Is elevated HbA1c a risk factor for infection after coronary artery bypass grafting surgery?

Yüksek HbA1c koroner arter bypass greftleme cerrahisi sonrası infeksiyon için bir risk faktörü müdür?

Deniz Göksedef, Suat Nail Ömeroğlu, Emine Şeyma Denli Yalvaç, Macit Bitargil, Gökhan İpek

Department of Cardiovascular Surgery, Medicine Faculty of Cerrahpaşa University, İstanbul

Background: The effect of glycosylated hemoglobin (HbA1c) and perioperative glucose levels on short term results following coronary artery bypass grafting surgery were compared.

Methods: One hundred and fifty patients (106 males, 44 females; mean age 61.69±10.06 years; range 37 to 84 years), who underwent coronary artery bypass grafting surgery in our clinic between April 2007 and December 2008, were enrolled in this study prospectively. Every patient including non-diabetics were managed with Portland protocol in the perioperative period.

Results: Mediastinitis was observed in two patients (1.3%). Elevated HbA1c levels do not affect the short term infectious complications, however the patients who had elevated perioperative glucose levels had higher incidence (0 vs 3%, p=0.01) of mediastinitis and local sternal infection (2.3% vs 12.1%, p=0.002).

Conclusion: Poor perioperative glucose management affects and increases the rate of postoperative infections as expected but elevated HbA1c levels do not cause any risks in infectious complications following coronary artery bypass grafting surgery.

Key words: Coronary artery bypass grafting surgery; glycosylated hemoglobin; Hemoglobin A1c; infection.

Amaç: Koroner arter bypass greftleme ameliyatı sonrasında glikosilat hemoglobin (HbA1c)'nin etkileri ve ameliyat sırası glikoz seviyelerinin erken dönem sonuçları karşılaştırıldı.

Çalışma planı: Nisan 2007 - Aralık 2008 tarihleri arasında kliniğimizde koroner arter bypass greftleme ameliyatı olan 150 hasta (106 erkek 44 kadın; ort. yaş 61.69±10.06 yıl; dağılım 37-84 yıl) ileriye dönük olarak çalışmaya dahil edildi. Diyabetik olmayan hastalar da dahil her hastaya ameliyat sırası glikoz kontrolü için Portland protokolü uygulandı.

Bulgular: İki hastada mediyastenit görüldü (%1.3). Yüksek HbA1c seviyelerinin erken dönemde enfeksiyoz komplikasyonları etkilemediği görüldü, buna karşın ameliyat sırası ortalama glikoz seviyesi yüksek hastalarda mediyastenit (%0'a karşın %3, p=0.01) ve lokal sternal infeksiyonlara (%2.3'e karşın %12.1, p=0.002) daha sık rastlandı.

Sonuç: Koroner arter bypass greftleme ameliyatı sırasında yapılan yetersiz glikoz kontrolü ameliyat sonrası enfeksiyöz komplikasyon sıklığını olumsuz etkiler, ancak yüksek HbA1c seviyeleri ameliyat sonrası infeksiyon komplikasyonu için herhangi bir risk oluşturmaz.

Anahtar sözcükler: Koroner arter bypass greftleme ameliyatı; glikosilat hemoglobin; hemoglobin A1c; infeksiyon.

The incidence of diabetes is increasing markedly and the World Health Organization estimates that by 2025, 5.4% of the world population would have diabetes.[1] Patients with diabetes represent a high-risk group for early and late cardiovascular surgical morbidity and mortality. Coronary revascularization prevalance is increasing up to 38% in this group of patients.[2,3] Perioperative morbidity and mortality in patients with diabetes following coronary artery bypass grafting (CABG) is high and these results have been demonstrated in several reports compared with nondiabetic patients.[4-6]

The relationship between glucose levels and cardiovascular disease may extend below the threshold currently defined as diabetes. Impairments in glucose metabolism, manifest as hyperglycemia, are associated with poor prognosis in the general population, in the

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Correspondence: Deniz Göksedef, M.D. İstanbul Üniversitesi Cerrahpaşa Tıp Fakültesi, Kalp ve Damar Cerrahisi Anabilim Dalı, 34098 Cerrahpaşa, İstanbul, Turkey. Tel: +90 212 - 414 30 00 e-mail: denizgoksedef@yahoo.com

absence of diabetes.[7] Glycosylated hemoglobin (HbA1c), a measure of chronic hyperglycemia, is a sensitive and reliable marker of impaired glucose metabolism.[8]

