions	435 (13.8%)
Worst lesion characteristic	
A	342 (10.9%)
B1	780 (24.8%)
B2	1,207 (38.4%)
C	817 (26.0%)
PTCA of vein graft	125 (4.0%)
Proximal LAD	702 (22.3%)
RCX	848 (27.0%)
Left main stem	41 (1.3%)
Unprotected left main stem	13 (0.4%)

Data are presented as number of patients.
LAD: left anterior descending branch of the left coronary artery, RCX: circumflex branch of the left coronary artery. In unprotected left main stem PTCA the LAD has not been previ ously revascularized with CABG

Procedural aspects

Intracoronary stents were used in 2,340 (74.4%) patients. The average stent length was 21.8 ±13.9 mm, the average minimal stent diameter was 3.3 ± 0.4 mm. Direct stenting was performed in 414 (17.7%) patients. In a small subset of pa tients, all treated for restenotic lesions, debulking devices (Rotablator and direc tional coronary atherectomy) were used. All patients who received a stent sub sequently received ADP receptor inhibitors for at least one month and aspirin indefinitely. Glycoprotein IIb/IIIa receptor antagonists were used in 820 (26.1%) patients of the total group and in 677 (28.9%) of all stented patients. Of the dia

betic patients 131 (28.5%) received glycoprotein IIb/IIIa receptor antagonists.

Clinical follow-up

Clinical restenosis occurred in 371 patients during the complete follow-up pe riod (Table 3). In 42 patients the event occurred within one month of the index intervention. Of them 31 (73.8%) were initially stented. These events all resulted from acute stent thrombosis, except for the death of whom this is unknown. The remaining 11 patients had occluding dissections. Excluding the events that occurred in the first month, clinical restenosis occurred in 346 (11%) of the pa tients: Kaplan-Meier restenosis event-rates at 9 and 12 months were 10.2 and 12.0%, respectively.

Table 3. Frequency of event rate during follow-up (N=3,146)

Event	<30 days (N=42)	>30 days (N=3,104)	Total (N=3,146)
Death of cardiac origin	6	33	39
Death from other causes	2	18	20
MI	5	22	27
TVR	21	304	325
Clinical restenosis*	25	346	371

**Some patients had more than one clinical event*

Predictors of clinical restenosis

Most established risk factors for premature coronary artery disease such as age, body mass index, gender, hypercholesterolemia and smoking were not associ ated with clinical restenosis after PTCA (Table 4). Furthermore, patients with a history of myocardial infarction, PTCA or CABG were not at increased risk for clinical restenosis. An increased risk for clinical restenosis was present in pa tients with diabetes (RR 1.51, 95% CI 1.16-1.96), hypertension (RR 1.28, 95% CI 1.04-1.59) and peripheral vessel disease (RR 1.82, 95% CI 1.13-2.92). Furthermore, patients with multivessel disease were at increased risk of clinical restenosis (RR 1.32, 95% CI 1.07-1.63), but not patients that underwent multivessel PTCA (RR

1.26, 95% CI 0.97-1.53). Suboptimal PTCA results with a residual stenosis of >20% of the luminal diameter (RR 1.36, 95% CI 1.01-1.82) and treatment of type C lesions (RR 1.3, 95% CI 1.04-1.63) also emerged as risk factors for clinical restenosis. In the stented group total stent length (RR 1.01, 95% CI 1.01-1.02) and minimal stent diameter (RR 0.67, 95% CI 0.45- 1.00) were associated with clinical restenosis (Table 5).

Table 4. Univariate predictors of a clinical restenosis: clinical variables (N=3,104)

	Clinical restenosis N=346	No clinical restenosis N=2,758	P-value	RR	95% CI
Age (years)	62.5 ± 10.5	62.1 ± 10.7	0.402	1.00	0.99-1.01
BMI (kg.m^{-2})	26.9 ± 3.7	27.0 ± 3.9	0.454	0.99	0.96-1.02
Male sex	250 (72.3%)	1,966 (71.3%)	0.768	1.04	0.82-1.31
Diabetes	69 (19.9%)	384 (13.9%)	0.002	1.51	1.16-1.96
Hypercholesterolemia	212 (61.3%)	1,678 (60.8%)	0.893	1.02	0.82-1.26
Hypertension	159 (46.0%)	1,100 (39.9%)	0.021	1.28	1.04-1.59
Current smoker	75 (21.7%)	687 (24.9%)	0.136	0.82	0.64-1.06
Family history	135 (39.0%)	963 (34.9%)	0.195	1.15	0.93-1.43
Previous MI	134 (38.7%)	1,105 (40.1%)	0.561	0.94	0.76-1.16
Stable angina	224 (64.7%)	1,855 (67.3%)	0.340	0.90	0.72-1.12
Peripheral vessel disease	18 (5.2%)	86 (3.1%)	0.014	1.82	1.13-2.92
Lipid lowering medication	185 (53.5%)	1,502 (54.5%)	0.725	0.96	0.78-1.19

