Original paper

Prognosis and long-term observation of a group of patients with acute coronary syndromes without ST-elevation (ACS-NSTEMI)

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Abstract

Introduction: The clinical assessment of patients with unstable angina is based not only on clinical symptoms, but also on concomitant diseases. The aim of this study was to investigate the adverse outcome in patients receiving successful treatment and discharged from the hospital.

Material and methods: The study group consisted of 53 consecutive patients after an incident of unstable angina (62±11 years, 29 men, 55%), among whom 17 patients were diabetics (32%). On admission, 61 clinical, electrocardiographic, echocardiographic, angiographic and laboratory factors were taken into consideration. We analysed the frequency of recurrent myocardial infarctions, recurrent ischaemia, the need for revascularisation and deaths during the follow-up of 23±2 months.

Results: The mortality rate was 9% and in 38% patients none of the above complications occurred. A univariate analysis revealed that age (p=0.005), diabetes mellitus (p=0.017), wall motion abnormalities in echocardiography (p=0.02), ST segment depressions on admission ECG (p=0.033), male gender (p=0.036) and the pattern of the mitral inflow (p=0.047) were predictors for adverse events. A multivariate analysis showed diabetes mellitus to be the strongest independent predictor of complicated outcomes (OR=9; p=0.008) beside a filling pattern of the mitral inflow (OR=1.9; p=0.03). The left ventricular end-diastolic diameter (p=0.016) was the only independent predictor of death.

Conclusions: Diabetes is the strongest prognostic factor in patients after incidents of unstable angina. Therefore, such patients should be considered for more extensive medical care.

Key words: arterial hypertension, hyperlipidaemia, diabetes mellitus, obesity.

Introduction

During the last years we have become witnesses to a considerable progress in exploring and comprehending the pathophysiological mechanisms of acute coronary syndromes (ACS). The most important consequence of that is a metabolic and oxygen imbalance of the heart muscle, which is a result of plaque rupture. The event is the elementary one in ACS. Additionally, it is concomitant with proembolic and peripheral microembolisation processes. The most important processes determining ACS occurrence include an imbalance of plaque and an overbalance of thrombotic factors, which increases the risk of formation of emboli on the eroding plaque. Both these reactions are strictly interconnected with each other.

An angioplasty procedure on unstable plaque with a growing embolus on its surface seems to be connected with a high risk of occurrence of early

AMS

and late complications. Therefore, some authors point out that the optimal strategy of treatment should be: "watchful waiting", especially in a group of patients in whom pharmacological treatment was applied before their admission to the Department of Cardiology with a haemodynamic laboratory. There are many methods of stratification in patients with ACS without ST-segment-elevation. Most of them are based on three groups of parameters, i.e. clinical gauging, new alterations in the ECG trace and biochemical parameters. Although the theoretical value of these methods is well established, their practical value is not so clear, especially without the context of cardiovascular stratification. An attempt at connecting knowledge and clinical practice was presented in the ACC/AHA guidelines published in 2002. Consequently, unstable patients can be divided into groups of high, intermediate and low risk of death or myocardial infarction [1]. During the last years, a completely new classification has been used in the bedside assessment of such patients, i.e. the "TIMI risk score", derived from the data of 7081 patients – participants of two multicentre, randomised trials [2, 3]. A very important factor in patients with unstable angina is a good stratification of risk due not only to cardiological, but also demographic and general medical data.

In the currently used ESC guidelines, the following parameters must be taken into consideration [4]:
1. The parameters of acute risk: recurrence of chest pain, depressions of ST-segment in ECG or its dynamic changes, high levels of cardiac troponins and an embolus in the coronary artery.
2. The parameters of postponed risk:
• **clinical:** age, history of myocardial infarction, CABG, diabetes mellitus, heart failure or arterial hypertension,
• **biological:** renal insufficiency (creatinine concentration or clearance), markers of inflammatory processes (CRP, fibrinogen, IL-6),
• **angiographic data:** left ventricular dysfunction and coronary artery changes.

In the present paper all the above parameters were taken into consideration, as well as those which had an important connection with the risk of complications in a long-term observation after the discharge.

The aim of the study was to assess the frequency of occurrence of complications in patients with ACS without ST-segment-elevation, in whom clinical stabilisation was attained during the hospitalisation period.

