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Значение индивидуальных целевых показателей HbA_{1c} для оценки гликемического контроля у больных СД2

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В настоящее время особое внимание уделяется достижению гликемического контроля у больных сахарным диабетом 2 типа (СД2) как фактору, определяющему риск развития макро- и микрососудистых осложнений СД. Современные руководства предполагают индивидуальный подход в выборе целевого уровня HbA_{1c} с учетом возраста и наличия осложнений.

Цель. *Оценить долю больных СД2, достигших целевых значений HbA_{1c}, исходя из индивидуальных целей.*

Материалы и методы. *Обследовано 2195 больных СД2. Пациенты были разделены на возрастные группы: до 45 лет, 45–64, старше 65 лет. В каждой группе были выделены две подгруппы: без осложнений и с осложнениями (острое нарушение мозгового кровообращения, острый инфаркт миокарда, стенокардия). Целевой уровень HbA_{1c}: до 45 лет без осложнений – <6,5%; до 45 лет с осложнениями и 45–64 лет без осложнений – <7,0%; 45-64 лет с осложнениями и старше 65 лет без осложнений – <7,5%; от 65 лет с осложнениями – <8%. Статистическая обработка материала проведена с использованием стандартного пакета программы Excel. Данные представлены в виде среднего ± стандартное отклонение.*

Результаты. *Получаемая сахароснижающая терапия: монотерапия диетой – 301 пациент (13,7%), препараты неинсулинового ряда (ПНИР) – 1335 (60,8%), комбинированное лечение ПНИР и инсулином – 319 (14,6%), монотерапия инсулином – 240 (10,9%) больных. В возрастной группе до 45 лет без осложнений целевых значений HbA_{1c} достигли 27,3% больных, с осложнениями – 25% больных; в возрасте 45–64 года без осложнений – 30%, с осложнениями – 35,2%; старше 65 лет без осложнений – 43%, с осложнениями – 55,6% больных.*

Заключение. *При индивидуализированном подходе к оценке достижения целей лечения по уровню HbA_{1c} при СД2 доля лиц, достигших целевых значений, выше, чем при традиционном подходе (HbA_{1c}<7,0%). Во всех группах отмечается достаточно высокий процент лиц, не достигших целей лечения, что свидетельствует о необходимости усиления сахароснижающей терапии.*

Ключевые слова: *сахарный диабет 2 типа; индивидуализированный подход; целевой уровень HbA_{1c}*

Significance of HbA_{1c} targets based on an individual approach to the treatment of patients with type 2 diabetes mellitus

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Background. *Over the past few years, special attention has been paid to achieving glycaemic control for type 2 diabetes mellitus (T2DM) patients, since it is a factor for determining the risk of developing macro- and microvascular complications of diabetes. Certain modern guidelines suggest an individual approach to the choice of HbA_{1c} target.*

Objective *of this study was to estimate the percentage of T2DM patients who have reached the HbA_{1c} levels. This was determined based on their age and the presence of severe complications.*

Materials and Methods. *A total of 2195 patients with T2DM were studied. The patients were divided into the following age groups: <45, 45–64, and over 65 years. Each group was subdivided into two subgroups depending on the presence of severe complications. The target level of HbA_{1c} was determined according to the subjects' age and the presence of severe complications: <45 years old without complications – HbA_{1c}<6.5%; <45 years old with complications and 45–64 years old without complications – HbA_{1c}<7.0%; 45–64 years old with complications and over 65 years old without complications – HbA_{1c}<7.5%; over 65 years old with complications – HbA_{1c}<8%.*

Results. *The following glucose-lowering therapy techniques were used for different groups: monotherapy with diet – 301 (13.7%) patients; oral antidiabetic drugs (OADs) – 1335 (60.8%) patients; combined treatment using OADs with insulin – 319 (14.6%) patients; and insulin monotherapy – 240 (10.9%) patients. The HbA_{1c} target was reached for 27.3% of patients in the group aged <45 years old without complications; in the group < 45 years old with complications for 25.0% of patients; in the group of 45–64 years old without complications for 30.0% of patients; in the group aged 45–64 with complications for 35.2% of patients; in the group ≥65 years old without complications for 43% of patients, and in the group ≥65 years old with complications for 55.6% of patients.*

