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Original research

Derivo embolization device in the treatment of unruptured intracranial aneurysms: a prospective multicenter study

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ABSTRACT

Background Flow diverters (FD) are used regularly for the endovascular treatment of unruptured intracranial aneurysms. We aimed to assess the safety and effectiveness of the Derivo embolization device (DED) with respect to long-term clinical and angiographic outcomes.

Methods A prospective multicenter trial was conducted at 12 centers. Patients presenting with modified Rankin Score (mRS) of 0–1, treated for unruptured intracranial aneurysms with DED were eligible. Primary endpoint was the mRS assessed at 18 months with major morbidity defined as mRS 3–5. Satisfactory angiographic occlusion was defined as 3+4 on the Kamran scale.

Results Between July 2014 and February 2018, 119 patients were enrolled. Twenty-three patients were excluded. Ninety-six patients, 71 (74%) female, mean age 54±12.0 years, were included in the analysis. Mean aneurysm size was 14.2±16.9 mm. The mean number of devices implanted per patient was 1.2 (range 1–3). Clinical follow-up at 18 months was available in 90 (94%) patients, resulting in a mean follow-up period of 14.8±5.2 months. At last available follow-up of 96 enrolled patients, 91 (95%) remained mRS 0–1. The major morbidity rate (mRS 3–5) was 3.1% (3/96), major stroke rate was 4.2% (4/96), and mortality was 0%. Follow-up angiographies were available in 89 (93%) patients at a median of 12.4±5.84 months with a core laboratory adjudicated satisfactory aneurysm occlusion in 89% (79/89).

Conclusion Our results suggest that DED is a safe and effective treatment for unruptured aneurysms with high rates of satisfactory occlusion and comparably low rates of permanent neurological morbidity and mortality.

Trial registration DRKS00006103

INTRODUCTION

Endovascular coil embolization is the preferred treatment modality for many patients with intracranial aneurysms since the results of the International Subarachnoid Aneurysm Trial showed better clinical outcomes with endovascular coiling than neurosurgical clipping in patients with ruptured aneurysms.[1] Nevertheless, incomplete aneurysm occlusion or recanalization of completely occluded aneurysms may occur after endovascular coiling in wide-necked or large-to-giant aneurysms as well as dissecting or fusiform aneurysms. Flow-diverting (FD) stents have been brought to clinical practice to circumvent these limitations and have proven helpful in the treatment of this group of aneurysms.[2]

A number of different FD stents have been designed and were brought to clinical practice. The Derivo embolization device (DED) is a second-generation FD with a novel surface finishing that is supposed to lead to reduced friction and low thrombogenicity.[3]

The purpose of this trial was to assess the safety and effectiveness of the DED with respect to long-term clinical and angiographic outcomes in a prospective multicenter trial.

METHODS

The data that support the findings of this study are available from the corresponding author on reasonable request.

Study design

The Derivo trial was an investigator-initiated, pragmatic, observational, post-market, multicenter clinical trial with prospective inclusion, open-label treatment, and open-label endpoint evaluation for clinical and angiographic outcomes. The study was conducted in 11 centers in Germany and one in Poland. The study protocol was approved by the leading ethics committee (Faculty of Medicine, University of Freiburg, 190/14) and the local ethics committees, and was authorized by the competent German and Polish authorities. The trial was registered in the German clinical trials register (DRKS00006103). The clinical investigational plan is enclosed as online supplementary file 1. Members of the trial steering committee and the local investigators designed the study, collected and analyzed the data, wrote the manuscript, and made the decision to submit the manuscript for publication.

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Patients

Patients were eligible for enrollment if they were ≥18 years of age and had unruptured intracranial aneurysms of any size located in the anterior or posterior circulation with an anatomy such that endovascular treatment with the DED was considered possible. Patient inclusion was limited to patients presenting with a modified Rankin Score (mRS) of 0 or 1. Patients were not eligible for enrollment if they had experienced a subarachnoid hemorrhage associated with a ruptured intracranial aneurysm within 60 days prior to the index procedure. The intended use of the DED is restricted to aneurysms that cannot be treated with other endovascular techniques or in aneurysms where the treatment risk is considered higher with other endovascular or neurosurgical techniques. Detailed inclusion and exclusion criteria are listed in the study protocol available as online supplementary file 1. We did not keep a log of patients screened for eligibility. All patients provided written informed consent. Patients had to be registered at the clinical trials unit in Freiburg prior to the procedure in order to be included in the analysis set of the trial.

