



Fixed Ratio Basal Insulin/GLP-1RA Combinations



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In this Issue...

The combination of basal insulin with glucagon-like peptide-1 receptor agonists (GLP-1RA) has recently been approved as an effective intensification strategy in type 2 diabetes. In this issue, Dr. Roopa Mehta from the Instituto Nacional De Ciencias Médicas y Nutrición Salvador Zubirán in Mexico City reviews recent publications describing the performance of this regimen against traditional intensification strategies (eg, basal-bolus and premix insulin), the clinical advantages and disadvantages of fixed ratio combinations of basal insulin analogues and GLP-1RA, and reports supporting the possibility that fixed-ratio combination (FRC) treatment may reduce glycemic variability and hypoglycemia risk.

LEARNING OBJECTIVES

- Describe characteristics of fixed ratio combinations (FRC) of basal insulin and glucagon-like peptide-1 receptor agonists (GLP-1RA).
- Compare basal insulin/GLP-1RA FRC with other intensification strategies.
- Explain how the simplicity of basal insulin/GLP-1RA FRC can overcome clinical inertia to medication intensification.

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Commentary & Reviews



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Guest Faculty Disclosure

Dr. Mehta has indicated that she has no financial interests or relationships with a commercial entity whose products or services are relevant to the content of this presentation.

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COMMENTARY

Since the advent of the incretin era and the introduction of insulin analogues, we have been inundated with new treatment options for type 2 diabetes. We are no longer just committed to lowering blood glucose levels; we now want to achieve other targets as well. These include treating patients in an individualized manner, designing medication regimens with low risk for hypoglycemia and weight gain, providing a better quality of life, improving patient-related outcomes, and if possible, positively impacting cardiovascular risk.

In treating type 2 diabetes, the need for basal insulin when oral anti-diabetic agents can no longer maintain glycemic control is well recognized. Intensification of basal insulin via either a basal-bolus regimen or a premix regimen is the traditional next step. Often clinical inertia is present at this stage because of fear of hypoglycemia or/and weight gain, as well as perceived treatment complexity.¹ The latest position statement of the American Diabetes Association has advocated intensification with the combination of basal insulin and a GLP-1RA.² This combination has been shown to have complementary effects, addressing the common drawbacks raised about intensification.

One key question is: how does this combination therapy of basal insulin + GLP-1RA compare to the other available options — namely basal-bolus, basal-plus, and premix insulin regimens? The reviewed 2017 article by Maiorino et al found that the combination therapy provided glycemic control comparable to basal-plus and basal-bolus regimens, with the advantages of greater weight reduction and a lower risk for hypoglycemia.³

Recently, two fixed-dose combinations of a basal insulin analogue and a GLP-1RA have been released.⁴ IDegLira is composed of the insulin analogue degludec (100 units/mL [U/mL]) combined with the GLP-1RA liraglutide (3.6 mg/mL) in a 3 ml pen device. IGlarLixi is composed of insulin glargine (100 U/mL) and the GLP-1RA lixisenatide (33 µg /mL) in a 3 ml pen device; two pen versions of this fixed ratio combination (FRC) are available (33 µg /ml and 50 µg /ml). Optimization of the dose involves slowly titrating up the basal insulin; as a result, there is a slow increase in dosage of the GLP-1 component, greatly reducing the nausea associated with this incretin class. The reviewed 2017 paper by Valentine et al discusses patient populations in whom these fixed-ratio combination (FRC) products may be particularly helpful.

Liakopoulou et al report on the results of a systematic review and meta-analysis of these FRCs.⁵ FRCs are more effective for glycemic control than their individual components. The advantages of the FRC include effective glucose lowering, low risk for hypoglycemia, less weight gain, and possibly lower insulin dose. In addition, these results are achieved with only one injection a day, simplifying intensification regimens. However, we must

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acknowledge that long-term data beyond a few years are unavailable, and the impact on cardiovascular risk among lower risk individuals is unknown. In addition, quality of life and cost effectiveness data would be of interest.