Conclusions. *The proportion of T2DM patients who have reached the HbA_{1c} target value using the individual approach was higher than that using the conventional approach (HbA_{1c}<7.0%). A high percentage of patients did not achieve HbA_{1c} targets in all groups,*

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indicating the need for antihyperglycaemic therapy.
Keywords: *type 2 diabetes mellitus; individual approach; HbA_{1c} targets*

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Taking into account the trend of continuous growth in the number of patients with diabetes mellitus (DM), one of the current main objectives of the health care system in many countries is the development of programs aimed at improving the treatment and preventive care for these patients. Therefore, special attention has to be given to the control of carbohydrate metabolism in patients with type 2 diabetes mellitus (T2DM) as a determinant of the risk of microvascular and macrovascular complications. In Russia, a new clinical consensus and algorithms for the specialised medical care for patients with DM [1] were adopted in December 2011; these recommend that the choice of individual treatment goals should be based on the level of glycated haemoglobin (HbA_{1c}) in accordance with the patient's age, presence of severe complications and risk of hypoglycaemic states.

Earlier evaluations of the quality of medical care in the region were based on the percentage of patients who achieved the average level of HbA_{1c} (≤7.0%). This approach is recognised as being inadequate because it did not consider the individual traits and goals for the treatment of patients with DM.

OBJECTIVES

The main objective of this study was to determine the proportion of patients with T2DM who achieved target HbA_{1c} levels using an individual therapy.

MATERIALS AND METHODS

The study was conducted in 12 municipalities of the Moscow Region through a survey among patients with T2DM under the auspices of the Diamobil program.

Diamobil is a mobile medical diagnostic module equipped with the necessary medical equipment to provide specialised endocrinological care to patients with DM. In the Moscow Region, Diamobil goes on a tour around the region 8 times per year and spends 10 days at each location. During this period, approximately 300 patients with T2DM are examined. The list of patients with DM was compiled by the specialists of the Vladimirsky Moscow Regional Clinical Research Institute; the patients were randomly selected from the Registry of patients with DM of the municipality. The levels of HbA_{1c}, creatinine and urea were determined and the lipid profile and ECG were recorded for all patients with DM. After the results of laboratory tests became available, the patients were examined by medical specialists (ophthalmologists, surgeons, cardiologists and endocrinologists).

We report the results of the survey for 2195 patients with T2DM, of which 1770 (80.6%) were women and 425 (19.4%) were men. To determine the individual treatment objectives, the patients were divided into the following age groups: <45 years, 45–64 years and ≥65 years. Each group was subdivided into 2 subgroups: the first subgroup included patients with T2DM without complications and the second subgroup included patients with complications such as acute cerebrovascular accident, acute myocardial infarction and angina pectoris.

The target levels of HbA_{1c} for each subgroup were established on the basis of the algorithms for specialised medical care for patients with DM [1] (Table 1).

HbA1c levels were determined using NycoCard Reader II (Axis-Shield, Norway) by borate affinity chromatography. The test is an NGSP-certified DCCT reference method.

General characteristics of the patients.

The average duration of T2DM in the patients examined was 9.4 ± 7.7 years. Of the 2195 patients, 699 (31.8%) had the disease for <5 years, 599 (27.3%) had it for 5–9 years, 438 (20.0%) had it for 10–14 years, 197 (9.0%) had it for 15–19 years and 262 (11.9%) had it for ≥20 years.

The mean BMI was 33.2 ± 6.1 kg/m^2. Normal BMI was reported for 6.7% patients; 24.7% patients were overweight and obesity I, II and III were found in 33.7%, 22.8% and 12.6% patients, respectively. Thus, 93.3% patients were overweight or obese; 12.6% patients had morbid obesity.

The patients were distributed into different age groups. The group aged <45 years included 59 (2.7%) patients [55 (2.5%) without complications and 4 (0.2%) with complications]. The group aged 45–64 year included 1291 (58.8%) patients [944 (43.0%) without complications and 347 (15.8%) with complications]. The group aged ≤65 years included 845 (38.5%) patients [419 (19.1%) without complications and 426 (19.4%) with complications].

