

MAŁGORZATA KOBUSIAK-PROKOPOWICZ, MARIA PREGŁOWSKA, ANDRZEJ MYSIAK

Admission Glucose Level, Left Ventricular Function and the Severity of Coronary Atherosclerosis in Patients with Acute Myocardial Infarction with and Without Diabetes

Stężenie glukozy podczas przyjęcia u chorych na zawał mięśnia sercowego a czynność lewej komory i stopień zaawansowania zmian miażdżycowych w tętnicach wieńcowych

Department of Cardiology, Wrocław Medical University, Wrocław, Poland

Abstract

Background. Prior studies have suggested that increased admission glucose is an independent predictor of both in-hospital and long-term mortality in patients with acute myocardial infarction (AMI), but the relationship between them is not well defined.

Objectives. This study was undertaken to assess the relationship between increased admission glucose in patients with ST-elevated AMI (STEMI) and left ventricular function and the degree of severity of atherosclerosis in diabetic/ impaired glucose tolerance (IGT) and non-diabetic patients with STEMI.

Material and Methods. The study group consisted of a total of 100 patients with AMI, 27 women and 73 men (aged 56–86 years), who underwent coronary angiography followed by angioplasty within 12 hours after the onset of chest pain. Plasma glucose level was measured at the time of hospital admission. Either diabetes type II or IGT were diagnosed in 52 patients – Group A. In 48 patients there was neither diabetes nor IGT – Group B. Then the patients were divided into 4 groups: Group 1 consisted of 37 diabetic/IGT patients with admission glucose level < 180 mg%; Group 2 – 15 diabetic/IGT patients with admission glucose level ≥ 180 mg%; Group 3 – 23 non-diabetic/IGT patients with admission glucose level < 140 mg%; and Group 4 – 25 non-diabetic/IGT patients with admission glucose level ≥ 140 mg%. The severity of atherosclerosis in coronary angiography and left ventricular ejection fraction (LVEF) were assessed.

Results. In Group A, anterior/anterolateral myocardial infarction were confirmed much more frequently than in Group B ($p < 0.05$). There was no difference between Groups A and B in the number of significantly narrowed coronary vessels; nor was there any significant correlation between admission glucose and the number of arteries blocked by coronary atherosclerosis in any of the groups. LVEF did not differ significantly between Groups A and B, nor was any significant correlation found between LVEF and admission glucose. Admission glucose in Group A showed a positive correlation with the patients' age ($r = 0.318$; $p < 0.005$) and gender (it was higher in men – $R = 0.415$; $p < 0.05$), while in Group B a positive correlation was found between admission glucose and BMI ($r = 0.294$; $p < 0.05$). Admission glucose in Group 3 showed a positive correlation with LVEF ($r = 0.451$; $p < 0.005$).

Conclusions. Admission glucose level in patients with STEMI does not reveal the severity of coronary atherosclerosis. Moreover, in patients with type 2 diabetes/IGT, admission glucose level does not correlate with LVEF in the early phase of myocardial infarction (*Adv Clin Exp Med* 2011, 20, 1, 57–64).

Key words: admission glucose level, diabetes, impaired glucose tolerance, ST-elevated AMI, acute coronary syndrome.

Streszczenie

Wprowadzenie. Badania analizujące zależność między podwyższonym stężeniem glukozy podczas przyjęcia do szpitala, występowaniem cukrzycy i rokowaniem przynoszą sprzeczne wyniki. Niektórzy wskazują, że zwiększona glikemia jest równorzędnym czynnikiem złego rokowania zarówno u chorych na cukrzycę, jak i z prawidłową gospodarką węglowodanową, w innych pracach podwyższona glikemia podczas przyjęcia wiązała się z gorszym rokowaniem jedynie u chorych bez uprzednio rozpoznanej cukrzycy.

Cel pracy. Ocena stężenia glukozy w surowicy podczas przyjęcia do szpitala w odniesieniu do czynności lewej komory serca oraz stopnia zaawansowania zmian miażdżycowych u chorych na zawał mięśnia sercowego z przetrwałym uniesieniem odcinka ST (STEMI).