A recent study by Bajaj et al investigated the effect of the combination of basal insulin with a GLP-1RA on glycemic variability.⁶ The investigators reported significantly lower variability and also lower hypoglycemia using this combination regimen compared with basal bolus and premix treatments. We can speculate that if glycemic variability translates to lower hypoglycemia risk, this may impact cardiovascular risk. However, further research is necessary in this area.

The final reviewed study is the head to head comparison of an FRC (IDegLira) with a basal-bolus regimen.⁷ This study is relevant as it clearly showed equivalent glycemic control but with a significantly lower risk of hypoglycemia, weight loss, and an insulin-sparing effect in favor of the FRC. All this was achieved with one injection vs potentially four a day.

Applying these findings to clinical practice, I believe FRCs offer an opportunity for both physicians and patients alike. The fact that glycemic control can be achieved without complex treatment regimens will impact clinical inertia and improve adherence. Titration is also relatively simple, something of particular importance for primary care doctors. Also, although the current guidelines recommend the FRC as an intensification option after basal insulin, it can also be used after failure of oral medications. The side effect profile is beneficial, with a low risk of hypoglycemia and weight gain, and the insulin-sparing effect provides another advantage.

In summary: the FRC of basal insulin with a GLP-1RA is a natural evolution in the process of improving glycemic control in people with type 2 diabetes and shows great potential for improving patient outcomes. Unfortunately, we lack long-term data, especially the effects of the combination on cardiovascular risk; in addition, the current high costs of these preparations will limit their use. However, I am confident that the use of this complementary combination will not only benefit patients but will also impact current treatment paradigms.

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Insulin and GLP-1RA Combination Therapy

Maiorino MI, Chiodini P, Bellastella G, Capuano A, Esposito K, Giugliano D. Insulin and glucagon-like peptide receptor agonist combination therapy in type 2 diabetes: A systematic review and meta-analysis of randomized controlled trials. *Diabetes Care*. 2017; 40: 614–624

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Current management guidelines in T2DM state that when basal insulin has been titrated to the fasting plasma glucose goal, but glycated hemoglobin (HbA1c) remains above target, treatment intensification is needed— either with the addition of mealtime insulin, changing over to premix insulin, or with the addition of a glucagon-like peptide receptor agonist (GLP-1RA).¹ The combination of basal insulin with a GLP-1RA shows complementary modes of action with potential benefits on glycemic control and metabolic profile.² This 2017 systematic review and meta-analysis evaluates the role of the GLP-1RA and insulin combination in the injectable treatment of type 2 diabetes mellitus (T2DM). In particular it addresses the following questions:

1. Is this combination therapy similarly effective in reducing HbA1c when compared with basal-plus or full basal-bolus regimens?
2. What is the role of the fixed-ratio combinations of GLP-1RA and basal insulin in this scenario?
3. Are there additional benefits of combination therapy on other aspects of diabetes control, including percentage of patients at HbA1c target, incidence of hypoglycemia, and weight change?

Studies were included if they were randomized controlled trials (RCT), compared short- and long-acting GLP-1RAs administered in association with insulin treatment to another injectable treatment strategy, were at least 12 weeks' duration of intervention, and assessed change in HbA1c, and/or the proportion of participants with HbA1c of < 7.0% (53 mmol/mol), or the number of participants with hypoglycemic events or weight change. Twenty-six RCTs with different designs were included: ten compared GLP-1RA with placebo on a background of basal insulin, three compared GLP-1RA with intensification of insulin on a background of different insulin regimens, two compared GLP-1RA + basal insulin vs basal-plus regimens, five compared GLP-1RA + basal or prandial insulin vs basal-bolus regimen, and six trials compared fixed ratio GLP-1RA/basal insulin analogue vs insulin intensification or GLP-1RA alone.