Procedures

Patients were treated with the DED, a self-expanding stent braided from 48 nitinol wires (Derivo embolization device, Acandis, Pforzheim, Germany). Procedures were performed under general anesthesia via a transfemoral approach. All patients were under double antiplatelet therapy (DAPT). Dosage, timing of DAPT, and testing for antiplatelet drug response as well as periprocedural administration of heparin followed the standard operation procedure at each center and were not pre-specified. The protocols for DAPT in the enrolling centers are outlined in online supplementary table 1. The DED was positioned through a 0.027 inch microcatheter via a bi- or triaxial approach. Additional coiling as well as balloon angioplasty after placement of the DED were left to the operators' discretion. Only devices that had received Conformité Européenne (CE) marking were used in the trial.

Clinical and radiological assessments

All patients underwent clinical examination and angiographic assessment of the underlying aneurysm. At the time of enrollment, the following parameters were collected: sex, age, and rupture status. Baseline data collected included number of aneurysms, aneurysm size (in mm), aneurysm neck size (in mm), dome-to-neck ratio, and aneurysm location. In addition, patients underwent a neurologic assessment using the modified Rankin Scale (mRS). After the endovascular procedure, data were obtained on the number and sizes of DED used, use of assist devices and additional coils, procedure-related complications, and the initial angiographic outcome. Study data were entered locally by the treating physician or a dedicated study nurse into the trial database via web-based electronic case report forms. Digital copies of angiographic images of the aneurysm before treatment, immediately after treatment, at 6 months, and at 18 months follow-up were sent to the clinical trials unit. Digital subtraction angiography (DSA) was preferred to magnetic resonance angiography (MRA), but MRA was considered acceptable for centers where angiographic controls routinely are performed with MRA. Imaging data were entered into the picture archiving and communication system in a pseudonymized way and reviewed by an independent senior neuroradiologist (MK>20 years of practice). Follow-up images were reviewed for degree of aneurysm occlusion according to the Kamran scale: complete occlusion (Kamran grade 4), neck remnant (Kamran grade 3), residual aneurysm with <50% filling (Kamran grade 2), residual aneurysm with >50% filling (Kamran grade 1), with satisfactory occlusion defined as Kamran grade3 or 4. The National Institute of Health stroke scale (NIHSS) was assessed in patients that had peri-procedural complications with subsequent stroke or in patients with the occurrence of new neurologic deficits during follow-up. All adverse and serious adverse events were reported in an electronic case report form. The mRS was assessed by the team treating the patient at 6- and 18-months' follow-up.

Study endpoints

Primary endpoint was the clinical outcome defined by the mRS at 18 months after aneurysm treatment. In patients where mRS at 18 months were not available, the last available mRS was used instead. Major morbidity was defined as any mRS 3–5. Secondary outcomes included:

1. Technical success: the participating centers reported on dual antiplatelet therapy, number of DED positioned, additional coiling, percutaneous transluminal angioplasty (PTA) after DED placement, time of procedure, and procedural complications. Core-laboratory assessment of angiographic data included determination of successful neck coverage, any coverage of side branches, degree of wall apposition, and long-term angiographic follow-up (12–18 months). In patients where angiographic long-term data was not available, we used the last available angiographic controls instead.
2. Clinical success: number of minor and major strokes immediately after flow-diverter implantation through to discharge, as well as during follow-up were collected. Minor stroke was defined as any new neurological deficit with NIHSS ≤3, whereas major stroke was defined as any new neurological deficit with an increase of NIHSS ≥4 or neurologic death.[4]

Statistical analysis

Patients were included in the full analysis set if they were: registered at the clinical trials unit before the intervention; gave informed consent; and were treated with the DED.

The primary endpoint, mRS at 18 months after treatment, was evaluated descriptively and summarized by the total number of patients in each category and the number of missing values. Relative frequencies were displayed as valid % (number of patients divided by the number of patients with non-missing values). Missing values were substituted by the last available observation of the patient (last observation carried forward).