Material and methods

The study group

The study group consisted of 53 consecutive patients admitted to II Chair and Department of Cardiology, Medical University in Lodz in 2001, with a diagnosed acute coronary syndrome without ST-

segment-elevation. The average age of the study group was 62±11 years (55% men); arterial hypertension was present in 66% of cases; diabetes mellitus in 32%; 32% of them were obese; the frequency of tobacco abuse was 13% and the family history of heart diseases was present in 6% of patients.

The following inclusion criteria were adopted:
• prolonged substernal pain not subsiding after nitroglycerin
• no elevation of ST-segment in the ECG tracing
• no recent LBBB

There following exclusion criteria were adopted:
• haemodynamically important valve defects, primary cardiomyopathies
• hepatic or renal failure
• other diseases which could jeopardise survival.

Treatment

In all patients the treatment was accordant with the current guidelines of the Polish Cardiac Society (acetylsalicylic acid, heparin, nitrates and betaadrenolitics were applied). In 32 (62%) patients coronarography was performed. It was in these patients in whom symptoms persisted and ECG relief was not observed despite pharmacological treatment. In 26% of patients at least one critical coronary artery stenosis was observed (min. 70% stenosis). An angioplasty procedure was performed in 31% of cases (in 8% – with stent implantation, in 6% – infusion of Gp IIbIIIa inhibitors was applied). Only one patient had no evidence of artery plaques in coronary arteries and in two patients no progression of the sclerotic process in coronary arteries was observed. In all those cases a very good early result of the procedures was achieved (TIMI 3 flow).

Clinical assessment

We analysed 61 clinical, laboratory, electrocardiographic and echocardiographic parameters. Among electrocardiographic ones the following were assessed: ST-segment depressions over 1 mV, T-wave inversion and/or new pathologic Q-wave and bundle brunch blocks.

In echocardiographic analysis we examined: intraventricular septum diameter, left ventricular ejection fraction, end-diastolic left ventricular diameter, mitral inflow pattern, E/A ratio, localisation of wall motion abnormalities and regurgitations.

The lipids profile, creatinine kinase and its MB fraction, troponin T level at admission and after 12 hours were also assessed. We also calculated the CK/CK-MB ratio.

Assessment of late complications

All patients were supervised in our Cardiological Outpatient Clinic. During an average observation period of 2 years (23±2 months), the occurrence of
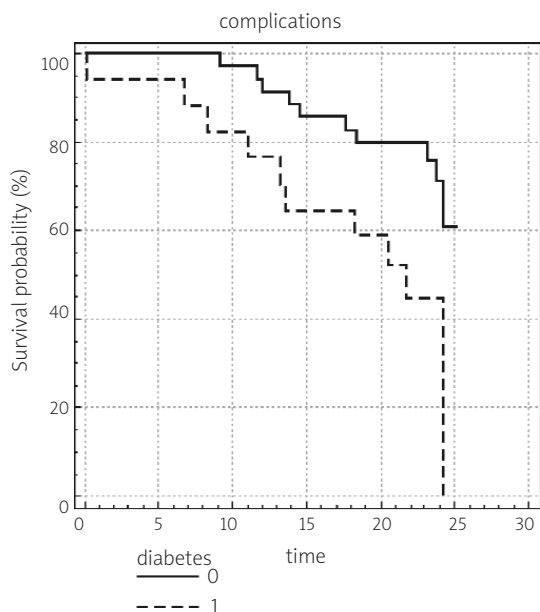
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Figure 1. Probability of an event-free survival (myocardial infarction, new hospitalisation due to cardiological reasons, new cardiac revascularisations, deaths) in Kaplan-Meier survival curves in groups of patients with and without diabetes

the following complications was assessed: myocardial infarctions, re-hospitalisations due to cardiological reasons, frequency of repeated cardiac revascularisations and deaths.

Statistical methods

All the data were assessed by uni- and mulitivariate stepwise logistic regression in Medcalc file 7.01 (Frank Schonjans, 2003) with a statistical significance at p<0.05.

Results

During the whole observation period five (9%) patients died, whereas twenty (38%) developed at least one of the complications assessed, i.e. myocardial infarctions, the need for re-hospitalisation due to cardiological reasons, repeated revascularisations and death. The frequency of the last complication in the group of patients with diabetes was 19% vs. 5.5% compared with the group without the disease (a strong statistical trend was observed; p=0.088; HR=0.29 calculated by means of the Kaplan-Meier method) and the frequency of any of the above complications was: 62.5 vs. 28% (p=0.018; HR=0.34 calculated from Kaplan-Meier) (Figure 1).

