

Randomized Trial of Atorvastatin for Reduction of Myocardial Damage During Coronary Intervention

Results From the ARMYDA (Atorvastatin for Reduction of MYocardial Damage during Angioplasty) Study

Vincenzo Pasceri, MD, PhD; Giuseppe Patti, MD; Annunziata Nusca, MD; Christian Pristipino, MD; Giuseppe Richichi, MD; Germano Di Sciascio, MD; on behalf of the ARMYDA Investigators

Background—Small myocardial infarctions after percutaneous coronary intervention have been associated with higher risk of cardiac events during follow-up. Observational studies have suggested that statins may lower the risk of procedural myocardial injury. The aim of our study was to confirm this hypothesis in a randomized study.

Methods and Results—One hundred fifty-three patients with chronic stable angina without previous statin treatment were enrolled in the study. Patients scheduled for elective coronary intervention were randomized to atorvastatin (40 mg/d, n=76) or placebo (n=77) 7 days before the procedure. Creatine kinase-MB, troponin I, and myoglobin levels were measured at baseline and at 8 and 24 hours after the procedure. Detection of markers of myocardial injury above the upper normal limit was significantly lower in the statin group versus the placebo group: 12% versus 35% for creatine kinase-MB ($P=0.001$), 20% versus 48% for troponin I ($P=0.0004$), and 22% versus 51% for myoglobin ($P=0.0005$). Myocardial infarction by creatine kinase-MB determination was detected after coronary intervention in 5% of patients in the statin group and in 18% of those in the placebo group ($P=0.025$). Postprocedural peak levels of creatine kinase-MB (2.9 ± 3 versus 7.5 ± 18 ng/mL, $P=0.007$), troponin I (0.09 ± 0.2 versus 0.47 ± 1.3 ng/mL, $P=0.0008$), and myoglobin (58 ± 36 versus 81 ± 49 ng/mL, $P=0.0002$) were also significantly lower in the statin than in the placebo group.

Conclusions—Pretreatment with atorvastatin 40 mg/d for 7 days significantly reduces procedural myocardial injury in elective coronary intervention. These results may influence practice patterns with regard to adjuvant pharmacological therapy before percutaneous revascularization. (*Circulation*. 2004;110:674-678.)

Key Words: angioplasty ■ trials ■ myocardial infarction ■ stents ■ angina

Myocardial necrosis, assessed by creatine kinase-MB (CK-MB) elevation, is relatively frequent after coronary intervention, occurring in up to 40% of cases.¹⁻⁴ Although most patients remain asymptomatic with no changes in cardiac function, even a mild release of CK-MB is associated with higher mortality during follow-up.^{2,3,5} Many treatment strategies have been proposed to address this issue, but procedural ischemic myocardial injury remains the most frequent complication after coronary angioplasty.⁴

Several randomized studies demonstrated the beneficial effects of therapy with HMG-CoA reductase inhibitors (statins) in patients with coronary disease or in normal subjects with hypercholesterolemia,⁶⁻⁸ and retrospective observational studies have suggested that pretreatment with statins might reduce the incidence of myocardial infarction after coronary intervention.⁹⁻¹¹ To date, there is no randomized, controlled study to evaluate the effects of statins given before coronary intervention on preventing myocardial injury.

Thus, we have performed the first randomized, placebo-controlled trial of pretreatment with atorvastatin before elective coronary intervention. In particular, we evaluated the effects of atorvastatin 40 mg/d, started 1 week before the procedure, on release of markers of cardiac damage (CK-MB, troponin I, and myoglobin) after percutaneous revascularization in patients with stable angina.

Methods

Patient Population and Study Design

This was a randomized, prospective, double-blind, placebo-controlled trial performed in 2 institutions. Inclusion criteria were presence of typical stable effort angina, positive stress test (either ECG, nuclear scan, or stress echocardiogram), and indication for coronary angioplasty. Exclusion criteria were acute myocardial infarction (<3 months); unstable angina; any increase in CK-MB, troponin I, or myoglobin above upper normal limit at the time of randomization; any increase in liver enzymes (AST/ALT); left ventricular ejection fraction <30%; renal failure with creatinine >3

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From the Interventional Cardiology Unit (V.P., C.P., G.R.), San Filippo Neri Hospital, and Department of Cardiovascular Sciences (G.P., A.N., G.D.S.), Campus Bio-Medico University, Rome, Italy.