A total of 847 (38.6%) patients received antihypertensive drugs as concomitant treatment; 83 (3.8%) patients received hypolipidaemic drugs, 1,155 (52.6%) patients received a combination of a lipid-lowering drugs and antihypertensive drugs and 110 patients (5.0%) did not receive any concomitant therapy.

Statistical analyses were performed using Microsoft Excel. The data are presented as mean ± standard deviation.

Table 1

Individual target levels of HbA_{1c} (%) depending on age and presence of severe complications

Complications	Age		
	<45 years	45–64 years	≥65 years
Without complications	<6,5	<7,0	<7,5
With complications	<7,0	<7,5	<8,0

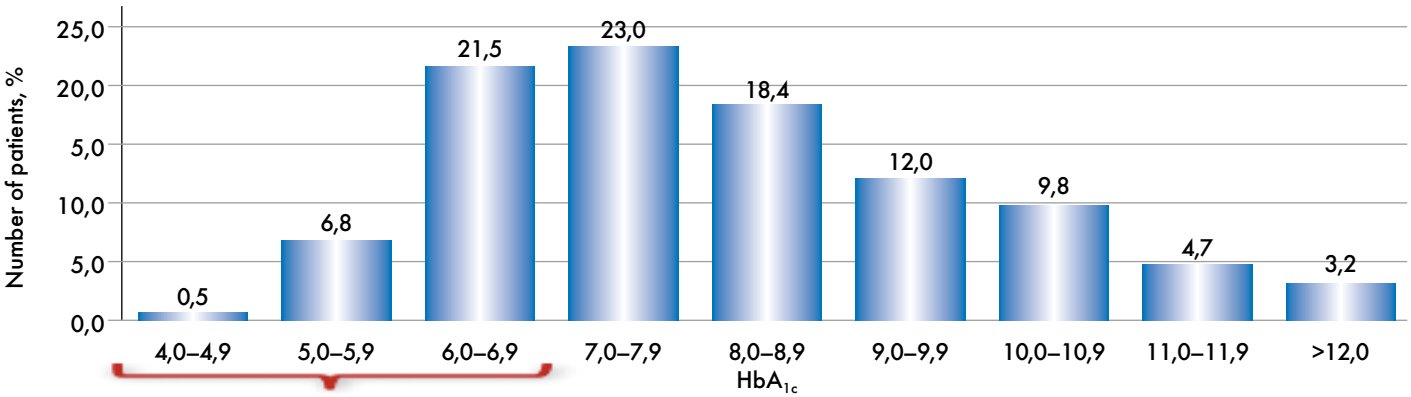

Figure 1. Distribution of the examined patients with T2DM according to HbA1c levels (%).

RESULTS

The mean HbA_{1c} level in the studied patients was 8.2% ± 2.9%. Of the total number of patients with T2DM, 28.8% achieved HbA_{1c} levels of <7.0% and 29.7% achieved the levels of <9.0%. The distribution of patients by HbA_{1c} levels is shown in Fig. 1.

In general, an individual target level of HbA_{1c} was achieved by 38.2% patients with T2DM. The highest percentage of patients who achieved the individual objectives of treatment was registered in the group aged ≥65 years; this percentage was 43.0% among patients without complications and 55.6% among patients with complications (Fig. 2). The lowest percentages were identified in the group aged >45 years, where the target levels of HbA_{1c} were achieved in 27.3% patients without complications and in 25.0% patients with complications. This is largely because the strictest target levels were provided for this group. In the group aged 45–64 years, 30.0% patients without complications and 35.2% patients with complications achieved the target levels. The percentage of patients who achieved the target levels was relatively higher in the subgroup with complications for both 45–64-year-old (30.0% and 35.2%) and 65-year-old patients (43.0% and 55.6%). This percentage was not significantly different between the subgroups for patients aged <45 years.

The average HbA_{1c} levels did not differ significantly among patients aged 45–64 years and those aged ≥65 years and were similar in patients with and without complications (Table 2). Among patients aged <45 years, the average HbA_{1c} levels were lower in those without complications than in those with complications. It should be noted that the results may be of limited value because of the paucity of patients in the younger age group with complications.

