Thrombolysis for pulmonary embolism: Past, present and future

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Summary

Patients with high-risk pulmonary embolism (PE), i.e. those with shock or hypotension at presentation, are at high risk of in-hospital death, particularly during the first hours after admission. A meta-analysis of trials which included haemodynamically compromised patients indicated that thrombolytic treatment significantly reduces the rate of in-hospital death or PE recurrence. Therefore, thrombolysis should be administered to patients with high-risk PE unless there are absolute contraindications to its use. Uncontrolled data further suggest that thrombolysis may be a safe and effective alternative to surgery in patients with PE and free-floating thrombi in the right heart. On the other hand, normotensive patients generally have a favourable short-term prognosis if heparin anticoagulation is instituted promptly, and they are thus considered to have non-high-risk PE. Generally, the bleeding risk of thrombolysis appears to outweigh the clinical benefits of this treatment in patients without haemodynamic compromise. However, within the group of normotensive patients with PE, some may have evidence of right ventricular dysfunction on echocardiography or computed tomography, or of myocardial injury based on elevated cardiac biomarkers (troponin I or T, heart-type fatty acid-binding protein). These patients have an intermediate risk of an adverse outcome in the acute phase of PE. Existing data suggest that selected patients with intermediate-risk PE may benefit from early thrombolytic treatment, particularly if they have a low bleeding risk. However, controversy will continue to surround the optimal treatment for this group until the results of a large ongoing thrombolysis trial are available in a few years.

Keywords

Pulmonary embolism, thrombolysis / thrombolytic agents, plasminogen activators, thrombosis, venous thrombosis

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Introduction: Thrombolysis in the context of pulmonary embolism severity

Morbidity and mortality associated with acute pulmonary embolism (PE) remain high in spite of the recent advances in cardiovascular imaging, and of the therapeutic options currently available. The annual incidence rate of venous thromboembolism has been reported to range between 23 and 69 cases per 100,000 population in epidemiological studies (1, 2), with approximately one third of these patients presenting with clinical symptoms of acute PE and two thirds with deep-vein thrombosis (3). Case fatality rates vary widely depending on the clinical severity of the thromboembolic episode (4–7), but according to the findings of large recent registries and cohort studies approximately 10% of all patients with acute PE die during the first 1–3 months after diagnosis (8, 9). In the United States, the Surgeon General has recently estimated that venous thromboembolism contributes to as many as 100,000 deaths each year (10). Overall, 1% of patients admitted to the hospital die of acute PE, and 10% of all hospital deaths are PE-related (11–13).

Acute PE covers a wide spectrum of clinical severity, with early mortality rates ranging between less than 1% and well over 50% (4–9, 14). The principal pathophysiological factor, which determines disease severity and therefore the patients' clinical course and risk of death over the short term, is the presence or absence of right ventricular (RV) dysfunction and failure resulting from acute pressure overload (15). Almost four decades ago, it was found that increased pulmonary artery pressure may develop in up to 60–70% of patients who suffer acute PE; importantly however, the extent of RV dysfunction, and of the resulting haemodynamic instability, is only roughly (and unreliably) related to thrombus burden and the severity of anatomical obstruction (16–18). This complexity is due to the involvement of numerous additional variables such as pulmonary vasoconstriction, platelet activation, and persistent myocardial injury despite maintained coronary flow to the right ventricle. Moreover, pre-existing cardiac or pulmonary disease may enhance the haemodynamic impact of an acute thromboembolic event (19–22). The interplay of all these factors, each one of which may be more or less pronounced in the individual patient, determines the development and extent of acute RV dysfunction. This latter event may in turn initiate a vicious circle of increased myocardial oxygen demand, myocardial ischaemia or even infarction, leftward septal displacement and left ventricular preload reduction, which ultimately lead to cardiogenic shock and death (15).