A univariate analysis of all the 61 parameters showed that the following ones had a statistical significance: diabetes (OR=0.33; p=0.017), age (OR=0.005; p=0.005), presence of ST-segment depressions on the ECG trace (OR=0.17; p=0.033) (Table I); male age (OR=0,094; p=0,036) (Table II); and any mitral inflow pattern abnormalities (i.e. <1.0 or >1.5) (OR=0.4; p=0.047) (Table III).

A multivariate predictive model obtained from the logistic regression model assessed the following parameters: clinical, biochemical, electrocardiographic and haemodynamic ones. The most important of them was diabetes (OR=0.11; p=0.008) (Table IV).

A positive correlation between CK and CK-MB levels and total mortality was observed. The maximum levels of CK correlated well with mortality at p value of 0.03 and CK-MB at 0.009; during the 2-year observation period (Table II).

The average CK-MB to CK ratio was 0.26. There was no difference among values of that parameter among the whole study group in terms of complications and the death rate. Nor did troponin T levels influence the uneventful outcome in long-term observation (p>0.05).

There was no correlation between the method of treatment and a complicated outcome in the study group.

Parameters significant for death frequency, obtained by means of the univariate analysis are shown in Tables I-III, whereas the only parameter that was significant for the occurrence of that event according to the multivariate logistic regression analysis was the end-diastolic left ventricular diameter (p=0.0016).

Discussion

According to the current Polish Society of Cardiology guidelines, acute coronary syndromes are

Table I. Electrocardiographic data of the study group

Parameter	Complications (-) n=33	Complications (+) n=20	p	Death (-) n=48	Death (+) n=5	p
ST depressions	25%	50%	0.033	34%	40%	0.39
T-wave inversion	59%	35%	0.045	53%	50%	0.08
Pathologic Q	37%	2%	0.095	27%	60%	0.07
RBBB	3%	5%	0.36	2%	14%	0.024
FA	9%	15%	0.27	10%	20%	0.27

RBBB – right bundle brunch block; FA – atrial fibrillation

Table II. Demographic and laboratory analysis of the study group in the context of complications and death occurrence in 12-month observation

Parameter	Complications (-) n=33	Complications (+) n=20	p	Death (-) n=48	Death (+) n=5	p
Male gender	21 (39.6%)	8 (15%)	0.036	25 (47%)	4 (7.5%)	0,129
Age	58.8±10.39	66.8±10.68	0.005	61.7±11.2	63.8±10.6	0,34
Diabetes	6 (11.3%)	10 (18.9%)	0.017	3 (5.6%)	14 (26.4%)	0,088
Duration of hospitalisation	6.6±4	6.7±4	0.46	6.6±6.6	4.1±3.3	0,49
HA	32 (60%)	20 (37.8%)	0.37	47 (88.7%)	5 (9.4%)	0,22
NYHA class	1.4±0.7	1.35±0.7	0.39	1.34±0.7	1.8±1.1	0,096
Hyperchole-sterolaemia	204.2±40.5	204.2±45.3	0.49	203.8±39.1	207.7±71.6	0,42
HDL	37±10	40±9	0.23	38±103 8±10	36±8	0,35
TG	200±104	165±90	0.12	185±98 185±98	219±135	0,25
CK first	208±334	407±1016	0.17	302±738 302±738	195±127	0,37
CK max	245±346	649±1348	0.07	326±739	1114±1806	0,033
CK-MB first	31±40	53±80	0.11	41±63	39±22	0,48
CK-MB max	37±42	84±147	0.065	44±64	156±249	0,009

HA – hypertensio arterialis; NYHA class – class of the NYHA scale; HDL – HDL-cholesterol concentration; TG – triglycerides concentration; CK first – the first measure of creatinine kinase; CK max – the maximum level of creatinine kinase; CK-MB first – the first measure of creatinine kinase-fraction MB; CK-MB max – the maximum level of creatinine kinase-fraction MB

