"One-Time" versus Staged Multivessel Intervention in Intermediate to Very High-Risk Patients with Non-ST-Segment Elevation Acute Coronary Syndromes

Xiaofan Yu, MD1,2,3, Yi Li, MD2, Qiancheng Wang, MD1, Ming Liang, MD2, Kai Xu, MD2, and Yaling Han, MD2

1Department of Cardiology, The Second Hospital of Dalian Medical University, Dalian, Liao Ning, 2Department of Cardiology, General Hospital of Shenyang Military Region, Shenyang, Liao Ning, 3Department of Cardiology, Anhui Provincial Hospital, Hefei, Anhui, China

Background and Objectives: To compare clinical outcomes of staged versus "one-time" percutaneous coronary intervention (PCI) in intermediate to very high-risk patients with non-ST-segment elevation acute coronary syndromes (NSTE-ACS) and multivessel coronary disease (MVD).

Subjects and Methods: 1531 NSTE-ACS patients with multivessel PCI and meeting the criteria of intermediate to very high risk were screened from a prospectively registered database obtained from General Hospital of Shenyang Military Region between 2008 and 2012. They were categorized into "one-time" PCI (n=859) and staged PCI (n=672) according to intervention strategy. The primary outcomes included a 3-year major adverse cardiac event (MACE), a composite of cardiac death, myocardial infarction (MI), and target vessel revascularization.

Results: At 3 years, no significant differences in MACE (20.8% vs. 19.7%, p=0.608) and cardiac death/MI (7.1% vs. 9.1%, p=0.129) were observed between the two groups. After propensity score matching, there was no statistical significance in MACE (18.9% vs. 21.8%, p=0.249); whereas cardiac death/MI was significantly lower in the staged PCI group (7.0% vs.11.1%, p=0.033). Ninety-day landmark analysis showed that the staged PCI group had a lower 90-day incidence of MACE (1.2% vs. 3.3%, p= 0.037) and cardiac death/MI (0.7% vs. 2.6%, p=0.031). For the 90-day to 3-year follow-up period, the incidences of MACE (17.9% vs. 19.1%, p=0.641) and cardiac death/MI (6.3% vs. 8.7%, p=0.191) were similar in both groups.

Conclusion: In intermediate- to very high-risk NSTE-ACS patients with MVD, staged PCI is superior to "one-time" PCI in terms of cardiac death/MI. (Korean Circ J 2016;46(6):774-783)

KEY WORDS: Acute coronary syndromes; Coronary artery disease; Percutaneous coronary intervention.

Introduction

Non-ST-segment elevation acute coronary syndromes (NSTE-ACS) are the most frequent manifestation of acute coronary syndromes (ACS). Its morbidity and mortality stays high and even equal to those of patients with ST-segment elevation myocardial infarction (STEMI) during long-term follow-up. Current guidelines propose risk stratification for tailoring treatment in patients with NSTE-ACS. In patients with intermediate- to very high-risk NSTE-ACS, routine invasive diagnostics and treatments are recommended. Multivessel coronary disease (MVD), a leading pathological foundation of intermediate to very high risk clinical manifestation, accounts for approximately 30–40% NSTE-ACS cohorts overall and is usually treated with invasive interventions. The American College of Cardiology/American Heart Association guidelines provide a class IIb recommendation that multivessel percutaneous coronary intervention (PCI), in contrast to culprit-only PCI, might be reasonable in NSTE-ACS patients undergoing PCI (Level of
Evidence: B).<sup>3</sup> This recommendation is based on reports of studies suggesting that multivessel PCI is superior to culprit vessel only PCI in terms of repeat revascularization.<sup>5-8</sup> However, there is still uncertainty as to whether non-culprit lesions should be treated at the time of culprit-lesion PCI for NSTE-ACS.<sup>3</sup> In the present study, we sought to examine clinical outcomes of “one-time” versus staged multivessel stenting in intermediate to very high-risk NSTE-ACS patients with MVD.