Materiał i metody. Do badania zakwalifikowano 100 kolejno przyjętych do kliniki Kardiologii chorych z ostrym zawałem mięśnia sercowego typu STEMI w wieku 41–86 lat, w tym 27 kobiet i 73 mężczyzn. Czas trwania dolegliwości dławicowych nie przekraczał 12 godz. Bezpośrednio po przyjęciu oznaczano stężenie glukozy w surowicy. U 52 chorych rozpoznano cukrzycę typu 2 lub upośledzoną tolerancję glukozy (IGT) – grupa A. U 48 chorych nie stwierdzono zaburzeń gospodarki węglowodanowej – grupa B. Chorych, w zależności od stężenia glukozy w surowicy podczas przyjęcia, podzielono na 4 grupy: 1 grupa – 37 chorych z cukrzycą/IGT z glikemią podczas przyjęcia < 180 mg/dl; 2 grupa – 15 chorych z cukrzycą/IGT z z glikemią podczas przyjęcia ≥ 180 mg/dl; 3 grupa – 23 osoby bez cukrzycy/IGT z glikemią podczas przyjęcia < 140 mg/dl; 4 grupa – 25 osób bez cukrzycy/IGT z glikemią ≥ 140 mg/dl. Wszystkim chorym wykonywano koronarografię oraz badanie echokardiograficzne z oceną frakcji wyrzutu lewej komory (LVEF).

Wyniki. W grupie A istotnie częściej niż w grupie B stwierdzano zawał ściany przedniej/przednio-bocznej ($p < 0,05$). W grupie B istotnie częściej niż w grupie A stwierdzano zawał ściany dolnej/dolno-bocznej ($p < 0,02$). W grupie A wykazano dodatnią korelację między stężeniem glukozy podczas przyjęcia a wiekiem ($r = 0,318$; $p < 0,05$) oraz płcią męską ($R = 0,415$; $p < 0,05$). W grupie B wykazano dodatnią korelację między stężeniem glukozy podczas przyjęcia a BMI ($r = 0,294$; $p < 0,05$). Nie stwierdzono istotnej statystycznie różnicy w liczbie zmian miażdżycowych w naczyniach wieńcowych między chorymi z grupy A a chorymi z grupy B. Nie stwierdzono istotnej statystycznie różnicy LVEF między chorymi z grupy A a chorymi z grupy B ($55,3 \pm 14,3\%$ vs $56,5 \pm 10,7\%$; pNS). W grupie 3 glikemia podczas przyjęcia korelowała dodatnio z LVEF ($r = 0,451$; $p < 0,005$). W żadnej z czterech badanych grup nie wykazano korelacji między stężeniem glukozy podczas przyjęcia a liczbą tętnic wieńcowych objętych zmianami miażdżycowymi.

Wnioski. Stężenia glukozy w surowicy podczas przyjęcia chorych ze STEMI nie identyfikuje stopnia zaawansowania miażdżycy naczyń wieńcowych oraz w grupie chorych na cukrzycę typu 2/IGT nie koreluje z czynnością skurczową lewej komory w ostrej fazie zawału (*Adv Clin Exp Med* 2011, 20, 1, 57–64).

Słowa kluczowe: glikemia, stężenie glukozy w surowicy podczas przyjęcia, cukrzyca, upośledzona tolerancja glukozy, zawał mięśnia sercowego, ostry zespół wieńcowy.

According to epidemiologic studies the number of people suffering from diabetes increased worldwide to 61 million between 1994 and 2000; by 2025 it is projected to be an estimated 380 million, which constitutes 4.5% of the whole population [1]. It has been established that ischemic heart disease is the main cause of death in diabetic patients. An analysis of the Euro Heart Survey on Diabetes and the Heart shows that 31% of patients with ischemic heart disease had been diagnosed with prior diabetes, while 22% of those with acute myocardial infarction (AMI) developed diabetes de novo [2].

Studies that analyze the relationship between higher admission glucose levels, diabetes presence and prognosis have produced inconsistent results. Some researchers claim that hyperglycemia in patients with acute coronary syndromes (ACS) brings the risk of less optimistic prognostic estimates of survival for both diabetic and non-diabetic patients. In other studies an increased admission glucose level is associated with less optimistic prognoses only for patients without prior diabetes [3, 4]. Lavi et al. have shown that within a group of 431 patients the risk of mortality was not due to diabetes, but to glucose level at admission. In-hospital and annual mortality was higher in non-diabetic patients with glucose levels > 126 mg/dl. Elevated plasma glucose of 1 mg/dl resulted in a 0.6% higher risk of death and a 2% higher risk that the subject

would need revascularization within one year [5]. The negative influence of hyperglycemia on the risk of death in patients with prior infarction, regardless of the presence of diabetes, has also been confirmed in studies by Dirkali et al. [6]. Gąsior et al. claim that every 18 mg/dl increase in admission glucose level increases the risk of mortality by about 6% in the course of annual observation [7].

