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Anticoagulant and Antiplatelet Use in Cataract Surgery and Combined with Posterior Vitrectomy

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1. Introduction

Patients receiving long-term anticoagulant and antiplatelet medications pose a clinical challenge when therapy needs intraocular surgery, including cataract surgery and vitrectomy [1-3]. Maintaining antiplatelet and anticoagulation places them at risk for serious bleeding complications, whereas discontinuing these medications puts them at risk of thromboembolic complications [4-6]. Currently, there is little consensus on the appropriate perioperative treatment of patients on long-term acetylsalicylic acid (aspirin) and warfarin therapy [7-9]. In this study, we compared the incidence of hemorrhagic and non-hemorrhagic complications and visual course of phacoemulsification alone and combined phacoemulisification and vitrectomy between patients who maintained or discontinued anticoagulant and/or antiplatelet medications.

2. Patients and methods

A total of 824 consecutive cases of 532 patients undergoing cataract surgery alone and of 69 consecutive cases of 69 patients undergoing combined cataract and vitreous surgery for the treatment of epiretinal membrane and macular hole who had been administered warfarin and/or aspirin for 6 months or longer between April 2005 and March 2009 were studied (Table 1). Before April 2007, all patients discontinued the drugs prior to the surgery. After

	Anticoagulant and antiplatelet medications	Number of patients (Number of cases)
Phacoemulsification alone group	Discontinuation subgroup	274 (421)
	Maintenance subgroup	258 (403)
Combined phacoemulsification and vitrectomy group	Discontinuation subgroup	33 (33)
	Maintenance subgroup	36 (36)

Table 1. Outline of patients with discontinuation and maintenance of anticoagulant and/or antiplatelet medications

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April 2007, all patients maintained the treatment at the time of surgery (Table 1). The discontinuation subgroups consisted of patients who ceased taking warfarin and/or aspirin 1 week before the surgery, with their therapies then restarted 2 days postoperatively. The study protocol and consent forms were approved by the Human Subjects Committee.

2.1 Surgical procedure and postoperative interventions

Cataract surgery

Phacoemulsification and intraocular lens implantation was performed through a superior sclerocorneal incision after scleral cauterization. Sub-Tenon anesthesia with 2% lidocaine (Xylocaine, Asteras, Tokyo, Japan) was employed using Fukasaku's blunt subtenon's cannula (Handaya, Tokyo, Japan). A standard phacoemulsification technique was used. In all cases, a three-piece hydrophobic acrylic intraocular lens (AcrySof™ MA30BM; Alcon, Fort Worth, TX, USA) was implanted. Sodium hyaluronate 1% (Healon, AMO, Santana, CA, USA) was used as viscoelastics.

Vitrectomy for epiretinal membrane and macular hole

A standard three port pars plana vitrectomy was performed in all patients after sub-Tenon anesthesia, phacoemulsification and intraocular lens implantation. We achieved a complete posterior vitreous detachment during pars plana vitrectomy using a vitreous cutter. For patients with epiretinal membrane, the membranes were removed with a slightly bent microvitreoretinal blade or internal limiting membrane forceps. For patients with macular hole, the internal limiting membranes around the macular hole were removed in assistance with triamcinolone acetonide or indocyanine green. Sulfur hexafluoride (20%) was used for gas tamponade. Patients remained in the prone position for 7-10 days postoperatively.

Postoperative management

In both groups, all patients were given topical levofloxacin, dexamethasone and diclofenac three times daily during the first 2 weeks, with the drugs then tapered off over the next 3 months.

Evaluation of outcomes

Before enrollment, patients had an ocular and systemic history taken as well as slit-lamp biomicroscopy, visual acuity, a physical examination, and dilated fundoscopy. Best-corrected visual acuity (BCVA) was measured, with the log of the minimum angle of resolution (LogMAR) then calculated and used for all statistical analyses. Intraocular pressure was measured using Goldmann applanation tonometry while a slit-lamp examination was used to clinically grade the preoperative nuclear sclerosis as per the method of Emery and Little [10]. After pupil dilation, ophthalmoscopic and slit-lamp biomicroscopic examinations were employed to assess retinal, vitreous and choroidal/suprachoroidal hemorrhages. For patients with epiretinal membrane and macular hole, we performed optical coherence tomography (OCT) scanning (OCT scanner 3000 and Cirrus, Humphrey Instruments, San Leandro, California) before and 1, 3, and 6 months after surgery. The fovea was identified as the patient's fixation point or with the fundus monitor in the OCT device. The cross-sectional images were normalized and smoothed using OCT plug-in software. Patients were also assessed intraoperatively and at every postoperative visit for the presence of general complications, which included cerebral events such as transient ischemic attack and cerebral infarction and hemorrhage,