Demographic and other baseline data including disease characteristics were summarized descriptively. Continuous data were given as arithmetic mean, SD, minimum, 25% quantile, median, 75% quantile, maximum, and the number of complete and missing observations. If appropriate, continuous variables were also presented in categories. Categorical data was evaluated in the same way as the primary endpoint. Adverse events (AE) were evaluated descriptively in the analysis population. Periprocedural AE and specific items requested in the electronic case report form describing treatment were evaluated jointly. Adverse events were coded using the Medical Dictionary for Regulatory Activities. All analyses were performed using version 9.2 of the Statistical Analysis System (SAS; SAS Institute, Cary, NC, USA). The statistical analysis plan is available as online supplementary file 2.

An interim analysis was undertaken after enrollment of 35 patients, which included assessment of trial data on procedure-related complications, AE, morbidity, and mortality. Results of this analysis were reviewed by the trial statistician and the trial coordinator in strict confidentiality with respect to predefined

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Table 1 Patient data and characteristics of aneurysms treated with the Derivo embolization device

Patients	96
Aneurysms	96
Women (%)	71/96 (74%)
Age (years, mean±SD)	54±12.0
Presentation	
Asymptomatic	61 (64%)
SAH from treated aneurysm >60 days	1 (1%)
Recurrent aneurysm after coiling, SAC, or failed clipping	14 (15%)
Baseline mRS	
mRS 0	72 (75%)
mRS 1	24 (25%)
Aneurysm size (mm)	
Mean±SD	14.2±16.9
<5 mm	14 (15%)
5–9.9 mm	36 (37%)
10–20 mm	33 (34%)
>20 mm	13 (14%)
Aneurysm neck size (mm)	
Mean±SD	7.7±9.6
Aneurysm partially thrombosed	
yes	18 (19%)
Location (%)	
ICA	82 (86%)
ACA	1 (1%)
MCA	1 (1%)
VA	8 (8%)
BA	4 (4%)
Morphology (%)	
Wide-neck saccular	77 (80%)
Fusiform/dissecting	19 (20%)

ACA, anterior cerebral artery; BA, basilar artery; ICA, internal carotid artery; MCA, middle cerebral artery; mRS, modified Rankin Scale score; SAC, stent-assisted coiling; SAH, subarachnoid hemorrhage; SD, SD deviation; VA, vertebral artery.

stopping criteria. Based on the results of their analysis the trial statistician and the trial coordinator advised the lead investigator (CAT) to continue with the trial. The primary endpoint had not been evaluated in the interim analysis.

RESULTS

Baseline characteristics

From July 17 2014, to February 19 2018, 119 patients were enrolled in 11 centers in Germany and one center in Poland. Recruitment was stopped after the pre-determined sample size was reached. Twenty-three patients were excluded from the analysis population for treatment-related criteria in 13, missing informed consent in seven, and double registration in three (online supplementary figure 1). Patient demographics, clinical presentations, and aneurysm characteristics are summarized in table 1.

The mean age was 54±12.0 years, 71 (74%) patients were women. Modified Rankin scores at presentation were 0 in 72 (75%) and 1 in 24 (25%). Median target aneurysm size was 14.2±16.9 mm with median neck size of 7.7±9.6 mm. Of 96 aneurysms 27 (28%) measured <7 mm in size, 33 (34%) were large (10–20 mm), and 13 (14%) were >20 mm. There were 77 (80%) aneurysms with saccular morphology, the remaining 19 (20%) aneurysms were fusiform. Eighty-four (88%) aneurysms were located in the anterior circulation with the intracranial internal carotid artery (ICA) being the predominant location (87%). Of 12 (12%) posterior circulation aneurysms eight (8%) were located at the vertebral artery, and four (4%) were aneurysms of the basilar artery.

