

Patients with non-ST-elevation myocardial infarction and without chest pain are treated less aggressively and experience higher in-hospital mortality

Joanna Zdzienicka, Zbigniew Siudak, Barbara Zawiślak, Artur Dziewierz, Tomasz Rakowski, Jacek Dubiel, Dariusz Dudek

2nd Department of Cardiology, Institute of Cardiology, *Collegium Medicum*, Jagiellonian University, Cracow, Poland

Abstract

Background: Lack of chest pain or atypical pain does not exclude acute coronary syndrome (ACS).

Aim: To assess demographic and clinical characteristic as well as treatment strategies in patients with atypical chest pain on admission in hospitals without on-site invasive facility (IF).

Methods: Twenty-nine community hospitals participated in the Registry of Acute Coronary Syndromes. A total of 2382 patients with ACS were enrolled. Patients admitted to hospitals with suspected ACS were stratified according to their pain symptoms as either typical (TS) or atypical which also included lack of pain (ATS).

Results: Of all patients with initial ACS diagnosis 152 (6.4%) presented without chest pain on admission. Patients from group ATS in comparison to group TS were more often women (49 vs. 39%; $p=0.01$), and less frequently had past medical history of coronary artery disease (54.3 vs. 72.5%; $p<0.0001$), myocardial infarction (15.2 vs. 32.1%; $p<0.0001$), arterial hypertension (65.6 vs. 74.5; $p<0.0001$) or renal insufficiency (1.3 vs. 5%; $p=0.04$). Invasive treatment was undertaken in 9.2% of patients from group ATS and in 14.6% from group TS ($p=0.049$). In-hospital mortality among all patients remaining in community hospitals for conservative treatment was similar in both groups (ATS vs. TS: 8.7 vs. 5.9%; $p=NS$). Among patients with typical and atypical symptoms the occurrence of ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI) and unstable angina (UA) was similar. Patients with NSTEMI and UA with atypical symptoms were less likely transferred for invasive diagnostic, for NSTEMI 9.4 vs. 18.1% ($p=0.03$) and for UA 6.1 vs. 12.9% ($p=0.04$). In-hospital mortality was similar among typical and atypical groups in STEMI and UA patients. However, it was significantly higher among NSTEMI patients with atypical chest pain treated conservatively (3.6 vs. 0%; $p=0.05$).

Conclusions: There is a significant group of ACS patients without chest pain on admission who are usually women with less severe past medical history. This subset of patients is treated less aggressively in terms of antiplatelet therapy and invasive approach. It is patients with diagnosis of NSTEMI who due to being misdiagnosed due to their atypical chest pain have poorer outcome.

Key words: pain, chest pain, acute coronary syndrome, registry

Kardiologia Polska 2007; 65: 769-775

Introduction

Acute coronary syndromes (ACS) cover a wide spectrum of clinical presentations, from unstable angina (UA) to ST-segment elevation myocardial infarction (STEMI), and are the main cause of increased morbidity and mortality worldwide [1]. The main, the most frequent and the most characteristic symptom of ACS is chest pain [2]. Ischaemic pain

results from an imbalance between blood supply (coronary flow) and myocardial demand (myocardial oxygen consumption) [3]. Typically, the anginal pain occurs in the retrosternal and/or precordial area and is usually deep, bloating, pressing or stabbing. It is usually described as a sensation of chest pressure, heaviness or burning in the chest. In some patients the pain might be located in an atypical area like the

Address for correspondence:

Dariusz Dudek MD, II Klinika Kardiologii Instytutu Kardiologii, *Collegium Medicum*, Uniwersytet Jagielloński, ul. Kopernika 17, 31-501 Kraków, tel.: +48 12 424 71 81, e-mail: mcdudek@cyf-kf.edu.pl

Received: 04 February 2007. **Accepted:** 25 April 2007.

upper abdomen or radiate to the elbows, jaw, shoulders, neck and back. Fainting, shortness of breath, increased perspiration, nausea and vomiting are considered anginal equivalents [2].

Acute coronary syndrome should not be excluded either in the absence of typical anginal pain or if the pain has atypical location. Clinically silent myocardial ischaemia or atypical clinical manifestation of MI represent an important type of ischaemic heart disease and are associated with poor prognosis [4-9].