and cardiovascular events such as deep vein thrombosis, myocardial ischemia, and myocardial infarction. Hemorrhagic complications were defined as subconjunctival hemorrhage and hyphema, or retinal, vitreous and choroidal/suprachoroidal hemorrhage. Hypotony was defined as an intraocular pressure of less than 4 mmHg after surgery, while the criteria of Teehasaenee and Ritch [11] were used to define shallow anterior chamber. An intraocular pressure spike was defined as an intraocular pressure on the first postoperative day that was greater than or equal to 3 mmHg higher than the level observed preoperatively.

2.2 Statistical analysis

A Student's t-test was used to evaluate the continuous variables, while a paired t-test was used was used to evaluate the difference in intraocular pressures between the follow-up intervals. All t-tests were two-tailed. Categoric variables were evaluated by using the chi-square test, the Fisher exact test, or the Spearman rank correlation, as appropriate. Results were defined as being statistically significant when $P < 0.05$.

For the pairing of groups, baseline values for age, sex, BCVA, and prothrombin time-international normalized ratio (PT-INR) were used for matching. When correlations between paired observations were noted, we used the F-test to examine the variances between the two populations.

3. Results

Baseline

Patient demographics are summarized in Table 2. No significant differences were found between the two subgroups for age, sex, or BCVA in the phacoemulsification alone group and the combined phacoemulsification and vitrectomy group. In patients who were administered warfarin, mean PT-INR was 1.94 ± 0.77 in the maintenance subgroup and 1.87 ± 0.62 in the discontinuation subgroup in the phacoemulsification alone group ($P = 0.3$) and 1.89 ± 0.57 in the maintenance subgroup and 2.23 ± 0.66 in the maintenance subgroup in the combined phacoemulsification and vitrectomy group ($P = 0.0249$).

3.1 Hemorrhagic and non-hemorrhagic complications

Phacoemulsification alone group: As seen in Table 3, there were no systemic complications or any significant intraoperative bleeding noted for the two subgroups. There were 87 eyes (21.6 %) in the maintenance subgroup and 46 eyes (10.9%) in the discontinuation subgroup that exhibited subconjunctival hemorrhage of greater than one quadrant ($P < 0.0001$). On the first postoperative day, microscopic hyphema was seen in 26 eyes (6.5%) in the maintenance subgroup and in 11 eyes (2.6%) in the discontinuation subgroup ($P = 0.0078$), whereas no apparent hyphema was found in the two subgroups. Within 1 week of the surgical procedure, all bleeding had stopped without affecting the visual acuity. There was also no vitreous or choroidal/ suprachoroidal hemorrhage found in either of the two subgroups. There were 5 posterior capsule rupture and 2 vitreous loss in the maintenance subgroup and 7 posterior capsule rupture and 3 vitreous loss in the discontinuation subgroup, respectively (posterior capsule rupture: $P = 0.6$; vitreous loss: $P = 0.7$) (Table 3). No significant differences were noted for the incidence of non-hemorrhagic intraoperative complications between the two subgroups.

Phacoemulsication alone group			
	Maintenance subgroup	Discontinuation subgroup	P
No.of patients (no. of eyes)	258 (403)	274 (421)	-
Age	74.3±7.7 (46 – 88)	73.7±8.4 (48 – 90)	0.4
Gender	135 females, 122 males	147 females, 127 males	0.8
Best-corrected visual acuity	0.313 (20/64.0) (0.01 – 0.8)	0.326 (20/61.3) (0.01 – 0.8)	-
LogMAR ± SD	0.505 ± 0.391	0.486 ± 0.393	0.5
Nuclear sclerosis	2.4 ± 0.8 (1 - 5)	2.3 ± 0.8 (1 - 5)	0.1
Administration			
Warfarin only	51 (83)	61 (96)	0.7
Aspirin only	194 (299)	197 (302)	
Both	13 (21)	16 (23)	
PT-INR	1.89±0.56 (1.17–3.54)	1.95±0.58 (1.20-3.47)	0.4
Duration of warfarin administration	4.2±2.1 (1 -14)	4.5±1.8 (2-12)	0.3