Elevated glucose level is a strong risk factor for both short and long term mortality after CABG.[4-6] An interest has been increasing to evaluate HbA1c levels before and after CABG surgery as well. Although HbA1c is a function of glucose metabolism for the last 3-4 months, it is shown in some studies that HbA1c is associated with both short and long term mortality following CABG as well as glucose levels.[9-12]

In this study our aim is to compare the effect of HbA1c and perioperative glucose levels on short term results following CABG surgery.

PATIENTS AND METHODS

In this study we prospectively collected data from our CABG candidates after institutional review board approval, and obtaining informed consent from every patient. Glycosylated hemoglobin levels were studied. During the perioperative period, glucose levels were monitored with Portland protocol. In order to identify the effect of HbA1c we designed a study to choose 75 consecutive diabetic, and 75 consecutive non-diabetic patients undergoing on-pump CABG. Data were collected between April 2007 to December 2008. During the same period 254 adult patients were operated in our clinic (Table 1).

Perioperative, intraoperative and postoperative variables were prospectively collected and saved to dedicated software with two surgical residents. After that, two independent observers checked the database and corrected the errors and missing data. Groups based on HbA1c and mean perioperative glucose levels were compared to each other with the collected variables. There was no group based on diabetes.

Study endpoint

Perioperative death, within a time period of 30 days following CABG operation was the primary endpoint. In hospital mortality was defined as the death of a patient after operation before discharge regardless of 30 day.

Outcomes

The primary aim of this study was to evaluate the effect of HbA1c on short term results following CABG surgery. Synchronous variables were collected as well to use them as risk modifiers in statistical analysis in short term analysis on mortality and morbidity.

Setting

We performed the study at Cerrahpasa Hospital, Istanbul, which is a tertiary care teaching hospital of the Istanbul University Cerrahpasa School of Medicine. The hospital is a well-known diabetic care center and our diabetic patient referral was 34.7% for the last three years.

Surgical technique

Radial and pulmonary arterial catheters were introduced under local anesthesia. Following endotracheal intubation, narcotic-based anesthesia was given. Median sternotomy was performed followed by routine aortic and right atrial two-stage cannulation. Standard cardiopulmonary bypass (CPB) technique was carried out using membrane oxygenators and moderate systemic hypothermia (30 ºC). Mean arterial blood pressure was kept between 50 and 70 mmHg during CPB. Myocardial protection was achieved by antegrade and retrograde cold blood cardioplegia. Heparin was administered 3.0 mg/kg and was neutralized with protamine, in a ratio of 1:3, within 10 min. after the end of CPB.

Blood glucose management

We managed every single patient with the Portland protocol regardless of a diagnosis of diabetes.

Definitions

Mean perioperative glucose (MPG) level: All recorded fasting glucose levels, divided by the number of samples. All glucose levels were recorded as fasting and non-fasting. During the evaluation process, we excluded the non-fasting values so as not to cause any false hyperglycemic conditions. Fasting glucose measurements were done at 5:30 AM, 11:30 AM, 17:30 AM and 23:30 PM, just before the meals and snacks.

Local infection (LI): An infection that was detected in the incisions that did not require surgical intervention such as debridement, suture placement or curettage. The term local infection does not mention the site, but does mention that the wound needed a follow up and/or antibiotic. The vacuum packed patients were not evaluated as local infection.

Table 1. Patients operated between April 2007 and December 2007

Operation	n	%
Coronary artery bypass grafting	180	70.8
Emergency surgery	14	5.5
Did not participate	12	4.7
Missing value	4	1.5
Study group	150	59.0
Valve ± great vessel	22	8.6
Congenital surgery in adult	20	7.8
Valve + coronary artery bypass grafting	5	1.9
Great vessel surgery	17	6.6
Total	254	100

Non-sternal infection (NSI): An infection which required surgical intervention such as debridement, suture placement or curettage, but not involving the mediastinum and the sternal incision.

Deep sternal wound infection (DSWI): An infection which took place in the surgical site of the mediastinum, and that required an open and/or vacuum assisted follow-up, a surgical debridement and/or sternal rewiring along with antibiotic supression.