Some scientific investigations emphasize that a 30-day prognosis (including in-hospital short-term prognosis) does not have much impact on long-term prognosis [8]. Observations by Ishihara et al. found that both diabetes as well as an increased admission glucose level (regardless of the presence of diabetes) significantly influence the risk of death in various time intervals. Admission glycemia ≥ 200 mg/dl increases the risk of death within a 30-day observation period, while diabetes substantially influences mortality in a three-year observation period [9]. Thus, during three years of observation the importance of the admission glucose level was less significant than diabetes [9]. The authors suggested that a high glucose level at admission in patients with and without diabetes should be perceived as two distinct sets of syndromes [9].

A high glucose level can impair micro-vessel coronary circulation, which results in more serious myocardial injury and worsening of systolic function [10, 11]. In several studies it has already been indicated that exposure to hyperglycemia or diabe-

tes protects the heart against ischemia and hypoxia [12, 13]. The influence of regulation of antiapoptotic factor Bcl-2 or inactivation of proapoptotic factor Bad has been discussed in an attempt to explain the cardioprotective effect of hyperglycemia [12, 14]. Nevertheless, the protective influence of hyperglycemia on ischemic heart disease and its functioning remains unexplained.

The aim of the study was to assess left ventricular function and the severity of coronary atherosclerosis in patients with acute myocardial infarction with persistent ST-segment elevation (STEMI) in relation to admission serum glucose levels.

Material and Methods

The study involved 100 patients with acute myocardial infarction with persistent ST-segment elevation (average age: 62.5 ± 11.6 years), including 27 females aged 49–81 (average age: 69.26 ± 9.5) and 73 males aged 41–86 (average age: 60.0 ± 11.3), admitted to Wrocław Medical University's Cardiology Department. The duration of their angina pectoris symptoms did not exceed 12 hours. The patients' profiles are presented in Tables 1–2.

A 12-lead electrocardiograph was performed along with a Troponin I (Tnl) test to diagnose myocardial infarction. Myocardial infarction with persistent ST-segment elevation (STEMI) was di-

Table 1. Patients' overall profile

Tabela 1. Charakterystyka badanych chorych

	Patients (Pacjenci) (n = 100)
Admission glucose level (Glikemia przy przyjęciu) mg/dl	163.24 ± 63.2
EF %	55.85 ± 12.7
BMI - kg/m ²	27.92 ± 4.2
Infarction zone (Umiejscowienie zawału) anterior, anterolateral, n (%) (przedni, przedsionkowy) inferior, inferolateral, n (%) (dolny, dolno-boczny)	36 (36) 64 (64)
Atherosclerotic changes (Liczba zmian miażdżycowych) 1, n (%) 2, n (%) 3, n (%)	43 (43) 21 (21) 36 (36)
Type 2 diabetes, n (%) (Cukrzyca typu 2)	36 (36)
IGT, n (%)	16 (16)

agnosed in accordance with the standards of the European Society of Cardiology [15].

Patients with severe cardiac insufficiency requiring intravenous infusion of inotropic drugs, those with stage 4 or 5 renal failure, those with

