European Heart Journal (2001) **22,** 1938–1947
doi:10.1053/euhj.2001.2627, available online at http://www.idealibrary.com on IDEAL®

The TRAPIST Study

A multicentre randomized placebo controlled clinical trial of trapidil for prevention of restenosis after coronary stenting, measured by 3-D intravascular ultrasound

P. W. Serruys[1], D. P. Foley[1], M. Pieper[2], J. A. Kleijne[3] and P. J. de Feyter[1] on behalf of the TRAPIST investigators

[1]*Department of Interventional Cardiology, Thoraxcenter, Erasmus Medical Center, Rotterdam, The Netherlands;* [2]*Heartcenter Bodensee, Kreuzlingen, Switzerland; and* [3]*Cardialysis, Rotterdam, The Netherlands*

Background Studies have reported benefit of oral therapy with the phosphodiesterase inhibitor, trapidil, in reducing restenosis after coronary angioplasty. Coronary stenting is associated with improved late outcome compared with balloon angioplasty, but significant neointimal hyperplasia still occurs in a considerable proportion of patients. The aim of this study was to investigate the safety and efficacy of trapidil 200 mg in preventing in-stent restenosis.

Methods Patients with a single native coronary lesion requiring revascularization were randomized to placebo or trapidil at least 1 h before, and continuing for 6 months after, successful implantation of a coronary Wallstent. The primary end-point was in-stent neointimal volume measured by three-dimensional reconstruction of intravascular ultrasound images recorded at the 6 month follow-up catheterization.

Results Of 312 patients randomized at 21 centres in nine countries, 303 (148 trapidil, 155 placebo) underwent successful Wallstent implantation, and 139 patients (90%) in the placebo group and 130 (88%) in the trapidil group had repeat catheterization at 26 ± 2 weeks. There was no significant difference between trapidil and placebo-treated patients regarding in-stent neointimal volume ($108{\cdot}6 \pm 95{\cdot}6\ mm^3$ vs $93{\cdot}3 \pm 79{\cdot}1\ mm^3$; $P=0{\cdot}16$) or % obstruction volume ($38 \pm 18\%$ vs $36 \pm 21\%$; $P=0{\cdot}32$), in angiographic minimal luminal diameter at follow-up ($1{\cdot}63 \pm 0{\cdot}61$ mm vs $1{\cdot}74 \pm 0{\cdot}69$ mm; $P=0{\cdot}17$), restenosis rate (31% vs 24%; $P=0{\cdot}24$), cumulative incidence of major adverse cardiac events at 7 months (22% vs 20%; $P=0{\cdot}71$) or anginal complaints (30% vs 24%; $P=0{\cdot}29$).

Conclusion Oral trapidil 600 mg daily for 6 months did not reduce in-stent hyperplasia or improve clinical outcome after successful Wallstent implantation and is not indicated for this purpose.
(Eur Heart J 2001; 22: 1938–1947, doi:10.1053/euhj.2001.2627)

Key Words: Restenosis, stent, trapidil, intravascular ultrasound, quantitative coronary angiography, randomized trial.

See page 1847 for the Editorial comment on this article

Introduction

Stenting reduces restenosis and repeat revascularization compared with balloon angioplasty in selected patients with single vessel coronary artery disease[1,2]. With increased rates of stent use and application to complex and multivessel disease, however, in-stent restenosis may be observed in up to one third of patients[3] and due to its indolence, prevention using effective antiproliferative measures remains a high priority.

The phosphodiesterase inhibitor, trapidil, a potent inhibitor of platelet derived growth factor and thromboxane A2 synthetase, inhibits cellular proliferation induced by platelet derived growth factor in-vitro and in-vivo[4–6] and was reported to reduce restenosis after coronary balloon angioplasty[7,8]. However, since post-angioplasty restenosis involves both rheologic and proliferative processes[9], we sought to evaluate the antiproliferative potential of trapidil post-stenting, using the

Revision submitted 29 January 2001, and accepted 31 January 2001.

Study supported by UCB SA, Brussels, Belgium.

Correspondence: Prof. P. W. Serruys, Erasmus Medical Center, Thoraxcenter Bd 408, Dr.Molewaterplein 40, 3015 GD Rotterdam, The Netherlands.

0195-668X/01/201938+10 $35.00/0

novel, recently described methodological approach of 3-D intravascular ultrasound measured in-stent neointimal volume as the primary end-point[10].

Methods

Primary end-point

Based on an expected in-stent neointimal volume of 125 mm^3 for Wallstents of 30 mm length[10–14], it was calculated that 240 evaluable patients would be necessary to detect a 30% reduction by trapidil, with 90% power (1-β), at two sided α of 0·05.

Study population

Patients with stable or unstable angina and/or documented ischaemia, scheduled to undergo single Wallstent implantation in a de novo coronary lesion $\leq$40 mm long in a vessel of 3–6 mm could be included. Exclusion criteria included: life expectancy <1 year, myocardial infarction within 7 days, left bundle branch block, side branch >2·0 mm, thrombus and left main lesion; those specific to trapidil therapy were: active peptic disease, bleeding disorder, stroke within 6 months and treatment with oral anticoagulants, ketanserin, ticlopidine, pentoxyphilline, calcium antagonists and molsidomine. The protocol was approved by the ethical board of participating hospitals and all patients gave written informed consent prior to inclusion.