RR: univariate relative risk according to the Cox' regression model. BMI: body mass index

Table 5. Univariate predictors of a clinical restenosis: lesion characteristics and technical aspects of the procedure (N=3,104)

	Clinical restenosis N=346	No clinical restenosis N=2,758	P-value	RR	95% CI
Multivessel disease	181 (52.3%)	1,251 (45.4%)	0.011	1.32	1.07-1.63
Residual stenosis>20%	53 (15.5%)	297 (10.9%)	0.042	1.36	1.01-1.82
Restenotic lesion	29 (8.4%)	179 (6.5%)	0.168	1.31	0.89-1.91
Total occlusion	60 (17.3%)	368 (13.3%)	0.125	1.24	0.94-1.65
Type C lesion	108 (31.2%)	694 (25.2%)	0.024	1.30	1.04-1.63
PTCA of vein graft	19 (5.5%)	104 (3.8%)	0.124	1.44	0.91-2.28
Proximal LAD	82 (23.7%)	607 (22.0%)	0.384	1.12	0.87-1.43
Left main stem	7 (2.0%)	34 (1.2%)	0.175	1.68	0.79-3.55
Glycoprotein IIb/IIIa inhibitor	98 (28.3%)	714 (25.9%)	0.094	1.22	0.97-1.55
Stenting	236 (68.2%)	2,073 (75.2%)	0.021	0.77	0.61-0.96
Direct stenting*	42 (17.8%)	367 (17.7%)	0.440	1.14	0.82-1.59
Total stent length (mm)*	24.6 ± 16.9	21.4 ± 13.3	<0.001	1.01	1.01-1.02
Minimal stent diameter (mm)*	3.23 ± 0.43	3.30 ± 0.41	0.05	0.67	0.45-1.00

*RR = univariate relative risk according to the Cox' model with 95 confidence intervals. LAD: left anterior descending branch of the left coronary artery, RCX: circumflex branch of the left coronary artery. * In the stented patient group*

In the multivariable model after backward selection algorithm, diabetes, hyper tension, multivessel disease, stenting, peripheral vessel disease and treatment of type C lesions prevailed as independent factors associated with clinical reste nosis (Table 6). The percentage variance explained by the 6 selected risk factors was 2.0%, and the percentage variance explained by all 14 factors in Table 6 was 2.5%.

Table 6. Multivariable predictors of clinical restenosis (N=3,104)

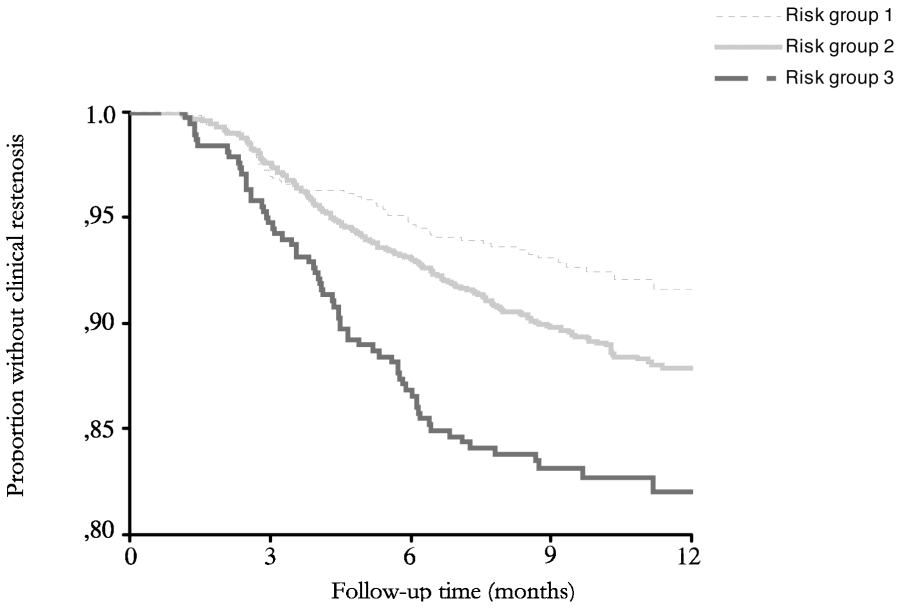
	Univariate RR		RR after backward selection	
Age	1.00	0.99-1.01		
Diabetes	1.51	1.16-1.96	1.39	1.07- 1.82
Hypertension	1.28	1.04-1.59	1.22	0.98- 1.51
Previous PTCA	1.26	0.97-1.63		
Stenting	0.77	0.61-0.96	0.75	0.60-0.94
Multivessel disease	1.32	1.07-1.63	1.24	1.00- 1.54
Peripheral vessel disease	1.82	1.13-2.92	1.72	1.07- 2.77
Residual stenosis >20%	0.74	0.55-0.99		
Type C lesion	1.32	1.06-1.64	1.32	1.05-1.66
Glycoprotein IIb/IIIa inhibitor	1.22	0.97-1.55		
Current smoker	0.82	0.64-1.06		
Total occlusion	1.24	0.94-1.65		
Restenotic lesion	1.31	0.91-1.90		
Multivessel PTCA	1.22	0.97-1.53		