Table 2. Diabetic and non-diabetic patients' profiles

Tabela 2. Charakterystyka chorych na cukrzycę i bez cukrzycy

	Group A Diabetic/IGT (Grupa A - cukrzyca/IGT)	Group B Non-diabetic/IGT (Grupa B - bez cukrzycy/IG)	Significance of differences (Istotność różnic)		
Admission glucose level (Glikemia przy przyjęciu) mg/dl	165.1 ± 59.8	155.2 ± 54.2	n.s.		
EF %	55.3 ± 14.4	56.5 ± 10.8	n.s.		
	Group 1	Group 2	Group 3	Group 4	
	55.3 ± 14.6	55.2 ± 14.4	57.5 ± 9.7	55.5 ± 11.9	n.s.
BMI - kg/m ²	28.2 ± 4.7		27.6 ± 3.7		n.s.
	Group 1	Group 2	Group 3	Group 4	
	28.2 ± 4.4	28.3 ± 5.7	26.9 ± 3.4	28.1 ± 3.9	n.s.
Infarction zone (Umiejscowienie zawału) anterior, anterolateral, n (%) (przedni, przedsionkowy) inferior, inferolateral, n (%) (dolny, dolno-boczny)	24 (46.2) 28 (53.8)		12 (25.0) 36 (75.0)		0.02 0,02
Atherosclerotic changes (Liczba zmian miażdżycowych) 1, n (%) 2, n (%) 3, n (%)	20 (38.5) 10 (19.2) 22 (42.3)		23 (47.9) 11 (22.9) 14 (29.2)		n.s. n.s. n.s.

systemic diseases of connective tissue, those with neoplasms, those who were undergoing either immunosuppressive or steroid treatment, and those with extremely elevated glycemia (> 400 mg/dl) were excluded from the study.

Type 2 diabetes and impaired glucose tolerance (IGT) were recognized on the basis of medical history: a prior diagnosis of type 2 diabetes or IGT and use of oral antidiabetic drugs and/or insulin. A diagnosis of either type 2 diabetes or IGT de novo was based on the standards of the Polish Diabetes Association [5]. The study also excluded the patients whose case history or observed glycemia level during hospitalization prevented an unambiguous diagnosis of type 2 diabetes/IGT or an absence of carbohydrate metabolism disorders.

The study was accepted by the appropriate Bioethical Committee. The subjects gave written informed consent before entering the study, in accordance with the recommendations of the Bioethical Committee, acting on the rules of Good Clinical Practice and the Helsinki Declaration.

Immediately after admission each patient's serum glucose concentration was checked after taking blood from the basilic vein as a standard procedure. All patients underwent coronography and then primary angioplasty in acute myocardial infarct with a stent. In the coronography narrowing of the left main coronary artery by $\geq 50\%$, and narrowing of the right coronary artery and the left coronary artery branches by $\geq 70\%$ were considered significant.

On admission all patients were given 300 mg of acetylsalicylic acid, and either 300 or 600 mg of clopidogrel orally, provided that neither of these drugs had been previously given by the ambulance personnel. During invasive procedures patients were given a 5000 IU dose of unfractionated intravenous heparin. During the initial 48 in-hospital hours patients underwent treatment in the Intensive Cardiac Care Unit. During the 24-hour period following admission, a beta-adrenolytic drug, ACE inhibitor and statin were introduced to the therapy unless there were contraindications for their implementation.

Within 48 hours of admission all patients underwent echocardiography using a Vingmed System 5 (General Electric) with a head signaling frequency of 2.5 MHz. The left ventricular ejection fraction was determined using the standard formula $EF = (LVEDV - LVESV)/LVEDV \times 100\%$. Both LVEDV and LVESV were assessed using the biplane Simpson's method, during which a computer determines the approximate volume of the left ventricle.

Study groups were established on the basis of the criteria described. Group A consisted of 52 pa-

tients, aged 41 to 86, diagnosed with diabetes type 2 or impaired glucose tolerance (IGT). Group B consisted of 48 patients, aged 42 to 81, who did not show any symptoms of carbohydrate metabolism disorders.

The patients were stratified into four groups according to diabetes type 2/IGT and admission glycemia level:

Group 1: 37 patients diagnosed with diabetes type 2/IGT, aged 44 to 79 (average age: 62.1), admission glucose < 180 mg/dl;

Group 2: 15 patients diagnosed with diabetes type 2/IGT, aged 41–86 (average age: 70.5), admission glucose ≥ 180 mg/dl;

Group 3: 23 patients without diabetes type 2/IGT, aged 42–81 (average age: 60.6), admission glucose < 140 mg/dl;

Group 4: 25 patients without diabetes type 2/IGT, aged 43–80 (average age: 60.4), admission glucose ≥ 140 mg/dl;