Medication and stent implantation

A loading dose of ticlopidine (500–1000 mg) was given 12–48 h before stenting, and continued at 500 mg daily for 1 month. A minimum of 1 h before, one tablet of trial medication was administered (to allow Cmax serum level at the time of barotrauma[15]). Aspirin 75–500 mg was continued indefinitely. After arterial access, heparin 10 000 units was given parenterally. The self-expanding coronary Magic Wallstent™ (Boston Scientific Corporation, Paris, France), was implanted after pre-dilatation and post-dilated to diameter stenosis of <20%. Intravascular ultrasound guidance was up to the treating physician, final post-procedural intravascular ultrasound being mandatory. After successful procedures, trial medication was given 8 h for 6 months, but withheld on the morning of follow-up exercise testing.

Angiographic and intravascular ultrasound procedures

Angiography in multiple projections was performed pre- and post-stenting and at the 6 month follow-up, and analysed at the angiographic core lab (Cardialysis, Rotterdam, The Netherlands) using the Cardiovascular Angiographic Analysis System (CAAS II) as described elsewhere[1,3,16]. Post-stenting and at the 6 month follow-up, stented vessel segments were examined with mechanical intravascular ultrasound (CardioVascular Imaging System (CVIS), Sunnyvale, CA, U.S.A.) using automated pullback at 0·5 mm . s^{-1}. A computer based contour detection program was used for automated 3-D reconstruction of the stented segment from up to 200 cross-sectional images. Lumen and stent boundaries are detected using a minimum cost algorithm. Total stent and lumen volumes were calculated as $V=\Sigma_{i=1}^{n} A_i \cdot H$, where V=volume, A=total vessel, stent or lumen area (as desired) in a given cross sectional image, H=thickness of the coronary artery slice, and n=number of slices[10–13]. Neointimal volume was calculated as stent volume − luminal volume.

Feasibility, reproducibility and inter- and intra-observer variability of this system have been validated in vitro and in vivo[12–14] and a prior multicentre randomized clinical trial has been performed using this methodology[10]. Where intravascular ultrasound at follow-up was not available, an imputation programme was used employing intravascular ultrasound post-procedure and quantitative coronary angiography at follow-up, to impute the intravascular ultrasound data at follow-up, as follows:

(1) Regression equations established the relationship between intravascular ultrasound and quantitative coronary angiography mean luminal and stent diameter at follow-up in all lesions with complete data.
(2) Stent length at follow-up was determined by intravascular ultrasound post-stent or quantitative coronary angiography at follow-up, also based on the r-square of regression equations applied in patients with complete data.
(3) Luminal volume=stent length * mean luminal area.
(4) Imputed stent volume=imputed stent length * imputed mean stent area.
(5) Imputed neointimal volume=imputed stent volume − imputed lumen volume.
(6) In cases of stent occlusion, it was assumed that the stent was completely filled with tissue, so neointimal volume='luminal volume'.

Imputed data were entered in the database blind before the treatment code was broken, using the following generated regression equations:

Total occlusions

[1] Imputed stent length follow-up=6·217+0·709 * Stent length post from intravascular ultrasound.
[2] Imputed mean stent area follow-up=2·353+0·916 * Mean stent area post from intravascular ultrasound.
[3] Imputed stent volume=Imputed stent length * imputed mean stent area; Imputed neointimal volume=Imputed stent volume.

Table 1 Summary of patient disposition

	Placebo	Trapidil
Randomized (safety population)	158	154
No stent implantation	3	6
Reason		
Guidewire did not cross	2	2
Lesion not suitable for stenting	1	3
Good result after balloon angioplasty	0	1
Stent implantation successful (intention-to-treat population)	155	148
No 6 month follow-up intravascular ultrasound available	33	23
Reason		
Intravascular ultrasound device could not cross	9	2
Patent vessel	4	0
Total occlusion	5	2
Technical problems intravascular ultrasound	3	5
Refused recatherization	7	11
Major adverse cardiac events	9	7
Other	5	3
Intravascular ultrasound not analysable	7	5
Analysable intravascular ultrasound at 6 months	115 (74%)	120 (81%)
Intravascular ultrasound imputation	22	11
Treatment compliance	116	104
Per protocol population	111 (72%)	102 (69%)

No total occlusion

[1] Imputed stent length follow-up=2·773+1·047 * Stent length follow-up from quantitative coronary angiography.
[2] Imputed mean stent area follow-up=2·353+0·916 * Mean stent area post from intravascular ultrasound.
[3] Imputed mean in-stent lumen diameter follow-up=0·624+0·880 * Mean lumen diameter follow-up from quantitative coronary angiography.
[4] Imputed lumen volume=2 * π * (0·5 * Mean in-stent lumen diameter)^2.
[5] Imputed stent volume=imputed stent length * imputed mean stent area.
[6] Imputed neointimal volume=imputed stent volume − imputed lumen volume.

Secondary end-points

Intravascular ultrasound measured minimum luminal diameter (mm) and minimal luminal cross-sectional area (mm^2) and quantitative coronary angiography measured minimum luminal diameter (mm) at follow-up, late loss, restenosis rate and loss index.

Clinical outcome

Major adverse cardiac events were defined as:

Cardiac death: All deaths were considered cardiac unless documented otherwise.

Myocardial infarction: Either: new abnormal Q waves (Minnesota code) not present at baseline, or elevation more than twice the upper limit of normal of CK and CK-MB.