**Subjects and Methods**

**Study population**

Between November 2008 and November 2012, a total of 12047 unselected patients who had undergone a PCI were prospectively registered in the PCI database of General Hospital of Shenyang Military Region. The database contained comprehensive information including clinical and angiographic characteristics, treatment strategies and clinical outcomes. Eligible patients had at least one intermediate to very high risk criteria with indication for invasive management defined by the 2015 European Society of Cardiology (ESC) guidelines for the management of NSTE-ACS<sup>2</sup>; 3 types of very high-risk criteria include recurrent or ongoing chest pain refractory to medical treatment, and recurrent dynamic ST-T wave changes particularly with intermittent ST-elevation and acute heart failure; 3 types of high-risk criteria include recurrent or ongoing chest pain refractory to medical treatment, and recurrent dynamic ST-T wave changes particularly with intermittent ST-elevation and acute heart failure; 3 types of intermediate-risk criteria include diabetes mellitus, renal insufficiency (Estimated glomerular filtration rate [eGFR] < 60 mL/min/1.73 m<sup>2</sup>), left ventricular ejection fraction (LVEF) <40% or congestive heart failure, early post-infarction angina, prior PCI, prior coronary artery bypass graft (CABG) and GRACE risk score>109 and <140. Exclusion criteria were patients who had chronic total occlusion; patients who had procedural failure (i.e., technical failure), including staged PCI patients who had procedural failure during the index PCI and scheduled for staging; patients who had cardiac shock, hemodynamically unstable or malignant ventricular arrhythmia; patients who had renal dialysis or a eGFR <30 mL/min/1.73 m<sup>2</sup>; staged PCI patients who had any major complication during the index procedure; patients who had a planned staged PCI >60 days. Our final population included 1531 patients from the database having NSTE-ACS with multivessel PCI (Fig. 1).

**Treatment**

All patients were given oral loading doses of aspirin (300 mg) and clopidogrel (300-600 mg) prior to PCI, unless they had already received antiplatelet medication. Interventional procedures were performed according to standard techniques and interventional strategies rested on the operators. The choice between complete or incomplete revascularization was also at operators’ discretion. The culprit lesion was identified by operators usually based on each patient’s electrocardiogram, angiographic imaging, echocardiogram and, if available, intravascular ultrasound (IVUS) and optical coherence tomography (OCT). A lesion was considered a culprit on angiography if at least two of the following morphological features suggestive of acute plaque rupture were present: intraluminal filling defects consistent with thrombus, plaque ulceration, plaque irregularity, dissection or impaired flow.<sup>29-31</sup> After the procedure, the use of aspirin lifelong was advised and clopidogrel was prescribed for 12 months. The study was approved by the hospital ethics committee and all patients gave written informed consent.

**Follow-up**

Clinical follow-up was performed via telephone or at an outpatient visit at 30 days, 6 months, and 12 months after the index procedure and annually until 3 years after the index procedure. Follow-up angiography was recommended to all patients 6 to 12 months after the index procedure, and repeat revascularization was performed, if clinically indicated.
Outcomes and definitions

The primary outcome was the incidence of major adverse cardiac events (MACE), defined as the composite of cardiac death, MI and target vessel revascularization (TVR) during 3-year follow-up. Secondary outcomes included MACE components, the composite of cardiac death or MI, definite/probable stent thrombosis, and any repeat revascularization.

MVD was defined as the presence of a significant atherosclerotic coronary artery stenosis (≥70% diameter stenosis) or a ≥50% stenosis of the left main coronary artery (left main disease) with additional significant stenosis (≥70% diameter stenosis) of at least one other coronary artery assessed visually during coronary angiography. Staged PCI is defined as the planned PCI of non-infarct vessel(s) within 60 days of the index PCI. eGFR was calculated from serum creatinine (sCr) concentrations using the modified glomerular filtration rate estimating the equation for Chinese patients with chronic kidney disease: eGFR (mL/min/1.73 m²) = 175×(sCr)⁻¹.23×(age)⁻⁰.₁⁷⁹×(0.⁷⁹ if patient is female). Anemia was defined as hemoglobin less than 12 g/dL for men or less than 11 g/dL for women. Early invasive intervention was defined as a coronary angiography performed within 24 h of hospital admission. Delayed invasive intervention was defined as a coronary angiography performed more than 24 h of hospital admission. Technical success was defined as the ability to cross an occluded or stenosed segment and successfully open the artery (restoration of thrombolysis in myocardial infarction [TIMI] flow grade 3) with a residual stenosis ≤30% by visual analysis. Cardiac death was defined as death that could not be attributed to a non-cardiac etiology. MI was defined as third universal definition of MI presented by The Third Global MI Task Force. TVR was determined as any repeated PCI or CABG to treat a previously stented vessel. Complete revascularization was defined when no visually estimated stenosis ≥50% for the left main and no stenosis ≥70% for other major arteries and/or their major branches at discharge. Stent thrombosis was classified as definite and probable according to definitions proposed by the Academic Research Consortium.