Based on these pathophysiological considerations and their prognostic impact, identification of patients with "severe" PE should focus on PE-related *early death risk* rather than reflect the volume, shape or anatomical distribution of intrapulmonary emboli as determined by various imaging modalities. Consequently, the recently updated guidelines of the European Society of Cardiology strongly advocate the replacement of previously used, potentially misleading terms such as "massive", "submassive", and "non-massive" PE, with *high-risk* and *non-high-risk* (the latter including *intermediate risk* and *low-risk*) PE (23, 24). According to this classification, high-risk PE indicates overt RV failure which results in refractory arterial hypotension and shock (i.e., systolic blood pressure <90 mm Hg, or a pressure drop ≥40 mm Hg for at least 15 minutes). This condition accounts for almost 5% of all cases of acute PE and is associated with a high risk of in-hospital death, particularly during the first hours after admission (5, 25, 26). On the other hand, in the absence of haemodynamic instability, patients are generally thought to have a favourable clinical outcome provided that the disease is diagnosed correctly and anticoagulation can be instituted without delay (non-high-risk PE) (14, 27). While consensus exists that thrombolysis is the treatment of choice in hypotensive patients with high-risk PE, uncertainty persists regarding the possible clinical benefits of this treatment form in normotensive patients (24, 28).

The present article reviews the history of thrombolysis, the evidence that has accumulated over the past 40 years on the benefits versus risks of this treatment option, and the current state of the art on thrombolytic treatment in the context of risk-adjusted management strategies for acute PE. Furthermore, by focussing on emerging tools and concepts for optimising the risk stratification of normotensive patients, it provides an outlook for the possible extension of thrombolysis to carefully selected cases of non-high-risk PE.

Thrombolysis: The past

Angiographic and haemodynamic benefits

In 1971, Miller et al. observed that streptokinase infusion over 72 hours resulted in a significant reduction of systolic pulmonary artery pressure, total pulmonary resistance, and the angiographic index of PE severity. In comparison, conventional heparin anticoagulation had no appreciable effect on these parameters during the first 3 days (29). Subsequently, a number of randomised trials (30–37) confirmed that fibrinolytic therapy rapidly resolves thromboembolic obstruction and exerts beneficial effects on haemodynamic indicators of cardiac function. For example, in the Urokinase Pulmonary Embolism Trial (UPET), which enrolled 160 patients and still remains one of the largest randomised thrombolysis trials in acute PE to date, urokinase (as bolus injection followed by infusion over 24 hours) was superior to heparin alone in resolving pulmonary artery thrombi (30). In another trial, 100 mg of recombinant tissue plasminogen activator (alteplase; rtPA) induced a 12% decrease in vascular obstruction at the end of the 2-hour infusion period, whereas no change was observed in patients receiving heparin (36). The effect of rtPA was associated with a 30% reduction in mean pulmonary artery pressure and a 15% increase in cardiac index. In 1993, Goldhaber et al. compared alteplase (100 mg infusion over 2 hours) to heparin alone in 101 patients, using echocardiographic indicators of RV pressure overload and dysfunction to evaluate PE severity (37). There was rapid improvement of RV function, as assessed by 24-hour echocardiographic follow-up and the absence of PE recurrence in the alteplase group.

Registry data suggest that as many as 92% of treated patients with acute PE may respond favourably to thrombolysis, judging by their clinical and echocardiographic improvement within the first 36 hours (38). The greatest benefit is observed when treatment is initiated within 48 hours of symptom onset (32), but thrombolysis can still be useful in patients who have had symptoms for as long as 6 to 14 days (39). On the other hand, it also needs to be emphasised that the haemodynamic benefits of thrombolysis over heparin are confined to the first few days after the initiation of treatment. In this regard, Dalen et al. reported in the late 60s that heparin anticoagulation alone (without thrombolysis) was capable of reversing pulmonary artery hypertension in most patients, even though improvement required three weeks or even longer (40). Trials which directly compared thrombolysis with heparin and included follow-up angiographic or echocardiographic studies showed that, one week after treatment, the improvement in the severity of vascular obstruction (30, 36) and the reversal of RV dysfunction (41) no longer differed between thrombolysis-treated and heparin-treated patients. It thus follows that thrombolysis needs to be considered only in those cases in which a high risk of *early* (i.e. within the first few hours or days after presentation) PE-related death is anticipated.

While the angiographic and haemodynamic benefits of thrombolysis are unequivocal, at least over the short term, the (presumed) favourable effects of thrombolysis on the clinical outcome of patients with PE could not be convincingly demonstrated so far. This partly relies on the fact that the majority of thrombolysis trials in PE were too small to address clinical end points. Even the most recent and largest of these trials failed to show a survival benefit (37, 42), possibly because they included "low-risk" patients whose mortality rate in the acute phase could not be further reduced by immediate recanalisation.