The aim of the study was to compare diagnostic and therapeutic procedures and the results of treatment in patients with ACS depending on the presence or absence of typical clinical manifestations of ACS, admitted to regional hospitals in Małopolska without 24h/7d cath lab availability.

Methods

Study group

On the basis of a written questionnaire, designed specially for the study, information about patients with initial diagnosis of ACS, admitted to regional hospitals in Małopolska, was collected and a Registry of Acute Coronary Syndromes in Małopolska was established [10, 11]. The questionnaire included demographic data, patient's history, clinical parameters on admission, treatment, transportation to cath lab to perform diagnostic procedures and PCI when appropriate, as well as the final diagnosis. The data came from patients hospitalised in 29 hospitals without a cath lab, including 7 hospitals in Cracow and 22 hospitals in the Małopolska region, in the period of April 2002 - February 2003.

Assessment of the nature of symptoms

For the purpose of this study, patients in whom there was a possibility to take their history were divided into the following two groups, depending on the nature of their clinical symptoms: patients with typical symptoms (TS) such as chest pain (in retrosternal and/or precordial area), radiating to the jaw and/or the neck and/or shoulders, lasting for at least a few minutes, relieved or not (MI) with nitroglycerin; and the second group including patients with atypical symptoms (ATS) such as the absence of chest pain or pain in an atypical location or equivalents of anginal pain (shortness of breath, fainting, nausea, vomiting, increased perspiration). Patients were qualified to either group by the physician admitting them to the hospital according to reported complaints. Only patients with confirmed diagnosis of ACS were included in the study. Both

groups were compared with respect to the data from the questionnaire.

Final diagnosis of the type of acute coronary syndrome

Patients were also divided into three groups depending on the final diagnosis: STEMI, NSTEMI and UA without rise in serum markers of myocardial necrosis. Considering the fact that the main dividing criterion was the presence or absence of distinctive clinical symptoms of ACS, the presence of typical changes in electrocardiogram and serum troponin determination were required to establish the final diagnosis.

Statistical analysis

Continuous variables were compared using Student's t-test, and parametric data – χ^2 test or Fisher's exact test. The differences were regarded statistically significant for p value <0.05. Continuous variables were presented as means \pm one standard deviation.

Results

Data on 2382 patients with confirmed diagnosis of ACS were collected in the Małopolska Registry of Acute Coronary Syndromes. A group of 152 (6.4%) patients presented with atypical pain on admission (ATS group), while the remaining 2230 (93.6%) patients had typical symptoms of ACS (TS group).

Demographics and patients' history

Table I compares demographic data of the ATS and TS groups. There were more women in the ATS group. Patients with ATS less frequently presented with a history of ischaemic heart disease, hypertension, dyslipidaemia, MI or renal failure than TS patients. The presence of each condition was assessed by the physician admitting the patient to the hospital, based on the patient's history, previous medical documentation and medications taken by the patient. Compared groups of patients (TS vs. ATS) did not significantly differ in terms of age or prevalence of diabetes mellitus.

Invasive treatment and in-hospital mortality in patients with initially conservative treatment

There was a difference in the percentage of patients referred to the cath lab for diagnostic purpose and percutaneous coronary angioplasty when appropriate between TS and ATS groups: fewer patients from the ATS group were sent to the cath lab than from the TS group (Figure 1). In-hospital mortality in patients treated conservatively in regional hospitals was similar in both groups (Figure 2).

Table I. Demographic data and patient's history of patients with ACS divided into the two groups: ATS and TS

Parameter	ATS	TS	p
Number of patients	152 (6.4%)	2230 (93.6%)	
Age [years] (mean±SD)	65.7±13.4	66.5±11.5	NS
Female gender	49	39	0.01
Patient's history:			
ischemic heart disease	54.3	72.5	<0.0001
myocardial infarction	15.2	32.1	<0.0001
heart failure	21.2	20.1	NS
Hypertension	65.6	74.5	<0.0001
Diabetes mellitus	18.5	23.3	NS
Dyslipidaemia	25.8	40.8	<0.0002
Stroke	7.9	5.5	NS
Smoking	26.5	28.7	NS
Renal failure	1.3	5.0	0.04
Coronary angiography in the past	2.6	9.6	0.004

Abbreviations: ACS – acute coronary syndrome, TS – patients with typical symptoms, ATS – patients with atypical symptoms

Final diagnosis

In patients with ATS and with TS the frequency of STEMI, NSTEMI and UA diagnosis was similar and as follows: STEMI: 32.2 vs. 32.8% (NS), NSTEMI 25.2 vs. 27.1% (NS), UA 42.6 vs. 40.1% (NS), respectively.