The results of the meta-analysis showed a beneficial effect of combination treatment of GLP-1RA and insulin compared with other injectable treatment strategies on HbA1c reduction and target, as well as weight reduction. Combination therapy (GLP-1RA + basal insulin) provided comparable glycemic control compared to basal-plus and basal-bolus regimens, with the additional advantages of greater weight reduction and a lower risk for hypoglycemia. Although short acting GLP-1RA reduced HbA1c by 0.32% and long-acting agonists by 0.60%, the final HbA1c levels achieved were similar to those with other injectable strategies. Fixed ratio combinations were significantly better than the individual components in achieving HbA1c reductions. There were no comparisons of fixed ratio combinations versus basal-plus or basal-bolus regimens. The authors acknowledge the following drawbacks: significant heterogeneity between studies, short duration of trials, industry funding, comparisons with placebo, open label (16 trials), and the lack of hard outcomes (microvascular and macrovascular complications). They concluded that GLP-1RAs alone or as titratable fixed-ratio combinations with basal insulin may represent a promising option to advancing basal insulin therapy or to initiating injectable therapy. However, more studies are needed before this becomes a standard of care in patients with T2DM.

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Fixed-Ratio Combinations IDegLira and IGlarLixi

Valentine V, Goldman J, Shubrook JH. Rationale for, initiation and titration of the basal insulin/GLP-1RA fixed-ratio combination products, IDegLira and IGlarLixi, for the management of type 2 diabetes. *Diabetes Ther.* 2017 Aug;8(4):739-752.



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In type 2 diabetes, timely intensification of treatment is necessary to maintain glucose control. When basal insulin alone is insufficient to achieve target HbA1c, control of post-prandial hyperglycemia can be accomplished with either rapid acting insulin or a premix regimen. Barriers associated with insulin intensification include fear of hypoglycemia and weight gain and reduced adherence due to regimen complexity.¹ Recently, a combination regimen of basal insulin and a GLP-1RA has been endorsed as an alternative strategy which may resolve some of these issues.²

This combination can address key defects in type 2 diabetes. Basal insulin decreases lipolysis in the adipocytes; GLP-1RAs augment insulin secretion, decrease glucagon secretion, and thus reduce hepatic glucose production. GLP-1RAs also improve insulin sensitivity in muscles, improve the incretin response by activating GLP-1 receptors throughout the body, and reduce appetite signaling.³ Systematic reviews analyzing the clinical performance of this combination have shown effective glucose control while minimizing hypoglycemia and weight gain.⁴

Fixed-ratio combinations of these products have been developed; these reduce the number of injections and permit a simplified intensification regimen. IDegLira is composed of the insulin analogue degludec (100 units/mL [U/mL]) combined with the GLP-1RA liraglutide (3.6 mg/mL) in a 3 ml pen device. IGlarLixi is composed of insulin glargine (100 U/mL) and lixisenatide (33 µg/mL) in a 3 ml pen device. However, two IGlarLixi coformulations have been developed: Pen A, with a ratio of 2 U of IGlar and 1 µg of lixisenatide; and Pen B, with a ratio of 3 U of IGlar and 1 µg of lixisenatide. Titration of both products is carried out in a similar fashion to basal insulin, with the slow titration of the GLP-1RA reducing the associated nausea. As there are no head-to-head studies of these products, the results of the clinical trial programs should not be compared, as the studies have different trial designs and populations.

The authors recommend target populations for fixed ratio combinations. The populations include those in whom HbA1c values remain high despite an acceptable FPG, those with glucose variability in the morning, and those whose total daily basal insulin dose is greater than 0.5 units/kg/day. Other patients who may benefit are those on basal insulin or GLP-1RA alone and those on basal-bolus regimens who would like to reduce the number of injections (potentially seven vs 28 per week). Compared with basal insulin, insulin/GLP-1RA fixed-ratio combinations are superior at reducing HbA1c, with the added advantage of weight neutrality or weight loss, as well as reduced hypoglycemia rates and possibly a reduction in basal insulin dose requirements.^{5,6} Only IDegLira has been compared with a basal-bolus regimen, showing effective HbA1c reduction and superiority in reducing weight, hypoglycemia rates, and insulin doses.⁷ Patients in whom intensification has been delayed because of fear of hypoglycemia or weight gain may also benefit; tackling this aspect of clinical inertia has also shown better patient reported outcomes.⁵ In conclusion, fixed ratio combinations show efficacy, safety, ease of use and reduced injection burden for patients.

