Delirium after primary percutaneous coronary intervention in aged individuals with acute ST-segment elevation myocardial infarction: A retrospective study

SHENG LI, XIAO-HONG ZHANG, GEN-DONG ZHOU and JIAN-FEI WANG

Department of Cardiology, The Third Affiliated Hospital of Anhui Medical University, Hefei, Anhui 230061, P.R. China

Abstract. The present prospective study aimed to investigate the incidence and risk factors of delirium after primary percutaneous coronary intervention (PCI) in older adults with acute ST-segment elevation myocardial infarction (STEMI). A total of 111 patients (age, ≥65 years) with acute STEMI following primary PCI were included in the present study. Neurocognitive testing was performed using the Mini-mental State Examination on the first day of hospitalization. Post-operative delirium was assessed using the Confusion Assessment Method for the Intensive Care Unit within the first four post-operative days. A total of 32 patients (28.8%) developed delirium after primary PCI. The independent predictors of delirium were older age [odds ratio (OR)=1.192, 95% confidence interval (CI)=1.07-1.328, P=0.001], living alone (OR=4.827, 95% CI=1.315-17.725, P=0.018), history of alcohol abuse (OR=3.875, 95% CI=1.168-12.857, P=0.026), longer duration of primary PCI (OR=1.152, 95% CI=1.077-1.232, P<0.001) and post-operative pain (current pain; OR=7.663, 95% CI=1.432-41.02, P=0.017). Compared to the patients without delirium, the participants who developed delirium had longer hospital stays and a higher rate of re-admission within 30 days after discharge. The mortality within one year after discharge (one-year mortality) was similar between patients with and without delirium. In conclusion, older patients (age, ≥65 years) with acute STEMI are at a relatively high risk of delirium following primary PCI. Higher age (≥65 years), living alone, history of alcohol dependence, longer length of primary PCI (>50 min) and post-operative pain (current pain) were determined to be risk factors for delirium after primary PCI in the present cohort.

Correspondence to: Dr Xiao-Hong Zhang, Department of Cardiology, The Third Affiliated Hospital of Anhui Medical University, 390 Huaihe Road, Luyang, Hefei, Anhui 230061, P.R. China
E-mail: xiaohongzhangdr@163.com

Introduction

Post-operative delirium is an acute neuropsychiatric clinical syndrome primarily characterized by disturbances in memory, thought, behaviour, perception, orientation and consciousness. This syndrome is a common and unrecognized condition after surgery in aged individuals (1). Delirium is not only a manifestation of clinical syndromes, but also associated with increased mortality (2), longer hospital stay, as well as a poorer physical performance and social functioning (3). Furthermore, ~25% of individuals aged ≥65 years have been reported to experience delirium during hospitalization (4,5). Given the projected aging of the population, a growing number of elderly patients may undergo surgery in the future. Therefore, post-operative delirium is likely to be more prevalent, and much attention must be paid to post-operative delirium in elderly patients.

The therapy of coronary heart disease mainly includes coronary artery bypass graft surgery and percutaneous coronary intervention (PCI). For coronary heart disease patients, post-operative delirium has been the most extensively investigated after coronary artery bypass graft surgery (6,7). The incidence of delirium in individuals with acute ST-segment elevation myocardial infarction (STEMI) within 12 h after primary PCI has not been determined in Chinese subjects, although primary PCI is increasingly common in older adults with acute STEMI. Thus, there is probably a large unrecognized population of older patients with STEMI who have developed delirium after primary PCI. The major objective of the present study was to investigate the incidence and risk factors of delirium in older adults (age, ≥65 years) with STEMI after primary PCI.

Patients and methods

Patients. The present prospective observational study was performed at the Department of Cardiology of the Third Affiliated Hospital of Anhui Medical University (Hefei, China), and the participants were enrolled between February 2014 and February 2016. The follow-up was performed at one year after discharge. In the present study, a diagnosis of acute STEMI was reached based on the following criteria: i) Chest pain that lasted for >30 min, and was not relieved by sublingual glyceryl trinitrate; ii) >0.1 mV of ST-segment elevation in two anatomically contiguous leads or >0.2 mV in leads V1

and V2; iii) elevated levels of MB fraction of creatine kinase or troponin-I at least three times the upper reference limit.

