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CASE REPORT

Management of Mitral Regurgitation in a Patient Contemplating Pregnancy

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Abstract

Management of rheumatic mitral regurgitation in a woman contemplating pregnancy presents unique challenges for the clinician. When tasked with taking care of this type of patient, attention needs to be paid to the patient's functional status to determine if symptoms are present. In addition to this clinical assessment, transthoracic echocardiography is also critical. It provides insight into the etiology of the mitral regurgitation, assesses for the presence of concomitant mitral stenosis or other valvular abnormalities, characterizes the severity of mitral regurgitation through an integrative approach and identifies high risk findings including progressive left ventricular (LV) dilation and LV dysfunction. Surgical intervention is recommended for symptomatic patients and in asymptomatic patients with evidence of progressive LV dilation and a LV ejection fraction of less than 60%. While the presence of pulmonary hypertension and atrial fibrillation have been shown to be risk factors in degenerative mitral regurgitation, the same has not been demonstrated in rheumatic mitral valve disease. While mitral regurgitation may be reasonably well tolerated during pregnancy, symptomatic patients are at higher risk for adverse maternal and fetal outcomes, and therefore, it is recommended that mitral valve surgery be performed prior to pregnancy. Once the decision has been made to proceed to surgery, mitral repair, performed at a Heart Valve Center of Excellence is recommended if possible due to improved outcomes. Mitral valve repair is possible in >80% cases of rheumatic mitral regurgitation. If repair is not possible, replacement with either a bioprosthetic or mechanical valve are reasonable options. There are advantages and disadvantages to each approach and the choice of prosthesis should be a shared decision between the patient and her treatment team.

Keywords: mitral regurgitation; valvular heart disease.

Clinical Vignette

A 35 year-old woman seeks advice regarding a planned pregnancy. She has known of a heart murmur since she was 10 years old. She is physically active, but during the past 3 months has been unable to keep up in her exercise class. She reports not having orthopnea, paroxysmal nocturnal dyspnea, or edema.

Physical examination: pulse rate of 60 per minute and regular; blood pressure of 110/73 mmHg; no jugular venous distention, carotid upstrokes normal; apical, holosystolic grade 3/6 murmur radiating to the axilla; no diastolic murmur audible; no edema.

Transthoracic echocardiogram: left ventricular ejection fraction (LVEF) of 60%; left ventricular

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end-systolic dimension (LVESD) of 40 mm, left ventricular end-diastolic volume (LVEDV) of 110 mL/m^2; left atrial volume of 40 mL/m^2; mitral valve with rheumatic deformity; mean transmitral gradient of 6 mmHg at a heart rate of 60 beats per minute, moderate to severe mitral regurgitation (MR); estimated right ventricular systolic pressure of 45 mmHg.

Brain natriuretic peptide: 334 pg/mL (upper reference limit 100 pg/mL).

Discussion

The patient is an otherwise healthy 35-year-old woman presenting with decreased exercise capacity. Her examination confirms the absence of overt congestive heart failure although her murmur is highly suggestive of significant MR. Her transthoracic echocardiogram shows a dilated left ventricle both by LVESD and by LVEDV (110 mL/m^2, the normal range for a woman her age is approximately 30–80 mL/m^2) [1] with an LVEF of 60%. In the setting of compensated significant MR, systolic function should be hyperdynamic (ejection fraction >60%) as the ventricle can eject blood into the lower-impedance left atrium. As a result, left ventricular (LV) function is inappropriately termed "normal." The mitral valve appears rheumatic (Figure 1A, B), with a mean transmitral gradient of 6 mmHg, which may reflect some degree of mitral stenosis, although increased transmitral flow from MR is likely the dominant contributor. There is also moderate pulmonary hypertension, reflective of secondary effects of the MR on the pulmonary vascular system. MR severity in this case was interpreted as moderate to severe, highlighting the challenge of semiquantitative transthoracic echocardiographic assessment. Use of an integrative approach is necessary, combining both qualitative and quantitative assessment, along with a careful search for secondary associated findings (Figure 2C, D). In addition to the inappropriately "normal" LVEF, LV dilation, and pulmonary hypertension, the presence of left atrial enlargement (40 mL/m^2, normal is <34 mL/m^2) [1] is also suggestive of chronic, severe MR. Finally, laboratory testing reveals an elevated brain natriuretic peptide level, which is associated with adverse events in patients with severe MR [4]. Taken together, her clinical presentation, physical examination findings, transthoracic echocardiogram, and laboratory testing results are all consistent with severe symptomatic rheumatic MR.

