Direct Stenting with TAXUS Stents Seems to be as Safe and Effective as with Predilatation

A post hoc analysis of TAXUS II

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Background and Method: Although direct coronary stenting does not improve angiographic outcome, it makes sense by reducing procedure times, radiation exposure and costs. Other potential advantages of direct stenting may be a reduction of myocardial ischemia time, which could be clinically relevant in high-risk patients. With the introduction of drug-eluting stents, however, concern arose that direct stenting would possibly damage the polymer coating and change or diminish the efficacy of the programmed drug release. Also, concerns about safety by preventing optimal apposition of single stent struts developed. It is the purpose of this paper to retrospectively analyze the data from the TAXUS-II Trial (536 patients) regarding patients with and without direct stenting. While predilatation was recommended per protocol, direct stenting was not forbidden: thus, direct stenting was performed in 49 patients (TAXUS n = 23, control n = 26).

Results: In the TAXUS groups, there was no significant difference regarding major adverse cardiac events (MACE; 7.5% vs. 4.3%), angiographic restenosis in the analysis segment (4.8% vs. 4.3%), late loss (0.28 ± 0.36 vs. 0.33 ± 0.30 mm) or intravascular ultrasound-(IVUS-)measured volume obstruction (7.95 ± 9.84% vs. 5.61 ± 7.91%) at six months between the predilated and directly stented patients. The same was true for the patients receiving the control stent. Compared with the directly stented control group, the statistically significant positive effects of TAXUS direct stenting were maintained, regarding angiographic restenosis in the analysis segment (4.3% vs. 30.8%), late loss (0.33 ± 0.30 vs. 0.80 ± 0.62 mm) or IVUS-measured volume obstruction (5.61 ± 7.91% vs. 22.50 ± 21.62%) at six months. MACE was reduced from 19.2% to 4.3%; due to the small number of patients this trend did not reach statistical significance. After predilatation, all parameters were significantly improved by the TAXUS stent.

Conclusion: Comparison of patients receiving TAXUS stents with or without predilatation revealed no differences in clinical, angiographic or IVUS parameters at six months. This suggests that direct stenting with the polymer-based paclitaxel-eluting TAXUS stent is feasible, safe and equally effective. Randomized trials comparing stenting after predilatation versus direct stenting with drug-eluting stents are warranted.

Key Words: Drug-eluting stents · Paclitaxel · Taxus · Restenosis · Direct stenting

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Direkt-Stenting mit TAXUS-Stents: So sicher und effektiv wie nach Vordehnung. Eine post-hoc-Analyse der TAXUS-II-Studie

Hintergrund und Methodik: Obwohl das koronare Direkt-Stenting das angiographische Kurz- und Langzeitergebnis nicht verbessert, macht es dennoch Sinn, da es die Prozedurzeiten, Strahlenexposition und die Kosten reduzieren kann. Andere mögliche Vorteile des Direkt-Stentings liegen in einer Reduktion der myokardialen Ischämiezeit, was bei Hochrisikopatienten klinisch relevant sein könnte. Mit der Einführung der Medikamente freisetzenden Stents kamen jedoch Beden-

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ken auf, dass ein Direkt-Stenting möglicherweise die Polymerbeschichtung beschädigen könnte und somit die Wirksamkeit vermindert. Auch eine eventuelle Beeinträchtigung der Sicherheit und Wirksamkeit durch Malapposition einzelner Stentstreben wurde diskutiert. Ziel dieser Arbeit ist es, die Daten der TAXUS-II Studie (536 Patienten) hinsichtlich des Direkt-Stentings retrospektiv zu analysieren. In dieser Studie war die Vordehnung zwar empfohlen, ein Direkt-Stenting aber nicht unerlaubt. Insgesamt wurde ein Direkt-Stenting bei 49 Patienten (23 in der TAXUS-Gruppe, 26 in der Kontrollgruppe) durchgeführt.

Ergebnisse: In der TAXUS-Gruppe war nach 6 Monaten zwischen den prädilatierten und den direkt-gestenteten Patienten kein signifikanter Unterschied hinsichtlich MACE (7,5 % vs. 4,3 %), angiographischer Restenose im analysierten Gesamtsegment (4,8 % vs. 4,3 %), late loss (0,28 ± 36 mm vs. 0,33 ± 30 mm) und in der IVUS-gemessenen prozentualen Obstruktion des Stentvolumens (7,95 ± 9,84 vs. 5,61 ± 7,91) erkennbar. Dasselbe galt auch für die Patienten, die einen unbeschichteten Kontrollstent erhielten. Im Vergleich zur direkt gestenteten Kontrollgruppe waren die statistisch signifikanten positiven Effekte des TAXUS-Direkt-Stentings unverändert erhalten: angiographische Restenose im gesamten analysierten Segment (4,3 % vs. 30,8 %), late loss (0,33 ± 0,30 vs. 0,80 ± 0,62 mm) und IVUS-gemessene Volumenobstruktion (5,61 ± 7,91% vs. 22,50 ± 21,62%). MACE wurde von 19,2 % auf 4,3 % reduziert, allerdings erreichte dieser eindeutige Trend aufgrund der kleinen Patientenzahl keine statistische Signifikanz. Nach Vordehnung waren in der TAXUS-Gruppe alle Parameter signifikant besser als in der Kontrollgruppe.

