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Perspective

Intracranial artery stenosis: Current status of evaluation and treatment in China

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Abstract

Intracranial artery stenosis (ICAS), a common cause of ischemic stroke, is a growing cause of concern in China. Recently, many epidemiological, etiological, pathophysiological, therapy, and diagnostic imaging studies have focused on ICAS, and guidelines and consensus on the diagnosis and treatment of ICAS have been published and updated by domestic experts. Such work is pivotal to our enhanced comprehension, diagnosis, and treatment of ICAS. In this review, we summarize the latest progress in the evaluation and treatment of ICAS in China.

Keywords: Intracranial artery stenosis; Evaluation; Treatment

Introduction

Stroke burden in China has increased over the last 30 years. Stroke is the leading cause of death in China. The incidence of ischemic stroke is estimated to be 69.6%, based on the Chinese intracranial atherosclerosis (CICAS) study,[1] and intracranial artery stenosis (ICAS) is estimated to account for 46.6% of all ischemic stroke cases.[2] Therefore, due attention should be paid to the problem.

Recently, many epidemiological, etiological, pathophysiological, therapy, and diagnostic imaging studies have focused on ICAS, and guidelines and consensus on the diagnosis and treatment of ICAS have been published or updated by Chinese experts.[3–10] Such work is fundamental to enhancing our understanding of ICAS, as well as improving the disease evaluation and treatment.

Epidemiology

In China, ICAS is estimated to account for 33–50% of all stroke cases, and more than 50% of transient ischemic attacks (TIA), contrary to Caucasian patients who are prone to extracranial carotid stenosis.[11–14] Both angiographic and autopsy studies suggest that intracranial artery lesions demonstrate higher severity

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than extracranial artery lesions in Chinese patients, similar to Japanese patients but different from Caucasian patients.[15,16] It remains unclear why the occurrence and severity of extracranial and intracranial lesions differ, and requires further investigation. Recently, a large, prospective, multicenter, hospital-based, cohort study, the CICAS study, indicated that the prevalence of ICAS was 46.6% in Chinese patients, consistent with previous research by Hong Kong-based academics.[2,12,13] According to the CICAS study, patients with ICAS experience more severe stroke at admission, have longer hospital stays, and higher risk of recurrent stroke.[2] The recurrent stroke rate was only 5% in the CICAS study patients with 70–99% stenosis, and lower than previous trials (23% in the WASID study and 12.2% in the medical arm of the SAMMPRIS study).[2,17–19] However, the occurrence rate was exceptionally high among patients with severe stenosis and multiple risk factors.[2,17–19] Moreover, the CICAS study reported both a geographic and gender variation in the distribution of ICAS in China; higher rates were recorded in northern China and women aged >63 years.[20] Northern patients were more likely,than the southern patients, to have both intracranial and extracranial lesions, multiple intracranial atheroscleroses, and occlusive lesions, which may be explained by the higher number of risk factors observed in northern patients, such as diabetes mellitus, hyperlipidemia, family history of stroke, smoking, heavy drinking, hyperhomocysteinemia, and overweight.[20]

Contrary to symptomatic ICAS, asymptomatic ICAS is often ignored. Wong et al studied 590 asymptomatic villagers in central rural China, and found 41 individuals (6.9%) with ICAS.[21] However, when the investigators applied transcranial Doppler (TCD) to screen 3057 patients with no history of stroke or TIA but at least one vascular risk factor, including hypertension, diabetes, or hyperlipidemia, they found that 385 patients (12.6%) had middle cerebral artery (MCA) stenosis.[22] These data suggest that asymptomatic ICAS is not uncommon, especially in patients with vascular risk factors. Moreover, ICAS was most common in young Chinese patients with ischemic stroke, likely due to high exposure to hypertension, smoking, dyslipidemia, and diabetes.[23,24] Thus, more attention and further studies are required for these special subgroups.

Etiology

Many studies indicate that vascular risk factors, including hypertension, diabetes mellitus, hyperlipidemia, family history of stroke and heart disorders, smoking, heavy drinking, hyperhomocysteinemia, and overweight, are associated with ICAS.[2,16,17,20–25] However, there are some inconsistencies in the data. Unlike the CICAS study, most studies are limited by, for example, small sample sizes and single-center, retrospective designs. Moreover, several studies have attempted to explain the different distributions of extracranial and intracranial stenosis between Asians and Caucasians, with inconsistent conclusions.[15,26–28] Thus, well-designed epidemiological studies are required to provide more valuable clinical information for enhanced patient management.

