Direct coronary stent implantation does not reduce the incidence of in-stent restenosis or major adverse cardiac events

Six month results of a randomized trial

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\textbf{Study objectives} To compare the long-term angiographic, clinical and economic outcome of direct stenting vs stenting after balloon predilatation.

\textbf{Patient population and methods} Four hundred patients with coronary stenoses in a single native vessel were randomized to direct stenting vs stenting after predilatation. A major adverse cardiac and cerebral event (MACCE) was defined as death, myocardial infarction, stent thrombosis, target restenosis, repeat target- and non-target vessel-related percutaneous coronary intervention, target lesion revascularization, coronary artery bypass surgery and stroke.

\textbf{Results} Stents were successfully implanted in 98.3\% of patients randomized to direct stenting vs 97.8\% randomized to stenting preceded by predilatation. The primary success rate of direct stenting was 88.3\%, vs 97.8\% for stenting preceded by balloon dilatation (P = 0.01). The angiographic follow-up at 6 months included 333 of the 400 patients (83\%). The binary in-stent restenosis rate was 23.1\% of 163 patients randomized to direct stenting vs 18.8\% of 166 patients randomized to balloon predilatation (P = 0.32). By 185±25 days, MACCE had occurred in 31 of 200 (15.5\%) patients randomized to direct stenting, vs 33 of 200 (16.5\%) randomized to predilatation (P = 0.89).

At 6 months, costs associated with the direct stenting strategy (Euros 3222/patient) were similar to those associated with predilatation (Euros 3428/patient, P = 0.43). However, procedural costs were significantly lower. It is noteworthy that, on multivariate analysis, a baseline C-reactive protein level >10 mg l\textsuperscript{-1} was a predictor of restenosis (odds ratio: 2.10, P = 0.025) as well as of MACCE (odds ratio: 1.94, P = 0.045).

\textbf{Conclusions} Compared to stenting preceded by balloon predilatation, direct stenting was associated with similar 6-month restenosis and MACCE rates. Procedural, but not overall 6-month costs, were reduced by direct stenting. An increased baseline CRP level was an independent predictor of adverse long-term outcome after coronary stent implantation.

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Introduction

Direct coronary stent implantation, defined as stenting without prior balloon dilatation, is a new treatment strategy for coronary artery disease, enabled by the development of advanced stent designs, and of delivery systems with lower crossing profiles, high securement and higher burst pressure ratings.1–11 Recent studies of direct stenting have confirmed its feasibility and safety, and its likelihood to shorten revascularization procedures and reduce the consumption of medical resources, thus increasing cost-effectiveness.1,3,6,9,11–17 In addition, results in rabbits have suggested that direct stenting of the iliac artery is associated with less vessel wall damage and endothelial denudation, as a result of fewer balloon inflations, and stimulation of the process of re-endothelialization, resulting in attenuated neointimal proliferation.18 However, few studies have examined the putative long-term advantages of direct stenting with respect to clinical and angiographic restenosis and cost-effectiveness. The purpose of this randomized study was to compare the angiographic, clinical and economic outcomes of direct stenting with stenting after balloon predilatation up to 6 months after the index procedure.

Patient population and methods

This study was approved by the Ethical Review Committee of the OLVG Hospital, and all participants had signed a written informed consent form. Between January 1999 and June 2001, 400 eligible patients with stable or unstable angina pectoris, and/or myocardial ischaemia due to a non-occlusive coronary stenosis of a single native vessel stentable and technically feasible for direct stenting were enrolled. Patients with complete chronic vessel occlusions, or ostial, bifurcation, or densely calcified lesions, or lesion length >30 mm, diameter <2.5 mm were not included in the study. Eligible patients were assigned 1:1 to either direct stenting or balloon predilatation using a computer-based randomization program.

Stent implantation procedure

The interventional cardiology staff of OLVG includes five operators who adhered to the same study protocol. Aspirin 500 mg, was administered before, and clopidogrel 300 mg after the procedure to all patients. Heparin, 10 000 U was given as an intravenous bolus at the beginning of the procedure, followed by additional hourly boluses of 5000 U. The use of glycoprotein IIb/IIIa receptor antagonists was left to the operators' discretion. The target lesion was accessed by standard techniques from the transradial, transfemoral, or transbrachial approach, and 6-F guiding catheters with appropriate curves were used. The target lesion was crossed with a 0.014-inch coronary guidewire. When performing pre- or post-dilatation, balloons of the shortest possible length were chosen to minimize the extent of vessel wall injury.