Schlussfolgerung: Der Vergleich von Patienten, die einen TAXUS-Stent mit oder ohne Vordehnung erhielten, ließ keinen Unterschied in den klinischen, angiographischen oder IVUS-Parametern nach 6-Monaten erkennen. Die Ergebnisse zeigen, dass das Direkt-Stenting mit dem Polymer-basierten, Paclitaxel-freisetzenden TAXUS-Stent gut durchführbar, sicher und genauso wirksam ist wie nach Vordehnung. Randomisierte Studien zum Vergleich des Direkt-Stentings mit Stenting nach Vordehnung für Medikamente freisetzende Stents sind wichtig.

Schlüsselwörter: Medikamente freisetzende Stents · Paclitaxel · Taxus · Restenose · Direktstenting

Introduction

Since the introduction of coronary stenting in 1987 [42] with its evidence of superiority over plain balloon angioplasty [2, 15, 18, 39, 41, 51], considerable efforts have been made to improve clinical outcome after percutaneous coronary intervention (PCI): while high-pressure stenting [13] and intravascular ultrasound-(IVUS-)guided stent implantation [32, 33] have failed to show a beneficial impact on angiographic or clinical outcome, the measurements of Doppler-derived coronary flow reserve (CFR) [1, 37] and of fractional flow reserve (FFR) [6, 28] were suggested. Furthermore, the technique of direct stent implantation (without predilatation) was believed to reduce trauma and, hence, restenosis [17, 30]. The improvements in mechanical properties of the latest-generation stents with their enhanced trackability and flexibility enabled the implementation of direct stent implantation for everyday use. Direct stenting can be safely performed in a broad spectrum of clinical and angiographic situations including patients with acute coronary syndromes and thrombus-containing lesions [10, 19, 20, 50]. Other potential advantages of direct stenting might be a reduction of vessel wall and myocardial ischemia time, which could be clinically relevant in specific patient subgroups (i.e., patients with severe left ventricular dysfunction and patients with left main coronary artery disease). In these patients, direct stenting may improve clinical outcome [7]. Furthermore, direct coronary stenting makes sense by reducing procedure times, radiation exposure and costs without increasing the risk to patients.

The major leap toward a reduction of restenosis after stenting was taken by developing drug-eluting stents [3, 4]. Regarding improvement of clinical outcome with paclitaxel-eluting stents, a polymer carrier has been shown to be essential [43]. However, concern arose that direct stenting would possibly damage the polymer coating and change or diminish the efficacy of the programmed drug release. Also, concerns about safety by preventing optimal apposition of single stent struts and/or damaging the drug-containing polymer developed.

The purpose of this paper is, to retrospectively analyze the data from the TAXUS-II trial regarding patients with and without direct stenting.

Method

The TAXUS stent was a slotted-tube stainless-steel stent (NIR, Medinol Ltd.) coated with a proprietary polymer (Translute) designed to control paclitaxel release with an initial burst phase over the first 48 h after implantation; a low-level, ten-day release phase followed [45]. Paclitaxel-eluting stents were coated with a total loaded dose of 1 µg/mm^2. Two paclitaxel-eluting release formulations were evaluated, TAXUS-SR (slow release) and TAXUS-MR (moderate release), the latter

having an eightfold higher ten-day drug release [45, 47]. Of the total loaded dose, approximately 90% remains sequestered within the SR polymer formulation and 75% within the MR formulation without further measurable paclitaxel release. The control stent was the uncoated NIR stent. Study stents included diameters of 3.0 and 3.5 mm and 15 mm length, premounted on 20-mm balloon delivery catheters.

TAXUS-II was a randomized, double-blind trial, conducted at 38 sites [11, 38, 49]. Eligible patients had stable or unstable angina or silent ischemia, were at least 18 years of age, and were acceptable candidates for PCI or coronary artery bypass grafting (CABG). Angiographic inclusion criteria specified a single de novo target lesion with estimated stenosis ≥ 50% and ≤ 99%, estimated length ≤ 12 mm, and location in a native coronary vessel ≥ 3.0 mm and ≤ 3.5 mm in diameter. Exclusion criteria included recent coronary intervention (≤ 30 days), left ventricular ejection fraction < 30%, evolving myocardial infarction (MI), unprotected left main coronary disease, or prespecified need to implant more than one 15-mm stent for full lesion coverage.

