ORIGINAL ARTICLE

Long-term clinical outcomes after placement of an implantable cardioverter-defibrillator: does the etiology of heart failure matter?

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KEY WORDS
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ABSTRACT

BACKGROUND European and American guidelines for the placement of implantable cardioverter-defibrillator (ICD) and cardiac resynchronization therapy defibrillator (CRT-D) in patients with heart failure (HF) remain unchanged despite controversy and ongoing debate on the etiology of HF. However, there are limited data on the long-term follow-up in patients who received primary defibrillator therapy with regard to ischemic cardiomyopathy (ICM) and nonischemic cardiomyopathy (NICM). The prognostic significance of the etiology of HF is not well established.

AIMS The aim of the study was to assess the predictive value of the cause of HF.

METHODS A total of 1073 patients with the first implantation of ICD / CRT-D between January 2009 and December 2013 from the COMMIT-HF (Contemporary Modalities In Treatment of Heart Failure) registry were selected for the study. Patients were divided into 2 groups depending on the etiology of HF: ischemic (n = 705; 65.7%) and nonischemic (n = 368; 34.3%). The primary endpoint was long-term all-cause mortality.

RESULTS The median follow-up was 60.5 months. The primary endpoint occurred more often in the ICM as compared with the NICM group (35.7% vs 26.6%; *P* = 0.008). A higher out-of-hospital mortality in patients with ICM tended to be statistically significant (15.5% vs 10.6; *P* = 0.05). The multivariate analysis revealed that, among others, an ischemic etiology of HF was an independent factor of long-term mortality (hazard ratio, 1.43; 95% CI, 1.30–1.81; *P* = 0.003). Other independent predictors for mortality are: age older than 65 years, impaired left ventricular ejection fraction, chronic kidney disease, atrial fibrillation, diabetes mellitus.

CONCLUSIONS In the real-world population, significantly worse survival of patients with ICM in comparison with those with NICM is observed, and an ischemic etiology of HF is a strong independent predictor of mortality among individuals following the placement of ICD / CRT-D.

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INTRODUCTION Prophylactic implantable cardioverter-defibrillator (ICD) therapy in patients with heart failure (HF) with left ventricular eject fraction (LVEF) of 35% or less significantly decreases the relative risk of death and remains standard care with class I recommendations in European and American guidelines, regardless of the etiology of HF.[1,2] However, despite a worse clinical profile and higher rate of concomitant diseases in patients with ischemic cardiomyopathy (ICM), the same clinical evaluation during follow-up after implantation regarding the frequency of in-clinic visits is recommended.[3,4]

In patients with nonischemic cardiomyopathy (NICM), the implantation of ICD in primary prevention is already considered controversial and remains in the center of the ongoing debate.[5,6] Following the recent publication of the DANISH (Defibrillator Implantation in Patients with Nonischemic Systolic Heart Failure) study, it is reasonable to ask whether we need to consider the etiology of HF before the decision

WHAT'S NEW?

The etiology of heart failure is a strong independent predictor of mortality in patients with heart failure after implantable cardioverter-defibrillator placement. Worse survival was observed in patients with ischemic, as compared with nonischemic, cardiomyopathy. Other independent predictors for mortality in patients with heart failure after implantable cardioverter-defibrillator placement are: age older than 65 years, impaired left ventricular ejection fraction, chronic kidney disease, atrial fibrillation, diabetes mellitus. It seems that patients with ischemic cardiomyopathy should be followed more frequently after the implantation of a cardioverter-defibrillator.

to apply ICD therapy or whether we should rethink guidelines with regard to this question.[7] On the other hand, recently published metanalyses, including DANISH, showed undeniable reduction in mortality related with ICD implantation in patients with NICM.[8,9]

All of the abovementioned investigations were based on comparisons between ICD and medical therapy. To the best of our knowledge, there is little evidence about long-term mortality after ICD implantation with regard to the etiology of HF from real-life settings and all-comers registries. Therefore, we conducted a trial of patients with ICM or NICM. The aim of this study was to compare long-term all-cause mortality in patients with impaired left ventricular function according to ischemic and nonischemic etiology.