An AVE S670 stent (Medtronic Inc. Minneapolis, MN) mounted on a rapid exchange delivery balloon with maximal securement and a <1 mm profile was used in all procedures. Stents as short as possible were chosen to avoid unnecessary wall coverage, and sizes were selected to reach a 1.1 to 1.2 stent/artery ratio. The burst pressure rating of the delivery balloon is 16 atm. The balloon pressure for final stent expansion was ≥14 atm. The use of additional postdilatation balloons was left to the operator's discretion, though not encouraged, and the implantation of multiple stents was discouraged. Crossover from direct stenting to predilatation was permitted when the stent could not be advanced through the stenosis. In such cases, standard balloon predilatation was performed, followed by further attempts to cross the lesion with the stent.

An optimal procedural result was defined as a residual stenosis <30% of the luminal diameter on online quantitative angiographic analysis (QCA) in the catheter laboratory.

Post procedure drug regimen

Intravenous heparin was generally infused overnight at a rate based on measurements of activated thromboplastin time, and was discontinued on the day after the procedure. Clopidogrel 75 mg day−1 was started on the day after the procedure, and continued for 1 month. Aspirin 100 mg day−1, was administered on the day after the procedure and continued for ≥6 months.

Quantitative coronary angiography

At each procedure, pre- and post-stenting angiographic images were obtained in at least two reproducible orthogonal views, free of vessel overlapping and foreshortening, for computer-assisted QCA analysis. Intra-coronary nitroglycerin 100–300 µg was injected before each cineangiographic recording, which were made before balloon dilatation, and/or immediately before and after stent implantation. During filming, the catheter tip had to be empty of contrast agent, the patient in mid
inspiration, and the table immobile. All angiograms were stored in a computer database and analysed offline, using the CAAS ’99 Camtronics (Philips Medical System, Eindhoven, The Netherlands), and analysed by an independent observer, according to an established protocol (Cardialysis, Rotterdam, The Netherlands). Regions of interest were chosen in the target vessel, and measurements of reference vessel diameter, minimal luminal diameter (MLD) and percent diameter stenosis (% DS) were made on end-diastolic frames. Lesion types were graded according to the American College of Cardiology/American Heart Association lesion characteristics classification. Lesion length, in mm, was measured as the distance between proximal and distal shoulders of the lesion. Tortuosity was defined as the presence of two or more bends \(>45^\circ\) proximal to the lesion.

Binary restenosis was defined as a luminal narrowing \(\geq 50\%\) at 6 months. MLD and % DS were measured within the stent's edges. Plaque volumes of target segments before and after the procedure and at 6 months were measured by computer-assisted quantitative coronary angiography. All unscheduled angiograms prompted by return of symptoms, abnormal stress testing, or other untoward coronary events, were also analysed.

**Endpoint definitions**

The primary endpoint of this study was to compare, up to 6 months, the composite incidence of major adverse cardiac and cerebral events (MACCE) in both groups. MACCE was defined as death from all causes, Q- and non-Q-wave myocardial infarction, stent thrombosis, target restenosis, repeat target- and non-target-vessel-related percutaneous coronary intervention (PCI), target lesion revascularization (TLR), coronary artery bypass graft (CABG) and stroke. Revascularization of the target lesion was defined as PCI or CABG performed for restenosis of the target lesion in association with recurrent angina, objective evidence of myocardial ischaemia or both. Procedural success was defined as TIMI grade III flow,\(^20\) <30% final, residual in-stent % DS, and absence of MACCE during the index hospitalization. Diagnosis of a Q-wave myocardial infarction was based on prolonged typical chest pain and documentation of new, \(>0.03\) s Q-waves on a standard electrocardiogram, recorded at baseline and before discharge of the patient from the hospital. Non-Q-wave infarction was defined as a blood creatine kinase, or its MB fraction, \(>twice\) the upper limit of normal with or without prolonged chest pain.

Additional endpoints were the comparison between the two groups of the success of the intended treatment strategy, final successful stent placement, procedural success rates, recurrent Canadian Cardiovascular Society (CCS) class III and IV angina pectoris and medical costs.\(^19\) The 6-month angiographic endpoints were in-stent binary restenosis and plaque volume of target lesion segment.

**Patient follow-up**

At 30 days, patients visited the outpatient department for assessment of their CCS anginal status, and recording of interim MACCE, coronary intervention, or clinical manifestations consistent with recurrent myocardial ischaemia. They also underwent follow up angiography for QCA at 6 months. The 6-month angiograms were waived in patients who had undergone an earlier clinically-indicated angiographic examination in which in-stent restenosis was detected. A 12-lead electrocardiogram was systematically recorded at each clinical visit, and other non-invasive tests as necessary.