The primary endpoint was the percent of the stent volume obstructed by neointimal proliferation measured by IVUS at six months. Secondary endpoints were major adverse cardiac events (MACE), including all death, Q-wave MI, non-Q-wave MI, and target vessel revascularization (TVR) at 1, 6, and 12 months. Non-Q-wave MI was defined as elevation of creatine kinase (CK) levels > 2 times normal with detectable CK-MB in the absence of pathologic Q-waves. TVR included all CABG and PCI performed on the target vessel. Target lesion revascularization (TLR) was performed to treat restenosis of the analysis segment (stent plus the 5-mm regions from the stent border). Quantitative coronary analysis (QCA) measurements at six months included binary restenosis (defined as ≥ 50% diameter stenosis), reference vessel diameter, minimum lumen diameter, percent diameter stenosis, and late lumen loss. To maintain blinding, TAXUS and control stents were indistinguishable by physical and radiographic appearance. Use of additional stents was permitted, if patency of the stented vessel was compromised. Second stents were of the same type as those originally assigned. Third stents, if necessary, could be of any type considered appropriate by the investigator, except for study stents. After stent placement, patients received clopidogrel 75 mg/d (or ticlopidine 250 mg twice daily) for at least six months and aspirin 75 mg/d, maintained indefinitely.

Between June 2001 and January 2002, 536 patients were randomized into two consecutive and independent cohorts: 267 patients in the SR cohort (TAXUS-SR n = 131, control n = 136) and 269 in the MR cohort (TAXUS-MR n = 135, control n = 134). Treatment and control groups in both cohorts were well matched for baseline demographics and clinical characteristics [11].

While predilatation was recommended per protocol, direct stenting was performed in 49 patients (TAXUS n = 23, control n = 26). After combining the two TAXUS groups (because of the relatively small numbers of patients with direct stenting), a post hoc analysis was performed to compare clinical, QCA and IVUS results at six months in these subgroups.

Statistical Analysis

Primary endpoint of the analysis was the six-month percent stented segment net volume obstruction, determined by IVUS. Event/success rates are number of patients with the outcome divided by the number of patients evaluable for the outcome. Clinical procedural success: using the assigned study device to achieve an in-target-lesion diameter stenosis < 30% in the average of two near orthogonal projections, as visually assessed by the physician, without the occurrence of in-hospital MACE. Six-month MACE: the proportion of patients who experience a MACE up to the six-month follow-up. MACE comprises death, MI including Q- and non-Q-wave MI, and TVR. Six-month restenosis: the proportion of patients who demonstrate ≥ 50% diameter stenosis of the target lesion by QCA performed at the angiographic core laboratory at the six-month follow-up. Six-month follow-up: 150–210 days. MLD: minimum lumen diameter; late loss: post-procedure MLD to Six-month MLD, MLD measured in the stented segment. The p-values are two-sided and from Student's t-test for continuous variables and Fisher's exact test for discrete variables. Difference = TAXUS – control. Confidence interval [CI] = difference ± 1.96 SE.

Results

The results are presented as TAXUS predilatation versus TAXUS direct stenting (Table 1), control predilatation versus control direct stenting (Table 2), TAXUS direct stenting versus control direct stenting (Table 3), and TAXUS predilatation versus control predilatation (Table 4).

Table 1. Comparison of patients receiving the TAXUS stent with and without predilatation. There were no statistically significant differences regarding MACE, angiographic and IVUS results. CABG: coronary artery bypass grafting; CI: confidence interval; IVUS: intravascular ultrasound; MACE: major adverse cardiac events; MI: myocardial infarction; MLD: minimum lumen diameter; QCA: quantitative coronary analysis; RVD: reference vessel diameter; TLR: target lesion revascularization; TVR: target vessel revascularization.

Tabelle 1. Vergleich der 6-Monats-Ergebnisse aller Patienten mit TAXUS-Stents, die entweder nach Vordehnung oder direkt implantiert wurden. Weder für MACE noch für die angiographischen und IVUS-Ergebnisse ergab sich ein statistisch signifikanter Unterschied. Erklärung der Abkürzungen siehe Text.

Efficacy measures	TAXUS predilatation	TAXUS direct stenting	Difference [95% CI]	p-value
Clinical procedural success	97.0% (227/234)	100% (23/23)	–3.0% [–5.2%, –0.8%]	1.0000
6-month MACE	7.5% (17/227)	4.3% (1/23)	3.1% [–5.9%, 12.2%]	1.0000
• Death	0.0% (0/227)	0.0% (0/23)	0.0% [0.0%, 0.0%]	Undef.
• Q-wave MI	0.0% (0/227)	0.0% (0/23)	0.0% [0.0%, 0.0%]	Undef.
• Non-Q-wave MI	1.8% (4/227)	0.0% (0/23)	1.8% [0.1%, 3.5%]	1.0000
• TVR, overall	6.2% (14/227)	4.3% (1/23)	1.8% [–7.1%, 10.7%]	1.0000
– TVR, non-TLR	2.2% (5/227)	0.0% (0/23)	2.2% [0.3%, 4.1%]	1.0000
– TVR, TLR	3.1% (7/227)	4.3% (1/23)	–1.3% [–9.9%, 7.4%]	0.5433
– TVR, CABG	0.9% (2/227)	0.0% (0/23)	0.9% [–0.3%, 2.1%]	1.0000
6-month restenosis (QCA)				
• Analysis segment	4.8% (11/227)	4.3% (1/23)	0.5% [–8.3%, 9.3%]	1.0000
• Stented segment	1.3% (3/227)	0.0% (0/23)	1.3% [–0.2%, 2.8%]	1.0000
6-month % stented segment net volume obstruction (IVUS)	7.95 ± 9.84 (208) (–0.05, 58.43)	5.61 ± 7.91 (22) (0.00, 31.46)	2.33 [–1.92, 6.58]	0.2835
6-month QCA				
• RVD (mm)	2.78 ± 0.41 (226) (1.90, 4.14)	2.67 ± 0.41 (23) (1.71, 3.63)	0.11 [–0.07, 0.29]	0.2188
• MLD (mm)	2.28 ± 0.43 (227) (0.00, 3.39)	2.13 ± 0.40 (23) (1.20, 2.81)	0.15 [–0.03, 0.33]	0.1083
• Diameter stenosis (%)	17.67 ± 10.89 (227) (–3.00, 100.00)	19.92 ± 10.11 (23) (4.00, 39.00)	–2.25 [–6.89, 2.39]	0.3429
• Late loss (mm)	0.28 ± 0.36 (225) (–0.54, 2.20)	0.33 ± 0.30 (23) (–0.08, 1.21)	–0.06 [–0.21, 0.10]	0.4709