Low cardiac output syndrome (LCOS): The condition that patient needs inotropic and/or intraaortic baloon pump (IABP) support due to low cardiac index (<2.2 lt/m^2/min).

Statistical analysis

We compared baseline patient characteristics and outcome variables across treatment groups, categorical variables by using chi square or Fisher's exact tests, and continuous variables by using T-tests or Wilcoxon rank-sum tests. We considered two-sided *p* values less than 0.05 to be statistically significant. We used SPSS for Windows (SPSS Inc., Chicago, IL, USA) version 15.0 for analyses.

RESULTS

There were 150 patients enrolled in our study and 53 (35.3%) were diabetic. Thirty-five (66%) of the diabetics and 22 (22.6%) of the non-diabetics (n=97) had elevated HbA1c levels (>7%; Fig. 1). The range of the HbA1c levels were between 3.2 to 11.4 mg/dL (Fig. 1).

We evaluated 12 preoperative and 15 intra- and postoperative data. All patients had complete revascularization.

The patients were divided into two groups according to HbA1c levels higher or lower to 7.0%. The first group had HbA1c levels lower than 7% and on univariate analysis, it was found that the prevalance of peripheral vascular disease (PVD) was higher in the second group with a 26.3% to 12.9% (p=0.03). All other variables listed in table 2 had no statistical difference including infections and early mortality. We could not demonstrate any difference between the groups designed by the level of HbA1c. However, on univariate analysis according to levels of MPG, the patients who had higher MPG (>126 mg/dl), had higher body mass indexes and higher prevelance of PVD. Renal dysfunction was also higher in the hyperglycemic group. The patients had higher preoperative urea (38.4 vs 43.5 mg/dl, p=0.002) and postoperative urea (47.4 vs 51.2 mg/dl, p=0.002) as well as preoperative creatinine levels.

Postoperative infections were seen in 16 patients (10.6%; Tables 2, 3). In HbA1c groups there were no statistical differences between each group including all subsets of infection. Deep sternal wound infection was seen in two patients, one patient from each group. However, in MPG groups, there was no patient with DSWI in the normoglycemic group. Two patients (3%) had DSWI in the hyperglycemic group (p=0.01). Local infection rate was significantly higher (2.3% vs 12.1%, p=0.002) as well in the hyperglycemic group.

The cross-match data of the study population is shown in table 4. Thirty-one of the 57 elevated preoperative HbA1c patients (54%) had MPG levels greater than 126 mg/dL. This group of patients had the highest incidence of all infections (12.2%) including subsets of LI (7%), NSI (3.5%) and DSWI (1.7%). All HbA1c groups had no difference in the incidence of infections, however MPG groups had higher rates of infection regardless of HbA1c levels. Local infection incidence was significantly higher in the hyperglycemic groups regardless of the HbA1c levels (p=0.002 in both HbA1c levels). Total infection rate was higher in hyperglycemic patients, but not higher in HbA1c groups.

Six patients (4%) died in the early period (Tables 2, 3). Five of them had perioperative myocardial infarction. One patient had multiorgan failure without having any cardiac problems. Glycosylated hemoglobin groups had similar mortality rates (4.3% vs 3.5%; p=0.811). Normoglycemic patients had only one mortality (1%), but the hypergylcemic group had five deaths (7.5%; p=0.044).

DISCUSSION

The American Diabetes Association has recommended the use of blood HbA1c as a method of assessing long-term glycemic control in diabetic patients.[13] Because red cell turnover is continuous (life span 90 to 120 days), HbA1c is not affected by short-term glycemic lability, and thus allows better assessment of glucose control over a 3 to 4 month period. The American Diabetes Association currently recommends that patients with diabetes aim for a target HbA1c of less than 7%,[14] whereas HbA1c levels of 4 to 6% are considered normal. Elevated HbA1c levels

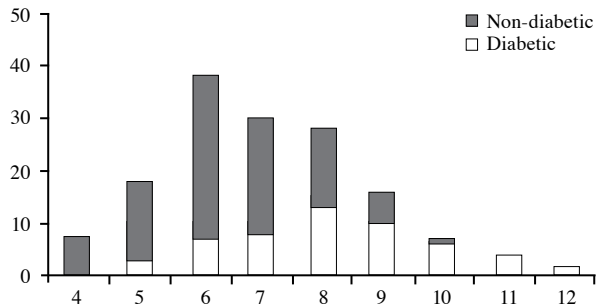

Fig. 1. HbA1c levels of the patients according to diabetic status. x-axis: HbA1c levels in percent; y-axis: Number of patients.