METHODS

Registry design The COMMIT-HF (Contemporary Modalities In Treatment of Heart Failure) registry is a prospective single-center observational registry (ClinicalTrials.gov identifier, NCT02536443) which was described elsewhere.[10] Data collection was based on the Polish healthcare provider registry. The study protocol was approved by an appropriate institutional review board and ethics committee; patient written consent was not required.

We included patients hospitalized with a diagnosis of systolic HF (LVEF ≤35%). Patients with acute coronary syndrome were excluded. Baseline characteristics of all individuals were collected from the hospital records. All data regarding implanted devices were annotated. All therapeutic interventions were individualized and based on the appropriate current European Society of Cardiology guidelines.[4]

Study population There were 1429 consecutive patients with HF included in the COMMIT-HF registry between January 2009 and December 2013. A total of 1073 patients with the first implantation of ICD or cardiac resynchronization therapy defibrillator (CRT-D) were selected for this study. Patients were considered to have HF of ischemic etiology if they had a history of myocardial infarction (including Q-wave or enzyme-positive myocardial infarction) or previous coronary artery interventions. All patient with risk factors for coronary artery disease (CAD) or older than 45 years of age underwent coronarography. Nonobstructive coronary lesions with no history of percutaneous coronary intervention or coronary artery bypass grafting surgery were insufficient for classification as ICM. Patients were divided into 2 groups: with ICM (n = 705; 65.7%) and NICM (n = 368; 34.3%). The following patients were excluded: with congestive HF as a complication of valvular heart disease, with devices implanted in other cardiovascular centers, with ICD or CRT-D implanted for other reasons than CAD or NICM (idiopathic ventricular fibrillation, hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, long-QT syndrome).

Data analysis and study endpoints The following variables were analyzed: gender, age, length of stay, type of prevention, type of implanted device (ICD, CRT-D), etiology of HF, functional class according to the New York Heart Association (NYHA) classification, comorbidities, previous revascularization in case of CAD, electrocardiographic parameters, and medication. The primary endpoint of this study was long-term all-cause mortality.

Statistical analysis Continuous variables with normal distribution were presented as mean (SD) and with nonnormal distribution as median (interquartile range). Categorical variables were presented as percentages. The continuous variables were compared using the *t* test or the Mann–Whitney test. The χ^2 test was used for categorical variables. The long-term mortality was analyzed using the Kaplan–Meier method. The prognostic relevance of the baseline variables on the occurrence of death in the observation period was assessed with a multivariable Cox proportional hazards regression model with results expressed as adjusted hazard ratios (HR) and 95% CI. We used a *P* value of 0.3 or less in univariate analysis to include a variable in the multivariable analysis model. Stepwise regression method with backward elimination was used in further analysis. A 2-tailed *P* value of 0.05 or less was considered significant. The SAS software (version 9.4, SAS Institute, Cary, North Carolina, United States) was used for all calculations.

RESULTS

Baseline characteristics The baseline clinical characteristics of the study groups are presented in TABLE 1.

Patients in the ICM group were more often male than in the NICM group (85.6% vs 74%; *P* <0.001) and were older (mean [SD], 64 [10] vs 53 [13]; *P* <0.001). Patients with ICM more often had diabetes mellitus (42.1% vs 32.6;

TABLE 1 Baseline clinical characteristics

Variable	Etiology of HF		*P* value
	Ischemic (n = 705)	Nonischemic (n = 368)	
Age, y, mean (SD)	64 (10.2)	52.8 (12.9)	<0.001
Male sex	604 (85.6)	273 (74)	<0.001
NYHA class II	282 (41.7)	147(42.1)	0.93
NYHA class III	267 (39.4)	136 (39)	0.93
ICD	487 (69.1)	240 (65.2)	0.23
CRT-D	218 (30.9)	128 (34.8)	0.22
DM	297 (42.1)	120 (32.6)	0.003
Chronic kidney disease	225 (31.9)	81 (19.3)	<0.001
AF	164 (24)	111 (31.4)	0.01
Hypertension	403 (58.9)	142 (40.2)	<0.001
Hypercholesterolemia	233 (34.1)	75 (21.2)	<0.001
Mix hyperlipidemia	112 (16.4)	35 (9.9)	0.21
Stroke	64 (9.4)	15 (4.2)	0.005
Hospitalization time, d, median (IQR)	6 (4)	6 (5)	0.81

Data are presented as number (percentage) unless otherwise indicated.