Evaluation of ICAS

The most widely used tools used for the diagnosis and assessment of ICAS include TCD, computed tomography angiography (CTA), magnetic resonance angiography (MRA), and digital subtraction angiography (DSA). However, whilst these techniques are able to measure arterial lumen stenosis, they cannot provide sufficient information on the characteristics of artery walls or plaques, or the status of collateral vessels and fractional flow, all of which play vital roles in predicting the risk of subsequent ischemic stroke.[29] More recent studies focus on atherosclerotic plaque morphology and hemodynamic assessment, and many new techniques, including high-resolution magnetic resonance imaging (HR-MRI), molecular imaging, intravascular ultrasound, and optical coherence tomography, have been developed.[29]

HR-MRI

HR-MRI is a non-invasive and effective tool to depict the vessel wall and plaque components. Xu et al demonstrated that HR-MRI can clearly display the wall structure of MCA, compensate for the limitations of MRA, and help to detect atherosclerotic lesions not visible via MRA.[30] By comparing the vessel wall properties of symptomatic and asymptomatic MCA stenosis using HR-MRI, investigators have found that symptomatic MCA lesions have a larger wall area, greater remodeling ratio, higher prevalence of expansive remodeling, and lower prevalence of constrictive remodeling, suggesting a possible correlation between the MCA wall features and clinical manifestations.[31] Moreover, MCA plaques tend to be located in the ventral and inferior walls, opposing the penetrating arteries orifices, whilst symptomatic MCA stenosis is characterized by superior rather than inferior plaques, especially in patients with penetrating infarction.[32]

Similarly, Sui et al also demonstrated that ventral and superior wall plaques are common in MCA stenosis with acute infarction.[33] Both studies indicate that plaque distribution may play an important role in stroke occurrence related to MCA stenosis.

In their research on intraplaque hemorrhage, Xu et al found that the occurrence rate of high signals on HR-MRI T1-weighted fat-suppressed images (HST-1), highly suggestive of fresh or recent intraplaque hemorrhage, was significantly higher in symptomatic versus asymptomatic MCA stenosis, although further pathological verification is needed.[34] Another HR-MRI research found that deep tiny flow voids (DTFVs)are commonly observed along MCA atherosclerotic occlusions, especially in asymptomatic patients, but are rarely detected in patients with large territorial infarctions or healthy control subjects.[35,36] Moreover, the distribution pattern of DTFVs is different from that of penetrating arteries or moyamoya collaterals.[35,36] These reports indicate that DTFV, a unique HR-MRI finding, is pathological but associated with relatively good outcomes, which may originate from new vessel network formation in response to chronic cerebral ischemia.[35,36] Thus, HR-MRI is a feasible and effective tool for evaluating the prognosis of MCA stenosis, and may provide new insight into the mechanisms of ICAS.

A recent study aimed to investigate the relationship between compensatory remodeling in symptomatic MCA stenosis with HR-MRI and TCD monitoring of microembolic signals (MESs); MESs were observed more frequently in the positive remodeling (PR) group than non-PR group and the authors hypothesized that PR may represent an early feature of plaque vulnerability and rupture.[37] This is the first study to explore vessel wall morphology in ICAS patients using MESs and HR-MRI.[37] Combining different techniques to assess plaque instability and evaluate subsequent stroke risk may be a valuable approach for prospective research.