### Table 1. Baseline characteristics

| Characteristic | Unadjusted | Propensity score adjusted |
|---------------|------------|--------------------------|
|               | One-time (n=859) | Staged (n=672) | p | One-time (n=420) | Staged (n=420) | p |
| Age (years)   | 62.7±10.4 | 62.6±10.0 | 0.756 | 62.8±10.3 | 62.7±10.0 | 0.770 |
| Gender (male) | 580 (67.5) | 496 (73.8) | 0.008 | 300 (71.4) | 306 (72.9) | 0.644 |
| BMI (kg/m²)   | 25.2±3.2 | 25.0±3.0 | 0.208 | 25.0±3.4 | 25.0±3.1 | 0.904 |
| Heart rate (bpm) | 73.8±11.4 | 74.0±11.7 | 0.795 | 73.6±11.1 | 73.8±11.8 | 0.770 |
| Atrial fibrillation, n (%) | 21 (2.4) | 20 (3.0) | 0.523 | 9 (2.1) | 10 (2.4) | 0.816 |
| Risk factors, n (%) | | | | | | |
| Anemia        | 76 (8.8) | 58 (8.6) | 0.882 | 30 (7.1) | 33 (7.9) | 0.694 |
| Diabetes      | 308 (35.9) | 256 (38.1) | 0.367 | 159 (37.9) | 159 (37.9) | 1.000 |
| Hypertension  | 561 (65.3) | 454 (67.6) | 0.355 | 281 (66.8) | 279 (66.4) | 0.884 |
| Hyperlipidemia| 384 (44.7) | 330 (48.9) | 0.086 | 203 (48.3) | 197 (46.9) | 0.679 |
| PAD           | 24 (2.8) | 19 (2.8) | 0.969 | 13 (3.1) | 12 (2.9) | 0.839 |
| Current smoker| 382(44.5) | 341 (50.7) | 0.015 | 213(50.7) | 210 (50.0) | 0.836 |
| Previous MI   | 172 (20.0) | 191 (28.4) | <0.001 | 105 (25.0) | 113 (26.9) | 0.529 |
| Previous PCI  | 203 (23.6) | 167 (24.9) | 0.580 | 109 (26.0) | 115 (27.4) | 0.640 |
| Previous CVD  | 68 (7.9) | 67 (10.0) | 0.160 | 42 (10.0) | 40 (9.5) | 0.816 |
| Type of NSTE-ACS, n (%) | | | 0.405 | | | 0.755 |
| UA            | 645 (75.1) | 492 (73.2) | 0.306 | 307 (72.9) | 310 (73.8) | |
| NSTEMI        | 214 (24.9) | 180 (26.8) | 0.114 | 114 (27.1) | 150 (31.2) | 0.262 |
| eGFR ≤60 mL/min/1.73 m², n (%) | 88 (10.2) | 78 (11.6) | 0.395 | 45 (10.7) | 38 (9.0) | 0.418 |
| LVEF ≤40%, n (%) | 13 (1.5) | 14 (2.1) | 0.400 | 9 (2.1) | 7 (1.7) | 0.614 |

BMI: body mass index, PAD: peripheral arterial disease, MI: myocardial infarction, PCI: percutaneous coronary intervention, CVD: cerebrovascular disease, Hb: hemoglobin, NSTE-ACS: non-ST-segment elevation acute coronary syndromes, UA: unstable angina, NSTEMI: non-ST-segment elevation myocardial infarction, eGFR: estimated glomerular filtration rate, LVEF: Left ventricular ejection fraction.
Statistical analysis