Correspondence to Prof Germano Di Sciascio, MD, Department of Cardiovascular Sciences, Campus Bio-Medico University, Via E. Longoni, 83, 00155 Rome, Italy. E-mail g.disciascio@unicampus.it

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mg/dL; history of liver or muscle disease; or previous treatment with statins. Patients undergoing current therapy with statins were also excluded. Between September 1, 2002, and March 1, 2004, a total of 912 patients underwent elective angioplasty for stable angina; 636 patients were excluded because of previous or current treatment with statins, 58 because of low ejection fraction, 39 because of contraindications to statin treatment (liver or muscle disease), and 26 because of renal failure. Thus, a total of 153 patients (age 64 ± 10 years, 107 men) fulfilling the inclusion criteria were scheduled for elective coronary intervention and were included in the study; 77 patients were randomized to placebo and 76 to atorvastatin (40 mg/d) starting 7 days before the planned intervention. Patients were randomized independently of their lipid levels. According to our standard protocol, all patients without contraindications were pretreated with aspirin (100 mg/d) and ticlopidine 250 mg BID at least 3 days before the procedure or with clopidogrel 300 mg at least 6 hours before the procedure. All patients continued ticlopidine 250 mg BID or clopidogrel 75 mg/d for 1 month (6 months for patients treated with drug-eluting stents). Before intervention, patients received weight-adjusted intravenous heparin with a target activated clotting time >300 seconds in the absence of glycoprotein IIb/IIIa inhibitor therapy and 200 to 300 seconds with glycoprotein IIb/IIIa, which was allowed at the operator's discretion.

Procedural success was defined as a reduction of stenosis to $<30\%$ residual narrowing. Blood samples were taken before and at 8 and 24 hours after the procedure to assay CK-MB (mass), troponin I (mass), and myoglobin; additional determinations were performed if any patient developed postprocedural symptoms suggestive of myocardial ischemia.

Measurements of CK-MB, troponin I, and myoglobin were obtained with the Access 2 Immunochemiluminometric assay (Beckman Coulter).¹² The upper normal limits were defined as the 99th percentiles of the normal population, with a total imprecision of $<10\%$, according to Joint European Society of Cardiology/American College of Cardiology guidelines.¹³ Normal limits were ≤ 4 ng/mL for CK-MB, ≤ 0.08 ng/mL for troponin I, and 80 ng/mL for myoglobin. C-reactive protein levels were assessed before coronary intervention (1 week after randomization) and at 24 hours after the procedure in 98 patients (50 in the statin group and 48 in the placebo group). C-reactive protein was determined by the KRYPTOR ultra-sensitive immunofluorescent assay (BRAHMS), with a detection limit of 0.06 mg/L. One-month clinical follow-up was obtained by office visit in all patients. Each patient gave informed consent to the study. The study was not supported by any external source of funding.

End Points

The primary end point was occurrence of myocardial infarction, defined as a postprocedural increase of CK-MB >2 times above the upper normal limit, according to the consensus statement of the Joint European Society of Cardiology/American College of Cardiology Committee for the Redefinition of Myocardial Infarction.¹³ Secondary end points included (1) any postprocedural increase of other markers of myocardial injury (CK-MB, troponin I, and myoglobin) above upper normal limits; (2) mean peak values of CK-MB, troponin I, and myoglobin after intervention; and (3) occurrence of all major adverse cardiac events (death, myocardial infarction, or need for unplanned revascularization) from the time of the procedure until 1 month of follow-up.