Chinese academics have also made substantial efforts to explore vertebral basilar artery stenosis using HR-MRI. Huang et al detected that plaques were mainly distributed at the ventral site of basilar arteries, away from penetrating artery orifices, suggesting that HR-MRI may provide precious information to avoid unnecessary endovascular therapy complications in the basilar artery.[38] Jiang et al utilized HR-MRI to guide endovascular interventions of basilar artery stenosis, reporting reduced risks of perforator stroke and iatrogenic dissection with HR-MRI.[39] These studies suggest that HR-MRI may directly delineate the anatomical relationship between plaque and penetrating artery orifices, and effectively guide endovascular therapy in basilar artery stenosis to avoid unnecessary complications. The researchers also investigated arterial remodeling of severe symptomatic basilar artery atherosclerosis with HR-MRI.[40] They found that PR was more commonly observed in patients with advanced basilar artery stenosis, and that PR compared to non-PR lesions have higher plaque sizes and represent a greater burden.[40]

Other technical progress in the assessment of ICAS

Recent advances in cardiology indicate that assessment of the hemodynamic impact of coronary artery lesions is superior to measuring stenosis in terms of guiding revascularization therapy and predicting outcome. This inspired neurologists to move from evaluating the degree of stenosis to exploring hemodynamic features when assessing ICAS.[29,41,42] Leng et al reconstructed computational fluid dynamics (CFD) models based on CTA images to assess the hemodynamic features of ICAS.[43] The investigators found that changes in shear strain rates and blood flow velocities across lesions significantly related to ischemic stroke in the territory at 1 year, potentially predictive of risk of stroke recurrence.[43] The first study in which pressure guidewire was floated across the intracranial lesion site to measure fractional flow reserve (FFR), a superior approach to anatomic stenosis for determining ischemic risk in coronary research, was conducted by a group of neurologists from China and the USA in ICAS.[44] The preliminary outcome indicated that fractional flow measurement across intracranial artery lesions with a pressure guidewire was technically feasible and safe.[44] Moreover, based on the CFD method, the researchers designed a non-invasive technique for computing the fractional pressure ratio (FPR), to evaluate the hemodynamic significance of severe ICAS; they found that this non-invasive parameter was comparable with the invasive parameter.[45] Although these outcomes are preliminary and require further confirmation, these results are promising in terms of guiding clinical decisions for the treatment of ICAS and patient selection for relevant clinical trials.

Recently, more attentions have been given to investigate collateral circulation and angiogenesis, as extensive research has confirmed their vital role in predicting prognosis and risk of ischemic events in patients with ICAS.[46,47] Previous studies indicated that angiogenesis can be induced by hypoperfusion in chronic cerebral ischemia.[48,49] Recently, Shu et al directly depicted angiogenesis with ^{68}Ga-NOTA-PRGD2[67] positron emission tomography/computed tomography (PET/CT), on the stenotic/occlusive artery side, in patients with severe ICAS. They found that the post-qualified event time interval can affect the extent of angiogenesis; hence, this is the first study to evaluate the collateral circulation route at the level of angiogenesis *in vivo*.[50] These studies of collateral circulation and angiogenesis may provide more information on the prognosis and adaption of treatment in ICAS patients.

Treatment

A large number of clinical trials on the treatment and management of ICAS have been undertaken or are currently underway. In general, ICAS treatment includes medication and revascularization while the medical treatments, involving antiplatelet therapy and management of vascular risk factors, are fundamental treatments.

Medical treatment

Risk factor management, including hypertension, diabetes mellitus, hyperlipidemia, smoking, heavy drinking, hyperhomocysteinemia, and overweight, plays a crucial role in the treatment and prevention of subsequent ischemic events associated with ICAS. Many studies have confirmed the relationship between ideal health behaviors and the lower prevalence of ICAS, yet detailed recommendations and criteria are still unclear.[51–53]

A number of studies indicate that hypertension, even pre-hypertension, is associated with a high prevalence of both asymptomatic and symptomatic ICAS.[54–60] However, relevant studies on blood pressure management in ICAS are limited. Although some trials, such as WASID and SAMMPRIS, suggest that blood pressure control is safe and beneficial in patients with ICAS, there is research indicating that over dose of hypotensive drugs increases the risk of stroke in patients with MCA stenosis.[61] Moreover, research indicates that stenotic lesions can affect the local hemodynamic environment and impair the capacity of dynamic cerebral autoregulation among asymptomatic and symptomatic patients with ICAS.[62,63] Thus, balancing the benefits of blood pressure control and the risks of hypoperfusion is still challenging. Hao et al found that the relationship between blood pressure on admission and outcomes in acute ischemic stroke patients with severe ICAS presented a U-shaped curve. In their study, patients with systolic blood pressures (SBPs) of more than 160 mmHg or less than 120 mmHg had an increased tendency toward death or disability, whilst patients with SBP of 120–159 mmHg had the lowest rates of adverse outcomes.[64]