Target lesion revascularization: Re-PTCA or CABG was required to be preceded by documentation of anginal complaints and/or objective evidence of reversible ischaemia.

Anginal status was documented at each visit and an exercise test was performed within 2 weeks prior to repeat angiography.

Treatment compliance was defined, using pill counting, by 90% intake of trial medication at 1 month and 80% at 6 months.

Analytical and statistical plan

The intention-to-treat population comprised patients undergoing successful stent implantation after at least one capsule of trial medication. The primary end-point was evaluated in patients undergoing follow-up catheterization. The per protocol population comprised patients with successful stenting and evaluable follow-up intravascular ultrasound, who were compliant with medication and follow-up.

Outcome measures were compared using chi-square or Fisher's exact test for categorical variables and two-tailed Student's t-test for continuous variables. Major adverse cardiac events are presented using the Kaplan–Meier method and compared using a logrank test.

Table 2 Baseline demographic characteristics of the intention-to-treat population

	Placebo n=155	Trapidil n=148
Male	109 (70%)	120 (81%)
Age (years)	60 ± 9·5	60 ± 9·7
Previous myocardial infarction	70 (45%)	68 (46%)
Q wave	40 (26%)	43 (29%)
Non-Q wave	30 (19%)	25 (17%)
Previous CABG	6 (4%)	10 (7%)
Previous PTCA	25 (16%)	26 (18%)
Diabetes mellitus	21 (14%)	20 (14%)
Insulin dependent	6 (4%)	5 (3%)
Non-insulin dependent	15 (10%)	15 (10%)
Hypertension	65 (42%)	62 (42%)
Hypercholesterolaemia	86 (55%)	79 (53%)
History of stroke	4 (3%)	2 (1%)
Family history of CAD	68 (44%)	55 (37%)
Peripheral vascular disease	9 (6%)	17 (11%)
Smoking history		
Never smoked	45 (29%)	42 (28%)
Previous smoker	67 (44%)	71 (48%)
Current smoker	41 (27%)	35 (24%)
Unstable angina	55 (35%)	54 (36%)
Braunwald classification		
IB	15 (10%)	13 (9%)
IIB	26 (17%)	27 (18%)
IC	6 (4%)	7 (5%)
IIC	8 (5%)	7 (5%)
Stable angina	90 (58%)	85 (57%)
Canadian Cardiovascular Society classification		
1	3 (2%)	3 (2%)
2	36 (23%)	31 (21%)
3	42 (27%)	41 (28%)
4	9 (6%)	10 (7%)
Silent ischaemia	10 (6%)	9 (6%)

CAD=coronary artery disease.

Results

Patient disposition (Table 1), demographics (Table 2), procedural intravascular ultrasound and quantitative coronary angiography (Table 3)

Patients exhibited a high frequency of risk factors and two thirds had complex lesions (type B2 or C). Target lesions were located less frequently in the left coronary artery, due to risk of imprisoning important diagonal or marginal branches. Wallstents were successfully implanted in 303 of the 312 randomized patients (Table 1). Additional stents were required in 17%. Mean implanted stent length was 30 ± 13 mm. Five patients experienced peri-procedural non-Q wave myocardial infarction and two underwent CABG before discharge.

Efficacy analysis (Table 4, Fig. 2)

Imputation was required in 33 patients. The primary end-point was evaluated in 89% and 88% of patients in the trapidil and placebo groups, respectively. There was no significant difference in in-stent neointimal volume or % obstruction.

Secondary end-points (Table 5, Fig. 1)

No significant difference was observed in the minimal lumen diameter (mm) or minimal luminal cross-sectional area (mm^2) by intravascular ultrasound, or in minimal lumen diameter (mm), late loss, loss index or restenosis rate by quantitative coronary angiography.

Major adverse cardiac events and anginal status at 7 months (Tables 6, 7; Fig. 3)

There was no significant difference in the cumulative incidence of major adverse cardiac events during follow-up (the majority being target lesion revascularization) or in recurrence of angina.

Compliance and side effects

Compliance, as defined above, was 76% in patients on trapidil and 83% on placebo at 1 month and 70% and 75% at 6 months. A total of 54% of patients in the placebo group and 67% in the trapidil group reported adverse experiences, gastrointestinal disturbances being observed in 24% of trapidil and 12% of placebo-treated patients.

Discussion

Previous studies reporting restenosis reduction by trapidil after balloon angioplasty[6,7] failed to convince the cardiology community to prescribe it for this purpose. These studies revealed various deficiencies including: small study size, large number of patients lost to follow-up or retrospectively excluded and suboptimal methodology (e.g. visual or calliper method of angiographic evaluation). Recognizing these shortcomings and that restenosis after balloon angioplasty is multifactorial, this trial set out to definitively investigate the putative antiproliferative effects of trapidil[4,5,8,17–19] after stent implantation where restenosis is a proliferative process and by using the most objective methodology currently available, namely 3-D intravascular ultrasound and serial quantitative coronary angiography.

Our findings, in contrast to the prior studies, indicate that trapidil in an adequate dose regimen fails to reduce restenosis, whether measured by intravascular ultrasound, quantitative coronary angiography or occurrence of major adverse cardiac events. A recent small trial comparing trapidil with aspirin post Palmaz–Schatz stenting in 118 patients also found no difference in clinical or angiographic results[20]. It appears likely that the benefit reported in the previously mentioned studies is serendipidous.