**Medical costs and effectiveness**

The balance between costs and effects was evaluated immediately after the procedure, and at 6 months. The costs of the initial procedure were calculated per patient, and averaged in both groups. Procedural costs included the materials and laboratory and staff time. Laboratory and staff time were calculated by multiplying the procedural time +30 min by Euros 17/min; the latter figure was based on time-tested cost estimates, obtained from a large data set collected by a company linked to the University Hospital of Rotterdam, The Netherlands (data unpublished). Materials included in the cost analysis were needles, sheaths, wires, guiding catheters, coronary guidewires, angioplasty balloons, pre-mounted stents and angiographic contrast agent. The balloon of the stent delivery system was not included in the overall count of balloons. Procedural effectiveness was expressed as the attainment of a postprocedural <30% DS of all lesions treated. Six-month costs were estimated by multiplying adverse clinical events by pre-estimated event costs (repeat PCI=Euros 4000, CABG=Euros 12 000, Q-wave MI=Euros 3000). Effectiveness at 6 months was defined as a MACCE-free status.
Statistical analysis

With a two-sided significance level set at 0.05 and an 80% power, it can be shown that the sample size of 400 patients will allow the detection of a minimum proportional treatment difference (MACCE) of 8% at 180 days. The primary analysis of angiographic, procedural and clinical outcomes was based on the intention-to-treat principle. For comparison of continuous non-paired variables between the treatment groups, the unpaired two-tailed Student’s t-test was used or, in case of skewed data, the Mann–Whitney U-test. Comparison of categorical variables or composite clinical end-points (any MACCE) between the two groups was performed using the Chi-square test. Event-free Kaplan–Meier curves were based on the absence of MACCE. Differences in survival time were assessed by the log–rank test. As events continued to occur 30 days after the 6-month follow-up, patients were censored at 210 days. A paired t-test or Wilcoxon Rank test was used to determine a potential gain or loss in mean luminal diameter. Spearman rank correlation testing (coefficient Rs) was performed to identify variables related to MACCE at 6 months and to binary restenosis. Logistic regression analysis was performed among these variables to detect predictors of MACCE and restenosis. Continuous variables were expressed as mean±standard deviation (SD) and/or as a percentage. Ninety-five percent confidence intervals (95% CI) were calculated for odds ratios. Statistical tests were carried out with the SPSS 10.0 statistical software package (Chicago, IL).

Results

Baseline demographics and lesion characteristics

In the 200 patients randomized to direct stenting, 238 lesions were treated, vs 231 lesions in the 200 patients randomized to predilatation. All baseline demographic, clinical and lesion characteristics were evenly distributed between the two treatment groups (Table 1).

Safety and efficacy

The ultimately successful vascular access was via the radial approach in 86.5%, femoral in 9.5%, and the brachial artery in 4% of the procedures. Direct stenting was successful in 210 lesions (88.3%), a significantly lower percentage than the primary success of stenting preceded by balloon dilatation (97.8%; P=0.01). In most unsuccessful direct stenting attempts, the stent could not be advanced through the stenosis because of marked vessel tortuosity and/or a densely calcified lesion. Nearly all lesions unsuccessfully stented directly, were successfully stented after predilatation, for a final success rate of 97.9%.

The ultimate procedural success rates, including the in-hospital MACCE rate, were 96% with direct...
stenting vs 94.5% with predilatation (ns). One patient treated by direct stenting died during emergency CABG after an unsuccessful procedure complicated by dissection of the left anterior descending coronary artery. Autopsy confirmed the presence of an acute anterolateral transmural myocardial infarction. Although no acute stent thrombosis occurred in the directly stented group, the no-reflow phenomenon was observed in one patient after stent implantation, and a second patient, who suffered a distal vessel occlusion, had to undergo further revascularization by emergency CABG. Four patients randomized to predilatation developed transient vessel closure complicated by myocardial infarction. In one patient, stent occlusion occurred 4 h after the procedure. Vascular complications were limited to femoral hematoma or false aneurysms. No patient suffered a stroke while in hospital.

Angiographic outcome and restenosis

Follow-up angiography was performed at 6 months in 333 patients (83%). Causes of missing follow-up angiograms included death (n=3), and patient refusal (n=64). Baseline, immediately post-procedural and 6-month angiographic measurements are listed in Table 2. Fig. 1 presents the cumulative distributions of acute gain, late loss and net gain for the two treatment strategies. At 6 months, the angiographic binary in-stent restenosis rates in 163 overall direct stenting attempts, 146 successful direct stenting attempts, and in 166 patients randomized to predilatation were 23.1, 21.9 and 18.8%, respectively (ns).

