Inhibition of Restenosis With a Paclitaxel-Eluting, Polymer-Free Coronary Stent

The European evaLUation of pacliTaxel Eluting Stent (ELUTES) Trial

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Background—The use of a stent to deliver a drug may reduce in-stent restenosis. Paclitaxel interrupts the smooth muscle cell cycle by stabilizing microtubules, thereby arresting mitosis.

Methods and Results—On the basis of prior animal studies, the European evaLUation of the pacliTaxel Eluting Stent (ELUTES) pilot clinical trial (n=190) investigated the safety and efficacy of V-Flex Plus coronary stents (Cook Inc) coated with escalating doses of paclitaxel (0.2, 0.7, 1.4, and 2.7 µg/mm² stent surface area) applied directly to the abluminal surface of the stent in de novo lesions compared with bare stent alone. The primary efficacy end point was angiographic percent diameter stenosis at 6 months. At angiographic follow-up, percent diameter stenosis was 33.9±26.7% in controls (n=34) and 14.2±16.6% in the 2.7-µg/mm² group (n=31; P=0.006). Late loss decreased from 0.73±0.73 to 0.11±0.50 mm (P=0.002). Binary restenosis (≥50% at follow-up) decreased from 20.6% to 3.2% (P=0.056), with no significant benefit from intermediate paclitaxel doses. Freedom from major adverse cardiac events in the highest (effective) dose group was 92%, 89%, and 86% at 1, 6, and 12 months, respectively (P=NS versus control). No late stent thromboses were seen in any treated group despite clopidogrel treatment for 3 months only.

Conclusions—Paclitaxel applied directly to the abluminal surface of a bare metal coronary stent, at a dose density of 2.7 µg/mm², reduced angiographic indicators of in-stent restenosis without short- or medium-term side effects. (Circulation. 2004;109:487-493.)

Key Words: stents • restenosis • paclitaxel

Percutaneous coronary intervention (PCI) with stents has become an accepted method for treating atheromatous coronary artery disease,1,2 reducing the incidence of clinical restenosis to <20%. However, in-stent restenosis due to tissue growth remains a therapeutic problem, particularly in certain subgroups,3 and restenosis almost wholly accounted for the advantage of surgery over stenting in the ARTS (Arterial Revascularization Therapies Study) trial.4

Prevention of recurrence may be possible by delivery of a drug via the stent to inhibit the proliferative process locally, thereby reducing systemic side effects. Studies in vitro and in animal models demonstrated that paclitaxel, which enhances polymerization of cellular microtubules and thus prevents mitosis and cell migration, reduced restenosis when delivered locally.5–7 Here, we report the European evaLUation of pacliTaxel Eluting Stent (ELUTES) trial, a multicenter, randomized, controlled, and triple-blinded clinical study designed to evaluate the efficacy (and safety) of a paclitaxel-eluting stent across a range of paclitaxel dose densities. The null hypothesis was that deployment of either bare metal stents or stents loaded with 4 doses of paclitaxel results in no difference in percent diameter stenosis at 6 months either between these doses or compared with controls.

Methods

V-Flex Plus coronary stents (Cook Inc) coated with paclitaxel applied to the abluminal bare metal surface by a proprietary process at 4 dose densities (0.2, 0.7, 1.4, and 2.7 µg/mm² stent surface area)
were compared with uncoated stents. Consenting patients with single de novo type A or type B1 lesions <15 mm length in a native coronary artery, who were candidates for coronary surgery if required, were entered into the study, and data were captured on standardized case report forms. Patients were excluded if they exhibited left ventricular ejection fraction <35%, were enrolled in another trial, were women of childbearing potential, had limited life expectancy, had hyperensensitivity to contrast or current antiplatelet therapy, had a history of bleeding diathesis or coagulopathy or would refuse blood transfusions, had myocardial infarction <72 hours previously, had chronic total occlusions, or had unprotected left main stenosis. Stents (16 mm long and 3.0 or 3.5 mm in diameter) were used in a predefined computer-generated tabulated random order, which ensured near-equal numbers in each of the 5 arms. The study was triple blinded (patient, interventionist, and angiographic core laboratory) and was overseen by a Data Safety Monitoring Board and Clinical Events Committee. An independent core laboratory (caas II system for dural and follow-up angiograms. Analysis included measurement to ensure identical follow-up image acquisition. Investigators reported Careful note was taken of procedural projection and table height to Intracoronary nitrate was administered before image acquisition. Careful note was taken of procedural projection and table height to ensure identical follow-up image acquisition. Investigators reported lesion morphology, side-brach involvement, dissections, and TIMI (Thrombolysis In Myocardial Infarction) flow. A blinded independent angiographic core laboratory used the CAAS II system for standard quantitative coronary angiography analysis of periprocedural and follow-up angiograms. Analysis included measurement to 5 mm beyond the stent edges to account for any so-called edge effect.