The inclusion criteria of the present study were as follows: i) A diagnosis of acute STEMI and a history of primary PCI, and ii) age of ≥65 years. The exclusion criteria were as follows: i) A Mini-Mental State Examination (MMSE) score of <15 before primary PCI, ii) history of drug abuse, iii) history of psychiatric disorders, iv) history of neurologic disease (including stroke), v) previous neuropsychological examination, vi) any severe visual or auditory disorder, vii) Parkinson's disease and viii) unwillingness to comply with the protocol or procedures. The primary PCI of all patients was performed by the same surgical team.

During the enrolment period, a total of 138 patients, who were aged ≥65 years, underwent primary PCI. Among these patients, 27 patients refused to participate this study. Hence, a total of 111 patients with acute STEMI following primary PCI were included in the present study (Table I). All patients enrolled in the present study were initially evaluated by MMSE on the day they were admitted to the hospital.

Measurement of delirium. Patients who were scored as 3-4 (i.e. arousable by verbal stimulation) based on the Richmond Agitation and Sedation Scale were assessed for delirium once daily by trained personnel using the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) method (8). This can only be used if a patient is arousable by voice without the requirement for physical stimulation. When performed by a well-trained healthcare professional, the CAM-ICU procedure only takes 1-2 min. This method has satisfactory sensitivity and specificity in detecting delirium (9).

The CAM-ICU method evaluates four features of delirium: i) Acute changes or fluctuations in mental state from baseline, ii) inattention, iii) altered consciousness and iv) disorganized thinking. The result of the CAM-ICU was positive if the patient exhibited features 1 and 2, and either feature 3 or 4. In the present study, patients were assessed by the same psychiatrists within the first four post-operative days (at 8 am, daily) (10).

Variables. The following pre-operative characteristics were recorded for each patient: Age, sex, educational level, determination of living alone, body mass index, smoking, history of major depression, history of alcohol abuse (use of three units or more of alcohol daily), history of hypertension, family history of coronary heart disease, history of myocardial infarction, history of PCI, history of diabetes, history of hyperlipidemia, localization of the patient's cardiac infarct (anterior or non-anterior), co-morbidity of arterial fibrillation, co-morbidity of chronic renal insufficiency, co-morbidity of acute left heart failure, co-morbidity of malignant arrhythmia, co-morbidity of electrical defibrillation, co-morbidity of hypotension/cardiac shock, cardiac arrest/cardiopulmonary resuscitation experience, laboratory tests at admission (pre-operative hemoglobin, total cholesterol, low-density lipoprotein, high-density lipoprotein, triglyceride, MB-isoform of creatinine kinase and troponin), peri-operative and post-operative characteristics (length of primary PCI), New York Heart Association classification (NYHA) (11) at 12 h after the operation, ST-recovery segment at 12 h after the operation, post-operative mechanical ventilation, intra-aortic

balloon pumping (IABP) after the operation, contrast-induced nephropathy, post-operative sleep disorders and post-operative pain [current pain, defined as Visual Analogue Scale/Score (VAS) (12) >4].

Statistical analysis. Statistical analyses were performed using SPSS version 16.0 for Windows (SPSS, Inc., Chicago, IL, USA). Values are expressed as the mean ± standard deviation or the frequency and percentage. Comparisons were performed using the t-test, Fisher's exact test, Chi-squared test and Mann-Whitney U-test. In the logistic regression analysis, forward stepwise (likelihood ratio) was performed to study the predictors of delirium. For this analysis, the presence or absence of delirium/mortality was introduced as a dependent variable, and all risk factors that differed significantly were introduced as independent variables.

Results

Incidence of post-operative delirium. The mean age of the patients was 68.95±12.16 years. Among the 111 patients, 58 (52.3%) were male. Overall, 32 of 111 participants developed delirium, and accordingly, the incidence of delirium after primary PCI in older adults (aged ≥65 years) with acute STEMI was 28.8%.