Patients with severe MR may remain asymptomatic for many years because of ventricular remodeling. In patients with severe degenerative MR (not rheumatic as in the patient presented here), the 8-year survival rate is more than 90% [5]. Among asymptomatic patients, those who develop a reduction in LV function or progressive LV dilation have worse outcomes (Table 1) [6, 7]. Not surprisingly, it has also been demonstrated that outcomes are worse in patients who are symptomatic, regardless of LV function [6, 7]. As such, the 2017 American College of Cardiology/American Heart Association valvular heart disease guidelines recommend mitral valve surgery in patients with severe primary MR who are symptomatic and in asymptomatic patients with LVEF of 30–60% and LVESD of 40 mm or greater [6]. In those asymptomatic patients whose LVEF remains greater than 60% and whose LVESD remains less than 40 mm but who have developed a serial decrease in LVEF or increase in LVESD, surgery is also recommended [6]. While atrial fibrillation and pulmonary hypertension have been identified as potential triggers for surgical intervention in nonrheumatic severe primary MR, it has not been shown that these are independent prognostic markers in patients with rheumatic mitral valve disease [3].

Management of valvular heart disease in the patient considering pregnancy poses additional considerations. Pregnancy is associated with significant hemodynamic changes [8]. As opposed to obstructive lesions, regurgitant valve lesions not associated with symptoms or LV systolic dysfunction are reasonably well tolerated up until delivery [9]. During labor, delivery, and the early postpartum period however, such patients can develop congestive heart failure and tachyarrhythmias because of the increase in venous return (autotransfusion) and systemic vascular resistance (from loss of the low-pressure uteroplacental circulation) [10]. A high threshold for valve intervention (transcatheter or surgical) during pregnancy is usually recommended, as procedural risks to the mother and baby can be substantial. Nevertheless, preexisting and/