Statistical Analysis

Statistical evaluation was performed using Statistica 5.0 PL software. The statistical analysis of selected parameters was carried out on the basis of the mean values of the determined variables and their standard deviations. In order to confirm normal distribution of data, the distribution of variables was investigated using the Shapiro-Wilks test. With samples that met this criterion, a further analysis was carried out using Student's *t*-test for paired and unpaired samples. With samples that did not display normal data distribution, the differences in distribution were investigated using the non-parametric *U* Mann-Whitney test. In order to evaluate the statistical significance of the qualitative changes, the highest reliability χ^2 test with Yates' modification and exact Fisher test were used. The correlation between the investigated variables was assessed, determining Pearson's linear correlation coefficient (Pearson's *r*) as well as using non-parametric correlation (Spearman's *r*). Differences were considered significant at $p < 0.05$.

Results

The results are presented in Tables 3–4.

Anterior/anterolateral myocardial infarction was found significantly more often among patients with diagnosed diabetes type 2/IGT (Group A) than in the non-diabetic Group B ($p = 0.02$). Similarly, inferior/inferolateral myocardial infarction was found significantly more often among B group subjects ($p = 0.02$).

Table 3. BMI, age and gender correlation in relation to admission glucose levels stratified into Groups A and B**Tabela 3.** Korelacja BMI, wieku i płci ze stężeniem glukozy chorych w grupach A i B

	Group A (Grupa A)		Group B (Grupa B)	
	Pearson's correlation	significance of differences	Pearson's correlation	significance of differences
BMI	r = 0.037	p n.s.	r = 0.294	p = 0.04
Age (Wiek)	r = 0.318	p = 0.02	r = 0.014	p n.s.
	Spearman's correlation	significance of differences	Spearman's correlation	significance of differences
Male gender (Płeć męska)	r = 0.415	p = 0.02	r = 0.049	p n.s.

Table 4. Correlation between LVEF and atherosclerotic changes in patients and admission glucose level, stratified into Groups 1 to 4**Tabela 4.** Ocena frakcji wyrzutowej i liczby i zmian miażdżycowych u chorych w odniesieniu do glikemii podczas przyjęcia w grupach 1–4

	Group 1 (Grupa 1)	Group 2 (Grupa 2)	Group 3 (Grupa 3)	Group 4 (Grupa 4)
	significance of differences	significance of differences	significance of differences	significance of differences
EF	n.s.	n.s.	r = 0.451 p = 0.003	n.s.
Atherosclerotic changes (Liczba zmian miażdżycowych)	NS	NS	NS	NS

Within Group A, a positive correlation between admission glucose level and age was shown ($r = 0.318$; $p = 0.02$). Furthermore, a positive correlation between the male sex and admission glucose level ($r = 0.415$; $p = 0.02$) was found. In Group B, a positive correlation was found between admission glucose level and BMI ($r = 0.294$; $p = 0.04$). No significant difference between Groups A and B was observed in the number of atherosclerotic changes in coronary arteries, nor was there a significant statistically EF difference between Groups A and B.

In Group 3, admission glucose levels showed a positive correlation with LVEF ($r = 0.451$; $p = 0.003$). None of the four groups in the study showed a correlation between admission glucose level and the number of coronary atherosclerotic arteries.

Discussion

High glucose concentration at admission may be an independent factor for an unfavorable prognosis in patients with myocardial infarction [3, 16]. However, despite strict regulations about procedures connected with patients suffering from substantially high glycemia during AMI, an increased glucose level in serum is not treated as an independent risk factor either in the risk range

resulting from the In Time II trial or the Morrow-Antman scale created on basis of In Time II [17]. In spite of the acknowledged advantages resulting from the use of insulin during AMI, no precise desired glycemia level, nor any tactics for glycemia optimization in patients with ACS, have been determined yet [18, 19].

Some previous investigations showed that patients with hyperglycemia had multi-vessel coronary artery disease and – more frequently – vessel reocclusion after angioplasty. In their research, Macin et al. analyzed the influence of glycemia levels on the risk of death in 565 patients with ACS [20]. The patients were divided into two groups with a quantified admission glycemia level of 128 mg/dl as the cutoff point. Those authors stated that glycemia levels over 128 mg/dl would mean death within a year of observation at a sensitivity of 85% and specificity of 62%. In addition, it was shown that the group of patients with glycemia levels over 128 mg/dl was at a three times higher risk of death in the long-term observation period [20]. While all the clinical and epidemiology data collected shows a negative influence of hyperglycemia, the data gathered during experimental research is controversial, and displays that animals with induced diabetes have significantly increased resistance to ischemic injury [21]. According to Malfitano et al., hyperglycemia within a group of rats with diabetes

decreased the risk of myocardial infarcted zone by 36%, improved the ejection fraction, lowered pro-inflammatory cytokines and apoptosis activation, and increased cell survival factor concentration, estimated 15 days after an induced infarction [22].