Risk factors. As presented in Table II, no significant difference was observed between the groups of patients with and without delirium with regard to sex, smoking status, history of major depression, history of coronary heart disease, history of hypertension, history of diabetes mellitus, localization of the cardiac infarct (anterior or non-anterior), co-morbidity of arterial fibrillation and co-morbidity of chronic renal insufficiency. Compared with non-delirious patients, those with delirium were older, had a lower educational level, a lower body mass index and more frequently had a history of alcohol abuse, myocardial infarction, PCI and hyperlipidemia. In addition, patients with delirium more frequently lived alone and had a higher rate of co-morbidity of acute left heart failure, malignant arrhythmia, electrical defibrillation, hypotension/cardiac shock and cardiac arrest/cardiopulmonary resuscitation. The data in Table III indicate that the levels of pre-operative hemoglobin, total cholesterol and low-density lipoprotein in the delirium group were similar to those in the non-delirious group. The participants with delirium had lower levels of high-density lipoprotein and higher levels of triglyceride, MB-isoform of creatinine kinase and troponin (Table III).

The intra-operative and post-operative characteristics are presented in Table IV. Delirious patients had a longer duration of primary PCI and more frequently had sleep disorders and post-operative pain (current pain), when compared with the non-delirious patients. In addition, no significant difference was observed in any of the other parameters, including NYHA at 12 h after the operation, ST-recovery segment at 12 h after the operation, post-operative mechanical ventilation and IABP after the operation (Table IV).

The result of the logistic regression indicated that an older age [≥65 years; odds ratio (OR)=1.192, 95% confidence interval (CI)=1.071-1.328, P=0.001], living alone (OR=4.827,

Table I. Statistical data regarding the patient selection for the present study.

Stage	n
Initial enrolment	138
Exclusion	
Primary PCI without screening	16
Participated in another study	1
Had no time	4
Had no interest/refused to participate	6
Finally included	111

PCI, percutaneous coronary intervention.

95% CI=1.315-17.725, P=0.018), history of alcohol abuse (OR=3.875, 95% CI=1.168-12.857, P=0.026), longer duration of surgery (>50 min; OR=1.152, 95% CI=1.077-1.232, P<0.001) and post-operative pain (current pain; OR=7.663, 95% CI=1.432-41.023, P=0.017) were independently associated with post-operative delirium (Table V).

Influence of delirium on hospital outcomes
Length of hospital stay. Participants who developed delirium had a longer mean hospital stay compared with that of the patients without delirium (10.2±1.8 vs. 6.9±1.3 days, Z=7.172, P<0.001; Table IV).

Mortality within one year after discharge (one-year mortality). The one-year mortality was similar between patients with and without delirium [3.1% (1/32) vs. 6.3% (5/79), Z=0.457, P=0.671; Table IV].

Readmission within 30 days after discharge. Of the 32 participants with delirium, four were readmitted to the hospital within 30 days (11%), while only one of the 79 participants without delirium was readmitted (1.9%; Z=4.326, P=0.038; Table IV).

Discussion

Delirium has become a research focus due to its profound consequences, such as longer hospital stay and higher hospitalization expenses (13). In addition, previous studies have demonstrated that understanding the incidence and risk factors of delirium is necessary to improve patient outcomes (14). The reported frequency of delirium ranges widely, depending on the location and type of studies that have investigated delirium. It has been reported that delirium occurs in 20-60% of patients in Intensive Care Units (15), 18-25% of oncology patients (16) and 8-36% of patients undergoing cardiovascular surgery (17). The incidence of delirium after primary PCI in patients with acute myocardial infarction has remained insufficiently investigated. According to a previous study, delirium or agitation were mentioned in physicians' or nurses' progress notes for 28% of hospitalized patients with acute myocardial infarction (18) in individuals aged ≥90 years. The incidence rate of delirium determined in the present study was 28.8%.

Since the present study was the first study in China to evaluate the incidence of delirium in patients diagnosed with acute STEMI who underwent primary PCI and were within the age group of ≥65 years, the prevalence data of the present study cannot be compared with other studies in China. However, the present result indicates patients aged ≥65 years with acute STEMI and subjected to primary PCI frequently present with delirium.

It is well known that post-operative delirium is an acute neuropsychiatric clinical syndrome primarily characterized by disturbances in memory, thought, behaviour, perception, orientation and consciousness, and mostly occurs within four days after surgery (19). In view of this, delirium assessment was performed by the same psychiatrists within the first four post-operative days in the present study.