Invasive treatment and mortality among patients with STEMI, NSTEMI and UA

Patients diagnosed with NSTEMI and UA and with ATS were significantly less frequently referred for invasive diagnostic catheterisation and invasive treatment than patients with TS (Figure 3). In-hospital mortality of patients diagnosed with STEMI and UA, treated less aggressively, was not significantly different between ATS and TS patients. However, in patients diagnosed with NSTEMI in whom conservative treatment was applied, mortality was significantly higher in the group with atypical symptoms (Figure 4).

Medical treatment of patients with STEMI, NSTEMI and UA

Figure 5 presents the pharmacological treatment of patients diagnosed with STEMI, NSTEMI and UA, divided into subgroups according to the presence or absence of typical anginal pain. In the ATS group, patients with each type of a final diagnosis were significantly less

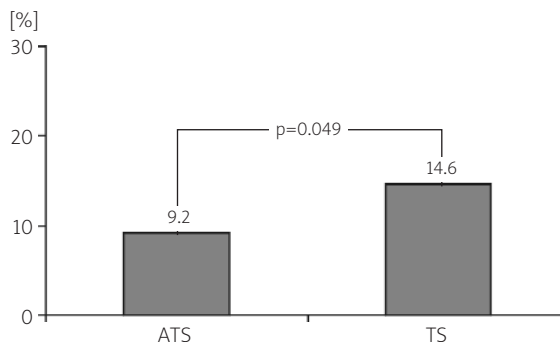


Figure 1. Patients with acute coronary syndrome and with atypical (ATS) and typical (TS) symptoms referred for invasive treatment

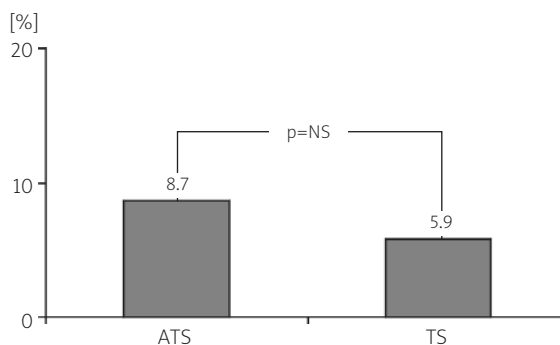


Figure 2. In-hospital mortality in patients with acute coronary syndrome in whom conservative treatment was applied, presenting with atypical (ATS) and typical (TS) symptoms

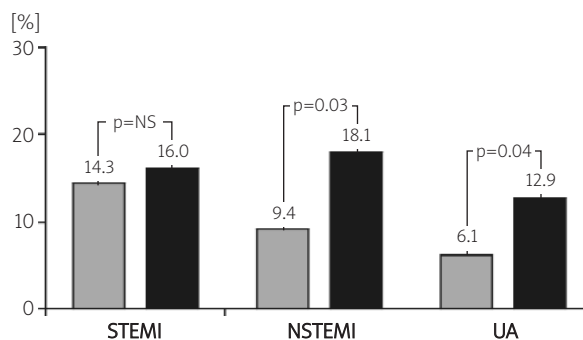


Figure 3. Patients with a final diagnosis of STEMI, NSTEMI and UA referred for invasive treatment, divided into subgroups of atypical (ATS – grey bars) and typical (TS – black bars) symptoms

Abbreviations: STEMI – ST-segment elevation myocardial infarction, NSTEMI – non-ST-segment elevation myocardial infarction, UA – unstable angina

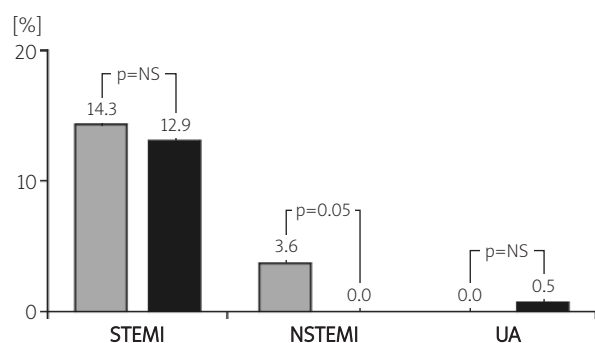


Figure 4. In-hospital mortality in patients in whom conservative treatment was applied, with a final diagnosis of STEMI, NSTEMI and UA, divided into subgroups of atypical (ATS – grey bars) and typical (TS – black bars) symptoms

Abbreviations: see Figure 3

frequently treated with statins, beta-blockers (except for patients with UA) and thienopyridine agents. Thrombolysis was used two times less frequently in patients with STEMI.

