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CARDIOPULSE

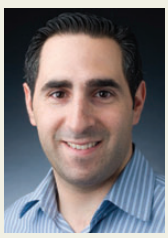
Warfarin increases stroke risk in atrial fibrillation

Warfarin increases risk of stroke among atrial fibrillation patients in first 30 days of use

Atrial fibrillation (AF) patients in the first 30 days of use. Patients with AF have nearly double the risk of suffering a stroke in the first 30 days after starting warfarin compared with non-users, according to a study of over 70 000 patients.

The study, published in the *European Heart Journal*,[1] found that the risk was particularly high in the first week after patients started taking the drug. In contrast, once the first 30 days had elapsed, the risk of stroke was halved in patients taking warfarin compared with non-users.

Randomized controlled trials of other anti-clotting drugs have suggested that there might be an increased risk of a stroke at the point when patients move from the trial drugs to warfarin. In addition, it has already been established that there is a possibility that warfarin leads temporarily to a hypercoagulable state. This is thought to be due to the different effects of warfarin on the production of certain blood clotting factors that are dependent on vitamin K.



Dr Laurent Azoulay, assistant professor in the Department of Oncology at McGill University (Montreal, Canada) and project leader at the Centre for Clinical Epidemiology, Lady Davis Institute, Jewish General Hospital in Montreal, led the research. 'There is no question that warfarin is highly effective in preventing strokes in patients with atrial fibrillation. Thus, our finding that the initiation of warfarin may be associated with an increased risk of stroke should not deter physicians and patients from using this drug, since this likely affects a small number of patients. Future studies should confirm our results, and identify the small subset of patients who may be at risk. However, the results of our study suggest that physicians should be vigilant when initiating warfarin, particularly in the first week of use', he said.

'An interesting finding was that patients with a history of stroke prior to their AF diagnosis were at higher increased risk of developing a stroke during the initiation of warfarin. This is consistent with the hypothesis that the risk may be highest in patients with hypercoagulable states, which provides insight on the possible biological mechanisms that may be at play in this association'.

'To our knowledge, this is the first population-based study to investigate whether the initiation of warfarin is associated with an increased risk of ischaemic stroke'.

The researchers analysed data from 70 766 patients aged 18 or over, who were diagnosed with AF between 1 January 1993 and 31 December 2008. The study was carried out using the UK Clinical Practice Research Datalink, the world's largest primary care database. The researchers followed the patients for up to 16 years until an ischaemic stroke, death, end of registration with their primary care practice, or end of the study period, whichever came first.

During that time, a total of 5519 patients experienced a stroke (2% per year). During the first 30 days after starting warfarin, there was a 71% (nearly double) increased risk of ischaemic stroke when compared with patients taking no anti-coagulant drugs. The highest risk was in the first week of use, peaking on the third day after starting warfarin when there was a 133% (2.3-fold) increased risk of stroke. After 30 days, the risk of stroke among the warfarin patients halved. If the patients had a history of previous ischaemic stroke, they had a 245% (2.5-fold) increased risk during the first 30 days.

The researchers believe that the reason for the difference in the effects of warfarin may be that while the drug blocks the activation of clotting Factors II, VII, IX, and X, it also deactivates two other proteins, C and S, which are anticoagulants. Rapid depletion of protein C, in particular, might lead to a temporary hypercoagulable state.

The senior author of the study, Prof. Samy Suissa, James McGill Professor of Epidemiology, Biostatistics and Medicine at McGill University (Montreal, Canada), said: 'While these findings need to be confirmed in other settings, it would be imperative to also investigate whether the newer popular anticoagulants also carry this early risk'. In the meantime, he suggests that 'a bridging strategy using heparin at the initiation of warfarin treatment could be considered as a way to reduce the increased risk observed in the first 30 days of use'.

The researchers hope to repeat the study using databases from other countries and settings.

Andros Tofield

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Aspirin still overprescribed for stroke prevention in atrial fibrillation

Latest data on European cardiologists' prescribing also reveals underuse of oral anticoagulants in the elderly and patients with paroxysmal atrial fibrillation

Aspirin is still over-prescribed for stroke prevention in atrial fibrillation (AF) despite the potential for dangerous side effects, according to the latest data on European cardiologists' antithrombotic prescribing.