The identification of risk factors is critical for implementing prevention efforts. Previous studies on subjects with non-cardiac general surgery have identified older age, alcohol abuse, abnormal electrolytes, thoracic or aortic surgery and poor cognitive or physical functional status as risk factors of delirium (20). In present study, it was indicated that older age, living alone, history of alcohol dependence, longer duration of primary PCI and post-operative pain (current pain) are risk factors for delirium after primary PCI in older patients with acute STEMI. Although the localization of myocardial infarction (anterior or non-anterior) is an important factor for the myocardial damage in subjects with acute myocardial infarction, the present results suggest that the localization of the myocardial infarction (anterior or non-anterior) is not a predictor of delirium after primary PCI, which was similar to the results of a previous study (21). In subsequent studies, more attention will be paid to this factor.

The results of the present study suggest that post-operative pain is an independent risk factor for delirium. Pain is frequently prominent in patients diagnosed with acute STEMI undergoing primary PCI, and pain gives rise to sleep disorders and neuroendocrine disorders, which are prone to causing delirium (22). The present study demonstrated that post-operative pain is an important risk factor for delirium, which requires careful consideration. Therefore, peri-operative pain optimization may be a strategy to reduce the risk of delirium and further research is required to test this hypothesis.

Previous studies have indicated that advanced age is one of the most consistent pre-disposing factors for the occurrence of delirium (23). Consistently, in the present study, advanced age was independently associated with the development of delirium in patients with acute STEMI after primary PCI. The mechanisms may be summarized as follows: First, older age is characterized by the aging of tissues and organs, an increase in the rate of frail subjects and an increased occurrence of cognitive decline and functional impairment (24). Frail elderly patients are more prone to several post-operative complications, including delirium. Second, the aged brain is more susceptible to anaesthetic effects and more sensitive to non-anaesthetic drugs (25). Finally, markers for activated microglia, including major histocompatibility complex class II, increase with aging (26), which may result in an inflammatory response in the brain. A study has also indicated that peripheral infections or pneumonia are closely associated with

Table II. Sociodemographic and clinical characteristics of patients with and without delirium.

Characteristic	Delirium (n=32)	No delirium (n=79)	P-value
Male (sex)	18 (56.3)	40 (50.6)	0.591[c]
Age (years)	75.47±13.16	67.99±11.27	<0.001[d]
MMSE score	26.23±3.42	27.13±3.11	0.154[a]
Education (years)	7.06±4.03	10.2±4.37	<0.001[a]
Living alone	10 (31.3)	6 (7.6)	0.003[c]
Body mass index (kg/m^2)	26.24±3.37	27.19±3.08	0.155[a]
History of major depression	1 (3.1)	5 (2.5)	0.671[c]
History of smoking	14 (43.8)	32 (40.5)	0.753[c]
History of alcohol abuse	11 (34.4)	12 (15.2)	0.024[c]
Family history of coronary heart disease	9 (28.1)	19 (24.1)	0.654[c]
History of myocardial infarction	10 (31.3)	9 (11.4)	0.012[c]
History of percutaneous coronary intervention	8 (25)	5 (6.33)	0.014[b]
History of hypertension	11 (34.3)	21 (26.6)	0.412[c]
History of diabetes	10 (31.2)	23 (29.1)	0.824[c]
History of hyperlipoidaemia	13 (40.6)	15 (18.9)	0.017[c]
Localization of the cardiac infarct (anterior)			0.812[c]
Anterior	17 (53.1)	40 (50.6)	
Non-anterior	15 (46.9)	39 (49.4)	
Combined atrial fibrillation	6 (18.8)	13 (16.5)	0.771[c]
Combined chronic renal insufficiency	9 (28.1)	17 (21.5)	0.457[c]
Combined acute left heart failure	6 (19.4)	3 (3.8)	0.026[b]
Malignant arrhythmia	7 (21.9)	5 (6.3)	0.04[b]
Electrical defibrillation	4 (12.5)	1 (1.3)	0.038[b]
Combined hypotension/cardiac shock	6 (18.8)	2 (2.5)	0.01[b]
Cardiac arrest/cardiopulmonary resuscitation experience	4 (12.5)	1 (1.3)	0.038[b]

Values are expressed as n (%) or the mean ± standard deviation. [a]Independent-sample t-test; [b]Fisher's exact test; [c]Chi-squared test; [d]Mann-Whitney U-test. The parameter which didn't obey normal distribution was analyzed using the Mann-Whitney U-test. The parameters which obeyed a normal distribution were analyzed using a t-test. MMSE, mini mental state examination.