Continuous variables were expressed as mean±standard deviation (SD), and categorical variables were expressed as number and/or percentages. For group comparisons, Pearson chi-square test or Fisher’s exact test was used for categorical variables. Student’s unpaired t-test or the Mann-Whitney rank-sum test, as appropriate, was used for continuous variables. To minimize the influence of confounders on outcome, we used propensity score matching analysis. Patients who underwent staged PCI were matched in a 1:1 ratio with patients who underwent a "one-time" PCI using the nearest neighbor matching, which were based on all available variables listed in Tables 1 and 2 except GRACE Score, IVUS used, OCT used, contrast volume, length of hospital, medication at discharge and dual antiplatelet therapy (DAPT) duration. A difference of <10% was regarded as acceptable. Time to event data with estimated event rates calculated by Kaplan–
Meier method were compared with the log-rank test. In addition, we performed Kaplan-Meier analyses at the landmark periods of 0 to 90 days and 90 days to 3 years to evaluate the effect of revascularization strategy on clinical outcomes at different time periods. All statistical tests were 2-tailed, and statistical analyses were performed with SPSS Ver. 20 software (SPSS Inc., Chicago, IL, USA).

**Results**

**Patients and treatments**

"One-time" PCI was performed in 56.1% (859/1531), and the remaining 43.9% (672/1531) had staged PCI. Of these, 80.7% (542/672) had staged non-culprit intervention during the same hospitalization and 19.3% (130/672) had planned staged non-culprit procedures after hospital discharge. The median delay of the staged PCI was 5 days (interquartile range [IQR], 3–9 days). As noted in Tables 1 and 2, male, previous MI, triple-vessel disease, and current smoking were associated with more staging. The volume of contrast media utilized during the index procedure in the staged PCI group was smaller (200 mL [IQR, 150–220 mL] vs. 200 mL [IQR, 200–300 mL], p<0.001) though the total volume utilized in the initial procedure plus staged procedure was greater (400 mL [IQR, 310–500 mL] vs. 200 mL [IQR, 200–300 mL], p<0.001). Medications at discharge were similar between both groups. Most patients took dual antiplatelet therapy (DAPT), which was consistent with the standard recommendation. After propensity matching, there were no statistically significant differences in preselected variables between the two groups.

**Clinical outcomes of unadjusted populations**

As noted in Table 3, Fig. 2A and Fig. 3A, MACE occurred in 132 patients (20.8%) in the staged group and 162 patients (19.7%) in the "one-time" group during 3-year follow-up (p=0.608). Rates of each component of 3-year cumulative MACE were similar between both groups. The estimated 3-year composite rate of cardiac death or MI was 7.1% in the staged PCI group compared with 9.1% in

| Table 3. 90-day and 3-year outcomes for unadjusted and adjusted populations |
|-----------------------------|------------------|------------------|------------------|------------------|
| **Outcomes** | **Unadjusted** | **Propensity score adjusted** |
| | **One-time** (n=859) | **Staged** (n=672) | **p** | **One-time** (n=420) | **Staged** (n=420) | **p** |
| 90 days, n (%) | | | | | | |
| MACE | 22 (2.6) | 13 (1.9) | 0.415 | 14 (3.3) | 5 (1.2) | 0.037 |
| Cardiac death or MI | 18 (2.1) | 8 (1.2) | 0.174 | 11 (2.6) | 3 (0.7) | 0.031 |
| Cardiac death | 6 (0.7) | 5 (0.7) | 0.914 | 3 (0.7) | 1 (0.2) | 0.318 |
| MI | 16 (1.9) | 7 (1.0) | 0.190 | 9 (2.1) | 3 (0.7) | 0.081 |
| TVR | 12 (1.4) | 7 (1.1) | 0.534 | 7 (1.7) | 4 (1.0) | 0.361 |
| Any revascularization | 18 (2.1) | 15 (2.3) | 0.854 | 9 (2.1) | 6 (1.4) | 0.432 |
| Definite/probable ST | 11 (1.3) | 4 (0.6) | 0.176 | 6 (1.4) | 3 (0.7) | 0.312 |
| 3 years, n (%) | | | | | | |
| MACE | 162 (19.7) | 132 (20.8) | 0.608 | 88 (21.8) | 74 (18.9) | 0.249 |
| Cardiac death or MI | 74 (9.1) | 43 (7.1) | 0.129 | 44 (11.1) | 26 (7.0) | 0.033 |
| Cardiac death | 41 (5.1) | 24 (4.0) | 0.294 | 19 (4.8) | 9 (2.5) | 0.067 |
| MI | 47 (5.8) | 28 (4.5) | 0.260 | 30 (7.7) | 20 (5.0) | 0.162 |
| TVR | 113(13.9) | 108 (17.3) | 0.103 | 58 (14.5) | 58 (14.9) | 0.971 |
| Any revascularization | 151 (18.6) | 141 (22.3) | 0.083 | 81 (20.4) | 80 (20.3) | 0.888 |
| Definite/probable ST | 16 (1.9) | 8 (1.3) | 0.295 | 9 (2.2) | 5 (1.2) | 0.280 |
| Acute (<24 h) | 5 (0.6) | 1 (0.1) | 0.178 | 4 (1.0) | 1 (0.2) | 0.178 |
| Subacute (1-30 d) | 5 (0.6) | 3 (0.4) | 0.708 | 2 (0.5) | 2 (0.5) | 0.990 |
| Late (>30 d) | 6 (0.8) | 4 (0.7) | 0.806 | 3 (0.8) | 2 (0.5) | 0.651 |