In the TAXUS groups, no significant difference was evident regarding MACE (7.5% vs. 4.3%), angiographic restenosis in the analysis segment (4.8% vs. 4.3%), late loss (0.28 ± 0.36 vs. 0.33 ± 0.30 mm), or IVUS-measured volume obstruction (7.95 ± 9.84% vs. 5.61 ± 7.91%) at six months between the predilated and directly stented patients (Table 1). The same was true for the patients receiving the control stent (Table 2).

Compared with the directly stented control group, the statistically significant positive effects of TAXUS direct stenting were maintained, regarding angiographic restenosis in the analysis segment (4.3% vs. 30.8%), late loss (0.33 ± 0.30 vs. 0.80 ± 0.62 mm), or IVUS-measured volume obstruction (5.61 ± 7.91% vs. 22.50 ± 21.62%) at six months (Table 3). MACE was reduced from 19.2% to 4.3%; due to the small number of patients this trend did not reach statistical significance (Table 3). After predilatation, all parameters were significantly improved by the TAXUS stent (Table 4).

Discussion

Clinical Outcome after Direct Stenting

Stent deployment is traditionally preceded by balloon angioplasty. Experimental studies, however, showed less trauma with direct stent implantation, demonstrating a minimization of endothelial injury with a reduction in neointimal hyperplasia [14, 29, 31]. This observation in animal studies might be based on sufficient endothelium left within the stented segment to allow repopulation with a much reduced requirement for endothelial proliferation and migration [30]. It was therefore hypothesized that if some endothelium is present in atherosclerotic vessels, stenting without predilatation may provide a means for dilating arteries while avoiding complete endothelial denudation [17]. The beneficial effects of direct stenting on restenosis as observed in animal experiments [17, 30], however, could not be extrapolated to the clinical setting:

Two larger retrospective analyses suggested that the in-hospital and long-term clinical outcomes in patients undergoing coronary intervention are equivalent when comparing stenting without balloon predilatation with balloon angioplasty followed by stenting [7, 52]. Two smaller randomized studies also failed to demonstrate a difference at one and six months [12, 26].

The PREDICT trial randomized 399 patients to direct stenting (S670, Medtronic-AVE) versus predilatation. Like in the other studies, there was no reduction in clinical or angiographic restenosis [5]. A Brazilian multicenter study randomized 411 patients (425 lesions) to undergo direct or conventional stent

Table 2. Comparison of patients receiving the bare control stent with and without predilatation. There were no statistically significant differences regarding MACE, angiographic and IVUS results. For abbreviations see Table 1.

Tabelle 2. Vergleich der 6-Monats-Ergebnisse aller Patienten, die einen unbeschichteten Kontrollstent entweder nach Vordehnung oder direkt erhielten. Erklärung der Abkürzungen siehe Text.