Relative Risk with 95 confidence intervals

To illustrate the prognostic value of this model we divided the sample of 3,104 patients into subgroups depending on the number of risk factors present in these patients. Since the model contained five risk factors (diabetes, hyperten sion, multivessel disease, peripheral vessel disease, type C lesion) we could con struct six subgroups. We disregarded whether these patients were stented or not because this was a procedural factor, which probably reflected suitability for

stenting. Since patients were not randomized for stenting, selection bias may have confounded this association. We also disregarded the fact that the prog nostic value of the five risk factors varied, because the variation was relatively small (smallest RR 1.22, largest RR 1.72). In Figure 1 these risk factor subgroups were further combined into three risk factor groups to illustrate the highest and lowest risk depending on the number of factors per individual. Group 1 had zero or one factor (n=700), group 2 two or three factors (n=2,018) and finally group 3 four or five factors (n=386). After one year group 1 had a clinical restenosis rate of 8.3%, whereas group 3 had a clinical restenosis rate of 17.6%.

Figure 1.



This Figure illustrates the absolute risk of clinical restenosis for a combination of risk factors. Risk group 1 n=700 included zero or one risk factor, risk group 2 n=2,018 two or three and risk group 3 n=386 four or five. Patients with zero or one risk factor have the lowest risk, whereas those with four or five risk factors have the highest risk see text .

Predictors of TVR

When we restricted the endpoint to TVR, diabetes (RR 1.58, 95% CI 1.20-2.09) and hypertension (RR 1.26, 95% CI 1.0-1.58) remained significant risk factors in the univariate analysis. Furthermore, residual stenosis more than 20% of the luminal diameter (RR 1.52, 95% CI 1.13-2.06), treatment of total occlusions (RR 1.35, 95% CI 1.01-1.81) and type C lesions (RR 1.29, 95% CI 1.01-1.64) were as

sociated with an increased risk of TVR. As expected, successful stent placement was associated with a lower TVR rate (RR 0.71, 95% CI 0.56-0.90). However, the presence of multivessel disease or peripheral vessel disease was not significantly associated with TVR.
In the multivariable Cox' proportional hazards model analysis diabetes and the treatment of total occlusions prevailed as independent risk factors for TVR after backward restriction algorithm. In contrast, current smokers were at a lower risk of TVR than non-smokers. (Table 7) The percentage variance explained by the five selected risk factors was 2.1%, and the percentage variance explained by all fourteen factors in Table 7 was 2.7%.

Table 7. Multivariable predictors of TVR (N=3,104)

	Univariate RR		RR after backward selection	
Age	1.00	0.99-1.01		
Diabetes	1.58	1.20-2.09	1.57	1.19-2.07
Hypertension	1.26	1.00-1.58		
Previous PTCA	1.24	0.94-1.63		
Stenting	0.71	0.56-0.90	0.78	0.60-1.02
Multivessel disease	1.15	0.92-1.44		
Peripheral vessel disease	1.37	0.77-2.44		
Residual stenosis>20%	1.52	1.13-2.06	1.34	0.96-1.86
Type C lesion	1.29	1.01-1.64		
Glycoprotein IIb/IIIa inhibitor	1.18	0.92-1.52		
Current smoker	0.77	0.58-1.02	0.76	0.58-1.01
Total occlusion	1.35	1.01-1.81	1.43	1.07-1.92
Restenotic lesion	1.39	0.94-2.07		
Multivessel PTCA	1.22	0.95-1.55		