Discussion

Acute coronary syndromes represent the leading cause of morbidity and mortality worldwide. Despite continuous improvements in both diagnostic and therapeutic techniques, the diagnosis of ACS and selection of optimal treatment has been a challenge for the front-line physicians due to the wide diversity and heterogeneity of symptoms. A detailed patient's history and integrated clinical assessment of each patient are of utmost importance. Attention should be paid to the changing demographic profile of societies, most importantly to the longer lifetime, particularly in developed countries and, as a consequence, different clinical manifestations of ACS in the elderly. Older patients experience decreased pain perception and present with comorbidities such as diabetes mellitus that might impede the diagnosis of ACS. It has been observed that such patients more often present with silent ischaemia that is associated with a worse prognosis [4, 6]. Additionally, the clinical assessment of older patients might be more difficult because of other coexisting disorders causing discomfort in the chest or shortness of breath, which might imitate anginal pain.

Our analysis of the Małopolska data demonstrates that the presence of atypical, painless ACS is not dependent on the age of patients. Stratification of patients according to the presence or absence of a typical anginal pain did not result in revealing statistically significant differences in the mean age of

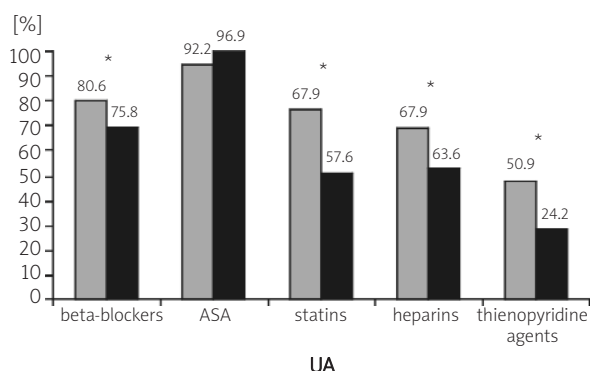
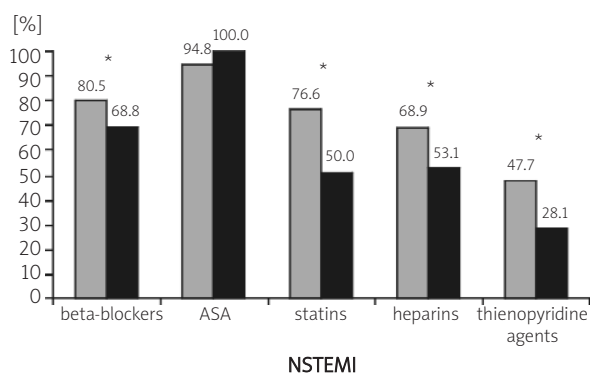
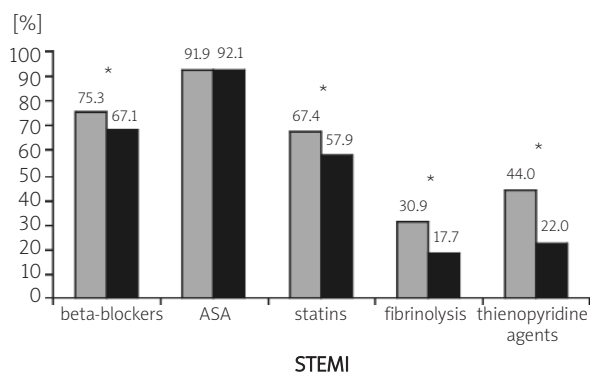


Figure 5. Pharmacotherapy of patients with STEMI, NSTEMI and UA with respect to the presence of atypical (ATS – grey bars) and typical (TS – black bars) symptoms

* $p < 0.05$

Abbreviations: see Figure 3

patients in both groups (ATS and TS), although such differences were shown in other studies [12].