Study Power and Statistical Analysis
To show reduction in 6-month angiographic %DS from 35% to 20% (with P<0.05 and 80% power), a minimum of 32 patients per group were required, with any 1 dose compared with control. Statistical analyses were prespecified and performed with Systat version 10 (SPSS). Continuous variables (%DS, minimal luminal diameter, and late loss) are reported as mean and SD. Standard ANOVA was used to analyze differences in continuous variables across the 5 groups. Multiple pairwise comparisons were performed between the groups with the Bonferroni correction to adjust for type I error. Dichotomous variables were reported in percent, and group-wise comparisons were performed with a Pearson’s χ2 test or Fisher exact test. All analysis was performed on an intention-to-treat basis that used all patients with available follow-up data.

Results

Patient Demographics and Characteristics
Between January 2000 and April 2001, 192 patients were enrolled, but for technical reasons, the stent could not be deployed in 2 patients. Of the 190 stented patients, 38 were randomized to control, and 37, 39, 37, and 37 patients were randomized to the paclitaxel-eluting stent groups (lowest- to highest-dose-density group, respectively). There were no significant baseline differences between groups, except for age (patients in the 0.2 μg/mm2 group were significantly older than those in the 2.7 μg/mm2 group [P=0.022]; Table 1). Lesion characteristics per group are shown in Table 1, with no difference between groups in lesion site or complexity (primarily B1), and most treated vessels were mildly tortuous and mildly calcified. There were no significant differences between groups in reference vessel size (2.90 to 3.03 mm) at baseline, and all lesions were of at least moderate severity (Table 2). Procedural data are presented for the 190 stented patients, and follow-up data are presented for all patients for whom they were available. Ten of the 190 patients required additional nonstudy stents (control, 2; 0.2 μg/mm2, 2; 0.7 μg/mm2, 2; 1.4 μg/mm2, 1; and 2.7 μg/mm2, 1).

Clinical and Angiographic Follow-Up at 6 Months
The mean time for 6-month angiographic follow-up was 187±18 (range 113 to 259) days. At 6 months follow-up, 1 patient had died (2.7 μg/mm2 group), and 14 patients had refused angiographic follow-up, with relatively even distribution among groups (control, 3; 0.2 μg/mm2, 3; 0.7 μg/mm2, 4; 1.4 μg/mm2, 2; and 2.7 μg/mm2, 2; Figure 1).

Angiographic Outcome
Six-month quantitative coronary angiography demonstrated benefit in the highest-dose-density group. %DS was 14.2±16.6% in the 2.7 μg/mm2 group compared with 33.9±26.7% in controls (P=0.006), and late loss was 0.11±0.50 versus 0.73±0.73 mm (P=0.002; Table 2). The cumulative distribution for minimal luminal diameter for the 2.7 μg/mm2 dose is shown in Figure 2. Binary in-stent restenosis (diameter stenosis ≥50% at 6-month follow-up) was reduced from 20.6% in controls to 3.2% in the 2.7 μg/mm2 group (P=0.056). Although there were no significant differences between intermediate groups for the primary end point (%DS), multiple pairwise comparisons with Bonferroni correction demonstrated that with respect to minimum lumen diameter, the 2.7 μg/mm2 group was significantly different from the 0.2 μg/mm2 group (P=0.032) and from the 0 μg/mm2 (control) group (P=0.014). Additionally, the late loss index in both the 2.7 and 1.4 μg/mm2 treatment groups was significantly less than both the control group and the 0.2 μg/mm2 group (2.7 μg/mm2 versus control, P=0.022; 2.7 μg/mm2 versus 0.2 μg/mm2, P=0.032; 1.4 μg/mm2 versus control, P=0.016). A trend to benefit with escalating doses was observed (Table 2; Figure 3).