Relative Risk with 95 confidence intervals

Risk predictors in stented patients

We performed a separate analysis for the 2,340 (74.4%) stented patients. Within this group, clinical restenosis rates at 9 and 12 months were 9.4% and 11.4% compared to 12.7% and 13.7% in patients treated with balloon angioplasty alone (log rank p=0.021). In the subgroup of patients treated with stents in combination with glycoprotein IIb/IIIa inhibitors the clinical restenosis rates at 9 and 12 months were 9.9 and 13.7% compared to 9.1 and 10.9% without (log rank p=0.28).

The mean total stent length in patients with restenosis was 24.6 ± 17.0 mm compared to 21.5 ± 13.4 mm in controls (RR 1.01, 95%CI 1.01-1.02). The mean minimal stent diameter was 3.2 ± 0.4 mm and 3.3 ± 0.4 mm (RR0.67, 95%CI 0.45-1.00), respectively. In the stented group diabetes, renal failure, peripheral vessel disease, multivessel disease, type C lesion, left main intervention, total stent length and minimal stent diameter emerged as univariate predictors of clinical restenosis. Additionally, previous MI was associated with TVR. In the multivariable model peripheral vessel disease (RR 2.24, 95% CI 1.31-3.82), stent length (1.02, 95% CI 1.01-1.03), larger minimal stent diameter (RR 0.65, 95% CI 0.44-0.96) and multivessel disease (RR 1.53, 95% 1.10-2.12) were independently associated with clinical restenosis. Furthermore, diabetes (RR 1.52, 95% CI 0.99-2.32), previous MI (RR 0.68, 95% CI 0.47-0.98), total stent length (RR 1.01, 95% CI 1.01-1.02), larger minimal stent diameter (RR 0.50, 95% CI 0.32-0.78) and multivessel disease (RR 1.37, 95% CI 0.96-1.95) were independently associated with TVR.

Discussion

Event rate

In this unselected series of patients, who were treated with contemporary intervention techniques in four Dutch university centers, we observed that the incidence of clinical restenosis after 9 and 12 months follow-up of the patients was 10.2 and 12.0%, respectively, considering that events within the first month are more likely to be attributable to subacute stent thrombosis and occluding dissections. These data are consistent with, for example, the recent ISAR-STEREO-2 trial, in which TVR rate was 12.3% in the favorable stent-diameter group in selected patients.[12] In a single center observational study between 1996 and 1999 (thus just preceding our observation period) a clinical restenosis rate of 14.8% in women and 17.5% in men was reported.[13] In the CART-1 trial evaluating antioxidant drugs in a selected population a clinical restenosis rate of 18.3% was found in the control group.[14] Clinical trials with drug-eluting stents report

more favorable results with clinical restenosis rates from zero to five percent in favorable lesions.[15;16] In contrast, the results of the SIRIUS trial, which randomized 1,058 patients to either bare metal stents or sirolimus-eluting stents and included more complex lesions, reported an overall rate of target-lesion revascularisation of 4.1% and any major adverse cardiac event occurred in 7.1%. This is still low, however restenosis is not yet totally eradicated.[17] Thus, although the results of drug-eluting stent trials are promising, the present study demonstrates that in daily practice, including patients with complex lesions, restenosis rates have decreased significantly compared to initial experiences.[18;19]

Risk factors

Previous studies in both the pre-stent and stent era have reported associations between different clinical variables and primarily angiographic restenosis. Diabetes is the most frequently reported factor that is consistently associated with an increased risk of restenosis.[20-22] Other frequently reported risk factors for restenosis include unstable angina[23], hypertension[24-26], multilesion PTCA[27], suboptimal procedural result[28], and total occlusions[29]. In this study we focused on clinically relevant restenosis and our model included exclusively clinical and morphological factors. Diabetes, hypertension, peripheral artery disease, multivessel disease and type C lesions were independently associated with clinical restenosis. When we restricted the analysis to TVR, diabetes and treatment of total occlusions were associated with an adverse prognosis. Furthermore, a suboptimal result increased the risk of TVR with 34%. The successful placement of an intracoronary stent was associated with a reduced risk of clinical restenosis and TVR. Thus, the patient characteristics that evolved as factors independently associated with clinical restenosis are largely in concordance with the experiences from previous studies. To our knowledge, the association of peripheral artery disease with clinical restenosis has not been reported before.