Gregory Y. H. Lip
(photo: S. Rogers)

Prof. Gregory Y.H. Lip, lead author of the European Society of Cardiology (ESC) study, said: 'The perception that aspirin is a safe and effective drug for preventing strokes in AF needs to be dispelled. If anything, you could say that giving aspirin to patients with AF is harmful because it is minimally or not effective at stroke prevention, yet the risk of major bleeding or intracranial haemorrhage is not significantly different to well-managed oral anticoagulation'.

He added: 'All the contemporary guidelines say that aspirin should not be used for the prevention of stroke in patients with AF. And yet our study shows that aspirin is still overprescribed in these patients'.

Stroke prevention is central to the management of patients with AF. As the most common cardiac rhythm disorder, AF occurs in 1.5–2% of the general population in the developed world and people over the age of 40 have a one in four lifetime risk of developing AF. Patients with AF have a five-fold risk of stroke, and when they do have strokes they lead to more death and disability.

Prevention of strokes in patients with AF is based on identification of risk factors. Patients with no stroke risk factors (i.e. CHA2DS2-VASc score of 0 in males or 1 in females) are considered 'low risk' and do not need any antithrombotic drugs. Patients with one or more risk factors should be offered effective stroke prevention, and thus be given an oral anticoagulant (warfarin or one of the novel oral anticoagulants). The use of aspirin, either alone or in combination with an oral anticoagulant, is not recommended.

The study was published in the *American Journal of Medicine* and provides the most up-to-date picture of prescribing of antithrombotic treatment by European cardiologists, which includes oral anticoagulation therapy (warfarin and the novel oral anticoagulants) and antiplatelet drugs (mainly aspirin).[1] The data are from the EURObservational Research Programme Atrial Fibrillation General Pilot Registry of >3100 patients in nine countries.

Overall, the study found that the use of oral anticoagulants has improved over the last decade since the last Euro Heart Survey was performed. Where oral anticoagulation was used, most patients (72%) were prescribed warfarin and just 8% were prescribed a new oral anticoagulant.

Prof. Lip said: 'Novel oral anticoagulant uptake is still a bit low, probably because of differences in regulatory approval, costs and access to drugs in different countries. But the main point is that overall oral anticoagulant uptake as a whole has improved in the last 10 years'.

Aspirin was commonly prescribed, either alone or in combination with an oral anticoagulant, when patients had myocardial infarction or coronary artery disease. The strongest reason for prescribing both drugs was coronary artery disease, which increased the use of combined therapy by more than eight-fold.

Prof. Lip said: 'Aspirin is still overused for stroke prevention in AF. ESC guidelines say concomitant aspirin should not be given to anticoagulated AF patients with *stable* vascular disease. The combination of drugs does not reduce cardiovascular events and stroke but does increase the risk of bleeding'.

Another worrying finding was that oral anticoagulants were underprescribed in elderly patients, with aspirin alone more commonly prescribed. Prof. Lip said: 'Elderly patients are at the highest risk for stroke and yet they are given aspirin which is not recommended and potentially harmful. There is a perception that elderly patients do not do well on anticoagulation. But a number of studies now, including the Birmingham Atrial Fibrillation Treatment of the Aged Study (BAFTA), have shown that in elderly patients warfarin is far superior to aspirin in preventing stroke'.

Patients with paroxysmal AF were less likely to receive oral anticoagulation compared with patients with permanent AF. Prof. Lip said: 'Cardiologists are continuing to underprescribe anticoagulation in paroxysmal AF and the belief that these patients are at less risk is another myth. ESC guidelines say that AF patients with stroke risk factors should receive oral anticoagulation irrespective of the type of AF'.Prof. Lip concluded: 'Our study of antithrombotic prescribing by cardiologists reveals a positive trend of increasing oral anticoagulant use. But worrying misconceptions and practices remain regarding aspirin, treatment of the elderly and paroxysmal AF'.

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Clinical Research in Cardiology: the official journal of the German Cardiac Society (Deutsche Gesellschaft für Herz-/Kreislaufforschung)

Clinical Research in Cardiology began as the '*Zentralblatt für Herzkrankheiten und die Erkrankungen der Gefäße*' by Max Hertz in 1909. Volume 3 was published 2 years later by Theodor Steinkopf Verlag, Dresden-Leipzig, in 1911.

