Nonarteritic anterior ischemic optic neuropathy (NAION) is the most prevalent optic nerve disorder among patients over 50 years of age, with sudden onset, painless visual loss, with an accompanying relative afferent pupillary defect and optic disc edema. Although the pathophysiology of NAION has not been fully elucidated, several risk factors have been considered, including advanced age, systemic hypertension, diabetes mellitus, and certain optic disc morphologies. An association between obstructive sleep apnea (OSA) and NAION has also been recognized. One prospective cohort study indicated that the relative risk of OSA among patients with NAION was 4.9; a later retrospective cohort study demonstrated that patients with OSA not treated with continuous positive airway pressure (CPAP) had a 16% increased hazard of developing NAION compared to patients without OSA. The following review will discuss the most recent understanding of the relationship between OSA and NAION, with implications for further research and prevention strategies.

**Keywords:** Optic nerve diseases, anterior ischemic optic neuropathy, sleep disorders, obstructive sleep apnea.

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**BACKGROUND**

**Clinical Characteristics of NAION**

Nonarteritic anterior ischemic optic neuropathy (NAION) is an ischemic insult to the anterior portion of the optic nerve, though an exact pathophysiology remains unclear. Classically, NAION presents with sudden, painless, monocular visual loss, most often in patients over the age of 50. Visual loss may affect central vision, peripheral fields, or both. Visual field deficits vary, but commonly, patients present with superior or inferior altitudinal field defects evident on automated perimetry. Interestingly, vision loss is most often noted upon awakening. Visual acuity on presentation may range from 20/20 to no light perception. Dyschromatopsia may be associated with NAION, with the level of color vision impairment coinciding with the degree of visual acuity deficit. Pain with eye movements is not a classic feature of NAION.

For a diagnosis of NAION to be made, the affected eye must exhibit a relative afferent pupillary defect. If bilateral NAION is present, a relative afferent pupillary defect will be absent, yet both pupils will react sluggishly to light. Optic disc edema evident on fundoscopy is another requirement for a diagnosis of NAION. The optic disc edema may be localized or diffuse, and the edematous area may be hyperemic or mildly pale (though not as pale as with arteritic anterior ischemic optic neuropathy). Nerve fiber layer hemorrhages are often visualized at the optic disc margins. In general, optic disc edema associated with NAION resolves in 4 to 8 weeks; if it fails to do so, an alternative diagnosis should be considered.

In a subset of NAION patients, the acute visual loss continues to decline over the following days to weeks. In the Isonic Optic Neuphthology Decompression Trial (IONDT), 45% of patients reported a subjective worsening of their vision over the course of 30 days; whereas other studies have indicated continued deterioration of vision in approximately 30% of affected patients. But this is not to say that a significant portion of NAION patients do not exhibit visual improvement. The IONDT also demonstrated that at 6 months following the initial onset of visual loss, 42.7% of patients improved ≥ 3 lines of visual acuity, versus 44.9% with little to no change and 12.4% with worsening of vision by ≥ 3 lines.

The rate of recurrent NAION, meaning a second, distinct ischemic event in the same eye, is low; in one study, 53 of 829 (3.6%) eyes experienced a recurrent NAION in 3-year follow-up. A sequential NAION, a separate ischemic event in the contralateral eye, is more common. In one published series, 24% of 83 patients with NAION developed sequential involvement of the contralateral eye in an average time of 2.9 years; similar rates of sequential NAION were found during the IONDT.

**Epidemiology of NAION**

NAION can occur at any age but is most prevalent among patients older than 50 years of age. The annual incidence of NAION among patients 50 years and older is between 2.3 and 10.2 per 100,000, with a prevalence of 0.54 per 100,000 patients of all ages. No specific gender predilection has been found, with both men and women affected equally. The majority of NAION patients, though, are Caucasian.

**Risk Factors Associated with NAION**

Several risk factors for the development of NAION have been proposed, including systemic vasculopathic risks such as systemic arterial hypertension, diabetes mellitus, hyperhemo-
cystinemia, and atherosclerosis. Studies have also revealed that NAION development may be related to optic disc morphology. A small cup-to-disc ratio and small optic disc size were frequently found among patients with NAION when compared to controls. The literature indicates that nocturnal arterial hypotension, particularly among patients with the aforementioned risk factors, may represent a precipitating (versus predisposing) factor in the development of NAION.