We demonstrated that significantly more women presented with atypical clinical manifestation of ACS, and a similar observation was made in the GRACE registry [12]. It has been observed that ischaemic heart disease in women develops at older age compared with men because of dyslipidaemia that is often a result of ovarian failure. A protective effect of

female sex hormones on the cardiovascular system results in a lower risk of ischaemic heart disease before menopause. In postmenopausal women the risk of ACS increases and is comparable to the risk in men [13].

It has been assumed that patients with diabetes mellitus more commonly present with a painless anginal episode. Autonomic neuropathy, which is a late complication of hyperglycaemia, has been considered the main cause [12, 14]. In our study, however, the percentage of patients with diabetes mellitus was similar in ATS and TS groups, suggesting the existence of other factors responsible for painless, atypical manifestation of ACS.

Patients without typical anginal pain were less often treated with modern antiplatelet agents. Less frequently, very often even twice less frequently than patients with typical pain, they received clopidogrel, which is used as a standard treatment in patients with ACS. The CURE study included clopidogrel in the standard medical regimen of ACS and found clopidogrel to significantly decrease the rate of myocardial infarction (ARR=1.5%, relative risk: 0.77 95% CI 0.67-0.89), cardiovascular death, acute heart ischaemia and stroke [15]. According to the guidelines on the management of NSTEMI ACS from 2002, clopidogrel should be recommended for the short- and long-term therapy of patients with ACS (for at least 9-12 months) [16, 17]. The less frequent use of statins should also receive special attention, as they play a substantial role in the treatment of ACS and plaque stabilisation, due to their pleiotropic, not only lipid-lowering actions.

Patients without typical anginal pain were significantly less frequently referred for invasive treatment. Coronary angiography allows not only the assessment of coronary anatomy and left ventricular function, identification of vessel or graft responsible for acute ischaemia, but most importantly, provides a possibility to make an optimal decision on the type of treatment in individual patients [2]. At the same time, higher in-hospital mortality was observed in patients in whom conservative treatment, that turned out to be insufficient was applied.

Taking into account the high prevalence of cardiovascular diseases, front-line physicians should always consider ACS in their differential diagnosis, even in the absence of typical symptoms, and plan appropriate tests. The number of patients with atypical manifestations of ACS receiving modern pharmacotherapy and invasive treatments might be increased by using such procedures and proper watchfulness. As a result, the mortality in these patients might be further reduced. Our analysis of the study data showed

that patients with atypical manifestation of ACS were constantly ignored in terms of a detailed and early diagnosis. It is even more striking when we realise that it is mostly women who present with atypical clinical manifestations of ACS, with no previous history suggestive of an increased risk of ACS. In view of the presented data, front-line physicians should pay more attention to establishing a detailed and more careful diagnosis and the treatment of such patients in emergency rooms. In the presence of a Pardee's wave, i.e. when STEMI is recognised, the clinical manifestations lead to the selection of an invasive treatment in these patients.

Conclusions

Patients with ACS without typical anginal pain constitute a minor but significant group of patients. These are usually women without a history indicating a high risk of coronary events. Patients with atypical symptoms are less frequently treated with modern antiplatelet agents and statins. Patients with diagnosed NSTEMI and atypical symptoms are less often referred for invasive treatment and in-hospital mortality is higher in those NSTEMI patients in whom conservative treatment is applied.

References

1. GRACE Investigators. Rationale and design of the GRACE (Global Registry of Acute Coronary Events) Project: a multinational registry of patients hospitalized with acute coronary syndromes. *Am Heart J* 2001; 141: 190-9.
2. Opolski G, Filipiak K. Obraz kliniczny ostrych zespołów wieńcowych i postępowanie przedszpitalne. In: Opolski G, Filipiak K, Poloński L (eds.). *Ostre zespoły wieńcowe*. Urban&Partner, Wrocław 2002: 33-7.
3. Gray HH. Wywiad w chorobach układu sercowo-naczyniowego. In: Gray HH, Dawkins KD, Morgan JM, et al. (ed.). *Kardiologia Via Medica*, Gdańsk 2003: 1-7.
4. Gregoratos G. Clinical manifestations of acute myocardial infarction in older patients. *Am J Geriatr Cardiol* 2001; 10: 345-7.
5. Herrick JB. Landmark article (JAMA 1912). Clinical features of sudden obstruction of the coronary arteries. By James B. Herrick. *JAMA* 1983; 250: 1757-65.
6. Calle P, Jordaens L, De Buyzere M, et al. Age-related differences in presentation, treatment and outcome of acute myocardial infarction. *Cardiology* 1994; 85: 111-20.
7. Sigurdsson E, Thorgeirsson G, Sigvaldason H, et al. Unrecognized myocardial infarction: epidemiology, clinical characteristics, and the prognostic role of angina pectoris. The Reykjavik Study. *Ann Intern Med* 1995; 122: 96-102.
8. Dorsch MF, Lawrance RA, Sapsford RJ, et al. Poor prognosis of patients presenting with symptomatic myocardial infarction but without chest pain. *Heart* 2001; 86: 494-8.
9. Canto JG, Rogers WJ, French WJ, et al. Payer status and the utilization of hospital resources in acute myocardial infarction:

- a report from the National Registry of Myocardial Infarction 2. *Arch Intern Med* 2000; 160: 817-23.
10. Dudek D, Siudak Z, Kuta M, et al. Charakterystyka kliniczna oraz leczenie pacjentów z ostrymi zespołami wieńcowymi w szpitalach bez pracowni kardiologii inwazyjnej. Małopolski Rejestr Ostrych Zespołów Wieńcowych 2002–2003. *Post Kardiol Inter* 2005; 1, 2: 97-106.
 11. Siudak Z, Dudek D, Kuta M, et al. Codzienna praktyka kliniczna w ostrych zespołach wieńcowych bez uniesienia odcinka ST w szpitalach rejonowych – rejestr w Małopolsce. *Folia Cardiol* 2005; 12: 21-31.
 12. Brieger D, Eagle KA, Goodman SG, et al. Grace Investigators. Acute coronary syndromes without chest pain, an underdiagnosed and undertreated high-risk group: insights from the Global Registry of Acute Coronary Events. *Chest* 2004; 126: 461-9.
 13. Rossouw JE. Hormonalna terapia zastępcza w okresie pomenopauzalnym a choroby sercowo-naczyniowe. In: Yusuf S, Cairns JA, Camm J, et al. (eds.). *Kardiologia faktów. Tom 1. Evidence-based. Centrum Wydawnictw Medycznych, Warszawa* 2005: 310-28.
 14. Foster DW. Diabetes. In: Fauci AS, Braunwald E, Isselbacher KJ, et al. (eds.). *Harrison's Principles of Internal Medicine. Tom III. Czelej, Lublin* 2000: 3467-500.
 15. Yusuf S, Zhao F, Mehta SR, et al. Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* 2001; 345: 494-502.
 16. Bertrand ME, Simoons ML, Fox KA, et al. Task Force on the Management of Acute Coronary Syndromes of the European Society of Cardiology. Management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J* 2002; 23: 1809-40.
 17. Braunwald E, Antman EM, Beasley JW, et al. ACC/AHA guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction – 2002: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients With Unstable Angina). *Circulation* 2002; 106: 1893-900.

Pacjenci z zawałem mięśnia sercowego bez uniesienia odcinka ST, którzy nie mają charakterystycznych dolegliwości bólowych, są częściej leczeni zachowawczo i cechują się wyższą śmiertelnością wewnątrzszpitalną

Joanna Zdzienicka, Zbigniew Siudak, Barbara Zawiślak, Artur Dziewierz, Tomasz Rakowski, Jacek Dubiel, Dariusz Dudek

II Klinika Kardiologii, Instytut Kardiologii, *Collegium Medicum*, Uniwersytet Jagielloński, Kraków

Streszczenie

Wstęp: Brak bólu wieńcowego lub nietypowe objawy bólowe nie wykluczają ostrego zespołu wieńcowego (ang. *acute coronary syndrome*, ACS).

Cel: Porównanie postępowania diagnostyczno-terapeutycznego i wyników leczenia w zależności od obecności lub braku charakterystycznej klinicznej manifestacji ACS u chorych z rozpoznaniem ACS, przyjętych do szpitali rejonowych w Małopolsce, które nie mają własnej pracowni kardiologii inwazyjnej dyżurującej w trybie 24-godzinny.

