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Effectivity of combined therapy that includes glutargine hepatoprotector in patients with comorbid permanent atrial fibrillation and liver disease on the background of longterm warfarin therapy

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Abstract
Atrial fibrillation (AF) is one of the most widespread rhythm disorders in the population and is considered that its frequency will continue grow because of aging of the population in the first place, and also with improving of diagnostics and treatment. So if in an age group to 55 years old it occurs in 1-1,5% persons, so in the persons older than 80 years reaches already 10-12%. Also famous risk factors are obesity, arterial hypertension, ischemic heart disease and valvular heart diseases. A significant role given to comorbide states and among them association of AF and chronic diffuse liver diseases and fatty hepatosis in particular is not enough studied nowadays. In the same time prevalence of fatty hepatosis became an epidemic according to the experts' assessment and is one of most frequent pathologies in clinical practice. A precise number of such patients is unknown and it is considered that it shakes in general population within 20-35% in west countries and this percent will rise without doubt. Data are collected that fatty hepatosis increases occurring of cardio-vascular diseases, especially in people with concomitant diabetes mellitus. He is also associated with early occurring as separate diastolic dysfunction of the left ventricle independent on other cardiometabolic risk factors, as well as higher frequency of hear failure development. It was also discovered a correlation between increased level of transaminases in blood, surrogate indicator of fatty hepatosis, and risk of paroxysmal AF.

Keywords: Comorbid pathology of the liver, atrial fibrillation, glutargine hepatoprotector, longterm warfarin therapy.

1. Introduction
Since fatty hepatosis and AF have common risk factors and lack of data about their association in the literature, the aim of our trial was study of effectiveness of kapicor/glutargine combination in treatment of patients with permanent AF and fatty hepatosis that get permanent therapy with warfarin.

2. Methods of the trial
156 patients with ischemic heart disease (IHD) complicated by comorbid permanent atrial fibrillation (AF) and liver pathology that were getting permanent therapy with warfarin long time were studied. These people were divided in two groups: to the first one people were included that were getting basic therapies (80 patients) according to Recommendations of Heart Rhythm Disorders Working Party of Ukrainian Cardiologists Association (2011); in the second group kapicor/glutargine combination in individually selected doses was added to the basic therapy (76 patients). Correction of therapy and observation were provided during two years. Selecting of patients into the trial was provided according to including criteria: patient agreement on participation in the trial and signing of presented informed consent form, patient's compliance, presence of clinical, laboratory and instrumental criteria of IHD and AF according to protocols of performing of medical aid for speciality «Cardiology». Into the trial persons with comorbidity of AF and such nosologies: fatty liver (fatty hepatosis), steatohepatitis, chronic cholecystitis and chronic cholangitis were included. Primarly diagnoses of chronic liver diseases were made on the base of clinical, biochemic and instrumental tests in inpatient departments according to protocols of performing of medical aid for speciality «Gastroenterology» (order of MoH of Ukraine №271 from 13.06.2005) [22] and Clinical Guideline (Kyiv, 2014). Into trials patients with IHD that formed because of AH, IHD and valvular pathologies of I-IIb degrees (according to Ukrainian Cardiologists Association

Classification (2000)) and functional classes I-III (according to New York Heart Association Functional Classification) were included. Exclusion criteria: patients with acute myocardial infarction, inflammatory diseases of heart layers, and patients that could not take oral anticoagulants for a long time because of different causes. Presence of viral hepatitis B or C, or positive indicators of viral hepatites B or C, confirmed cirrhosis or liver cancer, drug and alcohol dependence, HIV infection, somatic pathology in decompensating state, oncologic diseases were also excluded from the trial. Control group was formed from the patients with diffuse inflammatory liver diseases without heart rhythm disorders (38 patients).

The basis of as both experimental, as well as control groups was completed with patients with comorbid fatty liver dystrophy, 80,4 and 73,7% respectively. The lowest number of patients in the groups contained patients with chronic cholangitis (3, 7, 5, 3 and 4, 2%, respectively) and steatohepatitis (4, 8, 5, 3 and 3, 6%). The patients from all groups had similar division also according to gender and age features. The majority of examinated as in control, as well in experimental groups were males. If in the control one there were 24 males (63, 2%), so in first and second groups there were practically two thirds in each (69, 7%). Average duration of treatment with warfarine was 5, 9 years; optimal INR values were reached in both experimental groups with average warfarine dose 7, 3±1,3 mg/day. Therefore patients of these groups took aspirine doses 100 mg daily.