Bleeding complications

Pooled data from controlled thrombolysis trials in PE, which either compared thrombolysis to heparin alone or different thrombolytic regimens with each other (30, 34, 36, 42–49), revealed a 13% cumulative rate of major bleeding and a 1.8% rate of intracranial/fatal haemorrhage (50). On the other hand, major haemorrhage has been uncommon in the most recent (and largest) trials (37, 42), a fact which is in agreement with the observation that thrombolysis-related bleeding rates are lower when non-invasive imaging methods are used to diagnose PE (51). Fortunately, non-invasive diagnostic strategies have increasingly been adopted over the past 10 years thanks to

the technical advances in computed tomographic (CT) pulmonary angiography (23). While these data may appear reassuring, retrospective cohort studies and registries suggested a 36% incidence of major bleeding events and a 4% rate of intracranial/fatal haemorrhage (4, 5, 52, 53). These rates may be exaggerated, since registries are likely to include patients who have received thrombolysis despite the presence of formal contraindications (5). At the same time of course, it can be argued that registry data better reflect everyday clinical practice than controlled trials. In any case, all the results presented above highlight the critical importance of carefully defining the indications for thrombolysis in acute PE, particularly in patients who appear haemodynamically stable at presentation.

Thrombolysis: The present

Thrombolytic agents and regimens

Validated regimens of thrombolytic agents are shown in ▶Table 1, which also reviews the absolute and relative contraindications to thrombolysis. Regarding the performance of various thrombolytic regimens in head-to-head comparisons, the Urokinase-Streptokinase Pulmonary Embolism Trial (USPET) documented similar efficacy of urokinase (UK) and streptokinase (SK) infused over a period of 12–24 hours (49). In more recent randomised comparison trials (46, 47), 100 mg of rtPA infused over two hours led to faster angiographic and haemodynamic improvement compared to UK infused over 12 or 24 hours at the rate of 4,400 U/kg/h. However, the results no longer differed at the end of the UK infusion. Similarly, the two-hour infusion of rtPA appeared to be superior to a 12-hour SK infusion (at 100,00 U/h), but no difference was observed when the same SK dosage was also given over two hours (54, 55). Furthermore, two trials that compared the two-hour, 100 mg rtPA regimen with a short infusion (over 15 minutes) of 0.6 mg/kg rtPA reported a slightly faster improvement with the two-hour regimen at the cost of slightly (non-significantly) higher bleeding rates (44, 56). Thus, the thrombolytic regimens tested to date appear to be more or less comparable in terms of efficacy, but long infusion periods of the older thrombolytics SK or UK should generally be avoided.

Satisfactory haemodynamic results were obtained with double-bolus reteplase given as two injections (10 U) 30 minutes apart (57). Desmoteplase also appears to be a promising agent (58). Furthermore, a multicentre randomised pilot trial demonstrated the feasibility and safety of tenecteplase, given as a weight-adjusted bolus corresponding to the regimen recommended for acute myocardial infarction, in acute non-high-risk PE (59). However, none of these agents is officially approved for treatment of PE at present.

Thrombolysis in high-risk PE

In view of the high early mortality and complication risk associated with high-risk PE (5, 25, 26), existing guidelines (24, 28) and the overwhelming majority of experts and clinicians agree that patients who present with persistent arterial hypotension or shock are in need of immediate pharmacologic or mechanical recanalisation of the occluded pulmonary arteries. Pooled data from 5 trials which included haemodynamically unstable patients have suggested a significant reduction of death or PE recurrence after thrombolysis in this group (60). Thus, haemodynamically unstable patients with suspected high-risk PE should immediately receive a weight-adjusted bolus of unfractionated heparin while

Table 1: Thrombolytic agents, regimens, and contraindications (adapted from [23] with permission). * Unfractionated heparin should not be infused together with streptokinase or urokinase; it can be given during alteplase or reteplase administration. Low-molecular-weight heparins have not been tested in combination with thrombolysis in patients with pulmonary embolism. † Short (2-hour) infusion periods are generally recommended. ‡ Urokinase is available in some European countries, not in the United States. § FDA-approved regimen. ¶ Off-label use of reteplase. ∫ Off-label use of tenecteplase; this is the regimen recommended for acute myocardial infarction. A recent randomised pilot trial (58) found it to be safe and effective in non-high-risk PE.