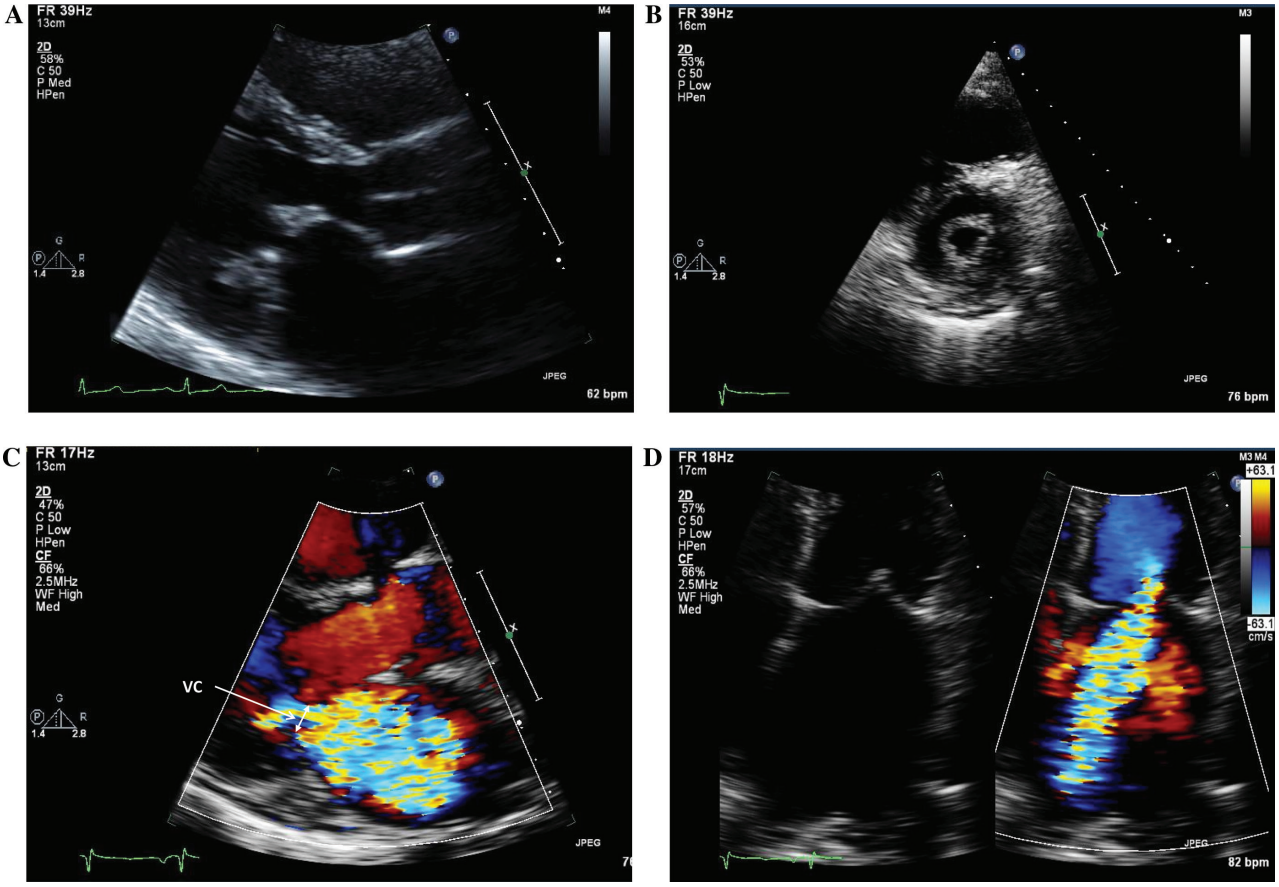

Figure 1 Echocardiographic Imaging of a Rheumatic Mitral Valve.
Rheumatic mitral valve disease is characterized by fusion of the mitral commissures as well as thickening of the leaflets and/or subvalvular apparatus. The resultant distortion of the mitral structures can result in mitral stenosis and/or mitral regurgitation. (A) Parasternal long-axis view of a representative rheumatic mitral valve. Fusion of the mitral commissures results in restriction of the leaflet tips. The basal and mid portions of the leaflets move apically during diastole, and this results in bowing and the characteristic "hockey-stick" deformity shown here. (B) Parasternal short-axis view of a representative rheumatic mitral valve. The medial and lateral mitral commissures are fused in rheumatic disease, resulting in a mitral orifice with a characteristic "fish-mouth" deformity. (C) Color Doppler image of a representative rheumatic mitral valve in parasternal long-axis view. Comprehensive mitral regurgitation assessment requires an integrative approach combining qualitative, semiquantitative, and quantitative assessment. The vena contracta (VC) is defined as the narrowest diameter of the flow stream. This represents a semiquantitative parameter for mitral regurgitation assessment. The VC shown here measures 7 mm, suggestive of moderate to severe mitral regurgitation (Table 1). (D) Color Doppler image of a representative rheumatic valve in apical views. Color jet area can be used as a qualitative means of assessment. It is important to note that in the parasternal view [shown in (C)], the jet area is quite large, but in apical views the jet area is far smaller because of the three-dimensional nature of the regurgitant jet. It is important to note that color jet area is highly dependent on the loading conditions and technical settings, and should not be used in isolation. When possible, quantitative methods, including the proximal isovelocity surface area method and/or quantitative Doppler methods, should also be included in a complete comprehensive assessment [2].

or pregnancy-related heart failure symptoms are associated with worse adverse maternal and fetal outcomes [11]. In the symptomatic patient with significant MR considering pregnancy, proceeding with mitral valve surgery before pregnancy is recommended [3, 12].

Once the decision has been made to proceed with surgery, what type of surgery is most appropriate? It is well established that the surgical risk of mitral valve replacement (MVR) for primary MR is higher than that associated with mitral valve repair and that outcomes are improved when surgery is performed at high-volume centers. In rheumatic mitral disease specifically, recent data suggest that successful repair is possible in more than 80% of cases of severe MR and should be attempted if possible [13].