Modulation of blood lipid and treatment with statin is currently a topic of great interest. A previous small sample trial showed that 54% (29/54) of stenosed intracranial vessels improved after treatment with 40 mg of atorvastatin per day, for at least 6 months, particularly in women.[65] Recently, a single-center, prospective, randomized, single-blind, parallel-group trial indicated that intensive doses atorvastatin therapy (40 mg/day) improved the serum lipid profiles, degree of stenosis, perfusion-related parameters, and probability of cerebrovascular events more effectively than low (10 mg/day) and standard doses (20 mg/day), without increasing adverse events, in patients with atherosclerotic ICAS.[66] Moreover, irregular use of statins has been found to be a risk factor for recurrent ischemic events in ICAS patients.[67] All these studies suggest that intensive statin therapy is safe and effective in Chinese patients with atherosclerotic ICAS. In addition, based on a subgroup analysis of CICAS patients, a low high-density lipoprotein cholesterol (HDL-C) level is associated with the development of ICAS. Thus, strategies for raising HDL-C level should be the focus of future work as well.[68]

With regards to the medical treatment of ICAS, dual antiplatelet therapy (DAPT) with clopidogrel plus aspirin is a topic receiving much attention at present. Subgroup analysis of an previous randomized, open-label, blinded-endpoint, multicenter trial, the Clopidogrel plus Aspirin for Infarction Reduction (CLAIR) study, indicated that DAPT for 7 days is more effective than aspirin alone for reducing the number of microembolic signals in acute stroke or TIA patients with ICAS.[69,70] The results of Clopidogrel in High-Risk Patients with Acute Non-disabling Cerebrovascular Events (CHANCE) trial verified that short-course DAPT in the acute phase, compared with aspirin alone, reduces the risk of recurrent stroke in patients with acute non-cardioembolic minor stroke or high-risk TIA, without increasing the risk of severe or moderate hemorrhage or intracranial hemorrhage.[71] A subgroup analysis of CHANCE indicated that although the rate of recurrent stroke in patients with ICAS is higher than those without ICAS, no significant difference in response to the 2 kinds of antiplatelet therapies between patients with ICAS or without was observed.[72] Thus, compared with aspirin alone, the efficacy and safety of DAPT for reducing the risk of recurrent stroke without increasing the risk of hemorrhage may be no different in patients with and without ICAS.[72]

Despite DAPT and risk factor management, recurrent ischemic events still occurred in some patients, possibly due to aspirin or clopidogrel resistance. Studies on the genetic variants associated with aspirin or clopidogrel resistance have found that *PON1rs662, P2Y12rs2046934, COX1rs1330344,* and *CYP2C19*3rs4986893* polymorphisms are associated with an increased risk of subsequent ischemic events, whilst *CES1rs8192950* mutations are associated with a decreased risk of ischemic events, in Chinese patients with either extracranial or intracranial stenosis.[73,74] Although these studies had relatively small sample sizes and included patients with extracranial disease, they demonstrate the important role of genetic polymorphisms in guiding antiplatelet therapy. For example, increasing drug dose, or switching to other antiplatelet drugs, may help to prevent subsequent ischemic events in patients with aspirin or clopidogrel resistance.

Endovascular intervention

Although antiplatelet therapy and management of vascular risk factors are effective and safe for the treatment on ICAS and prevention of subsequent stroke and TIA, some recurrent ischemic events still occur following aggressive medical treatment. Thus, revascularization may be an option for these subgroups. There are many devices applied in therapies for ICAS, including the Apollo stent, Gateway-Wingspan system, Enterprise stent, and coronary stent. A great many studies have demonstrated that angioplasty and stenting are safe and feasible, with high success and low periprocedural complication rates, in Chinese patients with ICAS.[75–84] However, most of these trials have limitations, such as small sample sizes, single–center and retrospective designs, and the absence of medication control groups.

With the publication of negative results in some large clinical trials, such as SAMMPRIS and VISSIT, endovascular therapy was not recommended as a primary treatment for patients with symptomatic ICAS; poor outcomes and high rates of perioperative complications were observed among patients treated with angioplasty and stenting compared with aggressive medical therapy.[19,85] Nevertheless, there were some limitations to these trials, such as defects in patients recruitment and poor operator experience. To resolve these problems (i.e. to reduce periprocedural complications and benefit patients), Chinese investigators carried out extensive studies.