Table III. Laboratory parameters in patients with and without delirium.

Parameter	Delirium (n=32)	No delirium (n=79)	P-value
Preoperative haemoglobin (g/l)	136.25±15.96	134.82±17.24	0.687[a]
Preoperative total cholesterol (mg/dl)	176.43±50.06	163.47±48.06	0.206[a]
Preoperative low-density lipoprotein (mg/dl)	107.68±39.22	99.82±41.27	0.359[b]
Preoperative high-density lipoprotein (mg/dl)	33.95±9.61	38.56±9.51	<0.001[a]
Preoperative triglyceride (ng/ml)	122.82±72.28	91.497±54.38	<0.001[b]
Preoperative MB-isoform of creatinine kinase (ng/ml)	75.71±78.13	39.86±58.87	<0.001[b]
Preoperative troponin (ng/ml)	40.13±25.78	23.71±22.36	<0.001[a]

[a]Independent-sample t-test; [b]Mann-Whitney U-test. The parameters which didn't obey a normal distribution were analyzed using the Mann-Whitney U-test and those that obeyed a normal distribution were analyzed using a t-test.

Table IV. Surgical and post-operative characteristics of patients with and without delirium.

Item	Delirium (n=32)	No delirium (n=79)	P-value
Length of surgery (min)	103.8±23.5	53.4±22.7	<0.001[c]
NYHA classification 12 h after operation (score ≥3)	6 (18.8)	5 (6.3)	0.102[a]
ST recovery segment 12 h after operation	10 (31.3)	32 (40.5)	0.487[a]
Post-operative mechanical ventilation	3 (9.4)	1 (1.3)	0.132[a]
Intra-aortic balloon pumping after operation	1 (3.1)	1 (1.3)	0.525[a]
Contrast-induced nephropathy	3 (9.4)	3 (6.3)	0.475[a]
Sleep disorder	19 (59.4)	23 (29.1)	0.003[b]
Post-operative pain [current pain (VAS >4)]	18 (56.3)	21 (26.6)	0.003[b]
Length of hospital stay (days)	10.2±1.8	6.9±1.3	<0.001[c]
Mortality within 1 year after discharge (%)	1 (3.1)	5 (6.3)	0.671[a]
Readmission within 30 days after discharge (%)	4 (11)	1 (1.9)	0.038[a]

Values are expressed as n (%) or the mean ± standard deviation. [a]Fisher's exact test; [b]Chi-squared test; [c]Mann-Whitney U-test. The parameters which did not obey a normal distribution were analyzed using the Mann-Whitney U-test and those that obeyed a normal distribution were analyzed using a t-test. NYHA, New York Heart Association; VAS, visual analog scale.

Table V. Predictors of delirium in the study sample (using univariate logistic regression analysis with reference category non-delirious).

Factor	B	S.E.	Wald	P-value	OR	95% CI
Age	0.176	0.055	10.201	0.001	1.192	1.071-1.328
Living alone	1.574	0.664	5.628	0.018	4.827	1.315-17.725
History of alcohol abuse	1.355	0.612	4.89	0.026	3.875	1.168-12.857
Length of surgery	1.127	0.625	5.32	<0.001	1.152	1.077-1.232
Post-operative pain (current pain)	0.078	0.035	11.38	0.017	7.663	1.432-41.02

B, estimated value of the model constant term; S.E., standard error of B; Wald, Wald Chi-square value; CI, confidence interval; OR, is odds ratio.

delirium in elderly people (27). Recently, the proportion of the population aged ≥65 years has rapidly increased (28). Thus, more medical care must be provided for delirium in patients aged ≥65 years.