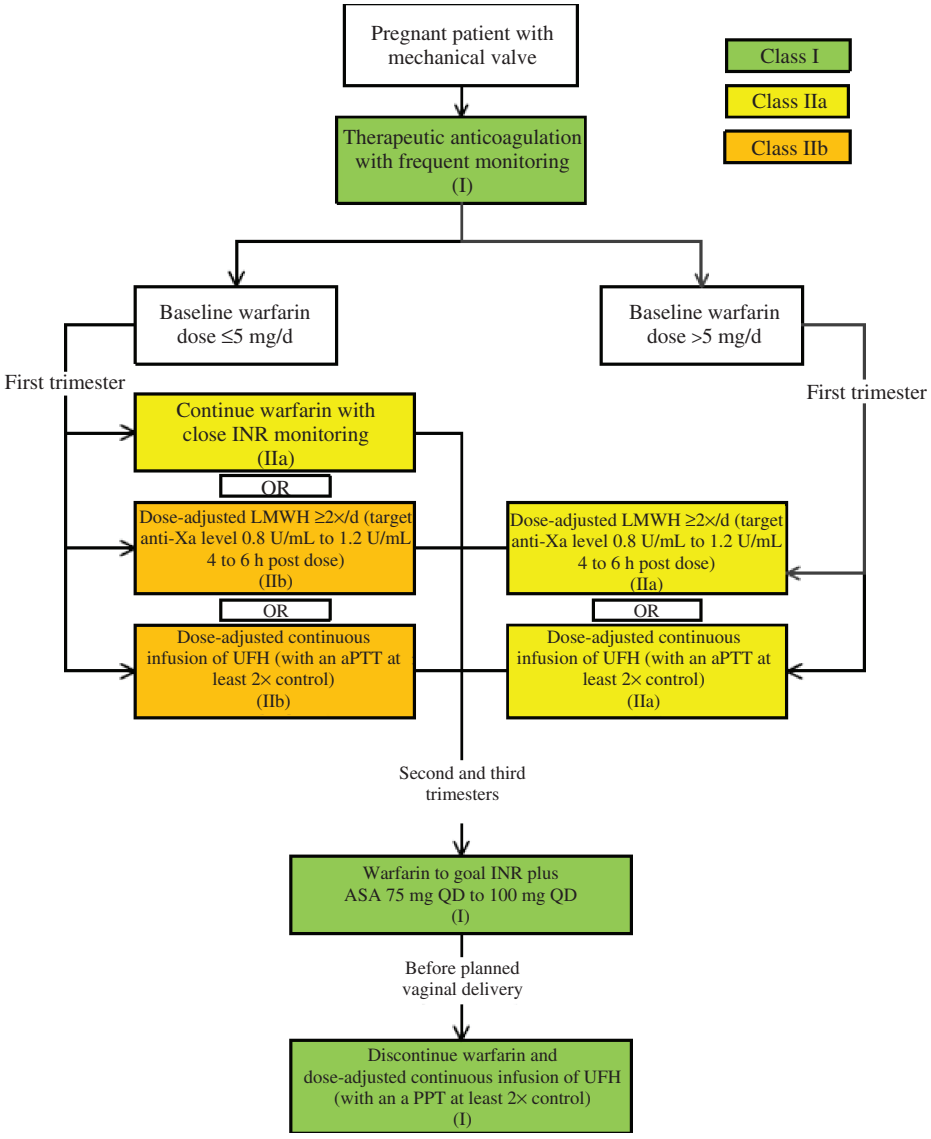

Figure 2 Anticoagulation Management Strategy for Pregnant Patients with Mechanical Heart Valves.
In patients with a warfarin dosage of 5 mg or less day, warfarin can be used in the first trimester (class IIa recommendation), although use of low molecular weight heparin (LMWH) with anti-Xa level monitoring or intravenously administered heparin is a reasonable alternative (class IIb). In patients with a warfarin dosage of more than 5 mg/day, LMWH with anti-Xa level monitoring or intravenously administered heparin can be used in the first trimester (class IIa recommendation). Regardless of the warfarin dosage, aspirin (75–100 mg/day) and warfarin should be used in the second and third trimesters until immediately before delivery (class I recommendation). aPTT, activated partial thromboplastin time; ASA, acetylsalicylic acid (aspirin); INR, international normalized ratio; QD, each day; UFH, unfractionated heparin. Reproduced with permission from Nishimura et al. [3].