Combined phacoemulsication and vitrectomy group			
	Maintenance group	Discontinuation group	P
No.of patients (No. of eyes)	36 (36)	33 (33)	
Age	63.8±7.1 (51 – 78)	64.6±7.2 (52– 76)	0.6
Gender	23 females, 13 males	20 females, 13 males	0.8
Epiretinal membrane	22	19	0.8
Macular hole	14	14	
Best-corrected visual acuity	0.290 (20/68.9) (0.08-0.5)	0.311 (20/64.1) (0.1-0.6)	-
LogMAR ± SD	0.537 ± 0.216	0.506 ± 0.193	0.5
Nuclear sclerosis	2.2 ± 0.6 (1 - 4)	2.1 ± 0.7 (1 - 3)	0.5
Administration			
Warfarin only	7	8	0.7
Aspirin only	26	22	
Both	3	3	
PT-INR	1.89±0.57 (1.31-3.14)	2.23±0.66 (1.38-3.46)	0.0249
Duration of warfarin administration	4.1±1.7 (2-8)	4.4±1.6 (2-7)	0.5

LogMAR ± SD: Log of the minimum angle of resolution ± Standard Deviation
PT-INR: prothrombin time-international normalized ratio

Table 2. Demographics of Patients

Combined phacoemulsification and vitrectomy group: Hyphema, apparent or microscopic, was seen on the first postoperative day in 15 eyes (41.7%) in the maintenance subgroup and in 3 eyes (45.5%) in the discontinuation subgroup (P = 0.6). Minor postoperative vitreous and retinal hemorrhage was found in 3 eyes (7.7%) and 6 eyes (15.4%) in the maintenance subgroup and in 2 eyes (5.6%) and 8 eyes (22.2%) in the discontinuation subgroup,

respectively (vitreous hemorrhage: P = 0.3; retinal hemorrhage: P = 0.3) (Table 3). Within 1 month of the surgical procedure, bleeding was not found without affecting the visual acuity. There was no vitreous or choroidal/suprachoroidal hemorrhage found in either of the two subgroups. No significant difference was found in non-hemorrhagic complications between the two subgroups (Table 3).

Phacoemulsification alone group			
	Maintenance group	Discontinuation group	P
	403 eyes	421 eyes	
Systemic complications			
Cerebral events	0 (0.0%)	0 (0.0%)	-
Cardiovascular events	0 (0.0%)	0 (0.0%)	-
Hemorrhagic complications			
Subconjunctival hemorrhage	87 (21.6%)	46 (10.9%)	< 0.0001
Hyphema (> 1mm)	0 (0.0%)	0 (0.0%)	-
Microscopic hyphema	26 (6.5%)	11 (2.6%)	0.0078
Vitreous hemorrhage	0 (0.0%)	0 (0.0%)	-
Retinal hemorrhage	6 (1.4%)	3 (0.7%)	0.3
Choroidal/suprachoridal hemorrhage	0 (0.0%)	0 (0.0%)	-
Non-hemorrhagic complications			
Intraoperative complications			
Early perforation	7 (1.7%)	9 (1.1%)	0.7
CCC tear	13 (4.0 %)	18 (4.3%)	0.4
Posterior capsule rupture	5 (1.2%)	7 (1.7%)	0.6
Vitreous loss	2 (0.4%)	3 (0.3%)	0.7
Nucleus drop	0 (0.0%)	0 (0.0%)	-
Early postoperative complications			
Hypotony	0 (0.0%)	0 (0.0%)	-
IOP spike	16 (3.9%)	13 (3.1%)	0.5
Corneal edema	8 (2.0%)	10 (2.4%)	0.7
Shallow/flat anterior chamber	0 (0.0%)	0 (0.0%)	-
Distorted pupil	2 (0.0%)	3 (0.0%)	0.7
IOL dislocation	0 (0.0%)	0 (0.0%)	-
Vitreous herniation	0 (0.0%)	0 (0.0%)	-
Retinal detachment	0 (0.0%)	0 (0.0%)	-
Endophthalmitis	0 (0.0%)	0 (0.0%)	-