In recent years, studies have increasingly focused on the influence of social support on the morbidity, mortality and quality of life (29). However, the effect of social support on post-operative delirium has rarely been studied. In the present study, patients who lived alone exhibited a higher risk of developing delirium. A variety of explanations have been offered to account for the association between living alone and delirium. First, isolated patients were reported to have lower incomes and hostility to society in America increased rates of smoking and less social support, compared with those living with company (30). These characteristics may result in delayed medical care for isolated individuals, causing their medical conditions to worsen. In addition, isolated patients may be significantly less likely to be married and have less confidence and receive fewer social visits, which may all contribute to psychological distress. In China, a growing number of elderly individuals live alone and undergo surgery (31), which may lead to an increasing occurrence of post-operative delirium in

the elderly. Therefore, more social support should be provided to elderly individuals living alone.

A prolonged operative time was identified as a significant risk factor for delirium in the present study. An increased duration of surgery is usually associated with an increased exposure to microemboli (32) and a systemic inflammatory response. Relevant studies have demonstrated that factors including endotoxins, cytokines and chemokines during the inflammatory process may have a key role in the pathogenesis of delirium (33,34). Therefore, it is likely that the increased duration of primary PCI may predispose patients to post-operative delirium due to increasing the systemic inflammatory response. However, there is currently no consensus regarding the standard or range of the operative time for primary PCI. Therefore, closer attention should be given to this factor in future studies.

In the present study, alcohol abuse appeared to be a significant risk factor for post-operative delirium. The present results may be partly explained by the suppressed immune defence associated with alcoholism and by the inhibited wound healing of chronic alcoholics (35). It should be pointed out that accurate quantitative data for alcohol

use were not provided by previous studies (36). In a study by Ouimet *et al* (37), alcohol abuse was defined as the daily use of >2 units per day, and was also demonstrated to be a multivariate risk factor for delirium. According to this, in the present study, the daily alcohol dependence was defined as the use of ≥3 units of alcohol daily.

In the present study, the neurocognitive testing of MMSE was performed on the first day of hospitalization and the results were similar for the two groups, indicating a similar pre-operative cognitive function in the two groups. In conclusion, delirium is common after primary PCI in older adults with STEMI, and aged individuals, living alone, history of alcohol dependence, longer duration of primary PCI (>50 min) and severe pain may be associated with a high risk of delirium. Delirium may be associated with a longer hospital stay and higher odds of re-admission. Thus, more effort should be made to prevent delirium in patients after primary PCI, particularly in older adults with acute STEMI.

Of note, the present study has certain limitations. First, the present study was a single-center study, and the present results require to be confirmed through multicenter trials with larger sample sizes. Furthermore, delirium assessment was only performed within the first four post-operative days, and not on all days of each individual's hospitalization. In addition, the occurrence of delirium prior to PCI was not assessed in the present study, and only neurocognitive testing via the MMSE was performed on the first day of hospitalization to assess the pre-operative cognitive function. Similar MMSE testing results in the two groups were considered to indicate a similar pre-operative cognitive function in the two groups, therefore suggesting that this factor had no marked impact on the results. Regarding the influence of delirium on hospital outcomes, only the indexes of readmission within 30 days after discharge and mortality within one year after discharge were used as end-points. Furthermore, the present study didn't observe all complications and comorbidities in the selected patients with acute myocardial infarction, which may have affected the results. A longer assessment may be needed to explore the incidence and risk factors of delirium after primary PCI in older patients (age, ≥65 years) with acute STEMI. In addition, these results may be affected by confounding, but potentially important factors, and in the present study, an adjustment for confounding factors selected *a priori* was performed based on a literature review (38).

In conclusion, the results of the present study indicated that older patients (age, ≥65 years) with acute STEMI are at a relatively high risk of delirium following primary PCI. Age (≥65 years), living alone, history of alcohol dependence, longer length of primary PCI (>50 min) and post-operative pain (current pain) were determined to be risk factors for delirium after primary PCI in the present cohort. Therefore, more attention should be paid to delirium following primary PCI in older patients (age, ≥65 years) with acute STEMI.

Availability of data and materials

The datasets generated and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

GDZ analyzed and interpreted the patient data, JFW analyzed the data, and SL and XHZ were major contributors in writing the manuscript. All authors read and approved the final manuscript.

Ethics approval and informed consent

The research protocol was in accordance with the guidelines of the World Medical Association's Declaration of Helsinki, and the present study was performed following the approval of the Ethics Committee of the Third Affiliated Hospital of Anhui Medical University (Hefei, China; no. 2014003). All subjects provided written informed consent.

Patients' consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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