Mean plaque volume at 6 months had returned to its baseline value in the direct stenting group, whereas it remained significantly lower in patients who had undergone stenting after predilatation (23.0±22.3 mm$^3$ vs 28.6±22.2 mm$^3$, $P=0.02$), despite equivalent mean minimal luminal diameters and percent diameter stenoses. At 6 months, the mean reference vessel diameter was significantly greater than at baseline in the overall study population ($P<0.001$ for both groups pooled), though not different between the two study groups.

One month and late clinical outcomes

The 1-month and late clinical outcomes are presented in Table 3. The 30-day MACCE rates were 4.5 and 5.5% in patients randomized to direct stenting and predilatation, respectively. No patient died after discharge from hospital. Two patients in the direct stenting group developed subacute stent thrombosis complicated by one Q-wave and one non-Q-wave myocardial infarction, respectively. There were no significant between-groups differences in clinical endpoints. The 30-day angina-free statuses were 71.9% in patients randomized to

| Table 2 | Immediate and 6-month quantitative coronary angiographic measurements in patients randomized to direct stenting (direct) vs stenting preceded by predilatation (predil) |
|-------------------------------|----------------------------------|------------------|------------------|------------------|
| **Measurement**                | **Direct** (n=238)               | **Predil** (n=231) | **P**           |
| Reference vessel diameter, mm  |                                  |                  |                 |
| Baseline                       | 2.87±0.61                        | 2.84±0.60        | 0.30            |
| After procedure                | 3.00±0.51                        | 2.99±0.51        | 0.68            |
| Six-month follow-up            | 3.23±0.69                        | 3.14±0.61        | 0.21            |
| Minimal lumen diameter, mm     |                                  |                  |                 |
| Baseline                       | 0.99±0.33                        | 1.00±0.30        | 0.68            |
| After procedure                | 2.57±0.47                        | 2.54±0.50        | 0.58            |
| Six-month follow-up            | 2.02±0.65                        | 2.02±0.68        | 0.93            |
| Percent diameter stenosis, %   |                                  |                  |                 |
| Baseline                       | 65.3±10                          | 64.7±8           | 0.50            |
| After procedure                | 14.7±8                           | 15.5±8           | 0.22            |
| Six-month follow-up            | 37.1±16                          | 36.2±16          | 0.54            |
| Plaque volume, mm$^3$           |                                  |                  |                 |
| Baseline                       | 28.4±21.0                        | 28.6±22.2        | 0.89            |
| After procedure                | 5.0±8.6                          | 5.1±6.5          | 0.84            |
| Six-month follow-up            | 29.1±28.3                        | 23.0±22.3        | 0.02            |
| Acute gain, mm$^3$             |                                  |                  |                 |
| Baseline                       | 1.58±0.47                        | 1.53±0.50        | 0.25            |
| After procedure                | 0.61±0.54                        | 0.58±0.48        | 0.57            |
| Late loss, mm                  | 1.0±0.62                         | 1.0±0.62         | 0.57            |
| Net gain, mm                   | 23.1                             | 18.8             | 0.32            |

Except for binary restenosis rate, values are mean±standard deviation. $P$ values reflect comparisons between Direct and Predil.

aAcute gain in minimal lumen diameter in each group was highly significant (paired t-test: $P<0.001$).
direct stenting vs 76.9% in patients randomized to predilatation (ns).

At the end of a mean observation period of 185±25 days, MACCE had occurred between study enrolment and the end of follow-up in 31 of 200 patients (15.5%) randomized to direct stenting, vs 33 of 200 patients (16.5%) randomized to predilatation (P=0.89). Cardiac arrest was presumed for
the single patient in the direct stenting group, whose cause of death had not been precisely determined. Kaplan–Meier event-free survival curves (Fig. 2) for patients randomized to direct stenting and predilatation were similar ($P=0.96$; log–rank test).

**Multivariate analysis**

Among 31 demographic, clinical and angiographic variables tested, diabetes mellitus (odds ratio: 2.35, 95% CI: 1.2–4.6, $P=0.014$), a smaller MLD after stenting as expressed in millimetres (odds ratio: 2.86, 95% CI: 1.5–5.4, $P=0.001$) and a C-reactive protein concentration $>10$ mg l$^{-1}$ (odds ratio: 2.10, 95% CI: 1.1–4.0, $P=0.025$) were independent predictors of restenosis (Fig. 3). The relation between MLD after stenting divided into subgroups and the binary restenosis rate is illustrated in Fig. 4.