Safety and Efficacy Data
There were no 30-day major adverse coronary events (MACE) in intermediate-dose groups. In the 2.7 μg/mm2 group, there were 3 events: a non–Q-wave infarct (day 0), a
stent thrombosis (day 8), and a death at day 10. There was 1 subacute stent thrombosis in the control group. Between 1 and 6 months, there were no additional deaths, bypass grafting, or Q-wave myocardial infarctions. One additional non–Q-wave myocardial infarction occurred in the 0.7 g/mm² dose group. There were 4 symptom-driven target-lesion revascularizations (TLRs) in the control group, 1 in the 0.2 g/mm² dose treatment group, 3 in the 1.4 g/mm² group, and 1 in the 2.7 g/mm² group who did not have binary in-stent restenosis but required the reintervention at 183 days for symptomatic persistent restenosis. The 1 patient in the 2.7 g/mm² dose treatment group who did have angiographic binary restenosis did not require reintervention. There were no further stent thromboses at 6 months.

One-Year Clinical Follow-Up

Between 6 and 12 months, there were no additional deaths, stent thromboses, or myocardial infarcts in any group. Bypass surgery was performed in 1 patient in each of the control and 0.7 g/mm² dose groups. One additional target lesion revascularization (PCI) was undertaken for persistent restenosis in the 2.7 g/mm² dose group and 1 for in-stent restenosis in the controls. Thus, at 12 months, there were 6 TLRs (16%) in controls and 2 (5%) in the 2.7 g/mm² group. Freedom from MACE was 82% in controls versus 86% in the highest-dose group (P=NS; Table 3). Despite the apparent higher event rate at lower concentrations of paclitaxel, all pairwise comparisons were nonsignificant.

Discussion

The processes that lead to neointimal hyperplasia after stenting are well understood.8,9 This tissue growth results in a 10% to 15% need for reintervention, with certain subgroups at an even higher risk of restenosis reaching rates of 45% if risks are combined.3,10–14 Paclitaxel is currently used primarily as systemic chemotherapy.15 It promotes stability of microtubules, and cell replication is inhibited in the G0/G1 and G2/M phases. Cell motility, shape, and transport between organelles may also be affected.

Preclinical data suggest paclitaxel has beneficial effects on the vessel response to injury. In animal models, late loss and intimal area are significantly reduced,6,7,16–18 but there is also an unwanted dose-dependent inhibition of reendothelialization,19 and additional adverse effects have been shown at high doses.7 In 1 study, stents coated with a cross-linked biodegradable polymer and loaded with different doses of paclitaxel reduced mean intimal thickness by 49% and 36% at doses of 42.0 and 20.2 µg per stent at 28 days but were associated with persistent intimal fibrin deposition, intrainti-
mal hemorrhage, and increased intimal and adventitial inflammation. We believed, therefore, that a dose-finding (efficacy and safety) human pilot study of paclitaxel-eluting stents was warranted, especially because available animal data failed to specify which dose may be beneficial. Further preclinical considerations included uncertainty about the impact of “release rates” in humans, not least because this trial involved the use of pure drug on the stent (ie, no polymer to modulate the release of the drug). As such, there was no release rate per se. Because the paclitaxel is in direct contact with the tissue, uptake is determined by the rate at which the drug crosses the cell membrane. In-house animal data showed