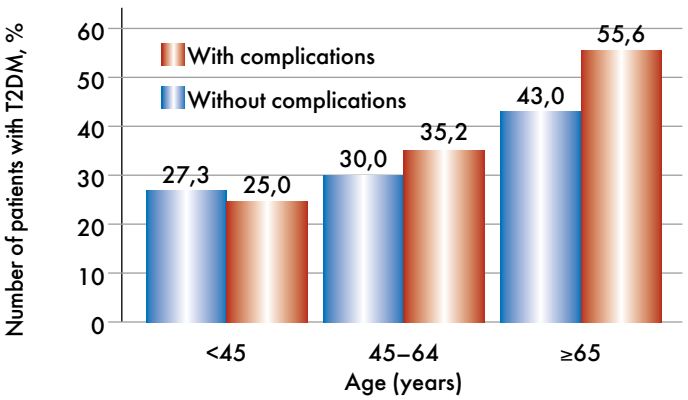

Figure 2. Percentage of patients with T2DM who achieved the individual target levels of HbA_{1c} (%) according to their age and presence of cardiovascular complications.

With respect to the type of hypoglycaemic therapy, most patients were treated with non-insulin antihyperglycaemic drugs (NIADs) (1335, 60.8%). The total number of patients receiving insulin therapy was 559 (25.5%), including those receiving combination treatment with oral antidiabetic drugs (OADs) and insulin (319, 14.6%) and patients receiving insulin monotherapy (240, 10.9%). A relatively high number of patients (301, 13.7%) remained on monotherapy with a special diet and did not receive any antihyperglycaemic drugs (Fig. 3).

In the group of patients receiving NIAD, 48.3% were treated with only 1 drug and 51.7% were treated with ≥2 NIADs.

Based on the structure of antihyperglycaemic therapy in the studied sample of patients, the results were comparable with the data from the Registry of patients with DM for the Moscow Region. The numbers of patients receiving

Table 2

Level of HbA_{1c} (%) and proportion of patients who achieved the individual target HbA_{1c} levels according to age and presence of cardiovascular complications

		<45 years	45–64 years	≥65 years
Without complications	Total number of patients (n)	55	944	419
	Mean HbA_{1c}, %	7,6±1,6	8,2±1,9	8,0±1,7
	Target HbA_{1c}, %	<6,5	<7,0	<7,5
	Patients who achieved the treatment goal, abs. (%)	15 (27,3)	283 (30)	180 (43)
With complications	Total number of patients, (n)	4	347	426
	Mean HbA_{1c}, %	9,4±2,8	8,4±1,8	8,3±5,4
	Target HbA_{1c}, %	<7,0	<7,5	<8,0
	Patients who achieved the treatment goal, abs. (%)	1 (25)	122 (35,2)	237 (55,6)

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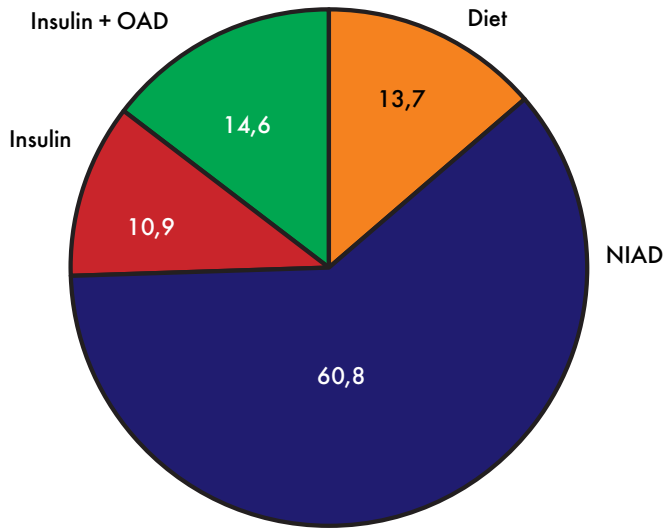

Figure 3. Structure of antihyperglycaemic therapy.

monotherapy with insulin (in the Registry, 9.0%) and patients on a special diet alone (in the Registry, 11.7%) were virtually identical.