The German Cardiac Society (DGK) was founded by Prof. Bruno Kirsch on 3 June 1927, during the '5th Seminar for Physicians about Arrhythmias of the Heart'.

Bruno Kirsch recalled the beginning of the German Cardiac Society on the 75th anniversary of the DGK in 2002[1] with the words, 'The whole process of establishing the Society didn't even take 3 minutes'.

In 1928 the journal became the official organ of the Deutsche Gesellschaft für Kardiologie (German Cardiac Society). After World War II the journal was reinstituted by Konrad Spang. The Society of Paediatric Cardiology, the Society of Cardiac Rehabilitation, and the subdivision of Cardiology of the German Internal Medicine Association chose the '*Zeitschrift für Kardiologie*' (*Journal of Cardiology*) as their official journal.

The journal was originally published in German, and then in 2005, the Board of the German Cardiac Society and the editors of the '*Zeitschrift für Kardiologie*' made the decision to publish all papers in English following a short transition phase. This was done to increase visibility of the scientists, in particular, researchers from Germany and to attract an international readership and international investigators to publish in the journal. In 2006 the name of the journal was changed to *Clinical Research in Cardiology*. Since then, the journal has been successfully converted to an internationally oriented journal published exclusively in English.

The following are the goals of *Clinical Research in Cardiology*:

(1) Publication of clinical studies in cardiology with high international and national recognition.
(2) Providing a platform for in-depth discussion of scientific controversies in clinical cardiology.
(3) Promotion of continuous medical education in clinical cardiology covering the broad spectrum of cardiovascular diseases.
(4) Providing clinicians with cases to foster practical education of students and doctors, and training of staff physicians.

Clinical Research in Cardiology is one of the numerous journals published under the patronage of the European Society of Cardiology, supporting European science in cardiology. Since 2006 the number of submitted papers has continuously increased and the rejection rate has remained high (*Figure 1*).