Efficacy measures	Control predilatation	Control direct stenting	Difference [95% CI]	p-value
Clinical procedural success	94.2% (228/242)	96.2% (25/26)	–1.9% [–9.9%, 6.0%]	1.0000
6-month MACE	19.1% (45/235)	19.2% (5/26)	–0.1% [–16.0%, 15.9%]	1.0000
• Death	0.4% (1/235)	0.0% (0/26)	0.4% [–0.4%, 1.3%]	1.0000
• Q-wave MI	0.0% (0/235)	3.8% (1/26)	–3.8% [–11.2%, 3.5%]	0.0996
• Non-Q-wave MI	4.3% (10/235)	3.8% (1/26)	0.4% [–7.4%, 8.2%]	1.0000
• TVR, overall	15.7% (37/235)	15.4% (4/26)	0.4% [–14.3%, 15.0%]	1.0000
– TVR, non-TLR	2.6% (6/235)	0.0% (0/26)	2.6% [0.5%, 4.6%]	1.0000
– TVR, TLR	13.2% (31/235)	15.4% (4/26)	–2.2% [–16.7%, 12.3%]	0.7618
– TVR, CABG	0.4% (1/235)	3.8% (1/26)	–3.4% [–10.9%, 4.0%]	0.1897
6-month restenosis (QCA)				
• Analysis segment	20.8% (49/236)	30.8% (8/26)	–10.0% [–28.5%, 8.5%]	0.3142
• Stented segment	17.9% (42/235)	26.9% (7/26)	–9.1% [–26.8%, 8.7%]	0.2895
6-month % stented segment net volume obstruction (IVUS)	21.82 ± 17.03 (220) (–0.00, 75.78)	22.50 ± 21.62 (24) (0.00, 77.07)	–0.68 [–8.06, 6.70]	0.8572
6-month QCA				
• RVD (mm)	2.62 ± 0.43 (233) (1.59, 4.12)	2.78 ± 0.54 (26) (1.95, 3.67)	–0.16 [–0.34, 0.03]	0.0929
• MLD (mm)	1.77 ± 0.53 (236) (0.00, 3.02)	1.85 ± 0.73 (26) (0.61, 3.26)	–0.09 [–0.31, 0.13]	0.4357
• Diameter stenosis (%)	32.52 ± 17.32 (235) (–9.00, 100.00)	34.30 ± 19.62 (26) (11.00, 72.33)	–1.78 [–8.89, 5.33]	0.6236
• Late loss (mm)	0.77 ± 0.45 (236) (–0.11, 2.63)	0.80 ± 0.62 (26) (–0.41, 2.19)	–0.03 [–0.22, 0.16]	0.7683

implantation [8]. Lesions with severe calcification were excluded. At six-month follow-up, the incidences of death (direct 1.4% vs. predilatation 2.5%), MI (5.3% vs. 5.0%), and TVR (8.2% vs. 10.5%) were similar in both groups [8].

In the BET study, 338 patients were randomly assigned to either direct stent implantation (DS+; 173 patients) or standard stent implantation with balloon predilatation (DS–; 165 patients) [9]. Procedural success was achieved in 98.3% of patients assigned to DS+ and 97.5% of patients assigned to DS– (p = n.s.), with a crossover rate of 13.9%. At six-month follow-up, the incidence of MACE including death, angina pectoris, MI, congestive heart failure, repeat angioplasty, or CABG was 5.3% in DS+ and 11.4% in DS– (p = n.s.).

The DISCO trial randomized 416 patients (446 lesions) to direct stent implantation or following balloon predilatation [22]. Patients > 75 years old, with heavily calcified lesions, bifurcations, total occlusions, left main lesions, and very tortuous vessels were excluded. Direct stenting was successful in 217/224 lesions (96.8%). There were no significant differences in MACE at follow-ups at 1, 6, and 12 months between the two groups. Angiographic reevaluation at six months was performed in 94% of the cases. Restenosis rate was 16.5% in direct stenting and 14.3% in predilated stenting (p = n.s.) [22].

The VELVET trial examined the six-month angiographic results of direct coronary stenting (Bx Velocity, Cordis J&J), and compared the 9-month safety, efficacy and cost of this strategy versus stenting after balloon predilatation [40]. The success rates of the intended delivery strategies were 87.9% and 97.9% for direct stenting and predilatation, respectively (p < 0.001), while the procedural success rates were similar (93.9% vs. 96.5%). Over a follow-up period of 9 months, MACE rates were 12.0% and 10.9% in patients randomized to direct stenting and predilatation, respectively (p = n.s.) [40].

The recently published ISAR-DIRECT trial was the largest of the randomized studies addressing this issue [23]. Sample size was calculated based on the following assumptions: a restenosis rate of 27% for conventional (= predilatation) stenting group (CS), a 30% reduction with direct stenting (DS), and a follow-up angiography rate of at least 75% [23]. Patients with acute MI, total vessel occlusions or vessel size < 2.5 mm were excluded. Calcification was not an exclusion criteria with 31.5% in the DS and 29.0% in the CS group. Complex lesions (B2/C) were present in 71.7% of the DS and in 72.2% of the CS group. In the 910 patients enrolled (native coronary vessels only), no significant difference was observed in the primary endpoint, the incidence of angiographic restenosis was 23.6% for DS and 21.0% for CS (p = 0.41; relative risk = 1.1; 95% CI = 0.8–1.5). The incidence of TVR was 17.3% among DS and 14.8%

Table 3. Comparison of patients receiving the TAXUS or the bare control stent by direct stenting. The differences regarding angiographic and IVUS results were statistically significant, proving the maintained efficacy of the TAXUS stent with direct stenting. Although MACE was reduced from 19.2% to 4.3%, this trend did not reach statistical significance due to the small number of patients. For abbreviations see Table 1.