The first multicenter, prospective, registry study of stenting for symptomatic ICAS in China demonstrated favorable outcomes; successful revascularization was observed in 97.3% of cases, and the 30-day rate of stroke, TIA, and death was 4.3%, lower than in the SAMMPRIS and VISSIT trials (14.7% and 24.1%, respectively).[19,85,86] Investigators attributed the positive results to the following: all operators were experienced and able to choose the appropriate stent, when both balloon-mounted and self-expanding stents were available, based on the anatomical features of vessel lesions; patients were required to have evidence of hypoperfusion, but no evidence of long lesions ($\geq$15 mm) or acute infarction within 3 weeks or severe vessel tortuosity.[86] Moreover, balloon-mounted stents were found to have lower degrees of residual stenosis than self-expanding stents, in accordance with a previous multicenter trial of stenting in ICAS.[86,87] The latter study also observed that Mori type B or C lesions potentially increase the risk of periprocedural stroke.[43,87] Another multicenter, prospective trial of stenting in patients with severe symptomatic ICAS also yielded acceptable results. The technical success rate and 30-day stroke and death rate were 100% and 2% respectively, better than those of the SAMMPRIS trial.[88] In this research, patients with ischemic events within 3 weeks or perforator strokes alone were similarly excluded, and the annual volume was greater than 30 procedures at each site.[88] A recent study on angioplasty and stenting with Wingspan in patients with symptomatic MCA stenosis indicated that the 30-day stroke or death rate at the learning stage was significantly higher than that at the technical maturation stage (16.0% *vs*. 4.1%). It is thought that high adverse events rate at the learning stage may be associated with insufficient experience and unskillful operation, highlighting the importance of the learning curve effect in avoiding perioperative complications.[89] Thus, the significance of patient selection and operator experience at high-volume sites in reducing the 30-day stroke and death rate was highlighted by these studies.

However, a common limitation of all these domestic clinical trials was the absence of a medication control group. Only one previous prospective, randomized, controlled, single-center trial compared the efficacy and safety of endovascular therapy with standard medical treatment in low-risk Chinese patients with symptomatic MCA stenosis.[90] Unfortunately, enrollment ceased early as there was no chance that endovascular treatment could be better than medication, despite the fulfilled enrollment.[90] Although the 30-day rate of stroke or death was only 2.8% in intervention group, lower than that in the SAMMPRIS trial, no significant difference was observed when the rate was compared with the medical group.[90] Likewise, another study that compared the stroke risk of stenting between severe and moderate ICAS patients indicated that only patients with severe stenosis may benefit from intervention therapy.[91] Thus, both reports did not recommend endovascular treatment among low-risk ICAS patients, which may be useful when devising a therapy strategy and patients selection criteria in subsequent clinical trials.

Studies on the complications associated with angioplasty and stenting in patients with ICAS are helpful for increasing operation success rates and preventing adverse periprocedural events. Jiang et al retrospectively investigated complications after endovascular treatment for patients with ICAS and associated risk factors, and found that there was a spectrum of periprocedural complications, including intracranial hemorrhage, stent thrombosis, posterior inferior cerebellar artery thrombosis, perforator stroke, embolic stroke, TIA from vasospasm, and dissection.[92] Moreover, the investigators found that preoperative perforator infarction adjacent to the stenotic segment might predict a high frequency of perforator stroke, as well as deterioration of perforator stroke after stenting placement in ICAS.[93] Furthermore, another research exploring the factors associated with perforator stroke after endovascular treatment in basilar artery stenosis reported that diabetes mellitus, time from last symptom procedure, and pre-procedure stenosis percentage may correlate with occurrence of subsequent perforator stroke after angioplasty and stenting.[94] In addition, Jiang et al detected that patients with severe basilar artery stenosis have a higher rate of stroke or death within 30 days of stenting placement compared with those with vertebral artery stenosis, and deemed that the discrepancy may be caused by the richer perforators originating from basilar versus vertebral arteries.[95] Despite these reports, a recent study indicated that endovascular therapy for severe symptomatic intracranial vertebrobasilar artery stenosis was safe when it was conducted by experienced operators at a high-volume stroke center.[96] There was also a research indicating that awake vertebrobasilar stenting under local anesthesia can help with timely detection of intraoperative TIAs and avoidance of irreversible perforator stroke.[97] Thus, enhanced understanding and aggressive management of periprocedural complications may reduce the occurrence of adverse events and enhance patient benefit.