<table>
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<th>Paclitaxel Dose Density, µg/mm²</th>
<th>0 (Control)</th>
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<th>0.7</th>
<th>1.4</th>
<th>2.7</th>
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<td>37</td>
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<td>39</td>
<td>37</td>
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<tr>
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<td>3</td>
<td>4</td>
<td>2</td>
<td>6</td>
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<tr>
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<td>35</td>
<td>37</td>
<td>31</td>
</tr>
<tr>
<td>Angiographic Binary Restenosis (％DS ≥50):</td>
<td>7 (20.6%)</td>
<td>7 (20.6%)</td>
<td>5 (14.3%)</td>
<td>5 (13.5%)</td>
<td>1 (3.2%)</td>
</tr>
</tbody>
</table>

**Figure 1.** Trial patient flow chart. F/U indicates follow-up; endpt, end point; SAT, subacute thrombosis; and NQMI, non–Q-wave myocardial infarction.
that the amount of drug remaining on the stent was 72±7% at 4 hours, 53±10% at 4 days, and 31±13% at 14 days. Preclinical data indicated that immediate, 1-week, and 1-month estimation of systemic blood paclitaxel was less than the sensitivity of the assay (20 to 40 ng/mL) even at the highest total dose (60 µg).

The ELUTES trial was therefore primarily a dose-evaluation study. Although it was unclear from animal models which dose would be beneficial in humans, we wished to stay below the maximum doses tested by the National Institutes of Health group7 that caused fibrin deposition and hemorrhage in the vessel wall. One group loaded paclitaxel by dipping the stent in ethanol/paclitaxel and then air-drying it, resulting in crystalline paclitaxel being deposited in uneven clumps.7 Furthermore, the Palmaz-Schatz stent used in these studies was structurally different from ours. Not withstanding these differences, compared with the stent we planned to use in ELUTES, their top dose (total dose 187 µg) was considered potentially “toxic,” and therefore the doses chosen for ELUTES were set at levels well below this, with a maximum total dose of 60 µg (2.7 µg/mm²). It might be argued that an abluminal dose of 60 µg is equivalent to 120 µg on both sides of the stent, and this is thus close to the dose loaded by Heldman’s group. However, even taking account of the lipophilic nature of the drug, which encourages tissue deposition, we believed that a 60-µg abluminal dose was still well within the 90 µg per stent side dose used by Heldman.

Given the potential toxicity of paclitaxel, it is encouraging that ELUTES demonstrated clinical safety, with reendothelialization appearing to have occurred, illustrated by the lack of late subacute thrombosis despite only 3 months of clopi-
this patient had no event. Therefore, for the highest-dose group, even with the patients with unevaluable angiograms at 6 months counted to allow for worst outcomes, there is no evidence that efficacy was associated with adverse MACE with this dose. Although not powered for clinical outcome, it is interesting that at 1 year, 2 clinically driven TLRs (PCI) were needed in the highest-dose group (5.4%), but 6 (5 PCIs and 1 CABG) were required in the control group (15.7%). The TLRs in the ELUTES highest-dose group were required for progression of disease outside and proximal to the stent (perhaps the consequence of using a 16-mm stent on a 20-mm balloon). All control-group TLRs were for diffuse restenosis within the stent itself.

The biological potency of the treatment was such that despite the planned angiographic numbers not being available in the highest-dose group, significant differences were reached, with a probability value of 0.006 (a 20% difference). Although angiographic loss to follow-up is always concerning, trial robustness in a blinded, randomized study such as ELUTES is supported by having independent safety and efficacy, data handling, and angiographic committees, and clinical follow-up was 100%. It is difficult to deal with missing angiographic quantitative data, but if all the unevaluable patients in the high-dose group were assumed to have developed binary restenosis (ie, diameter stenosis >50%) and all the unevaluable patients in the control group were assumed not to have been, then the unsubstantiated “worse case” for this trial would be 7 (18.9%) of 37 for the 2.7 μg/mm² dose density in ELUTES. The control and highest-dose diameter stenoses at follow-up were 33.9% and 14.1% (ELUTES) and 39% and 14% (ASPECT), showing similar biological responses despite different overall amounts of drug delivered (Figure 3) and indicating that dose density is more important than overall concentration or total dose.