Tabelle 3. Vergleich der 6-Monats-Ergebnisse der Patienten, die entweder einen TAXUS oder einen unbeschichteten Kontrollstent nach direkter Implantation erhielten. Die Unterschiede hinsichtlich der angiographischen und IVUS-Ergebnisse waren statistisch signifikant und belegen die unveränderte Wirksamkeit des TAXUS-Direkt-Stentings. Obwohl MACE deutlich von 19,2 % auf 4,3 % reduziert wurde, erreichte dieses Ergebnis aufgrund der niedrigen Patientenzahl nicht das statistische Signifikanzniveau. Erklärung der Abkürzungen siehe Text.

Efficacy measures	Direct TAXUS	Direct control	Difference [95% CI]	p-value
Clinical procedural success	100% (23/23)	96.2% (25/26)	3.8% [–3.5%, 11.2%]	1.0000
6-month MACE	4.3% (1/23)	19.2% (5/26)	–14.9% [–32.2%, 2.4%]	0.1944
• Death	0.0% (0/23)	0.0% (0/26)	0.0% [0.0%, 0.0%]	Undef.
• Q-wave MI	0.0% (0/23)	3.8% (1/26)	–3.8% [–11.2%, 3.5%]	1.0000
• Non-Q-wave MI	0.0% (0/23)	3.8% (1/26)	–3.8% [–11.2%, 3.5%]	1.0000
• TVR, overall	4.3% (1/23)	15.4% (4/26)	–11.0% [–27.2%, 5.1%]	0.3532
– TVR, non-TLR	0.0% (0/23)	0.0% (0/26)	0.0% [0.0%, 0.0%]	Undef.
– TVR, TLR	4.3% (1/23)	15.4% (4/26)	–11.0% [–27.2%, 5.1%]	0.3532
– TVR, CABG	0.0% (0/23)	3.8% (1/26)	–3.8% [–11.2%, 3.5%]	1.0000
6-month restenosis (QCA)				
• Analysis segment	4.3% (1/23)	30.8% (8/26)	–26.4% [–46.0%, –6.8%]	0.0256
• Stented segment	0.0% (0/23)	26.9% (7/26)	–26.9% [–44.0%, –9.9%]	0.0105
6-month % stented segment net volume obstruction (IVUS)	5.61 ± 7.91 (22) (0.00, 31.46)	22.50 ± 21.62 (24) (0.00, 77.07)	–16.88 [–26.46, –7.31]	0.0012
6-month QCA				
• RVD (mm)	2.67 ± 0.41 (23) (1.71, 3.63)	2.78 ± 0.54 (26) (1.95, 3.67)	–0.11 [–0.38, 0.16]	0.4323
• MLD (mm)	2.13 ± 0.40 (23) (1.20, 2.81)	1.85 ± 0.73 (26) (0.61, 3.26)	0.27 [–0.06, 0.61]	0.1175
• Diameter stenosis (%)	19.92 ± 10.11 (23) (4.00, 39.00)	34.30 ± 19.62 (26) (11.00, 72.33)	–14.38 [–23.30, –5.47]	0.0027
• Late loss (mm)	0.33 ± 0.30 (23) (–0.08, 1.21)	0.80 ± 0.62 (26) (–0.41, 2.19)	–0.47 [–0.75, –0.19]	0.0018

among CS patients (p = 0.29; relative risk = 1.2; 95% CI = 0.8–1.6). The combined incidence of death or MI at 1 year was 9.0% in the DS group and 7.0% in the CS group (p = 0.28) [23]. In this study, the Multi-Link stent (Guidant) was used in 54.8/59.5% (DS/CS), the AVE stent (Medtronic) in 22.4/19.8%, the Bx Velocity stent (Cordis, J&J) in 15.1/11.5%, the BiodivYsio stent (Biocompatibles) in 5.8/7.7%, and the BeStent (Medtronic) in 1.9/1.5%.

In unselected patients, direct stent implantation could be achieved in 80% of the cases [16]. If patients with noncalcified lesions were selected, direct stent deployment was possible in 97% of the cases [12]. In another study excluding patients with severe coronary calcifications and/or tortuosity of the lesion or the segment proximal to the lesion, direct stenting was successful in 96% of the patients [7]. With newer stent technologies, direct stenting also became feasible in patients with tortuous coronary artery lesions, calcified lesions and severe narrowings [27, 46] with success rates up to 98.5% [23].

Cost Saving with Direct Stenting

In a smaller prospective randomized study in patients with a single, noncalcified lesion in native coronary vessels, the procedural costs were significantly lower than those observed for patients treated conventionally [12]. The mean number of balloons was 1.4 ± 0.7 in the predilatation and 0.3 ± 0.7 in the direct stenting group [12]. In another study, direct stenting significantly reduced total procedural costs from € 2,210 ± 803 to € 1,305 ± 363 [7]. In the PREDICT trial, the decrease in angioplasty balloon use was 0.6 versus 1.3 balloons/case [5]. In the Brazilian study, direct stenting was associated with decreased use of balloons (0.15 vs. 1.09 balloons/lesion treated) [8], comparable to the significant reduction in the need of balloons in the ISAR-DIRECT trial from 1.4 ± 0.6 to 0.6 ± 0.5 [23]. The impact of direct stenting on needed contrast volume is not clear: while a decreased use of contrast dye from 255 ± 110 to 183 ± 96 ml was reported [7], contrast volumes in the Brazilian study did not differ between groups [8], as they did in the ISAR-DIRECT trial with 361 ± 136 ml in the DS versus 360 ± 141 ml in the CS group [23]. In the VELVET study, the cumulative costs up to 9 months revealed a trend towards mean savings of € 362 per patient in favor of the direct stenting strategy [40]; while in the BET Study, direct stenting conferred a dramatic reduction in procedure-related cost ($ 956.4 ± 352.2 vs. $ 1,164.6 ± 383.9; p < 0.0001) [9].