Obstructive sleep apnea (OSA), characterized by recurrent episodes of partial or complete upper airway obstruction causing cessation of breathing during sleep, is also a significant risk factor for the development of NAION. In their influential 1993 publication, Young et al. reported that of 602 middle-aged persons undergoing overnight polysomnography, 9% of middle-aged women and 24% of middle-aged men suffered from undiagnosed sleep disordered breathing (≥ 5 episodes of apnea or hypopnea/h of sleep). The authors also concluded that 4% of men and 2% of women in this age group “met minimal criteria for the sleep apnea syndrome,” indicating an apnea-hypopnea score > 5 and self-reported hypersomnolence. A more recent analysis of data collected from the 2005 National Sleep Foundation’s Sleep in America Poll revealed that of 1,506 respondents, 31% of men and 21% of women were at high risk for OSA according to the Berlin questionnaire. The percentage of respondents at high risk for OSA increased with increasing BMI, with 59% of individuals with BMI > 30 at high risk. The risk of OSA also increased linearly with increasing age. Additional risk factors for OSA include large neck circumference, craniofacial abnormalities, nasal obstruction, and increased pharyngeal tissue. The severity of sleep apnea may be increased by smoking, consuming alcohol, sleeping in the supine position, or engaging in minimal physical activity. Airway obstruction is corrected only after arousal from sleep, when airway muscle tone increases.

OSA is recognized as an independent risk factor in the development of daytime hypertension, with a recent study indicating a linear relationship between the odds of hypertension and severity of OSA. The Wisconsin Sleep Cohort Study provided prospective confirmation of this association, reporting that the apnea-hypopnea index (the average number of disordered breathing events per hour of sleep) is an independent predictor of daytime hypertension, with an odds ratio of 2.89 among patients with an apnea-hypopnea index > 15 per hour. Airway obstruction is corrected only after arousal from sleep, when airway muscle tone increases.

Mojon and colleagues published a seminal case-control cross-sectional study that sought to determine the prevalence of sleep apnea among patients diagnosed with NAION. Seventeen patients diagnosed with NAION (mean age: 64.6 ± 11.7 years), recruited from Switzerland and Boston, agreed to undergo overnight polysomnography, along with 17 control patients (mean age: 63.3 ± 11.0) who were referred for suspected restless leg syndrome; controls were matched according to age, gender, and cardiovascular risk factors. Sleep apnea syndrome was diagnosed and graded according to respiratory disturbance index (Normal, RDI < 10; Mild sleep apnea, RDI 10-20; Moderate sleep apnea, RDI 20-40; Severe sleep apnea, RDI > 40).

Twelve (71%) of 17 NAION patients were diagnosed with OSA, versus only 18% among matched controls. The elevated mean RDI among NAION patients compared with restless leg syndrome controls was statistically significant (25.3 ± 21.9 versus 9.2 ± 20.8, respectively). Mojon et al. also compared their OSA prevalence results to those of a larger random sample of men (741 subjects), aged 20-100 years of age and without NAION, published previously by Bixler et al. The prevalence of OSA among NAION patients in the study by Mojon et al. was significantly higher than the prevalence calculated from sleep studies among Bixler et al. subjects. In light of their comparisons between a previously reported control group and a current control group (restless leg syndrome suspects), in addition to similar prevalence rates obtained in two independent eye clinics (both Switzerland and Boston), the authors concluded that the elevated prevalence of OSA among NAION patients was “real and clinically significant.”

Palombi and colleagues further pursued the association between sleep apnea and NAION. Twenty-seven patients (18 men, 9 women, mean age 65 years), newly diagnosed with NAION, where recruited to undergo polysomnography. The authors found that “NAION was nearly always associated with sleep apnea,” with 89% of patients having an apnea-hypopnea index > 15 per hour. The prevalence of OSA among NAION patients was compared to the prevalence of OSA in the general population (5,615 subjects), published in a 2002 study completed by Young et al. The relative risk of OSA among NAION patients compared to members of the general population was 4.9.