Statistical Analysis

According to recent observational studies, previous treatment with statins can be associated with a reduction of periprocedural myocardial infarction of 50% to 90%.⁹ We expected an incidence of postprocedural CK-MB elevation of $\approx 30\%$ in the placebo group and 10% in the treatment group. Thus, a sample size of 120 patients (with 60 in each group) would provide 80% power to detect a difference with an alpha (probability value) of 0.05. Continuous variables between groups were compared by *t* test for normally distributed values (age, left ventricular ejection fraction); otherwise, the Mann-Whitney *U* test was applied (in particular, for CK-MB, troponin I,

TABLE 1. Main Clinical Features in the Placebo and Atorvastatin Groups

Characteristic	Placebo (n=77)	Atorvastatin (n=76)	<i>P</i>
Male sex, n (%)	67 (87)	64 (82)	0.53
Age, y	65 ± 10	64 ± 10	0.68
Diabetes mellitus, n (%)	15 (19)	21 (27)	0.36
Systemic hypertension, n (%)	56 (73)	58 (75)	0.96
Hypercholesterolemia, n (%)	32 (42)	32 (41)	0.92
Current smokers, n (%)	15 (19)	23 (28)	0.21
Family history, n (%)	9 (12)	15 (19)	0.28
Previous myocardial infarction, n (%)	15 (19)	19 (24)	0.59
Previous coronary intervention, n (%)	8 (10)	7 (9)	0.98
Previous bypass surgery, n (%)	2 (3)	6 (8)	0.14
Left ventricular ejection fraction, %	54 ± 7	54 ± 8	0.69
Multivessel coronary artery disease, n (%)	15 (20)	15 (20)	0.87
Blood creatinine, mg/dL	1.1 ± 0.2	1.1 ± 0.3	0.84
Aspirin, n (%)	74 (96)	75 (96)	0.65
Ticlopidine/clopidogrel, n (%)	75 (97)	76 (97)	0.50
β -Blockers, n (%)	26 (34)	26 (33)	0.91
ACE inhibitors, n (%)	47 (61)	47 (60)	0.95

and myoglobin values). Proportions were compared by χ^2 test or Fisher's exact test when appropriate. ORs and 95% CIs assessing the risk of periprocedural myocardial infarction associated with different factors were assessed by multiple logistic regression, adjusted for age; sex; use of β -blockers, ACE inhibitors, or glycoprotein IIb/IIIa inhibitors; diabetes; dyslipidemia; systemic hypertension; type of lesion (A/B1 versus B2/C); multivessel intervention; stent length; use of direct stenting; duration of balloon inflations; and use of high pressure after dilation. A probability value <0.05 (2 tailed) was considered significant. Analysis was performed with GB-STAT version 6 software. Results are expressed as mean \pm SD, unless otherwise specified.

Results

Study Population

Clinical and procedural variables in the atorvastatin and placebo groups are shown in Table 1 and Table 2, respectively. The 2 groups were similar with regard to age, sex, cardiovascular risk factors, clinical presentation (all patients had stable angina by study design), left ventricular function, renal function, and medical therapy at the time of the procedure. Coronary anatomy, lesion type, procedural characteristics (including total ischemia time), use of drug-eluting stents, diameter and length of implanted stents, and use of IIb/IIIa inhibitors were also similar. Procedural success was achieved in all patients of the placebo group and in all but 1 patient (99%) of the atorvastatin group (in 1 patient, a total chronic occlusion could not be crossed with the wire); no patient had no-reflow phenomenon or significant (≥ 2 mm) side-branch closure during the procedure. There were no in-hospital major complications (death or need for urgent revascularization). An increase above the upper normal limit of liver enzymes (AST/ALT) was observed in 1 patient in the atorvastatin group on admission for coronary intervention. In this patient, the drug was then discontinued; however, all patients completed the 7-day pretreatment period with ator-

TABLE 2. Procedural Features in the Placebo and Atorvastatin Groups

Characteristic	Placebo (n=77)	Atorvastatin (n=76)	P
Vessel treated, n (%)			
Left anterior descending	39 (51)	41 (53)	0.94
Left circumflex	17 (22)	15 (19)	0.81
Right coronary artery	20 (26)	19 (24)	0.96
Saphenous vein grafts, n (%)	1 (1)	3 (4)	0.62
Restenotic lesions, n (%)	2 (2)	3 (4)	0.99
Lesion type B2/C, n (%)	53 (69)	54 (69)	0.91
Chronic total occlusions (>3 months), n (%)	4 (5)	5 (6)	0.98
Multivessel intervention, n (%)	9 (12)	10 (13)	0.98
Type of intervention, n (%)			
Balloon only	1 (1)	3 (4)	0.62
Stent	73 (95)	72 (92)	0.75
Stent plus rotablator/atherectomy	3 (4)	3 (4)	0.63
Bifurcations with kissing balloon	6 (8)	7 (9)	1
No. of stents per patient	1.36±0.7	1.41±0.8	0.63
Stent diameter, mm	3.14±0.5	3.16±0.33	0.99
Total stent length, mm	20.7±10	24.0±13	0.12
Use of drug-eluting stents, n (%)	17 (22)	10 (13)	0.19
Direct stenting, n (%)	21 (27)	18 (23)	0.68
No. of predilations	1.6±1.8	2.0±2.2	0.19
Stent deployment pressure, atm	13.5±2.3	13.5±1.7	0.77
Duration of stent deployment, seconds	27±6	29±6	0.12
Total ischemia >120 seconds	12 (16)	15 (19)	0.67
Use of postdilatation, n (%)	14 (18)	18 (23)	0.58
Use of IIb/IIIa inhibitors, n (%)	12 (16)	19 (24)	0.24