Diabetes

Diabetes has been shown to be an independent risk factor for restenosis in several studies.[30;31] The clinical follow-up of diabetics is characterized by a higher incidence of death, myocardial infarction and reinterventions.[32] Furthermore, in five stent studies, including over 4,800 patients, the angiographic in-stent stenosis rate was consistently higher among diabetics than non-diabetics. Despite using a variety of stents over a broad range of patients, the overall 6-month angiographic restenosis rates were 36.8% and 26.3% for patients with and without diabetes, respectively (odds ratio 1.6, 95% CI, 1.4-1.9, p<0.001).[33] These findings are in concert with the presently reported adjusted relative risk of clinical restenosis of 1.4 (95% CI 1.07-1.82) and 1.6 (95% CI 1.19-2.07) for TVR.

Since diabetes is a consistent risk factor for restenosis, particularly diabetics would benefit from the drug-eluting stents. In the previously mentioned SIRIUS trial 26% of the patients were diabetics. The rate of in-segment stenosis was reduced from 50.5 percent to 17.6 percent, P<0.001; and the rate of target lesion revascularization was reduced from 22.3 percent to 6.9 percent, P<0.001. This represents an important advance in the management of patients with symptomatic ischemic heart disease. However, long-term safety and efficacy data are needed.[34]

Stenting

Stenting reduced both clinical restenosis and TVR (RR 0.75, 95% CI 0.60-0.94 and RR 0.78, 95% CI 0.60-1.02, respectively). Previously, several clinical trials have demonstrated that stenting reduces rates of clinical and angiographic restenosis; this reduction is clinically important.[18;19;35] Although our observation is in concert with previous observations, it should be kept in mind that this registry was not designed to evaluate the efficacy of intracoronary stenting. The use of stents was at the discretion of the operator and the reason to refrain from stenting was not evaluated. Therefore, in this observation selection bias cannot be excluded.

In stented patients increasing length of the stents and smaller vessel diameter have been reported to increase the risk of in-stent stenosis.[36] In this cohort these factors, total stent length and minimal stent diameter, were independently associated with both clinical restenosis and TVR.

Merits and limitations of the risk model

In this study, we constructed a multivariable risk model to predict clinical restenosis likelihood. As can be depicted from Figure 1, individuals with zero or one risk factor had a clinical restenosis rate at one year of only 8.3%, whereas those with four or five factors had a clinical restenosis rate of 17.6%. Therefore, the group of patients with the highest number of risk factors has twice the risk of clinical restenosis compared to those in the lowest category. These data suggest that individuals in the high-risk group might benefit most from new technology such as the drug-eluting stent.

Study limitations

Although nowadays clinical restenosis is considered the most important end point by patients as well as by regulatory agencies, a limitation of our study is the absence of angiographic data for all patients. We were not able to perform follow-up angiography and quantitative coronary angiography systematically, because of restriction of the ethical committee and limited funds.

Our prognostic model for clinical restenosis was developed using about twenty-five variables. In the univariate analysis we did not use a multiple testing correc tion method, which possibly inflated type-I error, in order to preserve power for the multivariable analysis.

Conclusions

This large unselected observational study shows that at present it is feasible to treat lesions that were previously considered to bare a high risk of long-term complications. In fact, in this series of daily clinical practice, including complex lesions, clinical restenosis occurred in only 10.2 and 12.0% of the patients after 9 and 12 months follow-up, respectively. This event rate should be considered in the interpretation of the studies on new devices such as drug-eluting stents. Although drug-eluting stents are very promising, long-term follow-up is missing. Furthermore, with the present costs of drug-eluting stents, using these stents in every suitable patient is impossible, since funds are limited. In order to tailor therapy to the individual patient and reduce costs, risk stratification can be very useful. Specific subgroups have a higher risk of restenosis. These subgroups may benefit most from new technologies. Although the risk increases with the num ber of clinical risk factors, it remains difficult to predict events solely based upon clinical risk factors, because the relative risks of the known clinical risk factors for restenosis are quite modest (in our study the highest RR was 1.7). Therefore, we expect that additional factors can be useful to stratify individuals further to tailored therapy. In this perspective, the quest for genetic risk factors has a po tentially important role.
In conclusion, clinical restenosis rate in an unselected patient population with complex lesions, is low, however not negligible. Individualizing therapy to pro vide the patient with an optimal intervention strategy seems useful, in order to improve the (cost) efficacy and avoid side effects of PTCA as much as possible.

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