Restenosis begets restenosis: implications for stent selection

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Background: Identifying the risk for restenosis is of critical importance in the stent selection process of patients undergoing percutaneous coronary intervention (PCI). Therefore, we sought to determine if a history of clinical recurrence (CR) after PCI increases the risk of CR after treatment of a *de novo* lesion in another coronary artery.

Methods: We retrospectively analysed all 12,763 patients who underwent PCI between 1993 and 2004 and selected patients with two or more interventions in two different native vessels. These patients were divided into two groups: patients without CR, and patients with CR after the first PCI. Clinical recurrence was defined as revascularisation of the target vessel by either PCI or CABG within one year.

Results: A total of 1010 patients with two or more interventions in two different native vessels were identified: 727 patients without and 283 patients with CR after the first PCI. Baseline patient characteristics and conventional risk factors were comparable between the two groups. Patients with a history of CR had a higher risk of CR after a second intervention in a second vessel (OR=3.4, 95% CI=2.3 to 4.9). A total of 112 patients also had a third intervention in a third native vessel: 12 patients with two CR, 30 patients with one CR and 70 patients with no CR after the first two interventions. CR rates in these patients were 50, 17 and 3%, respectively ($p<0.001$).

Conclusion: Patients with a history of CR have a markedly increased risk of developing CR after a second or third PCI in a different coronary artery. Therefore, in the decision-making process on whether to use a bare metal stent or drug-eluting stent, the history of CR is a simple and powerful aid. (*Neth Heart J* 2008;16:376-81.)

Keywords: angioplasty, coronary artery disease, restenosis, percutaneous coronary intervention, drug-eluting stents

Since the introduction of coronary angioplasty, restenosis has been a key problem after this procedure. In the early 1990s, intracoronary stenting was introduced to reduce complication as well as recurrence rates.^{1,2} Although this technique greatly improved immediate and long-term results, restenosis still remained a challenge. In 2002, drug-eluting stents (DES) were introduced to further decrease the risk of restenosis.³⁻⁵ However, the costs of these stents are high and cost-effectiveness of DES compared with bare metal stents remains an issue of debate.^{6,7} Furthermore, it has been shown recently that DES have an increased risk of developing late stent thrombosis.⁸⁻¹⁰ Therefore, an important field of research is to identify which patients will benefit in particular from DES and which patients will have a good outcome with a bare-metal stent.

The risk of developing restenosis is associated with several underlying conditions. The location of the lesion is important as ostial and bifurcation lesions are more prone to develop restenosis.¹¹⁻¹³ Also specific lesion characteristics such as calcification, severe angulation, long lesions and lesion complexity contribute to a higher risk of restenosis.¹³⁻¹⁸ Besides lesion and vessel characteristics, patients with diabetes and hypertension are at risk.¹⁹⁻²¹ Although still under investigation, also genetics seem to play a role in the pathway of restenosis.²²⁻²⁶ Finally, medications such as clopidogrel and abciximab have contributed to a significant reduction of short-term and long-term events.²⁷⁻²⁹

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Although not yet clarified, it is likely that some patients, by nature, are more susceptible to develop restenosis after percutaneous coronary intervention (PCI). Recently it has been shown that a history of PCI, within the target lesion or in other lesions, is associated with lower event-free survival.³⁰ Therefore, we hypothesise that patients with (compared with patients without) known restenosis as defined by clinical recurrence (CR) after a first PCI are more likely to develop CR after a second PCI in a different coronary artery.

Methods

Database collection

All patients undergoing a percutaneous coronary intervention (PCI) from January 1993 to July 2005 in the University Medical Center Groningen were selected

from our PCI database. From these patients, all patients who underwent PCIs in at least two different native coronary arteries (left anterior descending, left circumflex or right coronary artery) during the study period were included in our study group. Inclusion criteria were a first intervention after January 1993 and a second intervention before July 2004, in order to achieve appropriate follow-up after the second intervention. PCIs in left main coronary arteries and bypass grafts were excluded from the analysis. All PCI and CABG data from these patients with PCIs in at least two native coronary arteries were obtained. The study design is shown in figure 1.

Clinical recurrence

Clinical recurrence (CR) was defined as any attempt, successful or unsuccessful, to revascularise the target

Figure 1. Flow diagram of patient selection from PCI database and outcome after PCIs in the study group. This figure shows both study design (upper half) and study results (lower half). The pie charts show the clinical recurrence rates of the different groups analysed. PCI=percutaneous coronary intervention, LM=left main coronary artery, CR=clinical recurrence.

vessel, either by coronary bypass grafting or by PCI within a period from three days to one year of the first intervention. The day of the first intervention was labelled 'day 0' and the time to the following interventions was calculated in days. All patients with CR within a period of three days after the first PCI were considered to have an acute event and were excluded from further analysis. PCIs in the target vessel after more than one year were considered not to be due to restenosis but rather to the development of a new lesion in the target vessel. These were also left out of the analysis.