vastatin or placebo. After the procedure, all patients but the above-mentioned one were treated with atorvastatin (40 mg/d) irrespective of the initial randomization assignment. Lipid levels after 1-week treatment were not significantly different in the 2 groups. C-reactive protein levels at the time of the procedure were not significantly different in the 2 groups (2.6 ± 2.2 mg/L in the statin versus 6.4 ± 13.9 mg/L in the placebo group, $P=0.31$), although prevalence of patients with C-reactive protein >5 mg/L after 1 week of treatment was significantly lower in the statin group (10% versus 23%, $P=0.02$).

Markers of Myocardial Damage

Myocardial infarction by CK-MB elevation >2 times upper normal limit was detected after coronary intervention in 5% of patients in the statin group and in 18% of those in the placebo group ($P=0.025$). An increase of CK-MB above the upper normal limit occurred in 35% of patients in the placebo group versus 12% in the atorvastatin group ($P=0.001$); similarly, there were significantly higher proportions of patients with increases in troponin I (48% versus 20%, $P=0.0004$) and myoglobin (51% versus 22%, $P=0.0005$). Distribution of CK-MB and troponin I levels in the 2 groups is shown in Figure 1. In the 2 groups, mean preprocedural levels of the 3 markers were similar (and all were within the normal limits), whereas after coronary

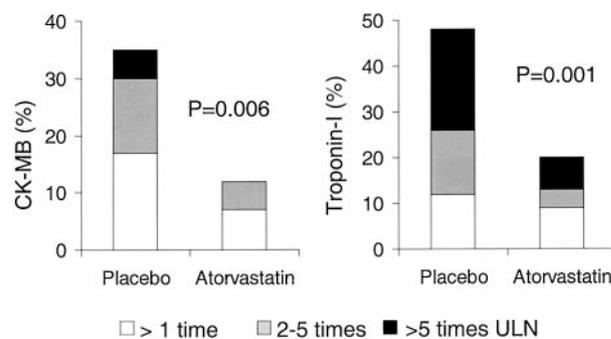


Figure 1. Incidence of postprocedural increase of CK-MB and troponin I >1 , 2 to 5, and >5 times above upper normal limit (UNL).

intervention, peak values of all markers were significantly lower in patients treated with atorvastatin than in those given placebo: CK-MB 2.9 ± 3 versus 7.5 ± 18 ng/mL ($P=0.007$), troponin I 0.09 ± 0.2 versus 0.47 ± 1.3 ng/mL ($P=0.0008$), and myoglobin 58 ± 36 versus 81 ± 49 ng/mL ($P=0.0002$), respectively (Figure 2).

At 1-month clinical follow-up, there were no other cardiac events in the 2 groups; thus, the occurrence of the composite end point of death, myocardial infarction, and repeat revascularization at 1 month depended entirely on periprocedural myocardial infarction (5% versus 18% in statin versus placebo, $P=0.025$).

Multivariate analysis (adjusted for age; sex; use of β -blockers, ACE inhibitors, or glycoprotein IIb/IIIa inhibitors; diabetes; dyslipidemia; systemic hypertension; type of lesion [A/B1 versus B2/C]; multivessel intervention; stent length; use of direct stenting; duration of balloon inflations; and use of high pressure after dilation) showed that pretreatment with atorvastatin significantly reduced the risk of periprocedural CK-MB release (OR 0.19, 95% CI 0.05 to 0.57); use of β -blockers, glycoprotein IIb/IIIa inhibitors, or ACE inhibitors was not associated with risk reduction (Figure 3).