Table 2. Preoperative and intra-postoperative variables according to HbA1c

Risk factor	HbA1c <7.0% (n=93)			HbA1c >7.0% (n=57)			*p*
	n	%	Mean±SD	n	%	Mean±SD	
Preoperative							
Mean age	–	–	62.7±9.09	–	–	61.2±10.4	0.27
Male/female	67/26	–	–	42/15	–	–	0.491
Hypertension	42	45	–	24	42.1	–	0.715
Hyperlipidemia	24	25.8	–	18	31.5	–	0.844
Body mass index (kg/m^2)	–	–	27.6±4.5	–	–	28.0±4.6	0.834
NYHA (mean class, ±SD)	–	–	2.4±0.9	–	–	2.3±0.8	0.215
Peripheral vascular disease	12	12.9	–	15	26.3	–	0,039
Previous myocardial infarction	22	23.6	–	15	26.3	–	0.715
Left main disease	9	9.6	–	4	7.0	–	0.575
Smoking history	28	30.1	–	18	31.5	–	0.85
Preoperative urea (mg/dL)	–	–	40.5±16.5	–	–	40.7±15.3	0.75
Preoperative creatinine	–	–	1.13±0.5	–	–	1.04±0.3	0.575
Intra-postoperative							
Atrial fibrillation	19	20.4	–	15	26.3	–	0.405
Extubation time (h)	–	–	9.06±10.15	–	–	8.4±8.4	0.405
Postoperative urea (mg/dl)	–	–	49.5±21.6	–	–	48.3±17.8	0.495
Postoperative creatinine (mg/dl)	–	–	1.42±0.74	–	–	1.27±0.4	0.061
Low cardiac output syndrome	12	12.9	–	8	14	–	0.098
X-clamp time (min)	–	–	67.0±28.1	–	–	71.2±37.5	0.06
Total pump time (min)	–	–	98.4±40.5	–	–	97.3±42.8	0.657
Left internal mammary artery	87	93.5	–	54	94.7	–	0.774
Mean graft	–	–	2.8±0.9	–	–	2.9±1.0	0.143
Perioperative blood products	–	–	1.4±0.9	–	–	1.5±0.7	0.097
Discharge time (day)	–	–	6.5±6.4	–	–	6.8±6.6	0.068
Mean glucose postoperative day 0-3 (mg/dl)	–	–	125.0±17.5	–	–	129.5±16.5	0.972
Early mortality	4	4.3	–	2	3.5	–	0.811
Infection							
Local infection (see text)	6	6.4	–	4	7	–	0.06
Non-sternal infection (see text)	2	2.1	–	2	3.5	–	0.744
Deep sternal wound infection	1	1	–	1	1.7	–	0.431
Total	9	9.6	–	7	12.2	–	0.8

HbA1c: Glycosialted hemoglobine; SD: Standart deviation; NYHA: New York Heart Association.

are associated with a reduced incidence of macrovascular and microvascular complications.[15,16]

Hyperglycemia promotes intravascular formation of reactive oxygen species (ROS) capable of quenching and inactivating nitric oxide once released by the coronary endothelium.[17] Reactive oxygen species are also formed and quenched within the myocardium as reaction products of intermediary metabolism. In the presence of hyperglycemia, excess myocardial ROS may be formed via nonenzymatic glycosylation of membrane and intracellular proteins. When produced in excess of the myocardium's reducing capacity, ROS may interfere with cardiomyocyte membrane transport, mitochondrial electron transport, and nuclear transcription, potentially leading to contractile dysfunction.[18] Importantly, this mechanism may also be relevant to an apparent synergy between hypertension and diabetes in the development of heart failure. Both hypertension and diabetes are associated in animal models with reactivation of a fetal gene program which includes a shift from - to - myosin heavy chain expression and downregulation of sarcoplasmic reticulum calcium adenosine triphosphatase (ATPase) transcription, which lead to impaired systolic and diastolic ventricular function, respectively. In the hypertensive heart, activation of the renin-angiotensin system also leads to increased production of angiotensin II capable of catalyzing the formation of ROS from glucose. In patients with both hypertension and diabetes, it might then be expected that chronic exposure to hyperglycemia would accelerate the transition from compensated to decompensated hypertensive cardiomyopathy by