Table 4. Comparison of patients receiving the TAXUS or the bare control stent after predilatation. The differences regarding MACE, angiographic and IVUS results were statistically significant, proving the known efficacy of the TAXUS stent in the subgroup after predilatation. For abbreviations see Table 1.

Tabelle 4. Vergleich der 6-Monats-Ergebnisse bei Patienten, die entweder einen TAXUS oder einen unbeschichteten Kontrollstent nach Vordehnung erhielten. Die Unterschiede hinsichtlich MACE, angiographischer und IVUS-Ergebnisse waren statistisch signifikant und dokumentierten die bekannte Wirksamkeit des TAXUS-Stents in der Untergruppe nach Vordehnung. Erklärung der Abkürzungen siehe Text.

Efficacy measures	Predilatation TAXUS	Predilatation control	Difference [95% CI]	p-value
Clinical procedural success	97.0% (227/234)	94.2% (228/242)	2.8% [–0.9%, 6.5%]	0.1807
6-month MACE	7.5% (17/227)	19.1% (45/235)	–11.7% [–17.7%, –5.6%]	0.0003
• Death	0.0% (0/227)	0.4% (1/235)	–0.4% [–1.3%, 0.4%]	1.0000
• Q-wave MI	0.0% (0/227)	0.0% (0/235)	0.0% [0.0%, 0.0%]	Undef.
• Non-Q-wave MI	1.8% (4/227)	4.3% (10/235)	–2.5% [–5.6%, 0.6%]	0.1738
• TVR, overall	6.2% (14/227)	15.7% (37/235)	–9.6% [–15.2%, –4.0%]	0.0010
– TVR, non-TLR	2.2% (5/227)	2.6% (6/235)	–0.4% [–3.1%, 2.4%]	1.0000
– TVR, TLR	3.1% (7/227)	13.2% (31/235)	–10.1% [–15.0%, –5.2%]	< 0.0001
– TVR, CABG	0.9% (2/227)	0.4% (1/235)	0.5% [–1.0%, 1.9%]	0.6178
6-month restenosis (QCA)				
• Analysis segment	4.8% (11/227)	20.8% (49/236)	–15.9% [–21.8%, –10.0%]	< 0.0001
• Stented segment	1.3% (3/227)	17.9% (42/235)	–16.6% [–21.7%, –11.4%]	< 0.0001
6-month % stented segment net volume obstruction (IVUS)	7.95 ± 9.84 (208) (–0.05, 58.43)	21.82 ± 17.03 (220) (–0.00, 75.78)	–13.87 [–16.53, –11.22]	< 0.0001
6-month QCA				
• RVD (mm)	2.78 ± 0.41 (226) (1.90, 4.14)	2.62 ± 0.43 (233) (1.59, 4.12)	0.16 [0.08, 0.23]	< 0.0001
• MLD (mm)	2.28 ± 0.43 (227) (0.00, 3.39)	1.77 ± 0.53 (236) (0.00, 3.02)	0.51 [0.43, 0.60]	< 0.0001
• Diameter stenosis (%)	17.67 ± 10.89 (227) (–3.00, 100.00)	32.52 ± 17.32 (235) (–9.00, 100.00)	–14.85 [–17.50, –12.20]	< 0.0001
• Late loss (mm)	0.28 ± 0.36 (225) (–0.54, 2.20)	0.77 ± 0.45 (236) (–0.11, 2.63)	–0.50 [–0.57, –0.42]	< 0.0001

Reduction of Procedure Time and Radiation Exposure with Direct Stenting

Radiation hazards are always an important issue in interventional cardiology [21, 24]. Omitting predilatation could substantially reduce the radiation exposure time.

Direct stenting reduced procedural time significantly from 59 ± 23 to 41 ± 20 min with a concomitant significant reduction in fluoroscopy time from 11 ± 7 to 7 ± 3 min [12]. In another study, radiation exposure time was also significantly reduced from 12.6 ± 7.6 min in conventional stent procedures to 8.7 ± 5.1 min with direct stenting [16]. In another study, direct stenting significantly reduced both, procedural time from 64 ± 46 to 45 ± 21 min and radiation exposure time from 16 ± 10 to 12 ± 9 min [7]. In the BET study, direct stenting significantly reduced the duration of the procedure from 635 ± 390 to 424 ± 412 s [9]. And in the DISCO trial, fluoroscopy and procedural time were significantly lower in direct stenting (6.4 ± 0.3 and 21 ± 0.9 min) than in predilated stenting (9.1 ± 0.4 and 27.5 ± 1.1 min) [22]. Similar results were obtained in a study matching a variety of "everyday patients" with and without predilatation [10]. In the just presented DIRECT-study (see below), procedural times were significantly shorter in the direct-stenting group (33 min vs. 45 min, $p < 0.01$).