Discussion

This is the first randomized trial to demonstrate that pretreatment with atorvastatin decreases the incidence of myocardial injury during coronary intervention compared with placebo; indeed, atorvastatin significantly reduced release of all markers of myocardial damage after coronary intervention, including myoglobin, troponin I, and CK-MB. Several randomized trials have shown that statins have beneficial effects on the incidence of long-term cardiovascular events in subjects with hypercholester-

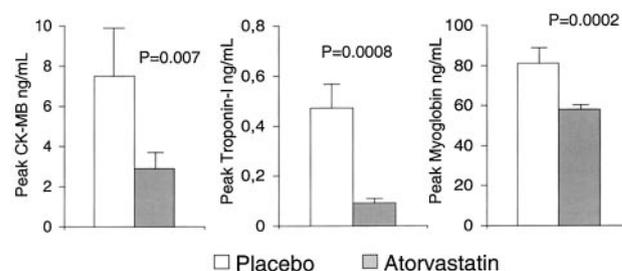


Figure 2. Peak values of CK-MB, troponin I, and myoglobin in statin vs placebo group. Data are mean \pm SEM.

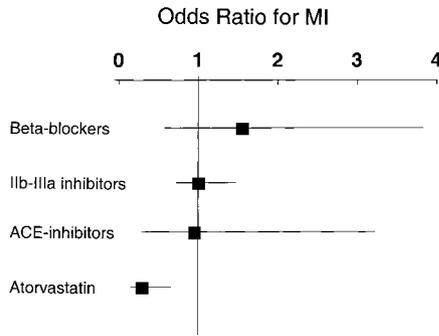


Figure 3. Results of multivariate analysis showing that pretreatment with atorvastatin significantly reduced risk of periprocedural myocardial infarction (OR 0.19, 95% CI 0.05 to 0.57). Use of β -blockers, glycoprotein IIb/IIIa inhibitors, or ACE inhibitors was not associated with risk reduction. MI indicates myocardial infarction.

emia, in patients with coronary disease, and in patients who underwent coronary intervention.^{6–8} In the latter group, statin treatment was generally started immediately after angioplasty;⁸ in addition, those randomized studies were not specifically focused on the effect of statins on periprocedural myocardial injury. In the present study, patients were started on atorvastatin therapy 7 days before coronary intervention regardless of their cholesterol levels. Previous observational studies have shown that pretreatment with statins may be associated with a reduction in myocardial infarction after coronary intervention;^{9,10,14} these retrospective, nonrandomized studies have included large numbers of patients, treated with different types of statins, with variable doses and with long (and largely unknown) duration of previous treatment. Conversely, the present study used a fixed dose of statin for a short time (atorvastatin 40 mg/d for 1 week) in a randomized fashion, and in multivariate analysis, this was the only factor that influenced reduction of periprocedural myocardial injury.

The present study included only patients with stable angina undergoing elective procedures and without previous treatment with statins. These strict inclusion criteria did exclude most high-risk patients, and it is possible that the benefit of statins may be even higher in high-risk populations (particularly in patients with unstable coronary syndromes), as suggested by a randomized trial evaluating high-dose atorvastatin started during acute coronary syndromes.¹⁵ The proportion of patients treated with IIb/IIIa antagonists was relatively low compared with standard practice in the United States; this reflects the elective nature of the procedures performed in patients with stable angina, as well as European practice patterns. However, the benefit of pretreatment with atorvastatin was similar in patients with and without IIb/IIIa inhibitor therapy. Moreover, all patients were pretreated with ticlopidine/clopidogrel, which confirms the benefit of statins in addition to the best current therapy. Multivariate analysis also confirmed that this benefit was independent of possible confounding factors and of other drug treatments, with an average risk reduction of 80%.