Table 2 Treatment characteristics

Dual antiplatelet therapy	96 (100%)
Number of DED implanted, mean (range)	1.2 (1–3)
Additional coiling	47 (49%)
PTA after DED placement	18 (19%)
Procedural time, mean±SD (range)	89±43 min (20-235)
Entire neck covered *	94 (98%)
Covered side branches *	89 (93%)
Complete wall apposition *	80 (84%)

Procedural time=groin puncture to final DSA; SD=SD deviation.
*Core-laboratory adjudicated data.
DED, Derivo embolization device; ; PTA, percutaneous transluminal angioplasty.

Procedure and core laboratory adjudicated baseline results

Treatment-related information is summarized in table 2.

All patients were under DAPT for the procedure. In 80 (82%) patients the effectiveness of DAPT was tested with either Multiplate test, Verify-Now, Platelet-Function-Assay (PFA-100), or vasodilator-stimulated-phosphoprotein-phosphorylation assay.

Successful DED placement was reported for all 96 patients. Forty-seven (49%) patients received additional coiling. The mean number of DED implanted per patient was 1.2 (range 1–3). Seventy-nine patients were treated with a single DED, 16 patients received two DED, and one patient had three DED implanted. In one patient a second DED was deployed, because the first DED moved proximally during initial placement. In the remainder >1 DED were used for reasons related to the underlying aneurysm (large aneurysm neck, fusiform aneurysm). Core-laboratory adjudication demonstrated complete neck coverage with the DED in 94 (98%) cases with complete wall apposition in 80 (84%) patients. A minor gap (<25% of the parent vessel diameter) was observed in seven (7%) patients, a major gap (>25% of the parent vessel diameter) was seen in eight (8%) patients. Thirty-four periprocedural complications were reported in 22 patients. Twenty-eight of these complications were related to the DED (table 3). A detailed overview of periprocedural complications, timing, management, as well as clinical consequences, and angiographic outcomes is provided in online supplementary table 2.

Primary endpoint

For the analysis population (n=96) mRS at 18 months were available in 90 patients. For six patients with missing mRS at 18 months we used mRS at 6 months in three, and mRS at discharge for the remaining three. The resulting mean follow-up period was 14.8±5.2 months. At last available follow-up 91 (95%) patients were mRS 0–1. Two patients were mRS 2, two patients were mRS 3, and one patient was mRS 4. The major morbidity rate (mRS 3–5) was 3.1% (3/96). No patient from our study sample had died. The mRS at baseline, discharge, through to last available follow-up are displayed in figure 1.

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Table 3 Periprocedural complications

Flow diverter could not be delivered through microcatheter	2 (2%)
Flow diverter did not open	3 (3%)
Flow diverter twisted	1 (1%)
Flow diverter displaced(proximally, distally)	6 (6%) [4, 2]
Fish mouthing of the DED *(proximal, distal)	11 (11.5%) [9, 2]
ICA dissection	1 (1%)
Parent vessel occlusion(thrombus, DED related)	4 (4%) [1, 3]
Multiple embolic infarcts	1 (1%)
Symptomatic intracranial hemorrhage	1 (1%)
Femoral artery pseudoaneurysm, groin hematoma, retroperitoneal hematoma	4 (4%)

*Eight cases signaled by core laboratory, three cases reported by enrolling center; ICA=internal carotid artery.
DED, Derivo embolization device.

Secondary endpoints

Technical success

Of the 96 patients 62 had angiographic follow-up at 18 months, for 27 patients the last available angiographic follow-up was used (median follow-up period 12.4±5.84 months). In three patients no angiographic controls were available, in four patients the core laboratory could not assess angiographic results based on the available imaging data. Core- laboratory adjudication revealed complete occlusion (Kamran grade 4) in 82% (73/89) patients and a neck remnant (Kamran grade 3) in 7% (6/89) resulting in a satisfactory occlusion rate of 89% (79/89). Residual aneurysm filling (Kamran grades 0–2) was seen in 11% (10/89). Angiographic outcomes are summarized in online supplementary figure 2. Angiographic outcomes in patients that received >1 DED did not differ from patients treated with a single DED (online supplementary table 3). However, the trial was not designed to address this question, therefore a final conclusion cannot be drawn.