Combined phacoemulsification and vitrectomy group			
	Maintenance group	Discontinuation group	P
	36 eyes	33 eyes	
Systemic complications			
Cerebral events	0 (0.0%)	0 (0.0%)	
Cardiovascular events	0 (0.0%)	0 (0.0%)	

Hemorrhagic complications			
Hyphema (> 1mm)	1 (2.8%)	0 (0.0%)	0.3
Microscopic hyphema	14 (38.9%)	15 (45.5%)	0.6
Vitreous hemorrhage	3 (7.7%)	2 (5.6%)	0.3
Retinal hemorrhage	6 (15.4%)	8 (22.2%)	0.3
Choroidal/suprachoridal hemorrhage	0 (0.0%)	0 (0.0%)	-
Non-hemorrhagic complications			
Intraoperative complications			
Early perforation	0 (0.0%)	0 (0.0%)	-
CCC tear	2 (5.6%)	1 (3.0%)	0.6
Posterior capsule rupture	0 (0.0%)	0 (0.0%)	-
Vitreous loss	0 (0.0%)	0 (0.0%)	-
Early postoperative complications			
Hypotony	0 (0.0%)	0 (0.0%)	-
IOP spike	4 (11.1%)	2 (6.1%)	0.4
Corneal edema	0 (0.0%)	0 (0.0%)	-
Shallow/flat anterior chamber	0 (0.0%)	0 (0.0%)	-
Distorted pupil	0 (0.0%)	0 (0.0%)	-
IOL dislocation	0 (0.0%)	0 (0.0%)	-
Retinal detachment	1 (2.8%)	0 (0.0%)	0.3
Endophthalmitis	0 (0.0%)	0 (0.0%)	-

Table 3. Incidence of hemorrhagic and non-hemorrhagic complications in the discontinuation and maintenance group

3.2 Visual acuity change

Phacoemulsication alone group: Mean BCVA before and at 1 month postoperative were 0.312 and 0.917 in the maintenance subgroup and 0.326 and 0.925 in the discontinuation subgroup, respectively (Table 4). The mean changes for the LogMAR BCVA during the 1-month postoperative period were -0.467 ± 0.339 in the maintenance subgroup and -0.453 ± 0.342 in the discontinuation subgroup. These differences were not significant between the two subgroups (P = 0.6) (Table 4).

Combined phacoemulsification and vitrectomy group: In patients undergoing surgery for the treatment of epiretinal membrane, mean BCVA before and at 6 months postoperative were 0.337 and 0.757 in the maintenance subgroup and 0.359 and 0.737 in the discontinuation subgroup, respectively (Table 4). The mean changes for the LogMAR BCVA during the 1-month postoperative period were -0.351 ± 0.173 in the maintenance subgroup and -0.312 ± 0.164 in the discontinuation subgroup (P = 0.5) (Table 4). In patients with macular hole, all patients had macular hole closure in the two subgroups. Mean BCVA before and at 6 months postoperative were 0.229 and 0.774 in the maintenance subgroup and 0.257 and 0.796 in the discontinuation subgroup, respectively (Table 4). The mean changes for the LogMAR BCVA during the 6-month postoperative period were -0.528 ± 0.195 in the maintenance subgroup and -0.491 ± 0.216 in the discontinuation subgroup (P = 0.6) (Table 4).

Phacoemulsification alone group			
	Maintenance group	Discontinuation group	
No.of eyes	403	421	
Baseline			
BCVA	0.312 (20/64.0)	0.326 (20/63.3)	-
Mean (LogMAR) ± SD	0.505±0.391	0.486±0.393	0.45
1day			
BCVA	0.849 (20/23.6)	0.853 (20/23.4)	-
Mean (LogMAR) ± SD	0.071±0.187	0.069±0.181	0.9
Change of LogMAR	-0.434±0.325	-0.415±0.328	0.4
1 week			
BCVA	0.899 (20/22.3)	0.903 (20/22.1)	-
Mean (LogMAR) ± SD	0.047±0.163	0.044±0.157	0.8
Change of LogMAR	-0.459±0.333	-0.442±0.340	0.5
1 month			
BCVA	0.917 (20/21.8)	0.925 (20/21.6)	-
Mean (LogMAR) ± SD	0.039±0.155	0.034±0.151	0.6
Change of LogMAR	-0.467±0.339	-0.453±0.342	0.6