Table 3 Baseline qualitative (pre-stenting) and quantitative (pre- and post-stenting) angiographic data and intravascular ultrasound assessment (post-stenting)

	Placebo n=155 patients	Trapidil n=148 patients
Qualitative angiography (n=303)		
Vessel dilated		
LAD	58 (37%)	48 (32%)
LCX	21 (14%)	26 (18%)
RCA	76 (49%)	74 (50%)
Lesion type (ACC/AHA classification)		
A	8 (5%)	11 (7%)
B1	52 (33%)	41 (28%)
B2	80 (52%)	83 (56%)
C	15 (10%)	13 (9%)
Quantitative angiography (n=299)	n=152*	n=147**
Pre-stenting		
Reference diameter (mm)	3·05 ± 0·47	3·00 ± 0·45
Minimal lumen diameter (mm)	0·95 ± 0·40	0·96 ± 0·35
Diameter stenosis (%)	68 ± 13	68 ± 11
Post-stenting		
Reference diameter (mm)	3·27 ± 0·43	3·23 ± 0·37
Minimal lumen diameter (mm)	2·77 ± 0·37	2·75 ± 0·33
Diameter stenosis (%)	15 ± 6	15 ± 7
Intravascular ultrasound post stenting (n=274)	n=136	n=138
Reference area (mm^2)	9·28 ± 3·78	9·41 ± 4·37
Minimal lumen area (mm^2)	6·11 ± 1·81	6·24 ± 1·89
Mean lumen area (mm^2)	7·79 ± 2·17	7·87 ± 2·09
Minimal lumen diameter (mm)	2·76 ± 0·41	2·79 ± 0·40
Projected minimal lumen diameter (mm)**	2·58 ± 0·40	2·59 ± 0·38
Stent symmetry ratio	0·91 ± 0·03	0·91 ± 0·03
Stent length (mm)	29 ± 14	29 ± 13
Stent volume (mm^3)	226 ± 135	228 ± 129

*Film not analysable due to overlap and foreshortening.
**Film not available for Corelab analysis.

Why did trapidil fail to prevent restenosis in this trial?

The reason for the failure of trapidil might be related to fundamental biological processes, drug pharmacokinetics, adequacy of the experimental basis and/or the clinical setting of the trial.

(1) Fundamental cell biology

Although stent restenosis may be considered a 'pure' proliferative process, interaction of multiple factors contributes to the ultimate formation of the neointima including clotting factors, cytokines, enzymes, growth factors, hormones, inflammatory cells etc. and probably other as yet unidentified molecules. Accordingly, even if the goal of a specific pharmacological intervention (e.g. inhibition of the Raf-1/MAP-kinase cascade by trapidil[8,19]), is successful, this could be counterbalanced by feed-back loops or other undefined pathways and be insufficient to inhibit the proliferative process.

(2) Pharmacokinetics

In contrast with the STARC trial[7], with pre-treatment of 3 days, there was no pre-treatment in this trial for logistic reasons, however, recent pharmacokinetic studies indicate that maximum plasma levels are reached 1 h after a single 200 mg tablet[15], so this should not be an issue. What may well be an issue is whether a sustained plasma level sufficient to inhibit hyperplasia could be reached by a three times daily dosage, since auto-induction of trapidil metabolism after repeated oral doses has been demonstrated, with an elimination half-life at steady-state of 1·19 ± 0·26 h[15].

(3) Adequacy of experimental models

The adequacy of the pre-clinical investigations as a basis for the balloon angioplasty studies could be criticised for being carried out in species no longer recognized as reliable forerunners for clinical evaluation (rabbit, rat, hamster[4,5]), using endothelial denudation, which is not a surrogate for single or double arterial injury, as is now considered appropriate.

(4) Appropriateness of the clinical setting

The Wallstent has been previously reported in non-randomized trials to be associated with a greater neointimal hyperplasia than other stents despite excellent acute results[3,11,14]. Continued stent self-expansion

Table 4 Six month follow-up intravascular ultrasound results

	Intention-to-treat without imputation		*P*-value	Intention-to-treat with imputation		*P*-value	Per protocol		*P*-value
	Placebo n=115	Trapidil n=120		Placebo n=137	Trapidil n=131		Placebo n=111	Trapidil n=102	
Ref. area (mm^2)	8·95 ± 3·71	8·56 ± 3·19	0·40	8·93 ± 3·69	8·56 ± 3·19	0·42	9·01 ± 3·76	8·55 ± 3·15	0·37
Min. lumen area (mm^2)	4·49 ± 2·11	4·05 ± 1·89	0·09	4·48 ± 2·10	4·05 ± 1·89	0·10	4·42 ± 2·05	4·01 ± 1·84	0·15
Mean lumen area (mm^2)	6·69 ± 2·49	6·07 ± 2·21	0·04	6·52 ± 2·46	5·95 ± 2·20	0·05	6·62 ± 2·44	5·89 ± 2·18	0·03
Min. lumen diameter (mm)	2·33 ± 0·56	2·21 ± 0·53	0·11	2·32 ± 0·56	2·21 ± 0·53	0·12	2·31 ± 0·54	2·20 ± 0·52	0·17
Proj. min. lumen diameter (mm)	2·18 ± 0·52	2·08 ± 0·49	0·11	2·18 ± 0·52	2·08 ± 0·49	0·12	2·17 ± 0·51	2·07 ± 0·49	0·16
Stent length (mm)	26 ± 11	28 ± 14	0·14	26 ± 11	28 ± 14	0·19	27 ± 12	29 ± 14	0·34
Stent volume (mm^3)	255 ± 134	276 ± 179	0·31	256 ± 134	274 ± 175	0·36	266 ± 135	279 ± 180	0·52
Luminal volume (mm^3)	117 ± 91	172 ± 108	0·92	163 ± 93	165 ± 108	0·70	169 ± 92	167 ± 112	0·74
In-stent neo-intimal volume (mm^3)	84 ± 69	104 ± 92	0·064	93 ± 79	109 ± 96	0·16	97 ± 81	112 ± 96	0·21
In-stent obstruction volume (%)	32 ± 15	36 ± 16	0·034	36 ± 21	38 ± 18	0·32	36 ± 22	39 ± 18	0·31