Abbreviations: AF, atrial fibrillation; CRT-D, cardiac resynchronization therapy defibrillator; DM, diabetes mellitus; GFR, glomerular filtration rate; HF, heart failure; ICD, implantable cardioverter-defibrillator; IQR, interquartile range; NYHA, New York Heart Association Classification

TABLE 2 Basic echocardiographic parameters

Variable	Etiology of HF		*P* value
	Ischemic (n = 705)	Nonischemic (n = 368)	
LVEF, %, mean (SD)	26 (5.7)	24 (5.6)	<0.001
Diastolic LV diameter, mm, mean (SD)	64.7 (8.8)	67.3 (9.3)	<0.001
Systolic LV diameter, mm, mean (SD)	52.3 (9.9)	56 (10.7)	<0.001
LVEDV, ml, mean (SD)	201.9 (86.1)	219.5 (87.2)	<0.001
LVESV, ml, mean (SD)	152.5 (74.3)	168.7 (76.5)	<0.001
Severe MVR	67 (11)	49 (15.8)	0.05
Severe TVR	31 (6.9)	27 (10.7)	0.1
Severe AVR	1 (0.8)	0	0.73
Severe AVS	4 (14.8)	1 (10)	0.87
LAA, cm^2, mean (SD)	27 (6.6)	30.1 (9.6)	0.01

Data are presented as number (percentage) unless otherwise indicated.

Abbreviations: AVR, aortic valve regurgitation; AVS, aortic valve stenosis; LAA, left atrium area; LV, left ventricle; LVEDV, left ventricle end diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end systolic volume; MVR, mitral valve regurgitation; TVR, tricuspid valve regurgitation

P = 0.003), chronic kidney disease (31.9% vs 19.3%; *P* <0.001), arterial hypertension (58.9% vs 40.2%; *P* <0.001), and hypercholesterolemia (34.1% vs 21.2%; *P* <0.001). Echocardiographic findings of the study group are presented in TABLE 2.

Patients in the ICM group, as compared with the NICM group, had significantly lower left ventricular end-systolic (52.3 mm vs 56 mm; *P* <0.001) and end-diastolic diameters (64 mm vs 67.3 mm; *P* <0.001), left ventricular end-systolic (152.5 ml vs 168.7ml; *P* <0.001) and end-diastolic volumes (201.9 ml vs 219.5 ml; *P* <0.001), and left atrium area (27 cm^2 vs 30 cm^2; *P* = 0.01). LVEF was significantly lower in the ICM group as compared with the NICM group (26% vs 24% *P* <0.001). No differences between groups were noted with regard

TABLE 3 Pharmacotherapy at baseline

Variable	Etiology of HF		*P* value
	Ischemic (n = 705)	Nonischemic (n = 368)	
β-Blockers	681 (97)	357 (97.3)	0.95
ACEIs	531 (76.2)	281 (77.2)	0.76
Sartans	59 (8.5)	29 (8.1)	0.89
Loop diuretics	572 (81.6)	327 (89.1)	0.002
Thiazide diuretics	29 (10.2)	39 (13.7)	0.2
MRAs	594 (84.9)	338 (92.1)	0.001
Statins	615 (88.1)	194 (53.7)	<0.001
Antiplatelets	619 (88.4)	117 (32.5)	<0.001
OACs	210 (30.1)	152 (42)	<0.001

Data are presented as number (percentage).

Abbreviations: ACEI, angiotensin enzyme converting inhibitor; ARB, angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonist; OAC, oral anticoagulant

to valve diseases. There were several differences in baseline pharmacotherapy (TABLE 3).

The etiology of heart failure and long-term prognosis The median (interquartile range) follow-up period was 60.5 months (43–77), and no patients were lost to follow-up for the primary outcome. The primary endpoint, death from any cause, occurred more frequently in the ICM group as compared with the NICM group (35.7% vs 26.6%; *P* = 0.008) (TABLE 4, FIGURE 2). A higher out-of-hospital mortality rate in patients with ICM tended to be statistically significant (15.5% vs 10.6%, *P* = 0.05), whereas cardiovascular and noncardiovascular mortality rates were comparable in the study groups (TABLE 4).