Although the gold standard for diagnosing OSA is polysomnography, such sleep studies are time-consuming, fairly expensive, and include a variety of invasive recordings. Therefore, Li and colleagues attempted to quantify the prevalence of OSA among NAION patients via telephone questionnaires (SA-SDQ), which have been validated against full polysomnography in terms of sensitivity and specificity. Seventy-three patients diagnosed with NAION, along with 73 age- and gender-matched controls, were given the verbal questionnaire. Questions addressed symptoms of OSA, as well as current weight, BMI, smoking status, etc.; a score of 36 for men and 32 for women served as the diagnostic cutoff for OSA (a score closer to 60 indicated a higher likelihood of OSA). Thirty percent of the NAION patients scored in the OSA range, whereas only 17.8% did so among the control group. Statistical analysis indicated that patients with NAION were 2.62 times more likely to have a SA-SDQ score consistent with OSA. These findings were consistent with results from the previously mentioned studies, though the magnitude of association was not as great.

The three preceding studies examined the prevalence of OSA among patients with NAION. Stein et al. investigated the co-
verse association—the prevalence of NAION among patients previously diagnosed with OSA.15 Stein et al. completed a retrospective, longitudinal cohort study utilizing billing records of 2.2 million managed care recipients in the United States. The incidence of NAION was determined among patients older than 40 years of age, who had been with the managed care network for at least one year, with at least one visit to an eye care provider during that time. Included patients must have received a diagnosis of sleep apnea prior to experiencing an NAION event.

Stein and colleagues found, after adjustment for confounding variables, that individuals diagnosed with sleep apnea and not treated with continuous positive airway pressure (CPAP) had a 16% increase in the hazard of developing NAION when compared to controls without sleep apnea.15 Otherwise, the adjusted hazard of developing NAION was not significantly different between those sleep apnea patients receiving CPAP treatment and controls without sleep apnea. Authors concluded that it may be beneficial for newly diagnosed sleep apnea patients to have a thorough ophthalmic examination to assess the possibility of coexistent optic neuropathy, especially those not treated with CPAP. Unfortunately, due to a lack of access to medical records, the incidence of NAION was not quantified based upon the severity of sleep apnea, and possible differences among those patients using and not using CPAP, with regards to their severity of sleep apnea, was not noted.15

The current standard of treatment for OSA remains CPAP during sleep, which serves as an airway splint to keep the airway patent.13 It has been demonstrated that the use of CPAP eliminates apneic episodes, improves fragmented sleep, and minimizes hemodynamic changes associated with OSA.11 Studies have also revealed that CPAP use improves blood pressure, alleviates the recurrence of cardiac arrhythmias and lessens the excess mortality among OSA patients who have suffered a stroke.12 In light of the abovementioned association between OSA and NAION, it is reasonable to hypothesize that if a patient with OSA is treated with CPAP, the probability of developing NAION would be less than if CPAP was not utilized. The findings of Stein and his colleagues substantiated this supposition.15

The value of CPAP treatment in the prevention of NAION was questioned by Behbehani et al. in their 2005 case reports.5

At Wills Eye Hospital in Philadelphia, PA, between 2002 and 2003, 108 patients were newly diagnosed with NAION. Three of those patients had been using CPAP prior to the diagnosis of NAION: (1) a 55-year-old male, treated for 2 years with a nasal CPAP machine at home; (2) a 57-year-old male treated for 6 years with a nasal CPAP machine; (3) a 50-year-old male treated with CPAP for 4 months prior to visual loss. All 3 patients suffered from hypertension; 2 had hypercholesterolemia, and 1 had diabetes. With no further studies investigating whether CPAP prevents NAION development, the utility of CPAP use for prevention of ocular complications of OSA remains speculative.

Blaivas and Uddin most recently published a novel case report of a 79-year-old male diagnosed with bilateral NAION, whose past medical history was significant for OSA and a euthyroid goiter for which the patient refused surgery for several years.16 Authors proposed that the goiter, demonstrated to decrease the tracheal tug refers to the slight caudal movement of the trachea during tidal breathing, which "tenses the upper airway soft tissues, serving to counter inspiratory upper airway collapse."18 In light of the patient’s BMI of 25 and his normal craniofacial structure, it was concluded that the patient experienced a rare cause of OSA, which ultimately resulted in bilateral NAION.