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Systematic Review of GLP-1RA/ Basal Insulin FRC

Liakopoulou P, Liakos A, Vasilakou D, et al. Fixed ratio combinations of glucagon like peptide 1 receptor agonists with basal insulin: a systematic review and meta-analysis. *Endocrine*. 2017 Jun;56(3):485-494.



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In the latest position statements, experts suggest that GLP-1 RAs might be preferred over prandial insulin in patients inadequately controlled with basal insulin because of their glycemic efficacy and safety profile in hypoglycemia.¹ This is a systematic review and meta-analysis of randomized controlled trials to investigate the efficacy and safety of fixed ratio combinations (FRC) of basal insulin with GLP-1RA.

Eight studies with 5732 participants qualified for inclusion in this analysis.²⁻⁹ Five studies assessed a fixed ratio combination of insulin degludec with liraglutide (IDegLira), and three studies assessed a fixed ratio combination of insulin glargine with lixisenatide (LixiLan). Study duration ranged from 24 to 52 weeks and participants' mean age and HbA1c at baseline ranged from 54.9 to 60.3 years and from 7.7 to 8.9%, respectively. Six of the trials used an open label design and all studies received industry funding.

Glycemic efficacy: The FRC was associated with better glycemic control compared with each individual component alone (change in HbA1c –0.31%; 95% CI –0.47 to –0.16; I₂ = 81 and –0.73%; 95% CI –0.87 to –0.58; I₂ = 74% compared with basal insulin and GLP-1 RA, respectively).² Transition from treatment with basal insulin to an FRC was associated with a reduction of 0.72% in HbA1c (95% CI –1.03 to –0.41; I₂ = 93%). Switching patients from treatment with GLP-1 RAs to a FRC produced a 0.94% reduction in HbA1c (95% CI –1.11 to

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–0.77). More patients achieve HbA1c targets with fixed ratio combinations.

Body weight: There is a beneficial effect transitioning from basal insulin to the FRC (change in weight –1.72 kg; 95% CI –2.29 to –1.14; I² = 73%) but a gain in weight changing over from a GLP-1 RA alone (change in body weight 2.27 kg; 95% CI 1.86–2.69; I² = 28%).

Hypoglycemia: Hypoglycemia definitions varied among studies; with IDegLira, a plasma glucose value < 56 mg/dL irrespective of symptoms; whereas with LixiLan studies, the definition was a plasma glucose ≤ 70 mg/dL associated with symptoms. Risk for hypoglycemia was similar compared with basal insulin (OR 0.89; 95% CI 0.74–1.06; I² = 53%), but was significantly increased in comparison with a GLP-1 RA (OR 5.89; 95% CI 4.23–8.21; I² = 0%). Severe hypoglycemia rates were low with the FRC (0.04%).

The FRC resulted in a 1% lowering in HbA1c compared to placebo. They have complementary effects rather than additive benefits and harms. The main limitation of this work is the high risk of bias because of the study designs, lack of blinding, and sponsorship bias. There was also a high degree of heterogeneity among studies, so the effect on clinically relevant outcomes (for example cardiovascular outcomes) could not be explored. In conclusion, the main advantage of FRC is their ease of use, allowing simpler treatment intensification; in the future, studies addressing quality of life and cost effectiveness are needed.