Table 5 Six month follow-up quantitative angiographic results (intention-to-treat analysis)

	Placebo n=155	Trapidil n=148	*P*-value
Reference diameter (mm)	2·89 ± 0·49	2·81 ± 0·44	0·13
Minimal lumen diameter (mm)	1·74 ± 0·69	1·63 ± 0·61	0·17
Diameter stenosis (%)	40 ± 20	43 ± 17	0·32
Late loss (mm)	1·04 ± 0·56	1·12 ± 0·53	0·23
Loss index (mm)	0·59 ± 0·33	0·64 ± 0·38	0·28
Mean lumen diameter (mm)	2·50 ± 0·53	2·36 ± 0·55	0·04
Minimum luminal cross-sectional area (mm^2)	2·79 ± 1·67	2·51 ± 1·65	0·18
Mean luminal cross-sectional area (mm^2)	5·36 ± 2·29	5·03 ± 2·87	0·31
Restenosis rate (%)	24	31	0·24
No Corelab quantitative coronary angiography analysis	18 (12%)	20 (14%)	

Table 6 Major adverse cardiac events until 250 days (clinical ranking) intention-to-treat

	Placebo n=155	Trapidil n=148
Death	1 (1%)	3 (2%)
Myocardial infarction	3 (2%)	2 (1%)
Q wave	1 (1%)	1 (1%)
Non-Q wave	2 (1%)	1 (1%)
CABG	2 (1%)	2 (1%)
Urgent	2 (1%)	0
Elective	0	2 (1%)
Target lesion revascularization	25 (16%)	25 (17%)
Major adverse cardiac event free	124 (80%)	116 (78%)

Wilcoxon Rank-Sum test: $P=0·71$.

Table 7 Anginal status assessed prior either to the 6 months scheduled angiography or prior to any intercurrent angiography followed by an intervention

	Placebo n=155	Trapidil n=148
Anginal complaints	35 (24%)	41 (30%)
Missing information	11 (7%)	11 (7%)
No anginal complaints and/or signs of ischaemia	109 (76%)	96 (70%)

Wilcoxon Rank-Sum test: $P=0·29$.

probably compensates for the hyperplasia[14], so that late clinical results have been found to be generally satisfactory[3,21]. However, a recent experimental study demonstrated that the proliferative response after stenting is not only greater, but also more prolonged, compared to balloon angioplasty[22]. This implies that post-stent restenosis may paradoxically be too aggressive to be affected by oral trapidil, particularly in the case of a self-expanding stent, with its continued expansion after implantation[14], as confirmed by increased stent volume from post stenting (226 ± 135 mm^3, Table 3) to follow-up (256 ± 134 mm^3, Table 4). Undoubtedly, an effective antiproliferative agent would be expected to exert a particular benefit after Wallstent or other self-expanding stent placement, where the continued self-expansion might then achieve even more favourable late lumen expansion.

Use of a primary intravascular ultrasound volumetric end-point

This methodology, although relatively new, has been extensively validated in vitro and in vivo[12–14] and previously applied in a randomized clinical trial evaluating the effect of abciximab on late restenosis after stenting[10]. Although angiography remains the cornerstone of coronary intervention, it is evident that intravascular ultrasound provides superior information on the vessel wall, plaque and lumen for mechanistic evaluation of therapies. 3-D intravascular ultrasound provides precise measurement of the target of therapy, namely the bulk of the restenotic lesion. Further, use of hyperplastic volume as the end-point allows evaluation of the trial hypothesis with a smaller sample size than would be needed using the classical quantitative coronary angiography parameter (minimal lumen diameter (mm)). This methodology has now also been meticulously applied to evaluation of outcome after coronary brachytherapy, providing previously unattainable pathophysiological insights[23]. The drawback is that intravascular ultrasound examination, using current technology, is not always possible in patients with severe restenosis or total or subtotal occlusion, or not carried out for other reasons (Table 1), leading to potential bias if there is imbalance between the groups. Recognizing this limitation, an imputation algorithm was prospectively designed in this trial and was applied to 22 patients in the placebo group and 11 in the trapidil group, who had an analysable follow-up angiogram and post-stent angiogram and intravascular ultrasound. For completeness, all available data both with and without imputation, is provided for both the intention-to-treat and per-protocol population, showing consistently that trapidil provided no benefit in reducing restenosis.