Table 1 provides a summary of the published epidemiological studies regarding the association between OSA and NAION.

### Table 1—Summary of published epidemiological investigations regarding the association between OSA and NAION

<table>
<thead>
<tr>
<th>Authors</th>
<th>Type of Study</th>
<th>Results</th>
</tr>
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<tbody>
<tr>
<td>Mojon et al.3</td>
<td>Case-control, cross-sectional</td>
<td>12 (71%) of 17 NAION patients diagnosed with OSA by polysomnography. 3 (18%) of 17 restless leg syndrome controls diagnosed with OSA by polysomnography.</td>
</tr>
<tr>
<td>Palombi et al.4</td>
<td>Prospective, cohort</td>
<td>24 (89%) of 27 NAION patients diagnosed with OSA by polysomnography. Relative risk of OSA among NAION patients: 4.9, compared to prevalence of OSA among general population.</td>
</tr>
<tr>
<td>Li et al.14</td>
<td>Case-control</td>
<td>30% of 73 NAION patients qualified as suffering from OSA by SA-SDQ (questionnaire). 17.8% of controls qualified as suffering from OSA by SA-SDQ. NAION patients 2.62 times more likely to have SA-SDQ score consistent with OSA, when adjusted for glaucoma, high cholesterol, and smoking.</td>
</tr>
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</table>

### PROPOSED PATHOPHYSIOLOGY LINKING OSA AND NAION

Nocturnal hypotension has long been implicated in the development of NAION, serving as the “final insult” among compromised optic discs.6,7 Hayreh et al. published a prospective report of 275 individuals with anterior ischemic optic neuropathy (AION), normal tension glaucoma, or primary open angle glaucoma who underwent 24-h ambulatory blood pressure monitoring. When all 3 optic nerve diseases were considered together, those individuals with visual field deterioration had sig-
significantly lower minimum nocturnal diastolic blood pressure. Hyperensive individuals on antihypertensive medications had significantly lower mean nocturnal systolic blood pressure, in addition to a larger mean percentage decrease in systolic, diastolic, and mean blood pressures during the night. The authors concluded that in an optic nerve head that is susceptible to vascular insufficiency, whether from altered autoregulation, arteriosclerosis, vasospastic disorders, systemic hypertension, or diabetes mellitus, nocturnal hypotension may no longer be simply a physiologic process; instead, may serve as “the straw that broke the camel’s back.”

In contrast, a study published by Landau et al. revealed contradictory results, indicating no significant difference in mean nocturnal decreases in blood pressure among NAION patients and controls. Thus, the role of nocturnal hypotension in NAION is not certain. Moreover, if nocturnal hypotension did play a role in the development of NAION, it may not be the reason as to why OSA, in particular, causes optic nerve damage. Previous studies have indicated that patients with OSA experience no nocturnal decrease in blood pressure, suggesting a limited or no role for nocturnal hypotension in the development of NAION among OSA patients.

Though extensively documented among cases of arteritic anterior ischemic optic neuropathy, Arnold found that histopathological evidence for infarction in the paralaminar regions of the optic nerve head, as well as occlusion of the short posterior ciliary arteries (SPCAs), in NAION is lacking. From the limited histopathological specimens of NAION that do exist in the literature, Arnold drew two conclusions regarding the pathogenesis of NAION: (a) Optic nerve head infarction is generally located in the retrolaminar region, implying that SPCA branches directly supplying the optic disc may be involved, rather than a primary role of the choroidal circulation. (b) A significant amount of NAION cases revealed cavernous degeneration, with accompanying mucopolysaccharide deposit that displaces optic nerve axons. The latter observation may imply focal compression as a contributing pathologic factor in the development of NAION.

Arnold described how fluorescein angiographic studies of NAION subjects report delayed filling of the prelaminar optic disc compared with normal controls and subjects with nonischemic optic disc edema. This finding suggests circulatory impairment in NAION as a primary process, rather than secondary to optic disc edema. Interestingly, fluorescein angiography also revealed, via “poorly correlated” filling of the optic disc and adjacent choroidal segments, that the level of vascular occlusion in NAION is located within the paraoptic branches of the SPCAs, after separating from the choroidal branches.