Meanwhile, it was found that a slightly higher number of patients were receiving insulin in combination with NIADs in the study sample compared with the data from the Registry (14.6% and 8.7%, respectively). Furthermore, a smaller number of patients were receiving NIAD monotherapy (60.8% and 70.6%, respectively).

Furthermore, 39.4% patients used metformin as the first-line antihyperglycaemic drug; a significant number of patients (59.2%) received monotherapy with sulfonylurea drugs (glibenclamide, 34.9%; gliclazide MB, 15.2%; glimepiride, 5.7% and gliquidone, 3.4%) and <1.5% patients received drugs from other groups (pioglitazone, 0.9% and drugs of the incretin family, 0.5%). Metformin was the most commonly prescribed drug for those receiving combined treatment with insulin and OADs (37.4% patients); slightly fewer patients (31.5%) received sulfonylurea drugs (glibenclamide, 21.9%; gliclazide MB, 4.8%; glimepiride, 3.2% and gliquidone, 1.6%). Pioglitazone in combination with insulin was prescribed in 0.3% patients. Furthermore, 30.8% patients received insulin in combination with ≥2 OADs.

Thus, metformin was the most commonly prescribed basic antihyperglycaemic drug (1162 patients or 52.9% of the total number of patients).

In each treatment group, most patients did not achieve their individual target levels, including those patients who received no medical antihyperglycaemic therapy (Table 3). This indicated the need for a more active treatment strategy for patients with DM and the early prescription of antihyperglycaemic drugs. The average HbA_{1c} level of patients on insulin therapy was >8.0% in all age groups, indicating that more active titration of insulin doses is needed, and if necessary, the patients should be transferred to a more intensive scheme of insulin therapy with additional short-acting insulin.

DISCUSSION

Analyses of the results showed that a sufficiently large percentage of patients with T2DM (71.2%) failed to achieve HbA_{1c} levels of <7.0%, which was comparable to the value reported for the entire Russian Federation (74.8%) [2]. On the other hand, 48.1% patients in the sample had HbA_{1c} levels of >8.0%, whereas according to other studies, similar HbA_{1c} levels were observed in 57.4% patients in the Russian Federation [3]. In some foreign countries, the situation is better; however, similar trends have been observed. In particular, according to the National Health and Nutrition Examination Survey (NHANES), only 50.0% patients with T2DM in the United States had HbA_{1c} levels of ≤7.0%; approximately 20.0% had HbA_{1c} levels ranging between 7.0% and 8.0% and approximately 30.0% had a severe decompensation of carbohydrate metabolism at the moment of examination, with HbA_{1c} levels of ≥8.0% [4]. These results suggested that the control over carbohydrate metabolism in patients with T2DM was insufficient. Although the achievement of HbA_{1c} levels of <7.0% or even <6.5% was not currently relevant for all patients with T2DM, the percentage of patients with HbA_{1c} levels of >8.0% or even >9.0% may characterise the quality of diabetes care in the region.

Intensive control of blood glucose levels has been associated with a reduced risk of microvascular complications, which cause disability and death in a large number of patients with T2DM. This has been proven in various studies such as UK Prospective Diabetes Study (UKPDS), Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) and Veterans Affairs Diabetes Trial (VADT) [5–8]. The role of intensive glycaemic control in the prevention of macrovascular complications

Table 3

Percentage of patients (%) who achieved target $Hb_{A1}c$ levels according to the antihyperglycaemic therapy

Antihyperglycaemic therapy	<45 years		45–64 years		≥65 years	
	without complications	with complications	without complications	with complications	without complications	with complications
Diet	16,7	0	47,8	65,6	75,8	83,9
NIAD	33,3	50	32,5	41,2	46,7	58
NIAD + insulin	0	0	8,6	14,9	8,3	33,9
Insulin	14,2	0	15,5	24,1	16,7	39
Total	27,3	25	30	35,2	43	55,6

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of DM is less clear [9]. It is possible that the reduced risk of macrovascular complications during intensive glycaemic control did not result from the deterioration of cardiovascular pathology due to hypoglycaemia in certain groups of people. On the contrary, highly intensive glycaemic control may be associated with increased cardiovascular mortality, which was demonstrated in the The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study [10]. On the other hand, it is obvious that the potential risk of development of hypoglycaemic responses in some patients should not stop a physician from prescribing strict treatment goals for patients with T2DM with a long life expectancy and without severe comorbidities.