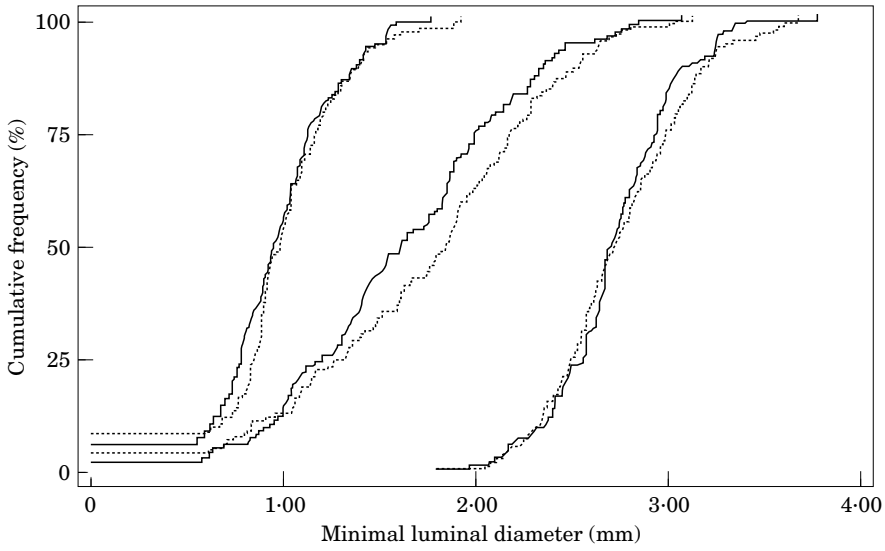

Figure 1 **Cumulative frequency distribution of minimal lumen diameter (mm) pre-, post- and follow-up. · · · = placebo group; —— = trapidil group.**

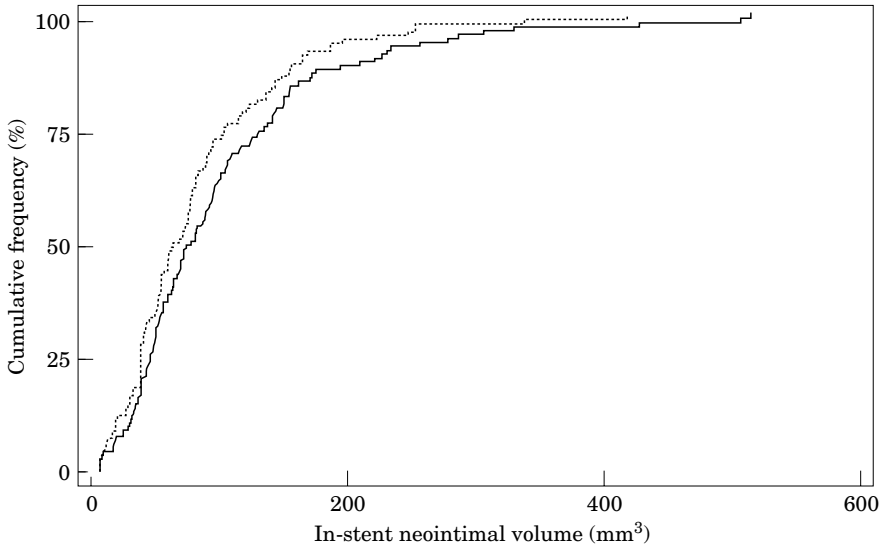

Figure 2 **Cumulative frequency distribution of in-stent neointimal volume. · · · = placebo group; —— = trapidil group.**

It deserves to be pointed out that although an evaluable follow-up intravascular ultrasound rate of 78% may seem relatively low, the rate of follow-up intravascular ultrasound examination in those eligible for re-catheterization was 86%, and of the patients who underwent repeat catheterization 88% had an evaluable intravascular ultrasound. These figures compare very favourably with angiographic follow-up rates in most multicentre restenosis trials over the years, and reveal the increasing willingness of a diverse range of physicians to apply intravascular ultrasound during catheterization. Impending enhancement of catheter design (e.g. reduction in crossing profile, use of imaging guidewires) and intravascular ultrasound imaging and recording technology, can only lead to further improvements in the general applicability of intravascular ultrasound.

Limitations

Full and complete compliance with trial medication and complete angiographic and intravascular ultrasound follow-up would be ideal in every such randomized trial, but is for all the known reasons unattainable. At 1 month, compliance, defined as 90% of intake of medication, was 76% for trapidil and 83% for placebo, which is less than ideal but the lack of a major imbalance means this is unlikely to have affected the study outcome. Poor

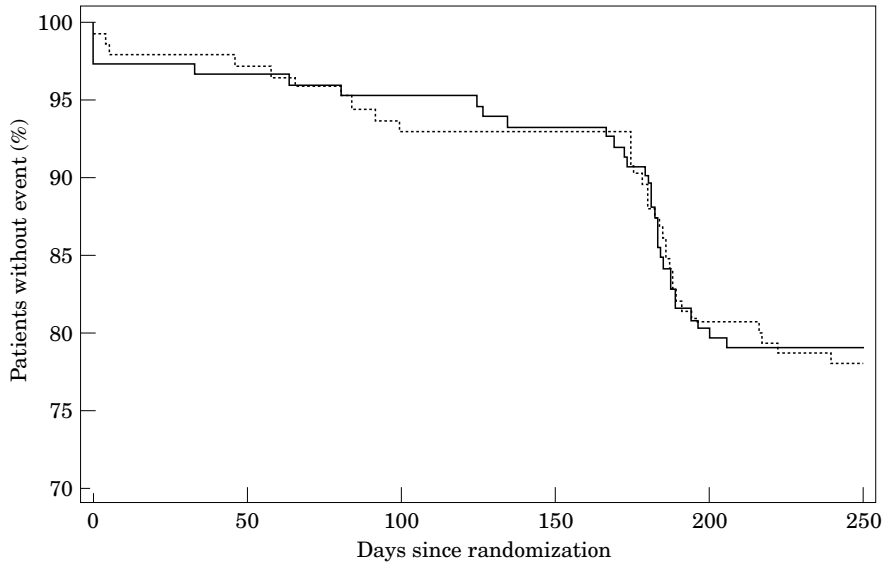

Figure 3 **Kaplan–Meier curves illustrating freedom from major adverse cardiac events during scheduled follow-up. · · · = placebo group; —— = trapidil group.**