Streptokinase*	250,000 U as a loading dose over 30 min, followed by 100,000 U per hour over 12–24 h	**Contraindications to thrombolysis (24)**
	Accelerated regimen: 1.5 million IU over 2 h†	*Absolute*
Urokinase*‡	4,400 U per kilogramme of body weight as a loading dose over 10 min, followed by 4,400 U/kg/h over 12–24 h	History of haemorrhagic stroke or stroke of unknown origin Ischaemic stroke in previous 6 months Central nervous system neoplasms Major trauma, surgery, or head injury in previous 3 weeks
	Accelerated regimen: 3 million U over 2 h†	
Alteplase*	100 mg over 2 h§	*Relative*
	Accelerated regimen: 0.6 mg/kg over 15 min	Transient ischaemic attack in previous 6 months Oral anticoagulation Pregnancy or first postpartum week Non-compressible puncture sites Traumatic resuscitation Refractory hypertension (systolic blood pressure >180 mm Hg) Advanced liver disease Infective endocarditis Active peptic ulcer
Reteplase*¶	Two bolus injections of 10 U 30 min apart	
Tenecteplase ∫	30 to 50 mg bolus over 5–10 sec adjusted for body weight:	
	<60 kg: 30 mg ≥60 to <70 kg: 35 mg ≥70 to <80 kg: 40 mg ≥80 to <90 kg: 45 mg ≥90 kg: 50 mg	

awaiting the results of further diagnostic work-up; if PE is confirmed, thrombolysis should be administered without delay. If thrombolysis is absolutely contraindicated or has failed, surgical embolectomy or catheter-based thrombus fragmentation and aspiration is a valuable alternative (61, 62) (▶Table 2).

Uncontrolled data also suggest that thrombolysis may be a safe and effective alternative to surgery in patients with PE and free-floating thrombi in the right heart (63, 64).

Thrombolysis in non-high-risk PE

At present, low-molecular-weight heparin or fondaparinux is considered adequate treatment for most normotensive patients with pulmonary embolism (▶Table 2). Routine thrombolysis is generally not recommended as a first-line therapeutic option, irrespective of the echocardiographic (or CT) findings or the biomarker levels. However, based on the results of the largest randomised thrombolysis trial to date (42), early thrombolysis may be considered in selected intermediate-risk patients with a high risk of death (due, for example, to pre-existing heart or respiratory failure) provided that they have no contraindications to thrombolytic treatment.

Is intermediate-risk PE the future of thrombolysis?

Defining intermediate-risk PE: detection of right ventricular dysfunction

As already emphasised, RV dysfunction is a crucial pathophysiological event and a determinant of prognosis in acute PE. Therefore, its early detection and reversal, *before* the patient develops haemodynamic instability and shock, would seem to be one of the top priorities in the management of the disease. Echocardiography is an imaging modality capable of detecting the changes occurring in the morphology and function of the right ventricle as a result of acute pressure overload. A number of registries and cohort studies could demonstrate an association between various echocardiographic parameters and a poor in-hospital outcome in terms of PE-related death and complications (14, 27, 37, 65, 66). The post-hoc analysis of a large international registry further suggested that echocardiographically detected RV dysfunction is an independent predictor of adverse outcome in normotensive patients (67). Nevertheless, the potential prognostic and, particularly, therapeutic implications of cardiac ultrasound findings for non-high-risk PE remain the subject of debate. The persisting uncertainty is mainly due to the lack of standardisation of the echocardiographic criteria and the absence of adequately powered, controlled studies focussing on normotensive (rather than unselected) patients with PE (68). Accordingly, a recent meta-analysis of five studies including a total of 475 normotensive patients with PE reported an only moderate overall negative (60%; 95% CI, 55–65%) and positive (58%; 95% CI, 53–63%) value of echocardiography for predicting early death, while also emphasising the limitations due to the clinical and methodological diversity of the pooled publications (69). The largest randomised thrombolysis trial in PE to date, which included 256 normotensive patients with RV dysfunction (mainly) detected by echocardiography, reported a significantly reduced incidence of the primary end point (30-day mortality or need for treatment escalation) in patients who underwent early thrombolysis as opposed to those treated with heparin alone. However, there was no significant influence of the type of treatment on mortality rates during the acute phase of PE (42). It is thus likely that additional information, beyond echocardiographic findings, may be needed before the decision can be made to treat a normotensive patient with acute PE aggressively (for example, with thrombolytic agents). Recent preliminary reports suggest that the prognostic value of echocardiography can be improved if combined with biomarkers