For stratification of disorder risk of cerebral circulation and bleeding CHA2DS2-VASc scores were used [6, 11, 17]. Therefore in all patients evaluation of anamnesis, complaints and clinical diseases courses was provided; additiomal evaluation of life quality was provided додатково with the help of «Chronic Liver Disease Questionnaire» (CLDQ). «CLDQ» was developed in Department of Gastroenterology (The Cleveland Clinic Foundation, USA) in 1999 by Younossi *et al*. as a specific instrument for examination of patients with chronic liver diseases [34]. It contains 29 questions and is divided into six scores, that evaluate such aspects of patients' health: «Abdominal symptoms» (AB) – questions 1, 5, 17; «Fatigue» (FA) – 2, 4, 8, 11, 13; «Systemic symptoms» (SS) – 3, 6, 21, 23, 27; «Activity» (AC) – 7, 9, 14; «Emotional function» (EF) – 10, 12, 15, 16, 19, 20, 24, 26; «Worry» (WO) – 18, 22, 25, 28, 29. Each question can be answered with from one (most affected) to seven points (least affected). Minimal amount of collected points is 29, maximal amount is 203. According to results physical, mental and emotional functions were evaluated.

Detoxic function of the liver was evaluated with the help of Wagner «Iris» IR analyzer (Germany) that uses infrared isotope spectroscopy. Metacetine [N-(4-methoxyphenol) acetamide] is derivate from phenacetin. Method principle consists in that that ^{13}C-metacetine undergoes fermentative demethylation and decarboxylation with participating of microsomal enzymes of P_{450} cytochrome in the liver. Final product of ^{13}C-metacetine methabolism is $^{13}CO_2$, which elimination intensity across the lungs lets to evaluate functional state of microsomal hepatocytes enzymes. Results of the trial were evaluated on the basis of $^{13}CO_2$ exhale volume in the end of 120th minute that formed during the change of ^{13}C-metacitine because of demethylation process to paracetamol and $^{13}CO_2$, which elimination intensity with exhaled air across the lungs lets estimate functional state of microsomal enzymatic hepatocytes systems. Absorption spectrum of studied gas was compared with reference absorption spectrum. During performing of ^{13}C-metacetine test metacetine powder is dissolved in 200 ml of fruit tea (less than 45 °C) because of its thermolability. Respiratory tests are received each 10 minutes during the first hour, and then each 20 minutes. Results received from analysis were presented in graphic form. Consequences about presence or absence of liver function disorders were made on the ground of comparison of $^{13}CO_2$ total concentration curve before finish of 120th minute of the trial with curves that were received during examination of healthy volunteers that represent upper and lower limits of norm. The cumulative dose of $^{13}CO_2$ on 120th minute 20-35% was considered as normal values. The corresponding liver function disorder was evaluated as pathologic affection of mild, moderate and severe degree.

3. Results and discussion

Observations of patients from experimental groups found that after year and particularly two years period of treatment with addition of kapicor/glutargine combination in individually matched doses examinees' feeling bettered fundamentally that manifested in the first place with decreasing of complaints as on cardiovascular system, as well as gastrointestinal tract. For example, if in patients of the first experimental group such symptoms like decreasing of capacity, fatigue are present in 57,5% and 61,3% cases, so in the second experimental group the amount of such patients after the first year treatment was less more then in two times. After two years treatment amount of patients with such complaints decreased more and contained 11, 9% and 18, 4% respectively. Also in the second experimental group amount of patients with dizziness and tinnitus decreased in half after two years treatment. The percent of patients with complaints on headache and memory disorders did not change practically in both experimental groups. So if in the first experimental group such patients contained 21, 3% and 27, 5%, then after one year observation they contained 18, 4% and 23, 7% in the second experimental group. After two years treatment of patients with such complaints minor decreasing was noted: 14, 5% and 19, 7% respectively. It is interesting that in the control group of patients (without rhythm disorders) pointing on memory disorders were only 7,9% that was almost in three times less than in both experimental groups. This difference can be explained with decreasing of cognitive properties because of microembolism of cerebral vessels that can be present in patients with AF [32, 16]. During observation of patients of the second experimental group a percent of patients with dream and psychoemotional sphere disorders decreased comparatively to the first experimental and control group. For example, in the first experimental group dream disorder in the night and also drowsiness during the day were pointed by 32,5% and 43, 8% patients, so after one year treatment such patients were in the second experimental group 18,4% each respectively. After two years treatment with addition of kapicor/glutargine combination in individually matched doses a percent of such patients decreased more and contained 10, 5% and 7, 9% respectively. In this group in the second year of observation also the least amount of patients was registered that were present with irritability and anxiety. Such patients were found 14, 5% and 11, 9% respectively. Comparatively in the first experimental group half of all interviewed complained on irritability: 58, 8%. Anxiety was noted in 38, 8%. It is worth to notice a low level of psychoemotional disorders in patients of the control group. If irritability was noted by 28, 9% of all interviewed, so complains on anxiety were at more