compliance with trial medication, even if there had been a positive trial outcome, of course augurs very poorly for subsequent successful clinical application, since patients included in trials are inherently better motivated and receive closer instruction and follow-up than in routine clinical practice.

According to the statistical plan, a total of 240 evaluable patients were required in the intention-to-treat population analysis and finally 268 patients were analysed for the primary end-point, including 33 patients in whom the follow-up intravascular ultrasound data had to be imputed from the in-built pre-defined protocol. Although we believe the imputation protocol to be unbiased, objective and currently the best method of obtaining intravascular ultrasound measurements where acquisition was impossible, the imbalance between the groups here is unfortunate and cannot be explained as more than a chance occurrence. For the purpose of the primary hypothesis, as stated already, there is incontrovertibly no beneficial effect of trapidil on the late results, in fact a trend towards more hyperplasia, if anything, is evident. However, such a conclusion would also be inappropriate given the previously mentioned limitations.

Conclusion

Trapidil did not reduce restenosis after successful Wallstent implantation, measured by three-dimensional intravascular ultrasound neointimal volume, or by angiographic indices or clinical events and is thus not indicated for this purpose. Follow-up intravascular ultrasound examination was found to be eminently applicable in the multicentre context and automated three-dimensional measurement presents a promising advancement for interventional trials. Further improvements in intravascular ultrasound catheter technology will be required to increase a successful application rate at follow-up catheterization.

References

[1] Serruys PW, de Jaegere P, Kiemeneij F *et al.* for the Benestent Study Group. A comparison of Balloon-expandable -stent implantation with balloon angioplasty in patients with coronary artery disease. N Engl J Med 1994; 331: 489–95.

[2] Fischman DL, Leon MB, Baim DS *et al.* the STRESS trial. A randomized comparison of coronary-stent placement and balloon angioplasty in the treatment of coronary artery disease. N Engl J Med 1994; 331: 496–501.

[3] Foley DP, Rensing BJ, Pieper M *et al.* on behalf of the Wellstent Native Investigators. Clinical and quantitative angiographic outcomes following elective implantation of the self-expanding Wallstent for longer coronary artery lesions-Final results of the Wellstent Native study. Int J Cardiovasc Interv 1999; 2: 171–9.

[4] Cercek B, Ebrahimi R, Dimayuga P, Khorsandi M, Forrester JS. Trapidil prevents rat smooth muscle cell proliferation in vitro and in vivo. J Am Coll Cardiol 1991; 17: 72A.

[5] Liu MW, Roubin GS, Robinson KA *et al.* Trapidil in preventing restenosis after balloon angioplasty in the atherosclerotic rabbit. Circulation 1990; 81: 1089–93.

[6] Okamoto S, Inden M, Setsuda M, Konishi T, Nakano T. Effects of Trapidil a platelet derived growth factor antagonist, in preventing restenosis after percutaneous transcoronary angioplasty. Am Heart J 1992; 123: 1439–44.

[7] Maresta A, Balducelli M, Cantini L *et al.* Trapidil, a platelet-derived growth factor antagonist, reduces restenosis after percutaneous transluminal coronary angioplasty; results of the randomized, double-blind STARC Study. Circulation 1994; 90: 2710–15.

[8] Wittpoth M, Bönisch D, Schrör K. Trapidil inhibits RAF-1 kinase in vascular smooth muscle cells via activation of protein kinase A (PKA). Circulation 1997; 96: I-558.

[9] Isner JM. Vascular remodelling. Honey, I think I shrunk the artery. Circulation 1994; 89: 2837–941.

[10] The ERASER investigators. Acute platelet inhibition with abciximab does not reduce in-stent restenosis (ERASER study). Circulation 1999; 100: 799–806.