Fig. 3 also shows that diabetes mellitus (odds ratio: 2.22, 95% CI: 1.1–4.4, $P=0.024$), triple vessel coronary disease (odds ratio: 2.27, 95% CI: 1.0–5.1, $P=0.049$), baseline CRP concentration $>10$ mg l$^{-1}$ (odds ratio: 1.94, 95% CI: 1.0–3.7, $P=0.045$), left anterior descending (odds ratio: 4.29, 95% CI: 1.9–9.6, $P<0.001$) and left circumflex (odds ratio: 4.46, 95% CI: 1.9–10.5, $P<0.001$) coronary arteries as target vessels, were independent predictors of cumulative MACCE up to 6 months.
A high baseline CRP also predicted an adverse outcome at 1 month (odds ratio: 4.20, \( P = 0.046 \)). Baseline CRP, expressed as a continuous variable, was not retained in our model, although it was separately associated with MACCE (Rs=0.15, \( P = 0.012 \)).

Costs and effectiveness

Direct stenting was associated with a reduced consumption of angioplasty balloons (0.4 vs 1.17 balloons/patient, \( P < 0.001 \)), thus, lower procedural costs (Euros 2545\( \pm \)914 vs 2763\( \pm \)842, \( \Delta C = -218, P = 0.01 \)), than with predilatation. There were no significant differences in overall costs after 6 months, owing probably to the wide variability of follow-up costs (Euros 3222\( \pm \)2713 vs 3428\( \pm \)2466, \( \Delta C = -206, P = 0.43 \)). Efficacy at 1 (\( \Delta E = 0.5\% \)) and 6 months (\( \Delta E = 1.0\% \)) was the same in both treatment groups.

Discussion

Technical progress in stent design in the past 10 years and in their delivery systems has eliminated the need for angioplasty balloons to predilate coronary lesions before stent implantation. This controlled trial examined the long-term angiographic, clinical and economic outcomes of this new strategy, known as direct stenting.

A primary implantation success rate of 88.3\% was achieved with direct stenting. The final procedural success rate, including 10\% of patients in whom balloon predilatation was ultimately needed, was 96\%, similar to the success rate observed in the group randomized to stenting after predilatation, and equivalent to that typically observed with standard methods in this type of patient population. Against our expectations based on results of animal studies, there seemed to be no long-term angiographic or clinical advantage conferred by direct stenting in this group of patients. Direct stenting did not reduce the incidence of binary restenosis, and mean plaque volume at 6 months was, in fact, higher in the directly stented lesions. The lower rate of restenosis observed in directly stented animals does not seem to be extrapolated to humans.

Early and long-term MACCE rates were comparably low, confirming that a systematic direct stenting strategy including provisional predilatation is associated with long-term results as favourable as those associated with a systematic strategy of stenting after balloon predilatation. The 6-month MACCE and binary angiographic restenosis rates were comparable to those reported in recently published stent trials.\(^{15}\) Long-term clinical outcomes cannot be compared with studies without protocol-mandated follow-up angiography, since the latter is highly sensitive in detecting restenotic lesions, leading to the performance of repeat PCIs in a higher percentage of patients.

On multivariate analysis a baseline serum CRP concentration >10 mg l\(^{-1} \), expressed as a binary variable, was an independent predictor of angiographic restenosis and MACCE, suggesting that a detectable inflammatory activity is associated with tissue proliferative responses within successfully implanted stents.\(^{15} \) As has been reported by others, post-procedural MLD, diabetes mellitus and triple vessel disease were independent predictors of restenosis and MACCE at 6 months.\(^{23} \)

The clinical outcomes were similar in both treatment groups. However, from an economic point of view, there was a short-term advantage of direct stenting, due to a modest, though statistically significant reduction in procedural costs. At 6 months, a small cost advantage persisted in favour of direct stenting, although it was no longer statistically significant as a result of the high variability in follow-up costs. This modestly lower cost associated with direct stenting has been reported by others.\(^{1,3,6,9,11,12} \)

Limitations of the study

Angiographic follow-up was not complete since several patients refused to undergo the protocol-mandated catheterization procedure, although all patients underwent clinical follow-up examinations. In addition, these results reflect the performance of a single institution. However, this results in more uniformity to the study.
In conclusion, in this relatively unselected patient population, direct coronary stenting and stent implantation preceded by balloon dilatation were associated with equally high overall procedural success rates. Likewise, the 6-month MACCE, binary angiographic restenosis and target lesion revascularization rates were not different between the two treatment intentions, and similar to those reported in recently published stent trials. There was a short-term benefit conferred by direct stenting, attributable to a modest reduction in procedural costs. An elevated baseline CRP level was a predictor of adverse outcome after coronary stent implantation, suggesting that an enhanced inflammatory activity is associated with an intimal tissue proliferative response within successfully implanted stents.

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