Table 2: Thrombolysis in contemporary management of acute pulmonary embolism. Modified from (24) and updated according to recent data. H-FABP denotes heart-type fatty acid-binding protein; LMWH, low-molecular-weight heparin or fondaparinux; MDCT, multidetector computed tomography (pulmonary angiography); PE, pulmonary embolism; RV, right ventricle; UFH, unfractionated heparin.

PE-related early mortality risk		Risk markers			Indication for thrombolysis ?
		Clinical: Shock or hypotension	RV dysfunction (Echo, MDCT, natriuretic peptides)	Myocardial injury (cardiac troponins, H-FABP)	
High (> 15%)		+	(+)	(+)	YES Alternative options: surgical / interventional thrombus removal Anticoagulation with UFH
Non-high	Intermediate (3–15%)	-	+	+	As a rule, No early thrombolysis Monitor clinical status and RV function Anticoagulation with LMWH
			+	-	
			-	+	
	Low (< 1%)	-	-	-	No thrombolysis LMWH or fondaparinux Outpatient treatment currently not recommended.

of myocardial injury (70) or integrated into risk scores which also include clinical parameters and natriuretic peptides (71).

Four-chamber views of the heart on multidetector-row computed tomography (MDCT), which is currently the preferred method for diagnosing PE in most institutions, may detect RV enlargement due to PE. In a large retrospective series of 431 patients, 30-day mortality was 15.6% in patients with RV enlargement (reconstructed 4-chamber views), defined as right/left ventricular dimension ratio >0.9, on MDCT, compared to 7.7% in those without this finding (72). A meta-analysis of two studies (with two different RV/LV diameter thresholds, 1.5 and 1.0) including 191 normotensive patients with PE reported a 58% (95% CI, 51–65%) overall negative and a 57% positive (95% CI, 49–64%) value of RV dilatation on CT for predicting early death (69).

Natriuretic peptides are released as a result of cardiomyocyte stretch and are very sensitive indicators of neurohormonal activation due to ventricular dysfunction. The biologically active C-terminal peptide 77–108 (BNP) and the inactive N-terminal fragment 1–76 (NT-proBNP) are detectable in human plasma, and their levels have been determined and evaluated in patients presenting with acute PE (73–76). In general, both BNP and NT-proBNP are characterised by very high prognostic sensitivity and a negative prognostic value which is probably even higher than that of the cardiac troponins (77). On the other hand, they exhibit a very low specificity and positive prognostic value in the range of 12 to 25% (77). Furthermore, the optimal cut-off levels of BNP (or NT-proBNP) for distinguishing between a prognostically "favourable" versus "unfavourable" result in patients with PE have not yet been prospectively determined (78). A recent meta-analysis of 13 studies found that 51% of the 1132 patients included had elevated BNP or NT-proBNP levels, and these were associated with an increased risk of early death (OR, 7.6; 95% CI, 3.4–17) and a complicated in-hospital course (OR, 6.8; 95% CI, 4.4–10) (79). Nevertheless, elevation of natriuretic peptides alone does not, by itself, justify more invasive treatment regimens. Evolving concepts of risk stratification suggest that the prognostic value of natriuretic peptides may be improved if they are combined with echocardiography (70), or integrated into risk scores which also include clinical parameters and echocardiography (71).