Clinical success

Four (4.2%) out of 96 patients from the analysis population experienced a major stroke. Two of these were related to proximal occlusion of the DED causing mechanical obstruction of the device and subsequent parent vessel occlusion. In two patients in-stent thrombosis occurred, in one patient 1 day after positioning of the DED, in a second patient 270 days after DED treatment when acetylsalicylic acid was discontinued. In three patients major stroke lead to a permanent morbidity (mRS 3–4), in one patient the neurological deficit improved to a mRS of 2. Another two patients had minor strokes (NIHSS 1+2). One minor stroke was related to a left temporal hemorrhage that occurred 9 days after the procedure associated with an NIHSS of 2. The second minor stroke occurred on the first post-operative day and was caused by multiple embolic infarcts. New neurological deficits from the procedure through to last available follow-up as well as the DAPT protocols of the corresponding patients are outlined in online supplementary table 4.

DISCUSSION

This prospective multicenter trial evaluated safety and effectiveness of the DED for the treatment of unruptured intracranial aneurysms.

Clinical outcomes and patient selection

Aneurysm treatment with the DED resulted in complete aneurysm occlusion in 82% of patients and was associated with permanent neurologic morbidity (mRS 3–5) of 3.1% and no mortality.

Brinjikji et al reported in 2013 data from a meta-analysis that included 1451 patients and 1654 intracranial aneurysms treated with FD which resulted in a complete aneurysm occlusion in 76% of patients with an associated procedure-related morbidity of 5.0% and a procedure-related mortality of 4.0%.[2] A recently published French prospective cohort study of 398 patients treated between 2012 and 2014 found comparable rates for permanent morbidity (5.9%) and a lower mortality (1.2%) at 12 months' follow-up. The core-laboratory adjudicated complete occlusion rate (Kamran 4) at 12 months was 68.4%.[5]

Complete occlusion rates at 12 months were 86.8 (79/91) for the Pipeline device in the prospective multicenter Pipeline for uncoilable or failed aneurysms (PUFS) trial that had initially enrolled 108 patients. Associated permanent morbidity and mortality rates were 2.8% and 2.8%, respectively.[6] Permanent neurologic morbidity and mortality were slightly higher in a prospective multicenter trial from 2015 assessing the first-generation Surpass FD in 165 patients with 6% and 2.7%, respectively. The reported complete occlusion rate was 75% at a relatively short follow-up period of median 6 months (range 1–38 months).[7] A more recent retrospective analysis of 531 patients treated with the Flow-Redirection Intraluminal Device reported in 2018 permanent morbidity in 0.8% and a mortality rate of 1.5%.[8]

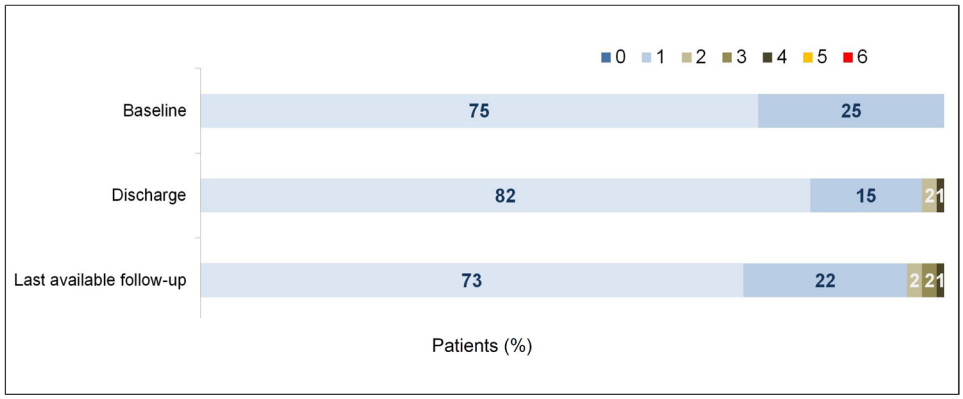

Figure 1 Scores on the modified Rankin Scale (n=96) distribution of scores at baseline, discharge, and last available follow-up (14.8±5.2 months) in the trial population.