Table 3. Preoperative and intra-postoperative variables according to mean glucose level

	MG (<126 mg/dL) (n=84)			MG (≥126 mg/dL) (n=66)			*p*
	n	%	Mean±SD	n	%	Mean±SD	
Preoperative							
Mean age	–	–	62.4±9.7	–	–	61.8±9.5	0.599
Male/female	67/18	–	–	42/23	–	–	0.054
Hypertension	35	41.6	–	31	46.9	–	0.427
Hyperlipidemia	22	26.1	–	20	30.3	–	0.554
Body mass index (kg/m^2)	–	–	27.0±3.7	–	–	28.7±5.2	0.029
NYHA (Mean class, ±SD)	–	–	2.3±0.9	–	–	2.4±0.9	0.638
Peripheral vascular disease	10	11.9	–	17	25.7	–	0.023
Previous myocardial infarction	20	23.8	–	17	25.7	–	0.713
Left main disease	9	10.7	–	4	6.0	–	0.34
Smoking history	22	26.1	–	24	36.6	–	0.148
Preoperative urea (mg/dL)	–	–	38.4±10.0	–	–	43.5±21.2	0.002
Preoperative creatinine	–	–	1.0±0.2	–	–	1.1±0.6	0.017
Intra-postoperative							
Atrial fibrillation	16	19.0	–	18	27.2	–	0.2
Extubation time (h)	–	–	7.8±7.8	–	–	10.0±11.2	0.072
Postoperative urea (mg/dl)	–	–	47.4±16.6	–	–	51.2±24.0	0.002
Postoperative creatinine (mg/dl)	–	–	1.3±0.3	–	–	1.4±0.8	0.014
Low cardiac output syndrome	8	9.5	–	12	18.1	–	0.021
X-clamp time (min)	–	–	67.8±30.9	–	–	69.7±33.5	0.081
Total pump time (min)	–	–	97.4±39.4	–	–	98.6±43.7	0.777
Left internal mammary artery	79	94	–	61	92.9	–	0.925
Mean graft	–	–	2.8±0.9	–	–	2.9±0.9	0.634
Perioperative blood products	–	–	1.4±0.9	–	–	1.5±0.7	0.097
Discharge time (day)	–	–	6.4±6.7	–	–	6.9±6.7	0.98
MG postoperative day 0-3 (mg/dl)	–	–	113.9±8.8	–	–	143.0±10.2	0.05
Early mortality	1	1.1	–	5	7.5	–	0.044
Infection							
Local infection (see text)	2	2.3	–	8	12.1	–	0.002
Non-sternal infection (see text)	2	2.3	–	2	3	–	0.445
Deep sternal wound infection	0	N/A	–	2	3	–	0.01
Total	4	4.7	–	12	16.1	–	0.005

MG; Mean glucose; SD: Standart deviation; NYHA: New York Heart Association.

accelerating myocardial oxidative damage. Potential evidence in support of this hypothesis may be found in the observation that patients with both diabetes and hypertension exhibit greater levels of cardiomyocyte necrosis in endomyocardial biopsy samples than those with either condition alone.[19]

Coronary artery bypass grafting surgery candidates found to have an increased blood glucose concentration can have stress-related hyperglycaemia, unrecognized impairment of glucose tolerance or diagnosed diabetes when they are admitted to hospital.[20] Studies of patients undergoing CABG procedures have shown that hyperglycaemia especially in this group of patients during the immediate postoperative period is a risk factor for developing sternal wound infection in patients both with and without a history of diabetes.[21]

Previously it was shown that elevated HbA1c levels are associated with an increased risk of postoperative superficial sternal wound infections and a trend for higher mediastinitis rate as well as hyperglycemia.[9] In our study of patients we did not demostrate the relationship between local and systemic infection with the elevated levels of HbA1c. All LI, NSI and DSWI rates were similar in each HbA1c subgroups. However, there was statistically significant relationship between local and also DSWI with poor perioperative glucose as expected (0 to 3%; p=0.01). Not only the high DSWI rates in hyperglycemic patients, local infection and NSI infeciton rates were higher than normoglycemic patients. Two local infections were seen in normoglycemic patients but hyperglycemic patients had eight (2.3% vs 12.1%, p=0.002). Hyperglycemic patients had higher