Analysis

Patients were divided into two groups. Group 1 contained patients without CR after the first PCI and group 2 contained patients with CR after the first PCI (figure 1). In both groups, data from the second PCI were obtained and patients were checked for CR after second PCI within the three days to one year period. When a third PCI in the third coronary artery was present, the same procedure was performed to analyse these patients.

Patient risk factors

All patient records were checked for major clinical risk factors. However, due to the retrospective nature of the study, we were not able to collect enough data to do a thorough analysis in all patients. Therefore, to evaluate clinical characteristics, we took a random sample of 200 patients: 100 patients in group 1 and 100 patients in group 2. Patients were selected in the following way: Working back from July 2004, for every month every first patient in group 1 and every first patient in group 2 with complete clinical data were selected and checked for all risk factors. This procedure continued until both groups contained of 100 patients with all risk factors completed.

Percutaneous coronary interventions

Angioplasty and stenting were performed according to standard techniques available at the time of the procedure. All patients received 300 mg aspirin and 5000 IU of heparin. The use of GPIIb/IIIa antagonists and clopidogrel was left to the discretion of the operator.

Statistical analysis

All continuous data are shown as mean values with standard deviation and all categorical data as frequencies with percentages. The independent samples t-test was used to compare continuous data from baseline and procedural characteristics between patients with and patients without CR. The χ^2 test was used to compare categorical variables between both groups. The odds ratio for developing CR after PCI 2 was calculated for patients with, compared with patients without a history of CR after PCI 1. For patients with a third PCI, the odds ratio for developing CR after PCI 3 was calculated separately for patients with one CR versus patients with

no CR after PCI 1 and 2, and patients with two CR versus patients with no CR after PCI 1 and 2. A p value of <0.05 was considered to be significant. Statistical analysis was performed using SPSS 11.0 for windows (SPSS Inc, Chicago, Ill).

Results

During the study period, a total of 12,763 patients underwent 19,284 PCIs in our institute. Of these 12,763 patients, 1010 had two or more percutaneous coronary interventions (total of 2.5618 PCs) in at least two different *native* coronary arteries and were included in the study group (figure 1). In total 727 patients did not have CR within the first year (group 1) and 283 patients did have CR within the first year (group 2).

The mean age was 61 ± 11 years in group 1 versus 62 ± 10 years in group 2 ($p = \text{ns}$). The percentage of females was 28 and 27%, respectively. The baseline characteristics of patients in group 1 and group 2 are displayed in table 1. Table 2 displays the lesion and PCI characteristics of both PCIs in group 1 and group 2. Figure 1 is a flow chart that embeds both the study design as well as outcome after PCIs in both groups. The data from a third PCI, when applicable, are also shown in figure 1. Patients with CR after the first PCI had a significantly higher risk of CR after their second PCI (OR=3.4, CI=2.3 to 4.9).

The impact of a clinical recurrence was even more pronounced when patients of either group were treated with a PCI in the third coronary artery. A total of 112 patients were treated in a third vessel. Patients with one CR out of two previous PCIs had a 16.7% clinical recurrence rate vs. 2.9% in patients with no CR in previous PCIs (OR=6.8, CI=1.2 to 37.3). When patients with a history of CR after both previous PCIs were treated in a third vessel, they had a 50.0% CR rate versus 2.9% in patients with no CR after both previous interventions (OR=34.0, CI=5.6 to 206.7).

Table 1. Baseline patient characteristics and conventional risk factors obtained from a random sample of 200 patients.

	Group 1	Group 2	P value
No. of patients	727	283	
Age (years)	60.9 $\pm$ 11.1	62.4 $\pm$ 10.3	0.06
Female (%)	28.2	27.1	0.76
Random sample (n)	100/727	100/283	
Risk factors (%)			
- Hypertension	39	48	0.25
- Hypercholesterolaemia	80	84	0.58
- Smoking	36	28	0.29
- Family history	47	56	0.26
- Diabetes Mellitus	15	21	0.36

The random sample consisted of 100 patients without (group 1) and 100 patients with (group 2) clinical recurrence after the initial PCI.

Table 2. Lesion characteristics of PCI 1 and 2 in all patients from both groups.