less, namely 18, 4%. A significant proportion of patients with AF and psychoemotional sphere disorders that was found by us during the trial echoes with data of other authors [19, 14]. Moreover these states are mutually aggravating. So there are data that presence of depression in a patient can be a cause of AF initiation possibly because of inflammation mechanism and oxidant stress [1]. It is also displayed that patients with depression have increased levels of acute phase inflammatory proteins, like C-reactive proteins and decreased level of anti-inflammatory cytokines, and this can be a cause of occurring of AF paroxysm [24, 9]. Bettering of functional state of the liver on treatment and decreasing in such way of tension of inflammatory response can be a basis of bettering of these patients' feeling [13, 18].

It is interesting to notice also a complaints dynamics from gastrointestinal tract. So in the control group (patients with chronic diffuse inflammatory liver diseases without cardiac rhythm disorders) nausea, feeling of fast filling with food and discomfort in right subcostal were stated in 23, 7%, 13, 4% and 47, 4% of all interviewed. In the same time patients with cardiac rhythm disorders that were on permanent warfarin and aspirin therapy with comorbid liver damage were already in two times and by some characteristics in three times more. Discomfort in the right subcostal and nausea were leading in this group and contained 91, 3% and 76, 3% respectively. Feeling of fast filling with food occurred more rarely (51, 3%) but still the percent of such people was significantly higher than in the control group (13, 4%). Addition of kapicor/glutargine combination in individually matched doses to basic therapy of these patients let significantly decrease the percent of patients with such complaints. So after the first year of such correction of basic therapy amount of patients that pointed nausea became 15, 8% in the second experimental group. In the second year there were no such patients, and the percent of patients with complaints on fast filling with food and discomfort in the right subcostal decreased from 21,1% and 15, 8% to 9, 2% and 11, 9% respectively.

It is worth to note that using in the second experimental group of therapy correction let decrease the percent of patients with so-called «subjective feeling of arrhythmia». So if in the first experimental group feelings of palpitation and disruptions in cardiac activity were noted by 86, 3% and 87, 5% patients, so after the first year of treatment correction there were such patients 76, 3% and 81, 6% in the second experimental group, and after the second year their amount decreased more and was already 53, 9% and 69,7% respectively. In the control group such complaints were made by 18, 4% and 2, 6% patients. It was possible also to optimize clinical objective symptoms in such patients. The most significant regress of clinical manifestations could be achieved from gastrointestinal tract. For example, if in the control group pain in the right subcostal during palpation occurred in 44, 7%, so in the first experimental group such patients were already more in two times, namely 88, 8%. Addition of kapicor/glutargine combination in individually matched doses let decrease already after the first year of observation the percent of this feature to 34, 2% and to 2, 6% after two years. Increased size of liver was typical for 65, 0% of patients from the first experimental group, and 21, 1% and 11, 9% after the first and second year of basic therapy correction respectively. More then in three times frequency of such feature as scleral icterus decreased in the second experimental group comparatively to the first one, in the same time ochrodermia did not found after two years of correction.