Table 4. A Change of Best-corrected Visual Acuity

4. Discussion

In patients who maintained warfarin and/or aspirin treatment, no increase was identified in potentially sight-threatening complications in the phacoemulsification group and the combined phacoemulsification and vitrectomy group compared with those who discontinued the treatment. In patients undergoing phacoemulsification alone, the incidence of subconjunctival hemorrhage and microscopic hyphema in the maintenance subgroup was significantly higher compared with the discontinuation subgroup; all subconjunctival hemorrhage and hyphema in both subgroups were self-limiting and spontaneously resolved within one week.

In patients undergoing combined phacoemulsification and vitrectomy, there was no significant difference in hemorrhagic complications between patients with and without interruption of anticoagulant and/or antiplatelet therapy. In patients undergoing cataract surgery alone, several investigators have demonstrated that the incidence of hemorrhagic complications was approximately 9-10% (range 0 to 36.1%, mean 13.0±13.3%) in anticoagulated patients without discontinuation of warfarin. Postoperative hemorrhagic complications typically consisted of mild hyphemae and subconjunctival hemorrhage, all of which were self-limiting and without further clinical consequences. [12-27]. Several studies have compared postoperative bleeding in anticoagulant-treated patients with that of normally coagulated patients. Even patients with normal coagulation undergoing cataract surgery may have postoperative hemorrhage. Patients without warfarin discontinuation have an approximately 3-fold greater risk for postoperative bleeding than normally anticoagulated patients who have cataract surgery [14,21,23-27].

The variance of the incidence of hemorrhagic complications previously reported may result from inconsistency of their definition and the duration and methods of their observation

[12-27]. Hemorrhagic complication rates may have also been influenced by the anesthestic and surgical techniques used. It is difficult to accurately measure risks of local anesthetic blockade in anticoagulated patients since anesthetic techniques varied as studies done after the late 1990s tended towards use of topical or sub-Tenon anesthesia [21-27], whereas, before then, retrobulbar or peribulbar anesthesia had been commonly used [13,15,20,21] Retrobulbar hemorrhage is more frequent even when anticoagulation is discontinued prior to surgery when compared to normally coagulated patients [27]. Prognosis for visual acuity with retrobulbar hemorrhage is generally good, provided an experienced surgeon is present to rapidly decompress the eye. However, sub-Tenon block and topical techniques appear safer still, and acceptable provided both patients and surgeons are satisfied. In the studies after the mid-1990s phacoemulsification was in common use [16,17,21-24,26,27]. Before then, the extracapsular extraction technique, which needed a larger wound and caused greater tissue injury and bleeding than the phacoemulsification technique, had been employed. [12-15,17,20]. However, hemorrhagic complication rates did not appear to differ based on surgical technique.

Benzimra et al. showed a significant increase in hemorrhagic and non-hemorrhagic complications without discontinuation of continuous antiplatelet medications [27], whereas other studies have demonstrated no increase [28-30]. These complications had no significant effect on visual improvement [27-30].

In this study, patients undergoing vitreous surgery with epiretinal and macular hole in combination with phacoemulsification were studied. Even normally coagulated patients undergoing vitrectomy have a risk of hemorrhagic complications from other diseases, including retinal detachment and proliferative diabetic retinopathy, which were hence excluded from this study. In patients without interruption of anticoagulant and/or antiplatelet medications, there were 14 microscopic hyphema and 6 retinal hemorrhages, whereas 15 microscopic hyphema and 8 retinal hemorrhage were found in patients who discontinued the medications. Most of the retinal hemorrhages occurred during the peeling of the epiretinal and internal limiting membranes, and hyphema developed from a postoperative prone position in patients who underwent macular hole surgery. Several investigators demonstrated the incidence of hemorrhagic complications in vitrectomy was less than 1% [31-35], the vast majority of which was transient vitreous hemorrhage, which was self-limiting and without any significant effect on visual improvement. There was only one potentially serious subretinal hemorrhage, which required retinotomy, in patients on anticoagulation [34]. Therefore, there has been no reported evidence that perioperative continuation of anticoagulant therapy may a deleterious impact on cataract surgery and postoperative visual improvement related to either continuation of anticoagulation or hemorrhagic complications [1-9].