	PCI 1 (n=1010)			PCI 2 (n=1010)		
	Group 1 (n=727)	Group 2 (n=283)	P value	Group 1 (n=727)	Group 2 (n=283)	P value
Stable angina	64.1	61.3	0.18	61.4	60.0	0.84
Unstable angina	28.2	27.3		33.9	35.7	
Myocardial infarction	7.7	11.3		4.7	4.3	
Vessel						
- LAD	34.1	42.9		34.6	28.0	
- LCX	31.0	30.1		35.7	37.6	
- RCA	35.0	27.0		29.8	34.8	
Lesion type						
- A	13.4	11.5	0.72	13.6	16.7	0.01
- B1	36.6	35.4		37.7	32.6	
- B2	22.2	21.9		22.2	30.7	
- C	27.8	31.2		26.4	20.1	
Diameter stenosis						
- <70 %	8.1	6.5	0.57	8.5	10.5	0.62
- 70-90%	48.0	50.5		52.9	55.6	
- >90%	29.3	31.5		30.7	27.6	
- Total occlusion	14.6	11.5		7.8	6.2	
TIMI before PCI						
- 0	14.6	11.5	0.30	7.8	6.2	0.15
- 1	4.9	3.9		5.7	3.5	
- 2	18.2	16.4		11.1	14.7	
- 3	62.3	68.2		75.3	75.5	
Max. diameter balloon	3.0±0.86	2.9±0.86	0.10	2.9±1.0	3.0±0.9	0.11
Max. inflation pressure	9.5±3.9	10.0±4.2	0.10	10.4±4.5	10.9±4.0	0.12
Stenting	50.8	54.3	0.33	66.0	62.3	0.27
TIMI after PCI						
- <3	7.9	7.5	0.87	5.3	7.6	0.35
- 3	92.1	92.5		94.7	92.4	
Residual stenosis						
- <20%	90.9	91.4	0.59	93.4	91.8	0.55
- 20-50%	7.5	7.8		6.0	7.8	
- >50%	1.6	0.7		0.6	0.4	

Group 1=Patients without clinical recurrence after the initial PCI, Group 2=Patients with clinical recurrence after the initial PCI. LAD=left anterior descending coronary artery, LCX=left circumflex coronary artery, RCA=right coronary artery, PCI=percutaneous coronary intervention.

Discussion

In this study we sought to assess the importance of a previous CR on the need for revascularisation after a second PCI in another coronary artery. Our results indicate that when a history of CR is present, this is an important risk factor for developing CR after PCI in a second coronary artery.

Multiple studies have reported a higher incidence of revascularisations in patients with a history of PCIs and/or CABGs.³⁰⁻³² These studies, however, did not focus on whether previous interventions were performed in the target vessel or in another vessel. By

dividing the coronary tree into three branches, we tried to eliminate the influence of a previous PCI on the new PCI. In this way, only the fact that a previous PCI was performed, and not the damage of the PCI itself, influences outcome after the subsequent PCI.

The role of genetic predisposition in developing restenosis is still not clear. Due to the complexity of the process, polymorphisms of a large number of pathophysiological regulation systems have been associated with restenosis such as: the renin-angiotensin system, platelet aggregation, the inflammatory response, matrix metalloproteinases, smooth muscle cell proliferation,

lipids and oxidative stress and nitric oxide.²²⁻²⁶ Although our study may support the concept of a genetic trait, the attribution of genetic predisposition remains unclear, but seems small compared with other major risk factors such as diabetes.

With the introduction of DES, the risk of restenosis has been reduced significantly.³⁻⁵ Although this reduction may not be totally independent of patient and vessel characteristics, there is evidence that DES reduce in-stent restenosis in all patients. However, DES are two- to four-fold more expensive compared with bare metal stents. This is a major strain on the budget of catheterisation laboratories. Furthermore, the issue of long-term efficacy remains. Recently, long-term results of DES stents have shown that the risk of late and very late stent thrombosis is higher than in bare metal stents.⁸⁻¹⁰ The identification of patients with increased as well as a decreased risk of CR is therefore of major clinical importance. In the 2005 ESC Guidelines for PCI, diabetes, long lesions, small vessels, vein grafts, and ostial and bifurcation lesions have a class I indication for the use of DES.³³ Our study may indicate that patients without previous CR are more likely than others to benefit from bare metal stenting. On the other hand, in patients with CR after a first (and/or second) PCI, a DES might be indicated for treating the disease and prevent clinical recurrence.

Limitations

This study was an observational study and therefore does not have the same impact as a prospective study. Also, there have been some major changes in PCI care, such as the routine use of stents, clopidogrel and of course the introduction of drug-eluting stents. Although these changes could influence outcome, this study reflects daily clinical care and the large study group and the long follow-up are well suited for evaluating this issue.

Another limitation is that PCIs were not analysed by segment, but rather by coronary artery. However, coronary artery lesions often expand over the borders of coronary segments and so PCI will not only influence one segment but also adjacent segments, if not the whole vessel. Therefore, by using a coronary artery-based instead of a segment-based analysis we have tried to eliminate the direct influence of prior interventions on a new PCI.

In this study, not all risk factors from all patients could be obtained. Therefore, a multivariate analysis was not performed. Although this is a major limitation, it does not weaken the clinical evidence of the impact of previous PCI outcome on clinical recurrence.

Conclusion

Patients are more prone to develop CR in a target lesion if they have a history of CR in a different coronary artery. In the decision-making process on whether to use a bare metal stent or DES, the history of CR is a simple and powerful aid. ■

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