In our study, compared with the average HbA_{1c} levels of <7.0%, individual target HbA_{1c} levels were achieved by a higher number of patients with T2DM (28.8% and 38.2%, respectively). A lower number of young patients (<45 years) achieved target HbA_{1c} levels, which was probably due to the fact that the strictest target levels were provided for this age group. These strict target levels were absolutely justified, because achievement of the optimal control over carbohydrate metabolism among this age group will contribute to the prevention of complications, such as those associated with morbidity and increased mortality among the active age groups.

The study demonstrated that in the group of young patients treated by a specific diet alone, the target HbA_{1c} level was achieved in only 16.7% individuals. Accordingly, the prescription of a more active antihyperglycaemic therapy would be required when the individuals are diagnosed with T2DM, particularly among young people, in the absence of severe comorbidities. Meanwhile, in the group aged ≥65 years, the number of individuals with satisfactory glycaemic control while receiving a specific diet was relatively high (75.8% for patients without complications and 83.9% for those with complications). This was due to the lower target glycaemic levels, which were easier to achieve, and probably better compliance with diets in older patients. Thus, the use of a diet as monotherapy is appropriate only for older patients, while HbA1c levels should be determined every 3 months and basic drug therapy should be added in order to achieve the target blood glucose level before DM complications occur and progress in young and middle-aged patients. Therefore, metformin, the basic drug for treating T2DM, should be prescribed more commonly. Until recently, the widespread use of metformin was limited because of the risk of side effects affecting the gastrointestinal tract. In addition, the fact that the drug should be administered 2–3 times per day reduced compliance in patients. The prolonged form of metformin, Glucophage Long, has recently been registered and widely prescribed in Russia. The risk of side effects affecting the gastrointestinal tract with this drug is much lower than that with the conventional form of metformin; in addition, treatment compliance is higher because of 1-per-day administration.

Taking into account the low percentage of patients with prescribed antihyperglycaemic therapy who achieved their individual treatment goals for each treatment group, an effective dose of NIAD should be prescribed. In the absence of target HbA_{1c} levels, a combination of drugs or NIAD combinations should be used more often.

A study performed in 7 European countries demonstrated that only 25.5% patients with T2DM receiving combination therapy with metformin and glitazones or sulfonylurea drugs had satisfactory indicators of carbohydrate metabolism [11]. This indicated that the timely addition of insulin treatment is important.

In our study, a low percentage of patients who achieved target HbA1c levels were detected among those were treated with combination therapy (insulin and OADs). The average HbA_{1c} levels for insulin therapy were >8.0% in all age groups. The low percentage of patients achieving target HbA1c levels was indicative of the late prescription of insulin therapy to patients treated with NIAD, inadequate titration of insulin doses and the need to teach patients about self-control of glycaemia and timely decision-making on the correct dose of insulin and insulin therapy scheme.

CONCLUSIONS

1. Compared with the conventional approach (HbA_{1c} levels of <7.0%), a higher proportion of patients with T2DM achieved the target levels when using the personalised approach to the assessment of target HbA_{1c} levels (28.8% and 38.2%, respectively).
2. A high percentage of patients who did not achieve the treatment goals were observed in all age groups, indicating the need for timely enhancement of antihyperglycaemic therapy.
3. A relatively low proportion of patients who achieved the treatment goals were observed among the young and middle-aged patients who received monotherapy with a special diet; therefore, earlier prescription of antihyperglycaemic drug therapy is recommended for this age group.
4. The lowest proportion of patients who achieved the personalised treatment goals was detected among patients receiving a combination therapy of insulin and OADs. This indicates the need for timely titration of insulin and revisions in the scheme of insulin therapy, with the possible addition of short-acting insulin.

DISCLOSURE INFORMATION

The authors declare that there is no conflict of interest.

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