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Differences in inclusion criteria and primary endpoints among these registries make a head-to-head comparison difficult. The trend toward improved clinical outcomes associated with FD treatment might reflect careful patient selection in the latest trials. Hanel et al recently published results of a prospective study on FD treatment of wide-necked small- and medium-sized aneurysms (mean 5.0±1.92 mm with 84.4% of aneurysms<7 mm) with the Pipeline device in 141 patients.[9] They had obtained a complete occlusion rate at 12 months of 76.8% with a major morbidity rate of 1.4% (2/141) and a mortality rate of 0.7% (1/141). 95% of aneurysms in their trial were located at the level of the ICA, only 5% of aneurysms were located in the posterior circulation (vertebral artery). In our trial the mean aneurysm size was considerably larger 14.2+−16.9 mm with only 28% of aneurysms<7 mm and 12% of aneurysms located in the posterior circulation. Both trials excluded patients with acutely ruptured aneurysm.

Low morbidity and mortality rates in our trial might be attributed to the fact that we limited inclusion to patients presenting with mRS of 0–1. Taschner et al observed a correlation between low mRS at presentation and a good clinical outcome in a subset of patients treated for posterior circulation aneurysms with FD.[10] The current data suggests that these findings might be transferable to aneurysms in other locations.

Our study corroborates results from the Brazilian prospective registry trial that evaluated the same flow-diverting device in 146 patients harboring 183 aneurysms. Trivelato et al reported comparably low morbidity and mortality rates of 3.4% (5/146) and 1.4% (2/146), respectively.[11] Baseline mRS was 0–1 in 86% (126/146), and ≥2 in 14% (20/146) with 3.3% (6/146) ruptured aneurysms. The percentage of patients treated for posterior circulation aneurysms was comparable. Mean aneurysm size of 6.7±5.1 mm was smaller compared with aneurysms treated in our trial which might explain the higher rate of complete aneurysm occlusion at 12 months of 89.2%.[11]

Technical properties

The DED is a single-layer FD consisting of a nitinol composite wire with platinum-iridium core. The surface of the wire is modified, named BlueXide, which is supposed to enhance corrosion resistance and lower thrombogenicity. The porosity of the DED is 65%, with a pore density of 15/mm^2. The proximal end of the DED is cut, whereas the distal portion of the device has flared ends. The DED is delivered through a 0.027 inches microcatheter.[3] According to the instructions for use provided by the manufacturer, the DED should not be used in patients who were not pretreated with antiplatelet agents before the procedure. The company does not suggest any specific anti-platelet protocol. In addition the DED is contraindicated in the acute phase after subarachnoid hemorrhage. To the best of our knowledge there are no reports on DED placement under antiplatelet monotherapy.

Our data does not determine whether the thrombogenicity of the DED stent is lower when compared with other FD available on the market. The number of in-stent thrombosis did not differ significantly from previous publications. Manufactured of nitinol, the DED displays advantages and disadvantages of the softer fabric when compared with FDs made of cobalt-chromium alloy. Even in tortuous anatomy the DED can easily be advanced through the 0.027 inches microcatheter. The softness of the material might be the explanation for the cases where the device would not open properly or twisted (online supplementary table 2). Correct sizing of the device is very important, since undersizing might lead to dislocation of the device. Undersizing seems also to have been associated with the cases of fish mouthing that we observed in our trial. Here the proximal part of the device seemed particularly prone to fish mouthing. Comparable observations were made in the Brazilian Derivo registry. They reported on 11 patients with periprocedural complications of which four were described as improper DED expansion.[11] Kraus et al reported results from a retrospective analysis of 42 patients treated for unruptured aneurysms with the DED. Delivery and deployment of the DED was successful in all patients.[12] They observed procedure-related adverse events in four patients – in one patient in-stent thrombus formation occurred related to incomplete proximal opening of the DED.[12]

Study limitations

Data for this trial was collected in a non-randomized fashion lacking a control arm making direct comparison with other aneurysm therapies impossible. It was designed as an international multicenter study in which patient selection was heterogeneous. Contrary to the angiographic follow-up data, clinical follow-up and serious AEs were self-adjudicated by physicians' participating sites.

CONCLUSION

Our results suggest that DED is a safe and effective treatment for unruptured aneurysms with high rates of satisfactory occlusion and comparably low rates of permanent neurological morbidity and mortality.

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the accuracy or integrity of any part of the work are appropriately investigated and resolved: All listed authors.

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