Values are presented as numbers and percentage. MACE: major adverse cardiac events, MI: myocardial infarction, TVR: target vessel revascularization, ST: stent thrombosis.
the "one-time" PCI group (p=0.129). In addition, no significant differences in the 3-year rates of any revascularization (22.3% vs. 18.6%, p=0.083) and definite/probable stent thrombosis (1.3% vs. 1.9%, p=0.295) were observed.

At the 90-day landmark analysis (Tables 3 and 4, Fig. 2C and Fig. 3C), no significant differences in terms of MACE, its individual components, any revascularization and definite/probable stent thrombosis were observed at the landmark period of 0 to 90 days and 90 days to 3 years.

**Clinical outcomes of propensity score-matched populations**

After generating a propensity score, 420 of the 672 patients who underwent staged PCI were matched with a patient, respectively, who underwent a "one-time" PCI. There were no differences in preselected variables for the propensity matched subjects (Table 1, 2). As noted in Table 3, Fig. 2B and Fig. 3B, at 3 years, there were no differences in MACE (18.9% vs. 21.8%, p=0.249); whereas there was a significantly lower incidence of cardiac death or MI (7.0% vs. 11.1%, p=0.033). The risk for cardiac death in the staged PCI group tended to be lower (2.5% vs. 4.8%, p=0.067). Other clinical outcomes including MI (5.0% vs. 7.7%, p=0.162), TVR (14.9% vs. 14.5%, p=0.971), any revascularization (20.3% vs. 20.4%, p=0.888), and definite/probable stent thrombosis (1.2% vs. 2.2%, p=0.280) were not significantly different between the two study groups.

The results of the 90-day landmark analysis for propensity score matched patients were shown in Tables 3 and 4, Fig. 2D and Fig. 3D.
Fig. 3. Kaplan-Meier assessment for the composite of cardiac death or MI for unadjusted (A) and propensity score matched (B) patients; 90-day landmark analysis of the composite of cardiac death or MI for unadjusted (C) and propensity score matched (D) patients. PCI: percutaneous coronary intervention, MI: myocardial infarction.

Table 4. Clinical outcomes from 90 days to 3 years after index PCI

| Outcomes                      | Unadjusted                  | Propensity score adjusted |
|-------------------------------|-----------------------------|----------------------------|
|                               | One-time (n, %) | Staged (n, %) | p       | One-time (n, %) | Staged (n, %) | p       |
| Between 90 days and 3 years   |                             |                           |         |                             |                           |         |
| MACE                          | 140/837 (17.6) | 119/655 (19.3) | 0.397   | 74/406 (19.1)   | 69/413 (17.9) | 0.641   |
| Cardiac death or MI           | 56/841 (7.1)     | 35/660 (6.0)     | 0.321   | 33/409 (8.7)    | 23/415 (6.3)   | 0.191   |
| Cardiac death                 | 35/853 (4.4)     | 19/663 (3.2)     | 0.230   | 16/417 (4.1)    | 8/417 (2.2)    | 0.117   |
| MI                            | 31/841 (4.0)     | 21/660 (3.5)     | 0.632   | 21/409 (5.6)    | 17/415 (4.6)   | 0.531   |
| TVR                           | 101/841 (12.7)   | 101/655 (16.4)   | 0.058   | 51/410 (13.1)   | 54/413 (14.0)  | 0.797   |
| Any revascularization         | 133/835 (16.9)   | 126/648 (20.5)   | 0.076   | 72/408 (18.6)   | 74/411 (19.1)  | 0.917   |
| Definite/probable ST          | 5/841 (0.6)      | 4/660 (0.7)      | 0.971   | 3/409 (0.8)     | 2/415 (0.5)    | 0.651   |