Detection of myocardial injury

Elevated cardiac troponin I or T levels, a sensitive and specific indicator of myocardial cell damage and microscopic myocardial necrosis, are found in up to 50% of patients with acute PE (80). Twenty studies published since 1998 with a total of 1985 patients were included in a meta-analysis which could show that cardiac troponin elevation was associated with an increased risk of death (OR, 5.24; 95% CI, 3.28–8.38) and major adverse events (OR, 7.03; 95% CI, 2.42–20.43) in the acute phase (81). However, the positive predictive value of cardiac troponin I or T elevation has been consistently low in cohort studies, so that troponin elevation does not necessarily indicate a poor prognosis (77). Moreover, a recent meta-analysis which focussed only on normotensive patients (a total of 1366 patients included in 9 studies) was unable to confirm the prognostic value of cardiac troponins in non-high-risk PE (82). Thus, based on the available data, the current opinion is that troponin elevation *alone* does not suffice to risk stratify normotensive patients with PE, and particularly to identify intermediate-risk patients who might necessitate early aggressive (for example, thrombolytic) treatment. A large ongoing randomised trial is currently investigating whether normotensive patients with right ventricular dysfunction, detected by echocardiography or CT, *plus* evidence of myocardial injury indicated by a positive troponin test, may benefit from early thrombolytic treatment (83).

Fatty acid-binding proteins (FABPs) are small cytoplasmic proteins which are abundant in tissues with active fatty acid metabolism, including the heart (84). Heart-type FABP (H-FABP) is particularly important for myocardial homoeostasis, since 50–80% of the heart's energy is provided by lipid oxidation, and H-FABP ensures intracellular transport of insoluble fatty acids. Following myocardial cell damage, this small protein diffuses much more rapidly than troponins through the interstitial space and appears in the circulation as early as 90 minutes after symptom onset, reaching its peak within 6 hours (85). These features make H-FABP an excellent candidate marker of myocardial injury (86), and preliminary data suggested that it may provide prognostic information superior to that of cardiac troponins in acute PE (87, 88). These data were recently confirmed by a study focussing on non-high-risk patients with acute PE (89).

Growth-differentiation factor-15 (GDF-15), a distant member of the transforming growth factor-β cytokine family, is an emerging biomarker for patients with cardiovascular disease. In particular, GDF-15 appears capable of integrating information both on RV dysfunction and myocardial injury in patients with acute PE. In a cohort study of 123 consecutive patients with confirmed PE, elevated levels of GDF-15 on admission were strongly and independently related with an increased risk of death or major complications during the first 30 days after diagnosis. Moreover, the prognostic information provided by GDF-15 appeared to be additive to that of cardiac troponins and natriuretic peptides, and to echocardiographic findings of RV dysfunction. GDF-15 also emerged as an independent predictor of long-term mortality (90).

Conclusions and outlook

Experts and recently updated guidelines agree that thrombolysis is indicated in high-risk PE, i.e. in patients with persistent arterial hypotension and shock at presentation, while low-molecular-weight heparin or fondaparinux is adequate treatment for most normotensive patients with non-high-risk PE (▶Table 2). Recombinant tissue plasminogen activator (alteplase), given as 100 mg infusion over 2 hours, is considered the treatment of choice for patients with PE, although regimens using urokinase or streptokinase also were shown to be efficacious in the past. Reteplase and tenecteplase, if eventually approved for PE, may turn out to be practical and useful alternatives. However, beyond the relatively small population of high-risk PE (5% of all patients) as a target population for thrombolysis, there is increasing awareness of the need for risk stratification of normotensive

patients and the search for an intermediate-risk group (91). Recent meta-analyses of cohort studies suggest that imaging of the right ventricle or biomarkers of myocardial injury *alone* may be insufficient for guiding therapeutic decisions. Instead, accumulating evidence appears to support strategies which combine the information provided by an imaging procedure (RV dysfunction on echocardiography or CT) with a biomarker test (RV myocardial injury indicated by elevated troponin I or T). Accordingly, a large multinational randomised trial has set out to determine whether normotensive, intermediate-risk patients with right ventricular dysfunction, detected by echocardiography or CT, *plus* evidence of myocardial injury indicated by a positive troponin test, may benefit from early thrombolytic treatment (EudraCT number, 2006–005328–18) (83). The primary efficacy end point is a clinical composite end point of all-cause mortality or haemodynamic collapse within the first 7 days. Safety end points are total strokes (intracranial haemorrhage or ischaemic stroke) within 7 days, and major bleeds (other than intracranial haemorrhage) within 7 days. Six-month follow-up is also being conducted. This study, which is already underway in 10 European countries, plans to enrol a total of 1,000 patients and will be completed in 2011.

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