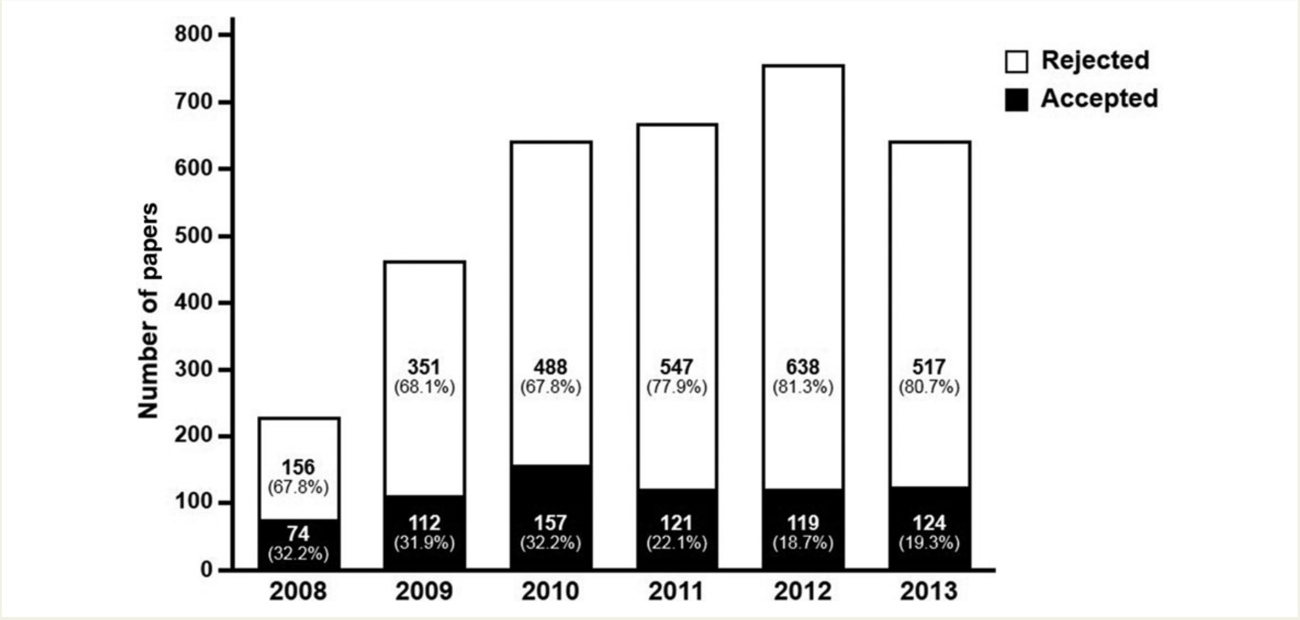

Figure 1 *Clinical Research in Cardiology*: final disposition of received manuscripts.

Table 1 Ten best published papers (2–11)

Rank	Article	Author
1	Foreword. Z Kardiol 91: Supp 4, IV/V (2002), Steinkopff Verlag 2002	Lüderitz B. and Arnold G.
2	Renal sympathetic denervation for treatment of electrical storm: first-in-man experience	Ukena C., Bauer A., Mahfoud F., Schreieck J., Neuberger H.R., Eick C., Sobotka P.A., Gawaz M., and Böhm M.
3	Everolimus-eluting vs. sirolimus-eluting stents: an updated meta-analysis of randomized trials	de Waha A., Cassese S., Park D.W., Burzotta F., Byrne R.A., Tada T., King L.A., Park S.J., Schömig A., and Kastrati A.
4	Platelet inhibition and GP IIb/IIIa receptor occupancy by intracoronary vs. i.v. bolus administration of abciximab in patients with ST-elevation myocardial infarction	Desch S., Siegemund A., Scholz U., Adam N., Eitel I., de Waha S., Fürnau G., Lurz P., Wetzel S., Schuler G., and Thiele H.
5	Local vs. general anaesthesia for transfemoral aortic valve implantation.	Motloch L.J., Rottlaender D., Reda S., Larbig R., Bruns M., Müller-Ehmsen J., Strauch J., Madershahian N., Erdmann E., Wahlers T., and Hoppe U.C.
6	Clues to detect tumour necrosis factor receptor-associated periodic syndrome among patients with idiopathic recurrent acute pericarditis: results of a multicentre study	Cantarini L., Lucherini O.M., Brucato A., Barone L., Cumetti D., Iacoponi F., Rigante D., Brambilla G., Penco S., Brizi M.G., Patrosso M.C., Valesini G., Frediani B., Galeazzi M., Cimaz R., Paolazzi G., Vitale A., and Imazio M.
7	Markers of oxidative stress after ablation of atrial fibrillation are associated with inflammation, delivered radiofrequency energy, and early recurrence of atrial fibrillation	Richter B., Gwechenberger M., Socas A., Zorn G., Albinni S., Marx M., Bergler-Klein J., Binder T., Wojta J., and Gössinger H.D.
8	Smoking restrictions and hospitalization for acute coronary events in Germany	Sargent J.D., Demidenko E., Malenka D.J., Li Z., Gohlke H., Hanewinkel R.
9	Prognostic value of mild-to-moderate pulmonary hypertension in patients with severe aortic valve stenosis undergoing aortic valve replacement	Zuern C.S., Eick C., Rizas K., Stoleriu C., Woernle B., Wildhirt S., Herdeg C., Stock U., Gawaz M., and Bauer A.
10	The risk-to-benefit ratio of transcatheter aortic valve implantation in specific patient cohorts: a single-centre experience	Puls M., Viel T., Danner B.C., Jacobshagen C., Teucher N., Hanekop G., Schöndube F., Hasenfuss G., Seipelt R.G., and Schillinger W.
11	A decade of developments in chronic heart failure treatment: a comparison of therapy and outcome in a secondary and tertiary hospital setting	Franke J., Zugck C., Wolter J.S., Frankenstein L., Hochadel M., Ehlermann P., Winkler R., Nelles M., Zahn R., Katus H.A., and Senges J.

The citation index is steadily rising, with the journal listed in ISI. The latest impact factor, published in 2013, was 3.6.