PCI: percutaneous coronary intervention, MACE: major adverse cardiac events, MI: myocardial infarction, TVR: target vessel revascularization, ST: stent thrombosis
The staged PCI group showed a lower 90-day incidence of MACE (1.2% vs. 3.3%, p = 0.037), mainly due to a lower composite rate of cardiac death or MI (0.7% vs. 2.6%, p = 0.031). The 90-day rates of MI did not differ significantly between the 2 study groups, but it presented a trend in favor of staged PCI (0.7% vs. 2.1%, p = 0.081). For the 90-day to 3-year follow-up period, both the incidences of MACE (17.9% vs. 19.1%, p = 0.641) and the composite of cardiac death or MI (6.3% vs. 8.7%, p = 0.191) were similar between the two groups. Cardiac death, TVR, any revascularization and definite/probable stent thrombosis did not differ significantly between the two groups at the landmark period of 0 to 90 days and 90 days to 3 years.

Discussion

To our knowledge, this is the first study to examine the efficacy of staged versus "one-time" approach in intermediate to very high-risk NSTE-ACS patients with multivessel PCI. Main findings of this study were as follow: in intermediate to very high-risk NSTE-ACS patients with multivessel disease, staged PCI was associated with a lower composite rate of cardiac death or MI compared with "one-time" PCI strategy. This benefit of staged PCI was more apparent in patients with multivessel disease has not been well established. Therefore, our patient inclusion criteria, which were based on ESC guidelines, selected NSTE-ACS patients with intermediate- to very high-risk features.

Our study had several limitations. First, this was a retrospective analysis from a prospective single center registry. The decisions for one-time vs. staged PCI were not based on a randomization but at physicians’ discretion, which resulted in obvious confounding and selection bias. Although we analyzed by adjusting many possible confounding factors, unmeasured confounding or selection bias might have influenced our findings. Second, in this study, all patients underwent PCI in the setting of antplatelet therapy with clopidogrel. When the new antplatelet agent ticagrelor is available, this finding deserves further investigation. Third, the relatively high frequency of angiography during the period between 6 to 12 months after the procedure could bias the MACE, especially TVR. However, this bias was limited, because the two groups had similar frequencies of follow-up angiography and because repeat intervention was guided by either recurrent angina or signs of ischemia that had progressed angiographically, even without angiina based on invasive or noninvasive testing. Fourth, our data were collected before current practice guidelines were published. Therefore, timing of invasive strategies were not run according to current guidelines. Fifth, given the low absolute number of events at 90-day follow up in the propensity score matched cohort, our study was not powered to detect significant differences in cardiac death, MI, TVR and stent thrombosis at 90 days. Last, considering follow-up angiography and routine cardiac biomarkers surveillance was not mandatory, therefore the incidence of MI might have been underestimated.

Conclusion

In intermediate to very high-risk NSTE-ACS patients with multivessel disease, staged PCI is superior to "one-time" PCI in poor clinical state or have concomitant comorbidities. PCI on the culprit lesion first and staged non-culprit PCI at a later date with optimal medical therapy usually results in the patient being stable and also allows clinicians to reassess the patient’s clinical and angiographic states.

Risk stratification is essential for the clinical decision-making process in NSTE-ACS patients. With respect to outcomes, periprocedural complications of intervention, as well as the long-term ischemic risk, remain higher in high-intermediate risk NSTE-ACS than in low-risk NSTE-ACS patients. When choosing the optimal treatment strategy in the individual patient with NSTE-ACS and MVD, general patient condition and concomitant comorbidities have to be taken into account. However, the optimal strategy for the management of NSTE-ACS patients with poor clinical presentation and multivessel disease has not been well established. Therefore, our patient inclusion criteria, which were based on ESC guidelines, selected NSTE-ACS patients with intermediate- to very high-risk features.
terms of the composite of cardiac death or MI. Our findings require further confirmation by randomized trial.

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