It is interesting that optimization of treatment reflected positively on the control of heart rate and blood pressure among the patients from the second experimental group. So if target control of heart rate in patients with permanent AF was reached without therapy correction only in half of patients, so already after one year treatment with addition of kapicor/glutargine combination such patients were two thirds, and after two years nearly 85%. Also the percent of patients that succeeded to reach optimal limits of AF changed in a positive way. In the second experimental group after two years of treatment correction the patients with increased AF were only 11%. Comparatively in the control group patients with arterial hypertension were 36, 9%, and in the first experimental group practically in two times more (66, 3%). Such improving/ is obviously bound with greater commitment of the patients to the therapy, including using of antihypertensive medicines. Also cardio- and vascular protective effects of active substance of kapicor – meldonium have significance [29, 8].

During the second evaluation of patients' life quality after one and two years basic therapy correction its improving was revealed in the patients of the second experimental group (pic. 1). Already after the first year of corrected therapy total score in all scales was significantly higher in second experimental group comparatively to the patients in that such correction was not performed and contained 140,5±7,5 points versus 112,1±10,7 points in the first experimental group, $p<0,05$. The most significant changes in this period that caused higher score were in scales «Systemic symptoms» (SS) and «Abdominal symptoms» (AB). In the first scale average score grew in the year of treatment from 15,2±2,0 to 25,5±1,7 points, $p<0,05$; in the second one from 9,2±1,8 to 14,6±1,6 points, respectively ($p<0,05$). In other scales positive changes were also noted that became more significant up to the finish of the second year of treatment correction.

The total score in all scales increased in average to 161,7±8,3. Comparatively in the first experimental group it was 112,1±10,7 points, $p<0,05$. In these patients anxiety indicator decreased and their psychoemotional state. So if in the scale «Emotional function» (EF) patients from the first experimental group collected in the average 37,5±2,7 points, so after the first year of treatment this indicator was already 40,6±3,4 in the second experimental group, and after the second year grew in 6 points (46,4±2,6), $p<0,05$. The patients of the second experimental group started to evaluate two times better their subjective experience in the scales «Abdominal symptoms» (AB) and «Systemic symptoms» (SS). The general state of these patients improved too.

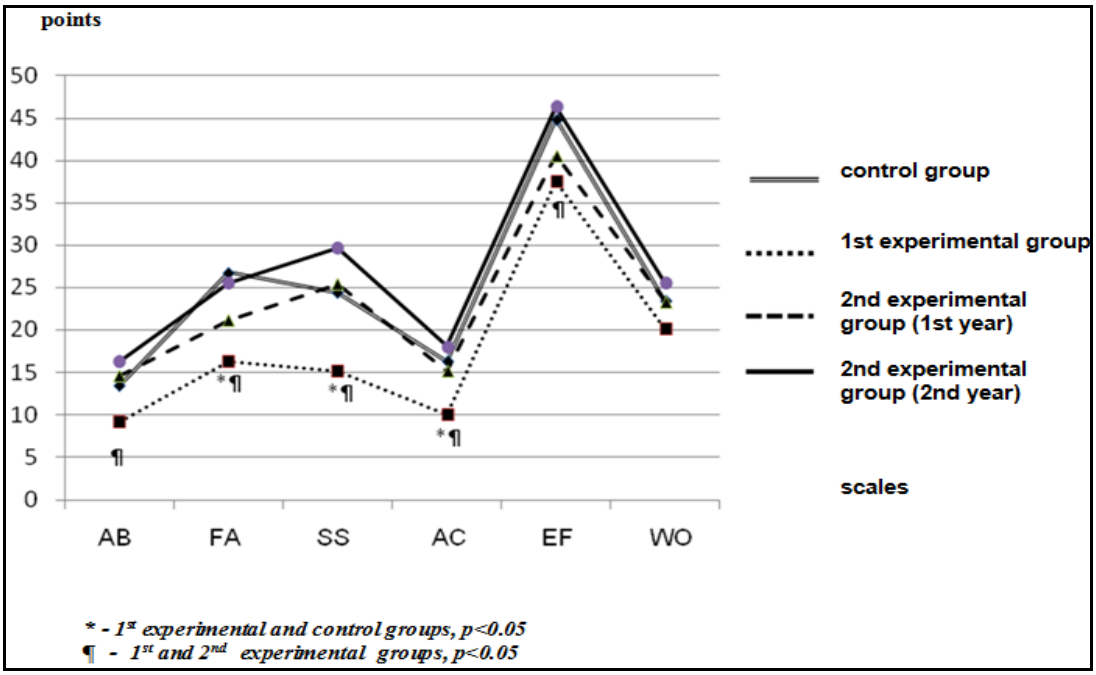

Fig 1: Classification of examined from control and experimental groups according to scales of questionnaire.