Table 4. Cross table for mean perioperative glucose and HbA1c

	MPG <126			MPG≥126			*Total*			*p* (MPG)
	n	%	*p*	n	%	*p*	n	%	*p*	
HbA1c <7	58	–	–	35	–	–	93	–	–	–
Local infection	2	3.4	–	4	11.4	–	6	6.4	–	0.002
Non-sternal infection	1	1.7	–	1	2.8	–	2	2.1	–	0.744
Deep sternal wound infection	0	0	–	1	2.8	–	1	1	–	0.698
Total	3	5.1	–	6	17.1	–	9	9.6	–	0.001
HbA1c ≥7	26	–	–	31	–	–	57	–	–	–
Local infection	0	0	–	4	12.9	–	4	7	–	0.002
Non-sternal infection	1	3.8	–	1	3.2	–	2	3.5	–	0.09
Deep sternal wound infection	0	–	–	1	3.2	–	1	1.7	–	0.07
Total	1	3.9	–	6	19.3	–	7	12.2	–	0.001
Total	84	–	–	66	–	–	150	–	–	–
p (Local infection)	–	–	0.054	–	–	0.098	–	–	0.43	–
p (Non-sternal infection)	–	–	0.544	–	–	0.47	–	–	0.666	–
p (Deep sternal wound infection)	–	–	0.956	–	–	0.17	–	–	0.098	–
p (Total)	–	–	0.433	–	–	0.331	–	–	0.543	–

MPG: Mean perioperative glucose; HbA1c: Glycosilated hemoglobine.

DSWI rate as well (p=0.01). This may suggest that microvascular complications of chronic hyperglycemia and/or diabetes have little or no effect on perioperative infectious complications when strict perioperative glucose control has been applied, MPG values of both HbA1c groups have no statistical difference (125.0±17.5 mg/dL vs 129.5±16.5 mg/dL; p=0.972) as well as infectious complications.

Renal functions were also evaluated in our study. We found that there was no difference between HbA1c groups in terms of pre- and postoperative renal indexes. In the MPG group, hyperglycemic patients had elevated pre- and postoperative urea and creatinine values than normoglycemic patients. There is no good explanation and this may be due to poor glucose control in diminished kidney function or that poor glucose management may induce renal impairment. Diabetic microangiopathy is a well known risk factor for renal dysfunction. We believe that the impact of poor glycemic control on kidney disease progression has not been well studied and should be the focus of future studies.[22]

Mortality rate among our patients was 4%. There was also no difference between the patients according to their HbA1c levels. Hyperglycemic patients had higher mortality rates than normoglycemic patients (7.5% to 1.1%; p=0.044). Preoperative glucose control did not affect short term mortality in contrast to previously published literature.[9]

Perioperative hyperglycemia in patients undergoing a cardiac surgical procedure adversly alter mortality, LCOS and infection rates.[23] Furnary stated in their study that diabetes is not the risk factor itself for mortality, LCOS, and infection, it is the hyperglycemia that causes these complications following open cardiac operations. Interestingly, careful blood glucose control lowers morbidity and mortality in intensive care patients irrespective of whether they have a diagnosis of diabetes or not.[17,24]

Conclusion, our study indicates that poor glucose control just a couple of months before surgery is not a risk factor for any LI, NSI and DSWI following CABG operations. Strict glucose control with aggresive perioperative glucose management is the key for controlling infections and early mortality as well even with elevated HbA1c levels. Poor perioperative glucose management affects and increases the rate of postoperative infections as expected but elevated HbA1c levels do not cause any risks in infectious complications following CABG operations.

Limitations

We did not evalutate follow-up data for mid and long term as well as survival statistics. Our data represents a single center experience. In addition to this, although we collected data consecutively from 150 patients, this number may not reflect the effects of perioperative glucose management and HbA1c levels. Futher studies including multicenter data with more patients are needed to show the importance of HbA1c.

Declaration of conflicting interests

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