There were differences between the ICM and NICM groups with regard to the incidence of stroke (6.2% vs 2.2%; *P* = 0.005) and myocardial infarction (25.7% vs 1.1%; *P* <0.001) (TABLE 4).

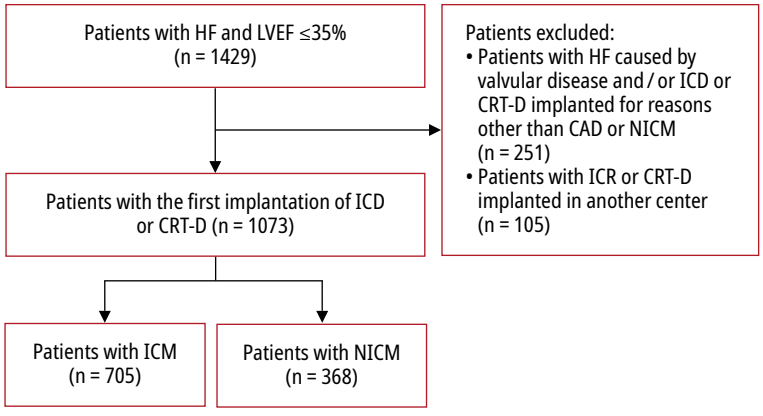

FIGURE 1 Study flow chart
Abbreviations: ICM, ischemic cardiomyopathy; LVEF, left ventricular ejection fraction; NICM, nonischemic cardiomyopaty; others, see TABLE 1

The multivariate analysis revealed that independent risk factors for mortality in paients with HF after ICD placement are: age older than 65 years, impaired LVEF (hazard ratio estimated for 1% increase in EF), chronic kidney disease (with glomerular filtration rate <60 ml/min/1.73 m^2), atrial fibrillation, diabetes mellitus. An ischemic etiology of HF was a strong independent factor of long-term mortality (HR, 1.43; 95% CI, 1.30–1.81; *P* = 0.003) (FIGURE 3).

DISCUSSION To the best of our knowledge, this is the first study to compare 2 different etiologies, ischemic and nonischemic, of HF in patients with ICD with regard to long-term follow-up. Additionally, the study population was derived from a real-life all-comers registry.

The overarching goal of this study was to evaluate the relationship between the etiology of HF and long-term prognosis in a large cohort of patients with ICD placed as primary prevention of sudden cardiac death. Thus, we performed a retrospective observational follow-up study in 1073 real-life patients, treated with an ICD or CRT-D and evaluated the differences in all-cause mortality as well as risk factors. All patients received optimal medical treatment and had ICD placed according to the current guidelines. The main clinical implications of our study are as follows: 1) patients with an ischemic etiology of HF as compared with nonischemic etiology have significantly worse clinical profile at the time of ICD placement; 2) after primary prophylactic ICD implantation, all-cause long-term mortality is higher in the ICM group in comparison with NICM; 3) ischemic etiology was a strong independent predictor of all-cause mortality; 4) other independent predictors for

TABLE 4 Characteristics of adverse events during follow-up

Variable		Etiology of HF		*P* value
		Ischemic (n = 705)	Nonischemic (n = 368)	
Mortality	All cause	252 (35.7)	98 (26.6)	0.008
	Cardiovascular	115 (16.3)	44 (11.9)	0.1
	Noncardiovascular	28 (4.0)	15 (4.1)	0.81
	Out-of-hospital	109 (15.5)	39 (10.6)	0.052
Stroke		44 (6.2)	8 (2.2)	0.005
Myocardial infarction		40 (5.7)	4 (1.1)	0.0005
Cardiology outpatient visits, mean (SD)		10.3 (7.3)	10.1 (7.6)	0.55
HF rehospitalization, median (IQR)		3 (4)	2 (3)	0.6

Data are presented as number (percentage) unless otherwise indicated.