Studies concentrated on some subtypes of ICAS patients play a part in patient selection and treatment, which is a hot issue as well. Intervention therapy for some lesions that are close to or across a bifurcation or with very tortuous proximal vessel may result in high risk of poor outcomes.[98] Miao et al reported that primary angioplasty was safe and feasible with a long-term benefit in this subtype of patients although concerns on high rate of dissection was still required.[98] Recently, a single-center, prospective study on angioplasty and/or stenting for a subgroup of symptomatic ICAS patients caused by hypoperfusion with poor collateral vessels suggested that results of individualized treatment according to arterial access and lesion morphology were acceptable.[99] Therefore, to choose proper devices and make individualized treatment approach based on characters of patients with ICAS is reasonable and beneficial.

In general, acute stroke subsequent to ICAS increases the risk of endovascular treatment. However, in some patients with acute intracranial artery occlusion, especially in posterior circulation, the consequence can be disastrous if timely recanalization of the occluded artery is not carried out. Gao et al reported the safety and feasibility of a combination of mechanical thrombectomy with angioplasty and stenting to treat acute basilar artery occlusion with underlying severe vertebrobasilar stenosis.[100] Furthermore, this group found that recanalization rates were high in patients with acute basilar artery occlusion treated by mechanical thrombectomy with a Solitaire Device; about one-third of patients had favorable outcomes.[101] Likewise, optimal treatment for chronic intracranial artery occlusion is controversial, and there are few relevant studies. Ma et al reported two cases of chronic symptomatic MCA occlusion treated with angioplasty and stenting; the long-term outcomes were acceptable, suggesting that endovascular treatment for chronic symptomatic MCA total occlusion is feasible, despite the potential risk of severe complications.[102] Recently, a retrospective study described the safety and feasibility of continuous indirect encephaloduroarteriosynangiosis (EDAS) bypass in anterior circulation arterial steno-occlusion.[103] Although the outcomes only provide initial evidence and further studies are required to confirm the results, this research provided an optional treatment for patients with ICAS who fail with medical or endovascular therapy.[103]

Of note, a recent study showed that, compared with medical treatment, angioplasty and stenting improved cognitive status and decreased serum levels of Aβ1-40 and Aβ1-40/Aβ1-42 ratio in patients with intracranial and/or extracranial artery stenosis.[104] A previous study confirmed that cognition and function declined faster in patients with moderate or severe ICAS, than in those without ICAS.[105] According to these studies, ICAS is a risk factor for dementia progression and treatment on the ischemic statues, given that ICAS might prevent the decline of cognitive function.

Conclusion and outlook

Although our understanding of ICAS has improved, there are still limitations in recent research that need to be addressed in future work. Firstly, more high-quality clinical trials on the safety and efficacy of medicine and endovascular treatment for ICAS patients are urgently needed in China. Secondly, although there are extensive results on the diagnosis and assessment of ICAS with HR-MRI, Chinese studies on intravascular ultrasound and optical coherence tomography are absent, and studies on the molecular imaging and measurement of hemodynamic feature are only preliminary. A wide gap still exists between our knowledge and that of the international and cardiological forum. Furthermore, most domestic research has concentrated on the treatment of severe ICAS (stenosis $\geq$70%), whilst patients with moderate (50−69%) or mild (<50%) stenosis have been ignored. Importantly, the rate of recurrent stroke in these patients can be as high as half according to the WASID study.[18] Finally, we should pay more attention to asymptomatic patients with ICAS, especially on the identification and screening of the subgroup at high risk of subsequent stroke and TIA. Maintaining asymptomatic ICAS, and preventing transformation to symptomatic ICAS, is important, but relevant studies are rare at present. Therefore, more large-scale and high-power studies are expected in the future.

Conflicts of interest

The authors declared no potential conflicts of interest.

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