The aim of the current study was to assess admission glycemia levels in relation to left ventricle function and the severity of coronary atherosclerosis. In patients with type 2 diabetes/IGT, no correlation was found between admission glycemia level and the number of coronary arteries influenced by atherosclerotic changes. In terms of the initial fall in contractility reflecting myocardial injury, there were no significant differences between the groups with and without type 2 diabetes/IGT. A lack of correlation between the size of the infarcted zone and admission glycemia levels in patients with diabetes was also confirmed by O'Sullivan et al., who analyzed the size of the infarcted zone on the basis of maximum troponin level in serum [8].

The current study is one of a number of research studies illustrating the potentially protective impact of hyperglycemia on myocardial injury in the course of myocardial infarction. Patients with carbohydrate disorders probably experience a sort of preconditioning along with the glycemia level changes that occur during their normal lives which results in a greater resilience to glucose level changes than non-diabetic patients have [23]. This has been also confirmed by the Japanese authors who compared ejection fraction (EF) changes in patients during acute myocardial infarction and prior to hospital discharge. Although the level of EF was initially the lowest among patients with carbohydrate metabolism disturbances, the reduction in its level during hospitalization was significantly lower in those patients than in non-diabetic patients. This indicates that patients with diabetes adjust better to changes in carbohydrate metabolism [24]. Similar conclusions were drawn by Stolker et al., who investigated the influence of admission glycemia levels on the presence of contrast-induced nephropathy. Among non-diabetic patients the risk of nephropathy increased significantly along with glycemia levels, while among diabetic patients no such correlation was revealed [25].

The current study also indicates that in patients without carbohydrate metabolism disturbances and with a normal admission glycemia level, glu-

cose concentration showed a positive correlation with EF. This creates one more aspect requiring further investigation; it may be a coincidence, but may also highlight the significance of the glucose delivery mechanism. King and Opie showed that glycolysis is advantageous for an ischemic heart, maintaining cellular membrane function, moderating arrhythmia and improving functional recovery [26].

In earlier studies it was demonstrated that glucose delivery played an important cardioprotective role in the myocardium's reaction to ischemia [27]. The key element to the improvement of myocardium function could be increased up-regulation of GLUT-1, which allows better glucose delivery in ischemia.

In conclusion it is worth mentioning some American researchers who suggested a cutoff point for hyperglycemia at admission in patients with myocardial infarction, and placed glycemia levels in the category of a continuous variable [28]. In a group of non-diabetic patients, an admission glycemia level over 110 mg/dl was connected with an increase in the 30-day mortality rate, while in a group of diabetic patients an increase in short-term mortality was observed only among those patients who presented with glycemia levels over 240 mg/dl. Annual mortality rates in the study were comparable [28], which is astonishing in the context of previously cited investigations. In their analysis those authors considered whether hyperglycemia creates a cause-and-effect element of unfavorable prognostic estimates in patients with myocardial infarction, or is merely a coincidental phenomenon. Nevertheless, the controversies surrounding hyperglycemia and the inability to determine a correlation between glycemia level, diabetes and prognosis indicate a need for further study.

Study Limitations

The relatively small group of patients limited our investigation, although in terms of both diagnostic and therapeutic aspects, the population studied was highly homogeneous.

The authors concluded that admission glucose level in patients with STEMI does not reveal the severity of coronary atherosclerosis; nor does it correlate with LVEF in the early phase of myocardial infarction in patients with type 2 diabetes/IGT.

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Address for correspondence:

Małgorzata Kobusiak-Prokopowicz
Department of Cardiology
Wroclaw Medical University
Pasteura 4
50-367 Wrocław
Poland
Tel.: +48 71 784 26 11, +48 71 784 26 12
E-mail: kobusiak@poczta.fm

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