Tesser et al. analyzed 3-dimensionally reconstructed serial sections of an optic nerve with NAION from a 70-year-old male who had a past medical history significant for peripheral vascular disease, congestive heart failure, and hypertension. The patient died 20 days after diagnosed with NAION. Results were indicative of a compartment syndrome mechanism of NAION development, similar to a possible compressive etiology suggested by Arnold. The resulting infarct was widest anteriorly, nearest to the optic nerve head, and confined to the intrascleral portion of the optic nerve. The infarct did not correlate to any single vascular territory and vascular inflammatory infiltrates or emboli were not evident. Though the results suggested a compartment syndrome pathogenesis of NAION, it is still believed that an initial ischemic event leads to edema formation within the confined space of the sclera, ultimately leading to mechanical compression of optic nerve fibers. Subsequently, it would appear that surgical decompression of the optic nerve may be beneficial in the prevention and/or treatment of NAION, yet previous publications demonstrated no benefit.

Proposed etiologies of NAION are summarized in Table 2. Though observational studies have indicated an epidemiological association between OSA and NAION, as described above, a causal relationship cannot be presumed. Today, research continues to more clearly define the way in which OSA may specifically contribute to an isolated vascular insult and/or compartment syndrome of the optic nerve disc. How OSA affects homeostatic, physiologic mechanisms may serve as guidance in efforts to deduce the exact role OSA plays within the pathogenesis of NAION. The following are proposed mechanisms by which OSA may contribute to the development of NAION (also outlined in Table 3).

1. It has been hypothesized that direct exposure of the optic nerve to OSA-induced hypoxia can lead to optic nerve damage. Interestingly, due to the excellent buffering capacity of the human body, changes in PaCO₂ and pH during apneic episodes generally remain insignificant compared to changes in PaO₂.

2. It is suspected that OSA leads to vascular dysregulation of the optic nerve. Nocturnal hypoxia secondary to repetitive apneic episodes is detected by carotid chemoreceptors, which subsequently fuels hemodynamic changes, particularly an elevation in blood pressure. Inspiratory efforts against collapsed airways decrease intrathoracic pressures, leading to increased venous return and subsequent increases in stroke volume and cardiac output. The same inspiratory efforts lead to arousal from sleep, with even further activation of the sympathetic system. Due to these intermittent sympathetic surges, transient elevations in blood pressure are evident in OSA, often accom-

### Table 2—Proposed etiologies of NAION

<table>
<thead>
<tr>
<th>Proposed Etiology</th>
<th>Authors</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Ischemic</td>
<td>Arnold⁶</td>
<td>Vascular occlusion within paraoptic branches of short posterior ciliary arteries after separating from choroidal branches.</td>
</tr>
<tr>
<td>- Nocturnal Hypotension</td>
<td>Hayreh et al.⁷, Landau et al.¹⁷</td>
<td>Contradictory results regarding difference in mean nocturnal decrease in blood pressure between NAION patients and controls.</td>
</tr>
<tr>
<td>Compressive</td>
<td>Arnold⁴, Tesser et al.¹⁸</td>
<td>Ischemic insult drives subsequent edema formation, contributing to optic nerve compression and infarction.</td>
</tr>
</tbody>
</table>

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been found at high serum concentrations among OSA patients.

Vascular endothelial growth factor (VEGF) and endothelin-1 have been shown to be active substances, especially nitric oxide and endothelin. Vasodilatation associated with OSA may also be due to an imbalance between vascular factors: a diminution in the production of reactive oxygen species, therefore allowing vascular endothelial damage with the development of oxidative stress.

Hypoxia-induced cerebral vasodilation may further impair autoregulation of the optic nerve, leaving the nerve susceptible to ischemic events.