[11] De Feyter PJ, Kay P, Disco C, Serruys PW. Reference chart derived from post-stent-implantation intravascular ultrasound predictors of 6-month expected restenosis on quantitative angiography. Circulation 1999; 100: 1777–83.
[12] Li W, von Birgelen C, Hartlooper A *et al.* Semi-automated contour detection for volumetric quantification of intracoronary ultrasound. In: Computers in Cardiology. Washington: IEEE Computer Society Press, 1994: 277–80.
[13] Von Birgelen C, Di Mario C, Li W, Schuurbiers JC *et al.* Morphometric analysis in three-dimensional intracoronary ultrasound an in vivo and in vitro study performed with a novel system for contour detection of lumen and plaque. Am Heart J 1996; 132: 516–27.
[14] Von Birgelen C, Airiian SG, de Feyter PJ, Foley DP, van der Giessen WJ, Serruys PW. Coronary Wallstents show significant late, post-procedural expansion despite implantation with adjunct high-pressure balloon inflatation. Am J Cardiol 1996; 132: 694–6.
[15] Harder S, Thürmann P, Hellstern A, Benjaminov A. Pharmacokinetics of trapidil, an antagonist of platelet derived growth factor, in healthy subjects and in patients with liver chirrosis. Br J Clin Pharmacol 1996; 42: 443–9.
[16] Serruys PW, Foley DP, de Feyter PJ. Quantitative coronary angiography in clinical practice. Dordrecht/Boston/London: Kluwer Academic Publishers, 1994.
[17] Ohnishi H, Yamaguchi K, Shimada S, Suzucki Y, Kumagai A. A new approach to treatment of atherosclerosis and Trapidil as an antagonist to platelet-derived growth factor. Life Sci 1982; 31: 2595–602.
[18] Tiell ML, Sussmann I, Gordon PB, Sanders RN. Suppression of fibroblast proliferation in vitro and of neointimal hyperplasia in vivo by the triazolopyrimidine, Trapidil. Artery 1983; 12: 33–50.
[19] Bönisch D, Weber AA, Withpoth M, Osinski M, Schrör K. Antimitogenic effects of trapidil in coronary artery smooth muscle cells by direct activation of protein kinase A. Mol Pharmacol 1998; 54: 241–8.
[20] Galassi AR, Tamburino C, Nicosia A *et al.* A randomized comparison of trapidil (triazolopyrimidine), a platelet-derived growth factor antagonist, versus aspirin in prevention of angiographic restenosis after coronary artery Palmaz-Schatz stent implantation. Catheter Cardiovasc Interv 1999; 46: 162–8.
[21] Ozaki Y, Keane D, Ruygrok P, vd Giessen WG, de Feyter P, Serruys PW. Six month clinical and angiographic outcome of the new less-shortening Wallstent in native coronary arteries. Circulation 1996; 93: 2114–20.
[22] Hanke H, Kamenz J, Hassenstein S *et al.* Prolonged proliferative response of smooth muscle cells after experimental intravascular stenting. Eur Heart J 1995; 16: 785–93.
[23] Sabate M, Marijnissen JP, Carlier SG *et al.* Residual plaque burden, delivered dose, and tissue composition predict 6-month outcome after balloon angioplasty and beta-radiation therapy. Circulation 2000; 101: 2472–7.

Appendix A

Members of the TRAPIST study committee

Steering Committee: P. W. Serruys, MD, Ph.D. (chair), A. Mignot, MD, R. Ott, MD, G.-A. van Es, MD, A. A. van den Bos, MD, B. Meier, MD, Y. Teunissen, Ph.D., P. de Feyter, MD PhD, C. van de Zwaan, MD, C. Kawai, MD, D. L. Clement. *Data Safety Monitoring Committee*: C. Kawai, MD (chair), J. Tijssen, Ph.D., P. de Jaegere, MD PhD. *Clinical Event Committee*: C. van de Zwaan, MD (chair), P. Klootwijk, MD, P. van der Meer, MD PhD. *IVUS-Angiographic Committee*: P. De Feyter, MD PhD (chair), T. Slagboom, MD, C. Vrints, MD. *Statistical analyses*: R. Melkert, MD, C. C. M. Disco, M.Sc.

Appendix B

Participating sites and investigators

The Netherlands: Thoraxcentre, University Hospital Dijkzigt Rotterdam: D. P. Foley, P. W. Serruys, P. de Feyter. Thoraxcentrum Ignatius, Breda: J. A. M. te Riele, P. C. H. Roose. OLVG, Amsterdam: E. Ronner, A. Scholte, G. J. Laarman, F. Kiemeneij. St Antonius Ziekenhuis, Nieuwegein: J. C. Kelder, M. Baars, H. W. M. Plokker, M. J. Suttorp. Catharina Ziekenhuis, Eindhoven: H. P. C. M. Heijmen, B. V. Nibbering, J. J. R. M. Bonnier. De Weezenlanden Hospital, Zwolle: H. Suryapranata, J. C. A. Hoorntje.
Belgium: OLVZ, Aalst: W. Wijns, B. De Bruyne, G. R. Heyndrickx. Clinique St-Jean, Brussels: M. Cascadot, P. Lafontaine, M. Vandormael. CHU Sart-Tilman, Liege: C. A. Martinez, V. Legrand. University hospital Antwerp, Edegem: C. Vrints. St Luc University Hospital, Brussels: C. Hanet, N. M. G. Debbas.
Germany: Universitätsklinikum Charite, Berlin: M. Beling, W. Rutsch. Medizinische Klinik University Münich, Münich: H. Mudra, J. Rieber.
France: Institute Cardiovasculaire Paris sud: M.-C. Morice, P. Dumas. Hôpital Broussais, Cedex 14, Paris: J.-L. Guermonprez, F. Ledru.
Switzerland: Herzzentrum Bodensee, Kreuzlingen: H. Franck, C. Schütz, M. Pieper.
Spain: Hospital Universitario San Carlos, Madrid: F. Alfonso, A. Delgado, C. Macaya.
United Kingdom: Kings College Hospital, Denmark Hill, London: M. R. Thomas, D. E. Jewitt.
Portugal: Hospital de Santa Cruz, Lisbon: R. Seabra-Gomes, J. M. P. da Silva Baptista.
Italy: Centro Cuore Colombus, Milan: A. Colombo, A. Amato.