On the other hand, in the PREDICT trial, there were only modest (approximately 10%) savings in fluoroscopy time [5]. In the Brazilian study, fluoroscopy time did not differ between both groups [8], like in the ISAR-DIRECT-trial with 12.5 ± 9.3 min in the DS versus 11.7 ± 7.9 min in the CS group, with identical procedure times (59.9 ± 27.3 vs. 59.3 ± 24.5 min) [23].

Direct Stenting with Drug-Eluting Stents

As this subanalysis has shown, direct stenting with TAXUS is as safe and effective as stenting with TAXUS after predilatation (Tables 1 to 4). Other data on direct stenting with drug-eluting stents are scarce: in the two pivotal studies with a clinical primary endpoint for the Taxus (TAXUS-IV [48]) and the Cypher (SIRIUS [25]) stents, direct stenting was not allowed. In E-SIRIUS [36] and C-SIRIUS [34], direct stenting, was allowed and left at the operator's discretion. In E-SIRIUS, direct stenting was performed in 26% [36], in C-SIRIUS in 31% of the cases [34]. The use of direct stenting in E-SIRIUS and C-SIRIUS may also have limited proximal edge trauma and subsequent restenosis in some patients [34]. The detailed results of the nonrandomized prespecified subgroup analysis of direct stenting in the E-SIRIUS study have been presented orally [35]: in the sirolimus group, 45 patients underwent direct stenting,

whereas 130 were predilated. After direct stenting, the in-stent MLD at eight months (= the primary endpoint of E-SIRIUS) was significantly increased from 1.36 to 2.30 mm with a mean reduction of late loss from 1.04 to 0.13 mm. After predilatation, the in-stent MLD at eight months was significantly increased from 1.31 to 2.19 mm with a mean reduction of late loss from 1.05 to 0.23 mm. One subacute stent thrombosis occurred in the sirolimus directly stented group and one in the sirolimus predilated group.

Just recently, another study for direct stenting with Cypher was presented as a late-breaking trial at the ACC March 7th 2004: the DIRECT-study (J. Moses et al.) compared the eight-months angiographic results (in-lesion late loss as primary endpoint) and six-months clinical follow-up in 225 patients treated with direct stenting with that of 412 historical controls who underwent predilatation in the SIRIUS trial. The eight-months binary restenosis rate was not different in-stent (3.6% vs. 3.2% for direct vs. predilatation) but showed a trend toward improved binary restenosis rates in-lesion (6.0% vs. 9.1%, $p = 0.30$). This trend was particularly strong in patients with small vessel sizes (8.3% vs. 18.3%, $p = 0.12$) and in patients with insulin-dependent diabetes, in whom the benefits of direct stenting were statistically significant, although the patient numbers were small with 14 patients directly stented and 20 after predilatation (0% vs. 35%, $p = 0.03$). The overall MACE rate at six months showed a nonsignificant positive trend for direct stenting (2.2% vs. 4.9%, $p = 0.21$). In this nonrandomized study using a historical control, the mean lesion length in the direct group, however, was significantly lower than in the predilatation group (12.4 mm vs. 14.7 mm, $p < 0.0001$) and mean stent/lesion ratio was significantly higher in the direct group (2.1 vs. 1.6, $p = 0.001$). There were no significant differences in stent thrombosis rates at six months between the two groups (0.4% vs. 0.2%, $p = 0.70$)

To date, an evidence-based improvement of clinical outcome has been shown only for the sirolimus-eluting Cypher and the paclitaxel-eluting TAXUS stents, with a level of recommendation of I B each [44]. Both stents release their drug from a polymer carrier.

Study Limitations

The major limitation of the present study is that it is a nonrandomized post hoc subgroup analysis. The criteria for selecting patients suitable for primary stenting were subjective and not part of a protocol. Therefore, an intrinsic bias cannot be ruled out, preferring patients with no or less calcified lesions and less tortuous vessels. This may explain the trend for a lower MACE rate (4.3% vs. 7.5%) and a lower in-stent restenosis rate (0.0% vs. 1.3%) in the directly stented TAXUS group (Table 1). Direct stent implantation without predilatation is more demanding than the conventional procedure, and more experience is required with the decision for direct stenting [7]. More data is needed to verify the impact of direct stenting with drug-eluting stents on restenosis rates and long-term clinical outcomes. Preferably, randomized trials of direct stenting versus stenting after predilatation with drug-eluting stents are warranted.

Conclusion

Comparison of patients receiving TAXUS stents with or without predilatation revealed no differences in clinical, angiographic or IVUS parameters at six months. This suggests that direct stenting with the polymer-based paclitaxel-eluting TAXUS stent is feasible, safe and equally effective with or without predilatation.

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