To date, it is believed that large variations in the concentration of blood oxygen and carbon dioxide may metabolically stress the autoregulatory ability of the optic nerve head. Riva et al. found that by autoregulation, through increased blood volume secondary to increased vascular capacitance, via recruitment of capillaries and/or increased in venous diameter, blood flow to the optic nerve head can remain steady until ocular perfusion pressure decreases to 15-20 mm Hg (or an intraocular pressure of 40-45 mm Hg is obtained). For the optic disc to experience hypoperfusion persistent enough to damage axonal fibers, impairment of this autoregulatory process, whether via arteriosclerosis or vasospasm, may very well play a role in NAION development.

In addition, the hypoxia-reoxygenation pattern associated with OSA contributes to oxidative stress with the production of reactive oxygen species, therefore allowing vascular endothelial damage. Optic nerve vascular dysregulation secondary to OSA may also be due to an imbalance between vasoactive substances, especially nitric oxide and endothelin. Vascular endothelial growth factor (VEGF) and endothelin-1 have been found at high serum concentrations among OSA patients. Hypoxia-induced cerebral vasodilatation may further impair autoregulation due to decreased cerebral perfusion pressure.

3. Elevated intracranial pressure during apneic spells may contribute to optic nerve head damage, directly or by circulatory compression. In one retrospective review of 18 adult males with idiopathic intracranial hypertension (IIH), 6 (33%) patients were identified as suffering from OSA; this prevalence was higher than the previously reported prevalence of OSA among the general male population. Also documented in the literature are 3 case reports of OSA patients with normal intracranial pressure during the day and “marked, frequent, and episodic elevation” in cerebrospinal fluid pressure over night (from 50 to 750 mm of water). Of importance, each episode of elevated intracranial pressure was preceded by an apneic or hypopneic episode. The authors proposed 3 possible mechanisms by which OSA may lead to elevated intracranial pressure, including (a) elevated central venous pressure leading to increased cerebrovascular volume, (b) increased systemic arterial blood pressure with accompanying elevated cerebroperfusion pressure, and lastly, (c) hypercapnia-induced cerebral vasodilation and ensuing decreased vascular resistance and increased cerebral blood flow. Questions remain as to whether OSA and IIH may be associated not by a causal relationship, instead, by their link to obesity.

Recognizing the association between OSA and NAION, though not fully clarified, has considerable implications for current medical practice. Ophthalmologists should be vigilant to ask NAION patients OSA screening questions and when necessary, to refer patients for polysomnographic studies. Simple screening questions are effective in differentiating what patients are most at risk of suffering from OSA, such as, “Are you sleepy during the day?" “Do you fall asleep more easily than normal?” “Does your partner comment that you snore loudly?” “Does your partner notice you gasping or choking at night during sleep?” “Has your partner witnessed any episodes where you stop breathing over night?”

A general medical examination completed by an ophthalmologist may also raise suspicion for underlying OSA, including systemic hypertension, obesity, increased neck circumference, large soft palate, and enlarged tonsils. But it is important to recognize that not all OSA patients are obese; instead, upper airway changes and retrognathia may indicate the diagnosis. Screening as described above is essential in preventing the profound cardiovascular and cerebrovascular effects secondary to OSA with the use of CPAP; the beneficial oculovascular effects of CPAP are not as definitive.

Likewise, general medical practitioners, pulmonologists, and sleep specialists should be cognizant of the risk of severe visual loss due to NAION among patients with OSA. Screening questions regarding visual function and early ophthalmic examinations are prudent, but what remains frustrating is the lack of prevention and treatment strategies.

This review highlights the need for further research. Larger sample size, retrospective or case-control studies to further quantify the association between OSA and NAION would be valuable but is not of imminent concern, for the association has been fairly well documented in the literature. The greatest need is for a more detailed understanding of the etiology of NAION and its pathophysiological link to OSA. It would be beneficial to examine more NAION eye specimens for histopathologic information which may guide new pathophysiologic hypotheses, in addition to considering the role individual differences in VEGF responses may have in this disease. Further investigation into the preventative measures of NAION is also necessary, especially a more thorough quantification of the prevalence of NAION among patients treated with CPAP. A closer look is needed, too, at the efficacy of preventing NAION with antihypertensives and diabetic medications. Additional research should be pursued so to one day provide protection for those at risk of developing NAION.
risk, and defense from progression or hope of reversal for those already affected by this potentially devastating disease.

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SUBMISSION & CORRESPONDENCE INFORMATION

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