It is interesting that treatment correction by adding of kapicor/glutargine combination helped for better control of INR in the patients of the second examination group. So if in the first experimental group such basic therapy correction was not provided a percent INR control in borders of «therapeutic window» 62,5% of the whole time, so after the first year of observation this percent grew in the second experimental group already to 75,0%, and after the second year to 83,3%. Such improving of control of INR indicator, and also better control of blood pressure let correct the classification of patients in the second experimental group according to main scales of risk factors and decrease risk of embolic damages (pic. 2).

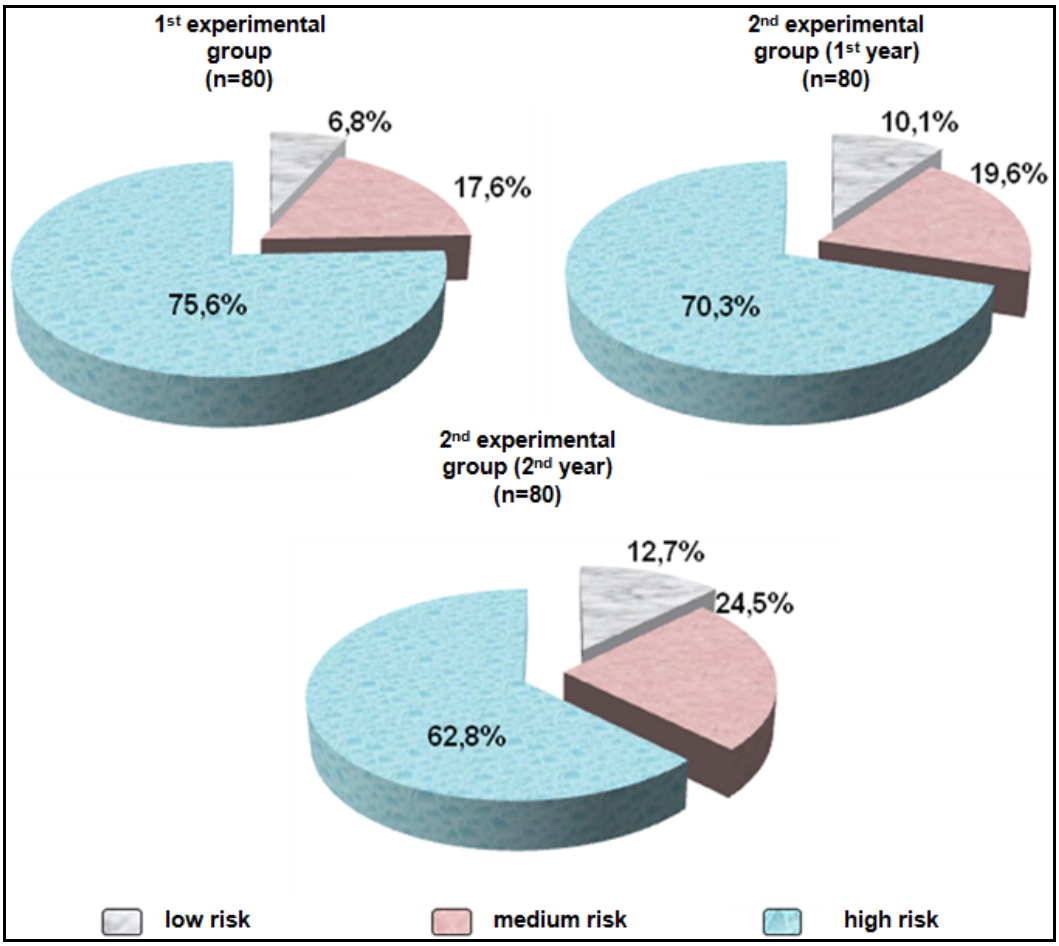

Fig 2: Classification of patients from the first and the second examination groups according to CHA2DS2-VASc scale.