Table 1 lists the 10 best published papers (nos. 2–11). The spectrum of these papers ranges from new topics, such as renal denervation, interventional cardiology with new stent developments, and antiplatelet therapies, as well as pericarditis, to well-established topics such as pulmonary hypertension and aortic valve interventions and heart failure. Original and well-performed studies as well as an active editorial and reviewer board have helped to support the goals of *Clinical Research in Cardiology* to encourage excellence in cardiovascular science and education. In addition, the journal promotes the visibility of the German Cardiac Society in particular, and of European Cardiology in general.


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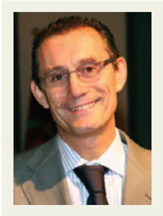
Septic shock in infective endocarditis

José Alberto San Román Calvar (Valladolid, Spain) and Isidre Vilacosta (Madrid, Spain) discuss their research, which they presented at the Acute Cardiac Care Congress late last year



José Alberto San Román Calvar

Isidre Vilacosta

Septic shock (SS) is one of the most fearful complications of infective endocarditis (IE). Scarce information exists about the development of SS and its impact on early outcome in these patients. Our group has investigated SS in a large, prospective, multicentre study of patients with IE published in the *EHJ*.[1] Seventeen per cent of a cohort of 894 episodes of IE had SS at some time during the course of the disease. A third of the patients with SS presented with this complication at admission, whereas two-thirds developed SS during hospitalization. Factors that were found to be independently associated with the development of SS were diabetes, acute renal insufficiency, *Staphylococcus aureus* infection, supraventricular tachycardia, large vegetation size (>15 mm), and signs of persistent infection.

It is well known that individuals with diabetes have a greater frequency and severity of infections. Abnormalities in cell-mediated immunity and phagocyte function are, among others, reasons to explain this increased susceptibility to bacterial infections. Not surprisingly, *S. aureus* infection was associated with SS. This virulent microorganism has been associated with poor prognosis and a high likelihood of SS from any origin. Acute renal insufficiency has also been related to the development of SS from any origin. The main mechanisms involved in the development of renal failure in severe sepsis include hypovolaemia, hypotension, and renal vasoconstriction. Prognostic implications of vegetation size are still a matter of controversy. How a bulky local infection leads to multi-organ dysfunction and hypotension is uncertain.

Importantly, we found that the combination of these factors allows clinicians to predict the risk of SS development. When adding signs of persistent infection (persistently positive blood cultures or fever after a week of appropriate antibiotics, with other possible foci of infection ruled out) to the presence of the aforementioned factors, the predicted risk dramatically doubled.

In our study, when analysing patients' outcome, subjects with SS underwent surgery much less frequently and had higher mortality than those without. Interestingly, patients with SS who underwent surgery had a mortality rate lower than those who received medical therapy alone. Do these results mean that all patients with IE and SS need to be sent to surgery? Probably not. It is not fully established if surgery improves prognosis in these patients, since surgery under these circumstances is associated with high mortality rates. The findings of our work have at least two practical considerations. First, patients with SS should not be routinely refused surgery, and secondly, our results reinforce a strategy of early surgery in patients who are at high risk for developing SS.

Another critical issue is how to differentiate cardiogenic shock from SS. In practice this is not an easy task. Some degree of myocardial dysfunction frequently accompanies severe sepsis, and cardiogenic shock and SS may sometimes co-exist, making the differential diagnosis difficult. To differentiate if a patient is in cardiogenic shock or in SS is of utmost importance, since a prompt intervention is usually recommended in the first case, providing satisfactory early and late results.[2,3] In contrast, emergency surgery for patients with SS is associated with high mortality.[1,3]

Understandably, surgery may be successful in fixing a 'local' complication causing cardiogenic shock, but it will have more difficulty combating an uncontrolled 'systemic' infection. Here again, experienced clinical judgement will be most necessary.

Jennifer Taylor MPhil

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Innovation in atrial fibrillation therapy

Pio Caso discussed imaging in left atrial appendage closure at EuroEcho-Imaging 2013

Pio Caso

Atrial fibrillation (AF) remains the most frequent arrhythmia in clinical practice and a major cause of morbidity and mortality.

The incidence of stroke increases markedly in AF with advancing age (1.5% at 50–59 years of age to >20% at 80–89 years of age), making AF a primary risk factor for stroke in these patients.