Table III. Echocardiographic data of the study group

Parameter	Complications (-) n=33	Complications (+) n=20	p	Death (-) n=48	Death (+) n=5	p
LVD (mm)	47.8±3.7	48.8±7	0.25	47.1±4.0	57.6±4.0	<0.0001
LVS (mm)	35.2±4.3	35.8±6.7	0.44	34.5±4.6	42.6±6.5	0.0004
EF (%)	48%	50%	0.2	50%	42%	0.041
RV (mm)	22.5±2.0	22.5±1.8	0.48	22.4±1.9	23.2±1.1	0.196
LA (mm)	38.4±5.5	39.3±5	0.3	38.3±5.3	42.6±3.7	0.043
E/A	0.7±0.3	0.9±0.6	0.047	0.7±0.3	1.6±1.2	0.00025
Anterior WMA	32%	26%	NS	26%	60%	NS
Lateral WMA	38%	42%	NS	37%	60%	NS
Inferior WMA	67%	63%	NS	60%	55%	NS
Posterior WMA	41%	36%	NS	33%	10%	0.051
Septum WMA	48%	52%	NS	48%	60%	NS
Apex WMA	35%	36%	NS	31%	80%	NS

NS – statistical nonsignificance; LVD – left ventricular end-diastolic diameter; LVS – left ventricular end-systolic diameter; EF – ejection fraction; RV – right ventricular diameter; LA – left atrium; E/A – E/A parameter; anterior WMA – anterior wall motion abnormalities; lateral WMA – lateral wall motion abnormalities; inferior WMA – inferior wall motion abnormalities; posterior WMA – posterior wall motion abnormalities; septum WMA – septum wall motion abnormalities; apex WMA – apex wall motion abnormalities

heterogeneous and are caused by many target factors, which is always associated with an exacerbation of ischaemic heart disease and may have a direct influence on myocardial infarction occurrence and sudden death.

The hitherto existing division of acute coronary syndromes which was based on the criteria of time and degree of symptoms became invalid due to the latest data [5]. Also, the classification of acute coronary syndromes, dividing them into non-Q-, Q-wave

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Table IV. Parameters of statistical significance after multifactor analysis

Parameter	Or	p
LVD (mm)	0.57	0.013
Posterior WMA	2.76	0.051
Lateral WMA	0.082	0.045
DM	2.2	0.008
E/A	4.91	0.03

LVD – left ventricular end-diastolic diameter; posterior WMA – posterior wall motion abnormalities; lateral WMA –lateral wall motion abnormalities; E/A – -E/A parameter

myocardial infarctions and sudden cardiac deaths, seems to be only of historical value nowadays.

Until the time of putting a new division into force, many terms existed, such as acute coronary syndrome, acute coronary status, acute coronary insufficiency, acute ischaemic events, acute coronary events, and it was not clear which of those terms were synonymous [6].

A contemporary definition of acute coronary syndromes mentions:
1) myocardial infarction,
2) unstable angina,
3) sudden cardiac death.
In clinical practice, there are two groups of patients:
1) with acute coronary syndrome with ST-segment elevation,
2) with acute coronary syndrome without ST-segment elevation.

Thanks to the increasing number of novel therapeutic methods – coronary angioplasty and modern drugs (inhibitors of platelets Gp IIbIIIa receptors) – the prognosis in patients with unstable angina has improved. The world trend of treating acute coronary syndromes by angioplasty caused evidently an increase in the number of coronary angioplasty procedures in our country (according to the data from the year 2002, as many as 83,000 coronarographies and 32,000 angioplasty procedures were performed).

The issue seems to be important due to the fact that in the majority of patients admitted to cardiology departments with acute chest pain, ST-segment elevation in ECG is absent.

If the above phenomenon coexists with an increase in cardiac markers, the diagnosis of acute coronary syndrome without ST-segment elevation is proposed [7]. In Poland, these figures are about 1 million patients with ischaemic heart disease and about 1 hundred with recently diagnosed myocardial infarction [8]. The prognosis in patients with acute coronary syndromes is based not only on their clinical status at admission, but also on concomitant diseases. The presence of arterial hypertension, hypercholesterolemia, obesity and diabetes clearly worsens it. The concomitance of each of the above factors increases the risk of complications in connection with percutaneous and surgical procedures [9].

According to the latest guidelines of the Polish Society of Cardiology, patients at high risk are those with pain whose duration exceeds 20 minutes, evidence of pulmonary haemostasis, hypotension, new or increasing mitral insufficiency murmur, ST-segment changes, T-wave changes, new pathologic Q-waves, angina symptoms in III or IV CCS class and an age of over 65 years [10-12]. Despite that, there are still many problems in estimating the prognosis in those patients, mainly due to a wide spectrum of clinical symptoms, other test results and a variety of concomitant diseases.