The greatest part of patients had high risk according to CHA2DS2-VASc scale as in the first experimental, as well as in the second experimental group. However after the first year of treatment correction the part of patients with high risk according to this scale was in 5% less, and after the second year in 15% less. Trials from last years show that presence of fatty hepatosis is an independent factor of increased formation of thrombi in the body that causes disorders of coagulation status and complications in optimal control of INR in patients with AF with comorbid liver injury [15, 23, 30]. Improving of functional state of the liver can be a cause of optimization of blood coagulation status in such persons.

Evaluation of metacetine breath test curve found improving of functional state of the liver (pic. 3).

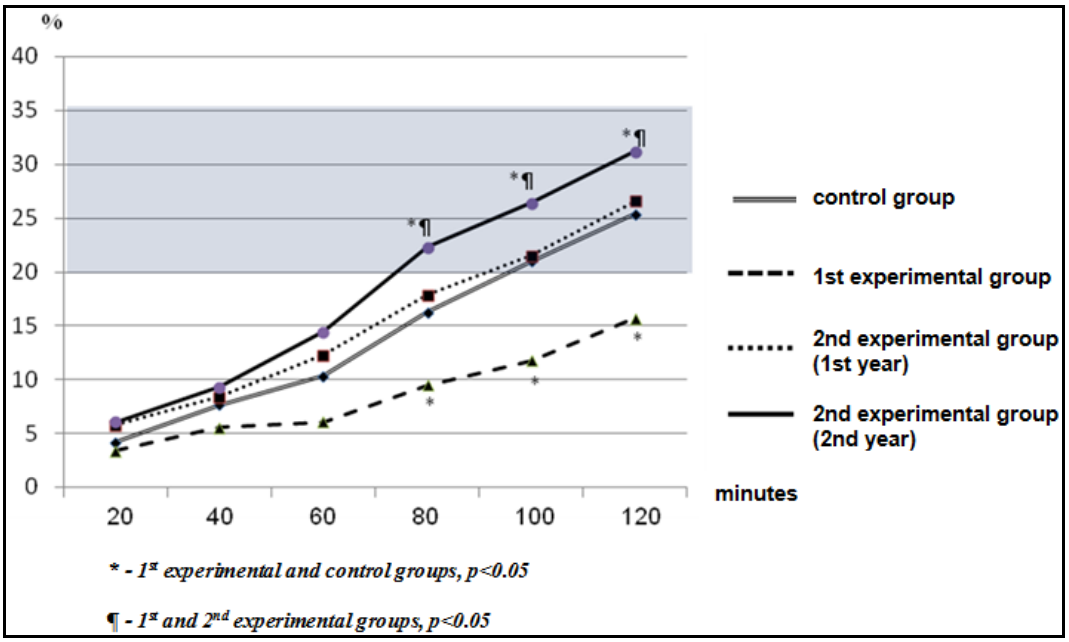

Fig 3: Classification of examined from the control and experimental groups according to the volume of cumulative dose according to the metacetine test results.

Therapy correction in the second experimental group let reach according to data of the first and the second year of observation normal values of cumulative dose in the 120th minute of the test that indicates good hepatoprotective potential of kapicor/glutargine combination. Positive action of these medications was noted also by other researchers Babak (OYA *et al.* 2013 OYA *et al.*2012 Prykhodko VYu *et al.* [2, 4, 25]. In our trial in the first experimental group cumulative dose was in the 120th min 15,7±1,6; in the second one at the end of the second year of therapy correction this indicator was in two times higher and was 31,2±1,6, p<0,05. Comparatively in the control group it was 25,4±1,3, p<0,05. It is worth to note that curves of the first and the second experimental groups (according to data as of the first, as well as for the second year of observation) started to diverge statistically reliable already from the 80th minute of the test. So in this minute cumulative dose in the patients of the first experimental group was 9,5±1,8, in the same time it was in patients of the second experimental group in the first year of observation 17,9±1,7, and after the second year 22,3±1,5, p<0,05.

4. Consequences

So it can be summarized that therapy correction with addition of kapicor/glutargine combination in individually matched doses leads to improving of clinical picture in patients with IHD complicated with permanent AF and comorbid liver damage that are on long warfarin/aspirin therapy promotes better control of heart rate and BP, labiality of blood INR indicator, improves function of the liver.

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