In this study, no systemic complications were noted in patients with and without anticoagulant and antiplatelet therapy in the phacoemulsication group and combined phacoemulsication and vitrectomy group. Many believe that there may be minimal risk of thromboembolism in patients whose anticoagulant therapy is discontinued for surgery [36]. Less than a half of reported hospitals continued antiplatelet or anticoagulant regimen at the time of surgery in Japan [37], although the majority of the Canadian Society of Cataract and Refractive Surgery members reported that they did not stop either warfarin or aspirin for cataract surgery during the perioperative period [38]. Current evidence suggests that warfarin therapy significantly improves prognosis in patients with atrial fibrillation with coexisting cerebrovascular disease, and those with non-tissue prosthetic heart valves [1].

Attempted cessation and recommencement of warfarin therapy may not only reverse anticoagulation for unpredictable periods of time but may also expose patients to a transient yet dangerous hypercoagulable state [39,40]. The discontinuation of warfarin does not prevent thromboembolism. There have been several documented cases of serious embolic complications, including deaths, after discontinuing warfarin therapy. Cosgriff reported that thromboembolisms occurred in14 of 17 patients (71% of cases) of dental extractions whose warfarin therapy was discontinued [41]. In 542 documented cases of discontinuing anticoagulant therapy for dental procedures, five cases (0.9%) had serious embolic complications, including four deaths [42]. Another study showed that discontinuation of anticoagulant therapy did not increase the incidence of thromboemobolitic events, but caused it to become serious and to increase the morbidity once the events occur [1]. However, in patients with cataract surgery, there was one (2.4%) thromboembolic complication in 36 cases of discontinuing anticoagulant treatment [14]. There were none (0%) in 208 patients discontinuing anticoagulant therapy whereas two thromboembolisms (0.4%) were reported in 524 anticoagulated patients and 15 thromboembolisms (0.08%) in 18,215 normally coagulated patients [21].

This study has important limitations. The study design was non-randomized, and the sample size of this study was relatively small and therefore not powered to detect small differences. Small sample size also precluded an assessment of safety. A large-scale randomized study is required to assess the safety of continuous anticoagulant and antiplatelet treatment associated with phacoemulsification alone and in combination with vitrectomy.

In cataract surgery blood vessels likely to cause persistent hemorrhage are unlikely to be encountered [6]. Although there is a theoretical risk of hemorrhagic complications after cataract surgery in patients at therapeutic levels of anticoagulation, the risk may be greatly outweighed by the risk and morbidity of thromboembolism after discontinuation of anticoagulant therapy [2-9]. There are several documented cases of serious thromboembolic complications, including deaths, in patients after discontinuation of anticoagulant therapy [41,42]. Patients receiving anticoagulant therapy who undergo cataract surgery have been reported to have more hemorrhagic complications than patients with normal coagulation. The vast majority of these complications are self-limiting and without significant effect on visual improvement. Ophthalmologists and physicians should collaborate closely in treating their patients who are taking anticoagulants, especially to make sure that the patient's INR is within the therapeutic range before cataract surgery [1-9]. Good surgical and anesthetic techniques and local measure, including cautery, to control bleeding are also important in all patients undergoing intraocular surgery, especially those receiving continuous anticoagulant and antiplatelet medications [3-9,23].

Although the sample size in each group was small, the current study demonstrated that (1) patients undergoing cataract surgery alone who maintained warfarin and/or aspirin experienced a significantly higher incidence of subconjunctival hemorrhage and hyphema compared with those who discontinued them; and (2) there was no significant difference in the incidence of intraoperative and postoperative complications and visual improvement between patients with and without interruption of anticoagulant and antiplatelet medications in patients undergoing cataract surgery alone and in combination with vitrectomy. Future study of a large population is needed to verify these observations. However, this information may be clinically valuable when treating patients with cataract and long-term administration of anticoagulant or antiplatelet medication.

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