Asymptomatic myocardial injury, assessed by postprocedural CK-MB elevation, is frequent during coronary intervention, occurring in 10% to 40% of cases.^{1–3} In the large majority of cases, only a small release of markers of myo-

cardial necrosis can be detected, without ECG changes or impairment of cardiac function.⁴ However, even small CK-MB releases are an expression of a true infarction, as assessed by contrast-enhanced MRI,¹⁶ and may be associated with higher mortality during follow-up.⁵ Treatments proposed to prevent myocardial injury during coronary intervention include nitrate infusion,¹⁷ intracoronary β -blockers,¹⁸ IIb/IIIa inhibitors,¹⁹ and adenosine,²⁰ but none of those (apart from the use of IIb/IIIa inhibitors) has changed current practice.

A controversial issue is the threshold at which a CK-MB elevation is associated with increased risk of adverse events. Most studies have found a good correlation between the degree of CK-MB elevation and mortality risk, with higher risk for patients with CK-MB >5 times above the upper normal limit.^{2,3,11} A recent meta-analysis, pooling data from 23 230 patients, showed that any increase of CK-MB above normal limits is associated with increased mortality.⁵ In particular, an elevation of CK-MB of only 1 to 3 times was associated with an excess mortality of 1.7% at 1 year; the excess mortality was 2.8% for CK-MB 3 to 5 times above the upper limit of normal and 7.4% for an increase >5 times above the upper normal limit.⁵ Similar results were obtained in a recent observational study on 8409 consecutive patients.¹¹ According to these data, an absolute reduction of 20% of CK-MB release, as observed in the present study, would translate into 6 lives saved per 1000 patients treated in 1 year. Although the association between CK-MB elevation and long-term mortality has been established, it remains to be demonstrated that preventing periprocedural necrosis would also correlate to a long-term mortality benefit. In previous observational studies, however, the benefit of statin pretreatment on periprocedural necrosis was primarily expressed as a long-term mortality reduction up to 30 months.^{9,10}

Troponin I has better sensitivity for myocardial damage than CK-MB and troponin T.²¹ Although the clinical significance of troponin I release after coronary intervention has been less extensively studied, observational studies have found a correlation between troponin I release and in-hospital adverse events,^{22,23} whereas a normal troponin I level after coronary intervention virtually excludes the risk of in-hospital complications.²² Furthermore, a recent study found that troponin I elevation was an independent predictor of major cardiac events at 1-year follow-up, particularly the need for repeat revascularization.²⁴ Thus, the effect of atorvastatin on troponin I release may be associated with significant clinical benefits. Finally, the protective effect of atorvastatin on myocardial injury, observed in the present study, is confirmed by the significant reduction of all 3 markers, including myoglobin.

The mechanisms underlying the beneficial effects of atorvastatin are not completely clear. A previous observational study has suggested that the antiinflammatory effect of statins may play a role, showing that the benefit was higher in patients with high C-reactive protein.¹⁴ Statins have important antiinflammatory effects *in vitro*²⁵ and *in vivo*,²⁶ and inflammatory status before angioplasty is associated with higher risk of periprocedural myocardial necrosis¹⁴ and adverse cardiac events during follow-up.^{27,28} The antiinflammatory effect of statins might contribute to reduce myocardial necrosis due to microembolization during coronary intervention;

this is supported by experimental evidence showing protective effects of statins on a model of ischemia/reperfusion, possibly by effects on microcirculation and cell adhesion²⁹ and platelet function,³⁰ and by the trend toward reduced C-reactive protein levels observed in the present study. A recent study observed that even a single dose of statins may significantly improve endothelial function;³¹ thus, even short-term treatment with statin may have important effects on endothelial function and on inflammation.³²

In conclusion, the present study shows that pretreatment with atorvastatin 40 mg/d for 1 week before coronary intervention may reduce periprocedural myocardial injury in patients with stable angina. The low cost and very low risk of this therapy may support its routine use in patients undergoing percutaneous revascularization.

Appendix

The following investigators and institutions participated in the ARMYDA trial:

Chairmen:

Vincenzo Pasceri, Giuseppe Richichi, San Filippo Neri Hospital, Rome; Giuseppe Patti, Germano Di Sciascio, Campus Bio-Medico University, Rome.

Investigators:

Christian Pristipino, Antonino Granatelli, Giulio Speciale, Francesco Pelliccia, Massimo Santini, San Filippo Neri Hospital, Rome; Annunziata Nusca, Andrea D'Ambrosio, Addolorata Carcagni, Marco Miglionico, Giordano Dicuonzo, Campus Bio-Medico University, Rome.

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