The new scale of complications after ACS mentioned in the introduction – the "TIMI risk score" – analysed the following parameters: age, risk factors of ischaemic heart disease, at least 50% coronary stenosis, administration of aspirin during the previous 7 days, currently diagnosed severe angina, ST-elevations over 0.5 mm and elevated cardiac markers levels. The presence of each of the above parameters is equal to 1 point of that scale (range 0-7). The risk of death, myocardial infarction and the need for emergency coronary revascularisation during 14 days was: 40.9% – in patients with 6-7 points; 26.2% – 5 points; 19.9% – 4 points; 13.2% – 3 points; 8.3% – 2 and 4.7% – 0-1 points [13-17]. However, its prognostic value can be applied only in the first two weeks after the incident of acute ischaemia.

Most complications which occur after acute coronary syndrome take place after discharge (57% during 8 months) [18]. Only 1/3 among them occurs during the hospitalisation period. Therefore, defining the group of patients at a particularly high risk of complications is important.

Among the risk factors under consideration diabetes is especially significant, because the proportion of patients with diabetes who undergo cardiac revascularisation reaches 25% [8].

The mortality data in the analysed group obtained by us are consistent with other authors (9% mortality) [19], only the proportion of patients with diabetes was more representative (32 vs. 25%). According to ESC data, 30-day mortality in acute coronary syndromes without ST-segment elevation was 3.5%, compared to 8.4% in patients with ST-elevation [20]. Only the finished GRACE Study brings similar data [12].

The main aim of our work was to assess the prognostic value of diabetes in the context of other parameters, such as hypertension, overweight, smoking abuse and family history. In the present paper, the prognostic value of the above factors and selected ECG and echo- data were also compared.

The division of acute coronary syndromes that was available not so long ago in the past was based

on the ECG tracing (presence or absence of ST-segment elevation), but it currently focuses on biochemical markers, such as troponins (T,I) and the BM fraction of creatinine kinase. Among the prognostically important parameters for patients after ACS, the most queries exist about ST-segment depressions. According to our data, they are of an important prognostic value in the risk assessment in that group of patients. The result is consistent with the TRIM trial [21] data on the association of ST-depression at admission with dismal prognosis during hospitalisation and 30 days after discharge. Very similar data come from the work of Cohen at al. [15] who revealed a worse 4-year survival of patients with ST-depressions exceeding 0.5 mm in ECG on admission.

Older age, diabetes, wall motion abnormalities and changes in ECG were good parameters of risk stratification [22]. Diabetes was a stronger predictor than the mitral filling pattern and wall motion abnormalities.

However, our results did not reveal diabetes to be associated with a higher rate of deaths, contrary to the end-diastolic left ventricular diameter and wall motion abnormalities.

There are not many data in the native literature on the topic discussed here in spite of the increasing number of patients hospitalised due to acute coronary syndromes. Also, there is little data about the occurrence of long-term complications after the exacerbation of ischaemic heart disease.

The association of diabetes with bad prognosis after ACS without ST-segment elevation, clearly revealed here, indicates the role of cardiological treatment even many months after discharge.

Study limitations

In spite of the existing limitations, among which the most important are: the small number of patients deriving from the same Centre, the omission of the latent phase of diabetes and the lack of assessments of glycosylated haemoglobin, the present study throws new light on the connection of diabetes with complicated cardiological outcomes.

Conclusions

The following parameters are associated with a high cardiological complication risk: recurrent ischaemia (based on changes on ECG), heart failure, elevated troponin levels, haemodynamic instability, severe ventricular tachycardia, ECG not allowing to assess ST-segment changes, and diabetes. According to the currently available guidelines, patients with at least one of above parameters should be referred for an invasive procedure.

The use of new diagnostic tools can facilitate not only the choice of the optimal therapy, but also good financial management. An uncomplicated outcome

of ischaemic heart disease in patients after an episode of exacerbation is rare, especially in a group of patients with diabetes, which was the strongest predictor of complications in our analysis.

That parameter remained statistically significant even after the multivariate analysis concerning such parameters as other risk factors or other clinical and laboratory parameters.

The presence of diabetes should play a pivotal role not only in the medical management during hospitalisation, but also in the treatment that follows, the frequency of check-ups after discharge and the referral for further treatment in outpatient clinics.

The optimal stratification should allow us to apply an optimal method of treatment and to state the prognosis.

The work was presented at the ESC Congress in Vienna: (Diabetes as the strongest predictor of complications after an incident of unstable angina in a 2-year follow-up". Eur Heart J 2003; 24 Suppl: 70.

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