The absence of polymer may or may not be an advantage. Although polymer may facilitate higher and more even drug delivery, the amount of drug delivered to the tissue may be governed more by the character of the tissue being targeted and the lipophilic nature of the agent. In this study, a “depot” of drug was sandwiched between stent and tissue and appeared to be effective on the basis of the various parameters of measured restenosis. Additionally, absence of polymer overcomes any concerns regarding its potential inflammatory or prothrombogenic effects.

There have been concerns regarding paclitaxel inhibition of reendothelialization, with its associated excess thrombotic risk. In ELUTES, there was no significant difference in the MACE-free rate between groups, although the study was not powered to demonstrate clinical benefit. Importantly, despite no antiplatelet therapy between 3 and 6 months, no stent thromboses occurred, unlike the Study to COmpare REsteno-sis between QueST and QuaDS-QP2 (SCORE),22 which used a large dose of paclitaxel derivative (4000 μg) and was stopped because of excess stent thromboses.

After completion of the ELUTES study, the RX Achieve Drug ELuting coronary stent systems In the treatment of patients with de NoVo nativE coronaRy lesions (DELIVER I),24 trial was undertaken with the trial dose based on the ELUTES highest dose, and the results have been presented in abstract form. It compared a 3.0 μg/mm² dose with controls in 1043 patients with target de novo lesions ≤25 mm. Although in-stent late loss was significantly less for the paclitaxel-loaded stent (0.81 versus 0.98 mm, P<0.003), this was clearly higher in the treated group than we have measured in ELUTES and was not low enough to drive a difference in angiographic restenosis (16.7% versus 22.4%, P=0.15). There were trends toward fewer TLRs (8.1% versus 11.3%) and repeat PCIs (7.0% versus 10.3%) in the paclitaxel group, but target-vessel failure, the primary end point, was not significantly different (11.9% versus 14.5%, P=0.13). The reasons for the success of ELUTES and failure of DELIVER are still being explored, but it has been suggested by the Principle Investigator O’Neill that it may relate to nonuniform use of glycoprotein IIb/IIIa inhibitors across groups and the presence of longer lesions.24 Additionally, the use of a different stent or a change in the facility for loading could have led to an inability to accurately load the stent with the effective (ELUTES) dose. It would appear from the late loss that not enough drug may have been loaded.

Paclitaxel, considering the ELUTES and Treatment of de novo coronary disease using a single pAclitaXel eULting Stent (TAXUS) trials and despite the DELIVER I results, is the second agent shown to benefit the vessel-wall response to stent trauma, the first being sirolimus in the RAVEL (Ran-domized study with the sirolimus-eluting Bx VElocity balloon-expandable stent in the treatment of patients with de novo coronary Lesions) trial.25 Recent studies have tested both sirolimus (SIRIUS; a multicenter randomized double-blind study of the SIRolImUS-coated Bx Velocity stent in the treatment of patients with de novo coronary lesions) and paclitaxel (TAXUS II) in slightly more complex lesions, and efficacy has been reported recently, extending the biological robustness of these agents. However, drug-eluting stents with these or other agents still need to be studied in patients with lesions at highest risk of restenosis, and longer-term uncertainty about the outcome for any of these agents justifies extended follow-up. Furthermore, the long-term importance
of the presence of polymer once the drug has eluted has yet to be evaluated in trials that have used this technology.

Conclusions
Available data suggest that local treatment of the target site with an antiproliferative drug may reduce restenosis. The ELUTES trial demonstrates that paclitaxel can be applied directly to a stent, and eluting from it significantly improves 6-month angiographic outcome. Paclitaxel in effective doses has a safety profile similar to control. Future study is warranted to address longer-term aspects of coated-stent technology for the elimination of restenosis.

Appendix

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References
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