In patients for whom repair is not possible, MVR is recommended with either a mechanical or a biological prosthesis. The advantage of a mechanical mitral prosthesis relates to its longer-term durability compared with a bioprosthesis, albeit with the need for anticoagulation with a vitamin K antagonist (VKA) with target international normalized ratio of 2.5–3.5 along with low-dose aspirin [3, 6]. Because of the high thrombotic risk with even short-term anticoagulation cessation, patients with mechanical MVR need to be bridged for noncardiac procedures [6]. Bioprosthetic valve durability has improved, with an average time to reoperation of approximately 12 years [14, 15]. Younger patients, however, are predisposed to accelerated valve degeneration [14]. After placement of a bioprosthetic mitral valve, patients are treated with a VKA for at least 3 months and then low-dose

Table 1 Stages of Primary Mitral Regurgitation (MR).

Grade	Definition	Echocardiographic parameters	Hemodynamic consequences	Symptoms
A	At risk of MR	• MR jet on color Doppler imaging <20% of left atrium • Vena contracta <0.3 cm	• None	• None
B	Progressive MR	• Central jet 20–40% of left atrium or late systolic eccentric jet • Vena contracta <0.7 cm • Regurgitant volume <60 mL • Regurgitant fraction <50% • EROA <40 mm^2	• Mild LA enlargement • Normal LV size • Normal PA pressures	• None
C1	Asymptomatic severe MR	• Central jet >40% of left atrium or holosystolic eccentric jet • Vena contracta ≥0.7 cm • Regurgitant volume ≥60 mL • Regurgitant fraction ≥50% • EROA ≥40 mm^2	• Moderate/severe LA enlargement • LV enlargement • Pulmonary hypertension (at rest or with exercise) • LVEF >60% • LVESD <40 mm	• None
C2	Asymptomatic severe MR	• Central jet >40% of left atrium or holosystolic eccentric jet • Vena contracta ≥0.7 cm • Regurgitant volume ≥60 mL • Regurgitant fraction ≥50% • EROA ≥40 mm^2	• Moderate/severe LA enlargement • LV enlargement • Pulmonary hypertension (at rest or with exercise) • LVEF ≤60% • LVESD ≥40 mm	• None
D	Symptomatic severe MR	• Central jet >40% of left atrium or holosystolic eccentric jet • Vena contracta ≥0.7 cm • Regurgitant volume ≥60 mL • Regurgitant fraction ≥50% • EROA ≥40 mm^2	• Moderate/severe LA enlargement • LV enlargement • Pulmonary hypertension (at rest or with exercise)	• Decreased exercise tolerance • Exertional dyspnea

Primary MR is a result of abnormalities in the mitral valve itself as is the case with rheumatic heart disease. In contrast, secondary MR results from progressive left ventricular (LV) dysfunction and annular dilation. Distinction between stage C1 and stage C2 is of particular importance in these asymptomatic individuals as the treatment strategies differ, with active surveillance being reasonable in the former and surgical intervention recommended in the latter.
EROA, effective regurgitant orifice area; LA, left atrial; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension; PA, pulmonary artery.
Adapted from Nishimura et al. [3, 6].

Table 2 Indications for Surgical Intervention for the Pregnant Patient with Severe Rheumatic Mitral Regurgitation (MR).

Class of recommendation	Recommendation
Class I	• MV surgery is recommended for symptomatic patients with chronic severe primary MR (stage D) with LVEF >30% • MV surgery is recommended for asymptomatic patients with chronic severe primary MR and LVEF of 30–60% and/or LVESD ≥40 mm (stage C2) • MV repair is recommended over MV replacement provided a successful and durable repair can be performed • MV surgery is recommended before pregnancy for symptomatic women with severe MR (stage D)
Class IIa	• MV repair is reasonable in asymptomatic patients with chronic severe primary MR and LVEF >60% and LVESD <40 mm (stage C1) if the likelihood for a successful repair is >95% with an expected mortality rate <1% when performed at a Heart Valve Center of Excellence • MV repair is reasonable in asymptomatic patients with chronic severe primary MR and LVEF >60% and LVESD <40 mm (stage C1) with a progressive increase in LV size or decrease in LVEF on serial imaging studies
Class IIb	• MV repair may be considered in patients with rheumatic MR if surgery is indicated if a durable and successful repair is likely or if the reliability of long-term anticoagulation management is questionable