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Glycemic Variability with Basal Insulin and GLP-1RA FRC

Bajaj HS, Venn K, Ye C, et al. Lowest glucose variability and hypoglycemia are observed with the combination of a GLP-1 receptor agonist and basal insulin (VARIATION Study). *Diabetes Care*. 2017;40: 194–200

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GLP-1RA drugs are associated with a low risk of hypoglycemia and are beneficial for postprandial glucose control and weight. GLP-1RAs may also be associated with less glycemic variability (GV) and hypoglycemia when combined with basal insulin.¹ The objective of this study was to determine whether patients with type 2 diabetes who had good, stable glycemic control (HbA1C < 7.5% [58 mmol/mol]) on a basal insulin + GLP-1 RA (BGLP) regimen demonstrate less GV and hypoglycemia compared with three common insulin regimens: basal insulin + oral drugs (BO), premixed insulin (PM), and basal-bolus insulin (BB).

Consecutive patients (n = 160) from three endocrinology clinics who met study criteria of type 2 diabetes, age 18- 80 years, body mass index \leq 45 kg/m², stable insulin regimen for a minimum of 6 months, and stable HbA1c value \leq 7.5% (58 mmol/mol) before study enrolment underwent six-day masked continuous glucose monitoring (CGM).

Hypoglycemia was defined as a sensor glucose concentration < 70 mg/dL on CGM. The primary outcome was the average daily glucose standard deviation (SD) over the measurement days.² Secondary outcomes included total glucose SD, daily average glucose, daily frequency, duration and time spent in hypoglycemia, daily percentage of time of hypoglycemia, and area under the curve (AUC) for hyperglycemia.

The baseline characteristics of participants were similar among groups. Almost 90% of subjects were on metformin; those on basal insulin were taking either glargine or detemir, and in the BGLP group almost all participants were on liraglutide. Baseline HbA1c was 6.9, 6.9, 7.0, and 7.0 in the BO, BGLP, PM, and BB groups respectively. All analyses were adjusted for age, body mass index, diabetes duration, and baseline HbA1c. Mean glucose was also similar between groups. The average daily glucose SD in the BGLP cohort (30.6 \pm 9 mg/dL) was significantly lower than in the other groups: BO, 34.2 \pm 9 mg/dL; PM, 36 \pm 10.8 mg/dL; and BB, 37.8 \pm 9 mg/dL. The total SD was also significantly lower in the BGLP group; 34.2 \pm 1.08 mg/dL, compared with 39.6 \pm 10.8, 41.4 \pm 10.8, and 43.2 \pm 10.8 mg/dL for the BO, PM, and BB cohorts, respectively. The proportion of patients with at least one reported hypoglycemia event was significantly lower in the BO and BGLP groups than in the BB group ($P < .01$). The time in hypoglycemia was lowest in the BGLP cohort at 2.9 min/ day (interquartile range [IQR] = 25.7) followed by the BO (7.3 min/day; IQR = 35.0), PM (23.6 min/day; IQR = 35.7), and BB (31.1 min/day; IQR = 67.0) cohorts.

In conclusion, the BGLP regimen showed the lowest glucose variability (compared to the three insulin regimens) and the most favorable hypoglycemia results (compared to PM and BB). Recently, GLP-1RA drugs have shown a beneficial cardiovascular role, with the LEADER trial (with liraglutide) showing a significant reduction in cardiovascular death and a lower risk for severe hypoglycemia.³ Since GV and hypoglycemia are possibly associated with oxidative stress and endothelial dysfunction, improvement in these parameters may play a role in a reduction in vascular events.⁴ Further research is needed to confirm the possibility of cardiovascular benefits, via improved GV and lower hypoglycemia, by using the combination of basal long-acting insulin and GLP-1 RAs.

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Efficacy and Safety Comparison: Basal Insulin/GLP-1RA FRC with a Basal Bolus Regimen

Billings LK, Doshi A, Gouet D, et al. Efficacy and safety of IDegLira versus basal-bolus insulin therapy in patients with type 2 diabetes uncontrolled on metformin and basal insulin; DUAL VII randomized clinical trial. *Diabetes Care*. 2018 Feb 26. pii: dc171114.