Abbreviations: see TABLE 1

mortality in patients with HF post ICD implantation were age older than 65 years, impaired LVEF, chronic kidney disease (with glomerular filtration rate <60 ml/min/1.73 m^2, atrial fibrillation, diabetes mellitus. Winkler et al[11] in their ICD or CRT-D population also observed similar results, although age and chronic kidney disease were significant only in univariate analysis. Advanced age (>65 years), atrial fibrillation, and impaired LVEF were risk factors in univariate and multivariate analyses previously presented by Stein et al.[12]

Although numerous guidelines differentiate between the HF etiologies with respect to the level of evidence on which their recommendations for ICDs as primary prevention are made (1A recommendation for an ischemic etiology, 1B for a nonischemic etiology), they recommend the same frequency of in-clinic visits for patients from both groups.[4,13]

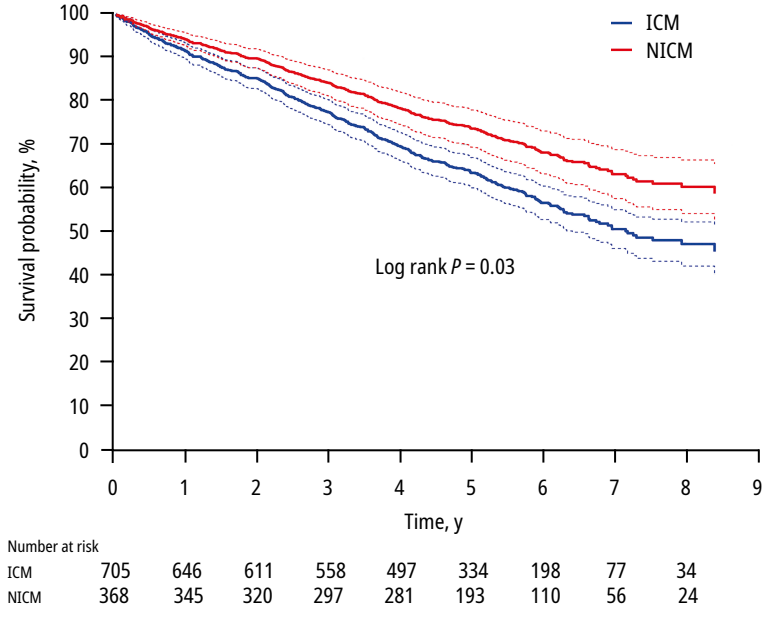

FIGURE 2 Kaplan–Meyer estimates of long-term all-cause mortality
Abbreviations: see FIGURE 1

This trial may be a premise for clinicians to implement a more frequent direct evaluation during follow-up and/or remote monitoring strategy after ICD implantation in patients with an ischemic etiology of HF. This concept, apart from the presented study outcomes, is also indirectly supported in a cohort of more than 1000 patients with ICM enrolled in the MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy).[14] The study showed that 9.5% of the study population had ischemic events during follow-up, mainly associated with acute coronary syndromes. Ischemic events after CRT-D implantation were independently associated with a more than 2-fold increase in the risk for subsequent HF and death.

Two previous studies[15,16] showed discrepant outcomes with neutral impact of ischemic etiology on mortality as compared with NICM. This could be explained by a few differences as compared with our trial: 1) there were less patients included—together in both trials there were 925 patients as compared with 1073 patients evaluated in the present study; 2) in one study, one-third of patients had a CRT-D and in the second, patients with CRT-D were excluded; 3) in both studies long-term follow-up was shorter as compared with our trial (mean, 40 vs 31 vs 60 months, respectively).