Symptomatic patients with severe MR are at increased risk of adverse events without surgical intervention, an observation that underlies the recommendation for surgical intervention in this population. Pregnant women with severe MR and preexisting heart failure symptoms are also at increased risk of adverse maternal and fetal outcomes [11], and therefore the class I recommendation remains, even in this population despite the challenges that may be present if mitral valve (MV) replacement is necessary.
LV, left ventricular; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension.
Adapted from Nishimura et al. [3, 6].

aspirin indefinitely, unless atrial fibrillation is present [6]. Patients undergoing mitral valve repair are treated similarly to those with bioprosthetic valves although their early thromboembolic risk is lower [16].

While a mechanical valve would be typically recommended in an otherwise healthy 35-year-old woman [6], her desire to become pregnant raises special considerations. Patients with mechanical heart valves who become pregnant are at high risk of thromboembolic complications likely due to the hypercoagulable state of pregnancy combined with the necessary alterations in anticoagulation management during this period [17]. Valve thrombosis is the most concerning complication, and carries a 20% risk of death [18]. While VKAs cross the placenta and are associated with adverse fetal outcomes (including miscarriage, stillbirth, and embryopathy), this effect is seen primarily at doses greater than 5 mg and is highest in the first trimester [19]. Low molecular weight heparin can be used with careful monitoring of anti-Xa levels, although there is some evidence to suggest that VKAs are more effective in preventing maternal mechanical valve thrombosis [19, 20]. Although often omitted, low-dose aspirin should be used in the second and third trimesters [18, 21]. Balancing these competing risks, the 2014 American College of Cardiology/American Heart Association guidelines put forth anticoagulation recommendations to best treat these complicated patients (Table 2) [3]. While these recommendations can help treat patients with mechanical heart valves safely through pregnancy, there remains a high risk of complications that warrant consideration of bioprosthetic MVR if mitral valve repair cannot be performed. The advantage of bioprosthetic MVR in this setting is the ability to avoid VKA therapy, while the main disadvantage is the need for repeated intervention in the future. At the current time, repeated intervention would involve a reoperative surgical MVR, although percutaneous (mitral valve-in-valve) procedures can be considered in patients who are not surgical candidates [22]. Additional transcatheter MVRs are

currently under investigation. There is no single correct option in this challenging patient population should a mitral valve repair not be feasible, and the choice of prosthesis should be the result of a shared decision making process involving the patient and her providers.

To return to the patient, she is a 35-year-old woman with severe rheumatic MR without significant stenosis, LV dilation, and an inappropriately "normal" LVEF presenting with progressive decline in exercise tolerance. Assuming that her history has been obtained carefully to exclude other causes of decreased exercise tolerance, it is reasonable to conclude that she is symptomatic from her severe MR. On the basis of the adverse pregnancy-related outcomes, as well as longer-term cardiovascular outcomes, surgical intervention is recommended. She should be evaluated by an experienced mitral valve surgeon, and a mitral valve repair should be performed if possible. If repair is not possible, replacement with either a bioprosthetic or a mechanical mitral valve should be considered, with advantages and disadvantages weighed carefully. There is no single correct answer for all patients, and a shared decision making process is necessary to reach the optimal solution for each individual patient. Regardless of the surgical intervention selected, she will need to continue with antibiotic prophylaxis for the prevention of recurrent rheumatic carditis until at least age 40 years (and potentially longer depending on her residual exposure to group A streptococcus), as well as before dental procedures for the prevention of infective endocarditis [23]. While the decision to proceed with surgery can seem straightforward when presented in a clinical vignette such as this, it is often more complicated in "real life." The symptoms are not always clear, echocardiographic assessment can be technically challenging, and the ability to predict reparability can be limited. While the data and guidelines serve an important role in helping craft recommendations for patients, the final treatment plan ultimately requires a multidisciplinary shared approach between the patient, cardiologist, cardiac surgeon, and maternal-fetal medicine specialist.

Conflict of Interest

The authors declare no conflict of interest.

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