The left atrial appendage (LAA) plays a fundamental role in the formation of atrial thrombus in patients with AF. In patients with non-rheumatic AF, thrombi were found in 12.5% of patients and the LAA is the origin of at least 90% of all left atrial (LA) thrombi.

Stroke prevention in patients with AF has largely been based on the use of anticoagulation with warfarin, which reduces the risk of stroke by 60%, and more recently on the use of novel anticoagulants such as dabigatran.

A significant proportion of patients with AF, from 30 to 50%, do not receive anticoagulation due to relative or absolute contraindications in clinical practice, including the risk or fear of treatment-induced bleeding.

Left atrial appendage surgical ligation in patients undergoing cardiac surgery may be an attractive choice for reducing stroke risk. In addition, LAA closure can now be achieved through different approaches such as thorascopic LAA ligation and, more recently, percutaneous LAA occlusion.[1,2]

Cardiac imaging can be used in LAA closure before, during, and after the procedure.

Before the procedure

There are data that support the procedure, data that contraindicate the procedure, and data about the LAA anatomy that can improve the procedure.

Data that support the procedure are, first, the profile of LAA contractile dysfunction and, second, the specific morphology at risk. Left atrial appendage contractile dysfunction is visible by transoesophageal echocardiography (TOE): low flow velocities increase risk (the risk of thrombi is five times more if the velocities of the LAA appendage are <20 cm/s), and risk is higher in the presence of echo contrast (grade 3 or 4) and by dilatation of the LAA. The specific morphology at risk is seen by cardiac computed tomography or cardiac magnetic resonance: the chicken wing morphology was strongly associated with the absence of a history of stroke ($P < 0.0001$); on the other hand, the cactus morphology increases risk by 4.5 times, the windsock morphology by 4.08 times, and the cauliflower morphology by 8.0 times.[3]

Data that contraindicate the procedure: contraindications are thrombosis of appendage, intracardiac mass, endocarditis, giant appendage, intra-appendage membrane, pericardial effusion, patent foramen ovale, septal aneurysm, and atheroma in the aortic arch.[4]

Data about LAA anatomy to improve the procedure: it is necessary to localize surrounding structures such as the left superior pulmonary vein, the Marshall ligament, the entrance of the left appendage (morphology and diameter of ostium, plus length and width), distance between the ostium and the mitral valve (vestibular length 5–14 mm), and that between the ostium and left upper pulmonary vein (6–23 mm), localization of the circumflex artery, the number of LAA lobes, and localization of the pectinate muscles. All of these data are better shown by 3D echocardiography with TOE.

During the procedure

Transoesophageal echocardiography can be used to guide the procedure, but it is necessary to use anaesthesia. During the procedure echo makes it possible to follow puncture of the interatrial septum (better seen by 3D echo), handling of the catheters, opening the device, the criteria of device detachment (position, stability, size, and sealing), post-device detachment, and device recapture if required.

During trans-septal puncture, echo guides the puncture in the posterior and central zone of the foramen ovale (3D is better than 2D). After trans-septal puncture, echo guides the sizing of the left appendage (evaluation only when LA pressure >10 mmHg) and handling of the catheters (progress slowly and carefully because the LAA lateral wall is very thin).

In implantation, it is necessary to evaluate the position, stability, sizing, and sealing, and to ensure that the position and shape of the device is correct. The external disc of the device must remain fixed in the LAA ostium, including after the traction test. The external disc has a diameter of 4–6 mm greater than the body of the implanted device. It is important to visualize the shape of the device to assess its stability, gently retracting the guide and releasing control, to observe whether the device returns to its original position. If the device is moved to an unacceptable position or compression is not enough, it must be recaptured.

After the procedure

Possible complications are heart rupture, periprocedural stroke, and incorrect positioning of the device. Heart rupture is related to trans-septal puncture or appendage perforation with visualization of immediate pericardial effusion; possible complications are detachment and recapture of the device under the guidance of TOE. Periprocedural stroke is a possible complication and TOE can visualize a thrombus on the device. Risk factors for thrombosis are $CHADS_2$ score ≥ 3; $CHA_2DS_2VASC_2 \geq 6$; higher platelet count; and ejection fraction <50%.[5]

Jennifer Taylor MPhil

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