The first 2 primary prevention ICD trials (CAT [Cardiomyopathy Trial] and AMIOVIRT [Amiodarone Vs Implantable Cardioverter-Defibrillator] trial) were stopped untimely, partially because mortality rates were lower than predicted.[17,18] The SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial) demonstrated a mortality benefit of prophylactic ICD placement in various patient groups, including patients with both ischemic and nonischemic cardiomyopathy. Amiodarone compared with

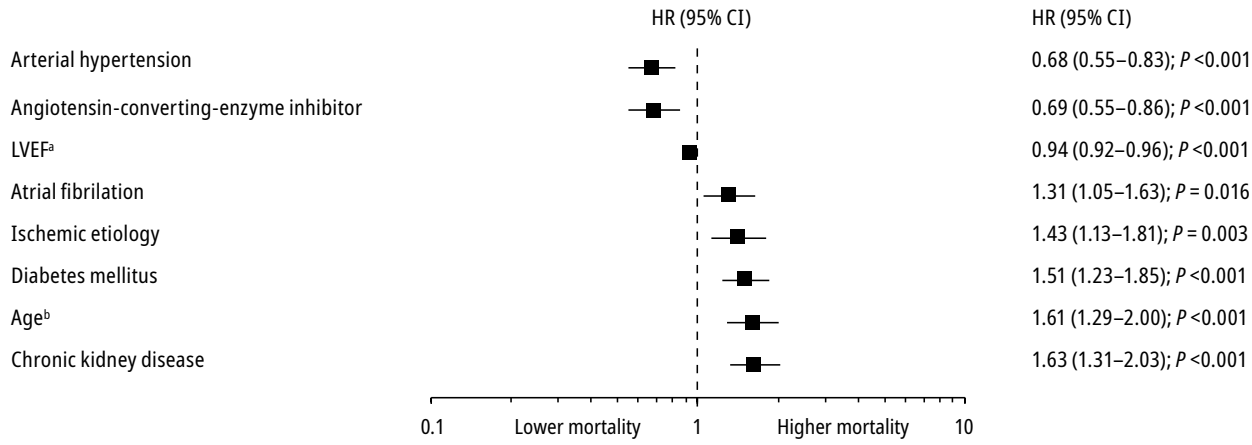

FIGURE 3 Predictors of all-cause mortality in the entire study population (the results of the Cox proportional hazards model)

a Hazard ratio estimated for 1% increase in ejection fraction

b 65 years and older

Abbreviations: HR, hazard ratio; see FIGURE 1

placebo was associated with a similar risk of death and the ICD group had a decreased risk of death during a 5-year follow up. Outcomes did not vary based on the ischemic or nonischemic etiology of HF.[19]

The 2004 DEFINITE (Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation) trial included 458 patients with nonischemic dilated cardiomyopathy with LVEF of 35% or less, NYHA classes II and III symptoms, and a history of nonsustained ventricular tachycardia. In the DEFINITE trial, ICD implantation jointly with standard medical therapy resulted in decreased mortality compared with standard medical therapy. The reduction was significant only in patients with NYHA class III.[20]

The more recently published DANISH trial questions ICD implantation in patients with a nonischemic etiology of HF. Køber et al[7] found that the prophylactic ICD placement in patients with symptomatic systolic HF not caused by CAD does not reduce the rate of death from any cause more than standard clinical care. However, in the subgroup of patients who were younger than 68 years of age, the mortality rate from sudden cardiac death was lower in the ICD group than in the control group. The neutral influence on all-cause mortality in this trial could be partially explained by the high percentage of patients with a CRT-D enrolled in the trial (nearly 60%) and its potential positive electromechanical, hemodynamic, and clinical response as presented in landmark trials.[21] Additionally, recently published meta-analyses of randomized controlled trials compared implantation of ICD in primary prevention with medical treatment in NICM patients, comprising the DANISH trial, found that primary prevention ICDs reduce all-cause mortality in patients with left ventricular dysfunction both in the ICM and NICM groups.[9,22]

Limitations The most important limitation is that this study is a single-center observational study derived from a real-life practice with inherent weakness related to retrospective analysis. The results of our multivariate analysis may be biased due to the potential impact of important factors that are not available in our database. Nevertheless, all data on primary and secondary outcomes were obtained without loss to follow-up.

Conclusions In the presented study, worse survival in the ICM as compared with the NICM in real-world population was observed. An ischemic etiology of HF was a strong independent predictor of long-term mortality. We believe that more frequent clinical evaluation (including remote monitoring for instance) should be considered in patients with ICM and a ICD in primary prevention of sudden cardiac death. Well-designed randomized controlled trials are required to reassess our findings and the concept mentioned above.

ARTICLE INFORMATION

CONFLICT OF INTEREST None declared.

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