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Many patients with type 2 diabetes remain on basal insulin without intensification of their treatment because of concerns such as increased hypoglycemia risk, weight gain, and treatment complexity.¹ Using a GLP-1RA with basal insulin is a recognized intensification strategy. When the nonfixed dose combination of basal insulin with a GLP-1RA was compared with a basal-bolus regimen, investigators reported a noninferior HbA1c reduction, lower hypoglycemia rates and better weight outcomes.² To date, no other study had compared the performance of a basal insulin analogue/GLP-1RA FRC to a basal bolus regimen. This 2018 study assessed the efficacy and safety of initiating insulin degludec/liraglutide FRC (IDegLira) versus basal-bolus insulin (BB).

Adults with type 2 diabetes and a glycated hemoglobin between 7.0–10.0% (53–86 mmol/mol) and a stable dose of insulin glargine U100 (IGlar U100) (20-50 units/day) and metformin (ideally ≥ 1500 mg/day) were included. This was an open label, multinational, treat-to-target, parallel arm, 32-week study. Participants were randomized to either IDegLira (insulin degludec 100 units/mL and liraglutide 3.6 mg/mL, in a 3 mL prefilled FlexTouch pen) or IGlar U100 (insulin glargine 100 units/mL solution, in a 3 mL prefilled Solostar pen) and insulin aspart. IDegLira was administered once daily at any time, and patients were started on 16 units degludec/0.58 mg liraglutide and titrated twice weekly to a maximum dose of 50 units degludec/1.8 mg liraglutide. Glargine was initiated at the pretrial dose, and aspart was initiated with 4 U/meal, with no maximum titratable dose for either agent.

The primary endpoint was change in HbA1c from baseline to week 26 of treatment: IDeglira showed noninferiority compared to the BB regimen (estimated treatment difference was -0.02% [95%CI -0.16, 0.12], $P < .0001$). IDeglira was statistically superior in lowering hypoglycemia rate (risk ratio 0.39 [95% CI 0.29, 0.51], $P < .0001$) and weight reduction (ETD -3.6 kg [95% CI -4.2-2.9], $P < .0001$). There was also an insulin-sparing effect in favor of IDeglira, with a mean daily dose of 13 units less of basal insulin and 45 units less of total insulin. Nausea was infrequent in the IDeglira arm due to the slow titration. Furthermore, in the majority of patients, glycemic targets were reached with one injection of IDeglira vs three to four with BB. A greater proportion of patients achieved composite treatment targets (glycemic control with no hypoglycemia or weight gain) with IDeglira than BB (OR 12.56 [95% CI 6.46, 24.45], $P < .0001$).

This study is the first to show that the FRC is an efficacious, well-tolerated alternative to BB as a titration regimen. The advantages include significantly less hypoglycemia and weight gain, lower insulin dose, and fewer injections (possibly permitting greater adherence). These findings may have an impact on intensification clinical inertia, allowing a more opportune management of patients with diabetes.

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References:

1. Khunti K, Millar-Jones D. [Clinical inertia to insulin initiation and intensification in the UK: a focused literature review](#). *Prim Care Diabetes*. 2017; 11:3–12.
2. Rosenstock J, Fonseca VA, Gross JL, et al; Harmony 6 Study Group. [Advancing basal insulin replacement in type 2 diabetes inadequately controlled with insulin glargine plus oral agents: a comparison of adding albiglutide, a weekly GLP-1 receptor agonist, versus thrice-daily prandial insulin lispro](#). *Diabetes Care*. 2014;37:2317–2325.

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KEY TAKEAWAYS

- The combination of basal insulin with a GLP-1RA is an effective intensification strategy.
- The fixed-ratio combination of a basal insulin analogue with a GLP-1RA is more effective than the individual components. In addition, the FRC shows the same degree of efficacy as a basal-bolus regimen, with a low risk for hypoglycemia, less weight gain, and potentially a lower insulin dose. In addition, glycemic control is achieved with only one injection a day, simplifying the intensification regimens.
- The FRC shows lower glycemic variability than three other common insulin regimens (basal insulin + oral drugs, premixed insulin, and basal-bolus insulin), and is associated with a lower risk of hypoglycemia. There are benefits that may translate into a lower cardiovascular risk.

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