Metodyka: Dwadzieścia dziewięć szpitali rejonowych wzięło udział w Małopolskim Rejestrze Ostrego Zespołu Wieńcowych. Zebrano dane o 2382 chorych z ACS. Dla potrzeb niniejszej analizy chorych objętych Rejestrem podzielono na podstawie objawów klinicznych na dwie grupy: grupę chorych z dolegliwościami charakterystycznymi (ang. *typical symptoms*, TS), za które przyjęto ból w klatce piersiowej (okolica zamostkowa i/lub przedsercowa), promieniujący do żuchwy i/lub szyi, i/lub ramion, trwający co najmniej kilkanaście minut, ustępujący lub nie (zawał serca, MI) po podaniu azotanów, oraz grupę chorych z dolegliwościami niecharakterystycznymi (ang. *atypical symptoms*, ATS), czyli pacjentów niezgłaszających bólu lub z bólem o nietypowej lokalizacji, ewentualnie z ekwiwalentami bólu dławicowego (duszność, omdlenia, nudności i wymioty, poty).

Wyniki: U 152 (6,4%) chorych z rozpoznaniem ACS nie stwierdzono typowych objawów bólowych (grupa ATS). W tej grupie chorych w porównaniu z grupą chorych z TS było więcej kobiet (49 vs 39%; $p=0,01$), rzadziej występowały wcześniejsze epizody dławicy piersiowej (54,3 vs 72,5%; $p < 0,0001$), przeżyty MI (15,2 vs 32,1%; $p < 0,0001$) oraz niewydolność nerek (1,3 vs 5%; $p=0,04$). Leczeniu inwazyjnemu poddano 9,2% pacjentów z grupy ATS i 14,6% z grupy TS ($p=0,049$). Śmiertelność wewnątrzszpitalna dla chorych z ACS leczonych zachowawczo w szpitalach rejonowych była podobna w obu grupach (ATS vs TS: 8,7 vs 5,9%; $p=NS$). Wśród pacjentów z ATS i z TS rozpoznanie ostateczne MI z uniesieniem odcinka ST (STEMI), MI bez uniesienia odcinka ST (NSTEMI) oraz niestabilnej dławicy piersiowej (UA) było podobne – dla STEMI 32,2 vs 32,8% (NS), dla NSTEMI 25,2 vs 27,1% (NS) oraz dla UA 42,6 vs 40,1% (NS). Chorzy z rozpoznaniem NSTEMI i UA z ATS byli istotnie rzadziej niż chorzy z TS kierowani do diagnostyki inwazyjnej oraz ewentualnego leczenia inwazyjnego do pracowni hemodynamiki w Krakowie, odpowiednio dla NSTEMI 9,4 vs 18,1% ($p=0,03$) i dla UA 6,1 vs 12,9% ($p=0,04$). Śmiertelność wewnątrzszpitalna dla chorych leczonych zachowawczo w grupie STEMI i UA nie różniła się istotnie statystycznie między grupami ATS i TS. Jedynie wśród chorych z NSTEMI zanotowano istotnie częstsze zgony w grupie chorych z ATS leczonych zachowawczo (3,6 vs 0%; $p=0,05$). Fibryniliza w STEMI była prawie 2-krotnie rzadziej stosowana (30,9 vs 17,7%; $p=0,01$).

Wnioski: Chorzy z ACS bez charakterystycznych dolegliwości bólowych stanowią niewielką, ale istotnie wyróżniającą się grupę chorych. Są to częściej kobiety z mniej obciążającym wywiadem chorobowym. W grupie chorych z ATS stosowano mniej agresywne leczenie przeciwpłytkowe oraz rzadziej terapię statyną. Chorzy z grupy NSTEMI z ATS byli rzadziej kierowani do leczenia inwazyjnego i charakteryzowali się wyższą śmiertelnością wewnątrzszpitalną w stosunku do chorych z NSTEMI z TS również leczonych zachowawczo.

Słowa kluczowe: ból, stenokardia, ostry zespół wieńcowy, rejestr

Kardiologia Pol 2007; 65: 769-775

Adres do korespondencji:

Dariusz Dudek MD, II Klinika Kardiologii Instytutu Kardiologii, *Collegium Medicum*, Uniwersytet Jagielloński, ul. Kopernika 17, 31-501 Kraków, tel.: +48 12 424 71 81, e-mail: mcdudek@cyf-kr.edu.pl

Praca wpłynęła: 04.02.2007. Zaakceptowana do druku: 25.04.2007.