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Risk Stratification and Invasive Strategy in NSTE-ACS

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1. Introduction

Under the heading of acute coronary syndrome (ACS), we include myocardial infarction with ST segment elevation (STEMI), myocardial infarction without ST segment elevation (NSTEMI) and unstable angina (UA). Given the similar pathophysiological mechanisms, clinical manifestations, diagnostic and therapeutic algorithm UA and NSTEMI are sorted into a common group of ACS without ST segment elevation (NSTE-ACS). ACS is a serious clinical disease, which is associated with higher mortality than stable angina pectoris. High proportion of patients die of sudden death in the early hours of ACS (especially STEMI), before admission to the hospital, therefore it is difficult to assess the real incidence of ACS. The incidence of ACS also depends on the sensitivity of the humoral markers of myocyte necrosis. The annual hospital admissions rate for NSTE-ACS is estimated from the results of registers and surveys about 3 per 1000 inhabitants. The proportion of STEMI represents approximately 20% of NSTE ACS.

1.1 NSTE-ACS

Acute coronary syndromes without ST segment elevation constitute a clinically heterogeneous group. Pathophysiological basis of NSTE-ACS is usually unstable atherosclerotic plaque (with rupture, erosions and inflammatory changes) and the presence of intracoronary thrombosis. Intracoronary thrombus has a high content of platelet and (unlike in STEMI) is non-occlusive or intermittently present. In the USA were hospitalized for ACS 1.57 million patients per 1 year, of which 0.33 million were admitted for STEMI and 1.24 million for NSTE-ACS (0.57 mil. for NSTEMI and 0.67 million for UA). In the same year were performed in the U.S. 1,297,000 coronary angiographies and 658 000 PCIs (Rosamond W et al., 2007). Based on analogous application of these statistics data, it can be expected the annual incidence of 5500 STEMI and 20 600 NSTE-ACS (9500 NSTEMI) in the Slovak Republic.
According to data from the registers of ACS, invasive diagnostics was currently performed in less than half of patients with NSTE-ACS (Fox KA et al., 2003, Bhat DL et al., 2004, Kovar F et al., 2010). Assessment of the benefits of invasive management strategy in NSTE-ACS based on the data from randomized trials is difficult because of number of reasons. High proportion of patients originally enrolled in the conservative arm is then treated invasively and in addition, there were significant differences in the timing of invasive diagnosis in individual studies (less than 2.5 hours to 7 days)) (Cannon CP et al., 2001; Fox KA et al., 2002; Neumann FJ et al., 2003).

The recently published study ICTUS did not present significant difference between groups treated within invasive or conservative arms in terms of mortality, reinfarction or rehospitalization rate for period 1 and 3 year follow-up (22.7% versus 21.2%, p = 0.33). There was observed an increased incidence of early myocardial infarction (15% versus 10%, p = 0.005) among invasive managed patients. During initial hospitalization, however, 76% of patients in the invasive group and 40% of patients scheduled for conservative treatment underwent revascularization procedure (Hirsh A et al., 2007).
Similarly, meta-analysis of more than 4500 patients from randomized trials has suggested that routinely indicated coronary angiography compared with more conservative strategy was associated with increased incidence of early mortality (1.8% vs. 1.1%, p = 0.007) and combined endpoint of death and reinfarction (5.2 % vs. 3.8%, p = 0.002). Long term monitoring however, favored an invasive strategy with a reduction of death and reinfarction (12.2% versus 14.4%, p = 0.001) (Mehta SR et al., 2005).
Some clinical trials were able to document benefit of invasive strategy in NSTE-ACS patients with an increased troponin level in the beginning, but not at its normal levels (Diderholm E et al., 2002, Lagerqvist B et al., 2006).
In a recently published meta-analysis of more than 8300 patients with NSTE-ACS, there has been documented benefits of timely invasive procedure compared with conservative management in order to reduce mortality (4.9% vs. 6.5%, p = 0.001), nonfatal myocardial infarction (7.6 % vs. 9.1%, p = 0.012) over a 2 year follow-up period, without increasing risk of myocardial infarction within 1 month (Bavry AA et al., 2006). Reduction of mortality rate in the early invasive strategy was present during the 5- year follow-up periods in FRISCO II and RITA 3 trials as well (Fox KA et al., 2005; Lagerqvist B et al., 2006).

2. RISC score

As has been pointed out previously, NSTE-ACS is a heterogeneous group of diseases. Coronary angiography can reveal severe stenosis of one or more coronary arteries, narrowing of the left main coronary artery, presence of intracoronary thrombi (FRISC II investigators, 1999; Kovar F et al., 2003, 2004). These facts reflect current recommendations of the European Society of Cardiology (ESC), which emphasize the need for early (and repeated as necessary) risk stratification in patients with NSTE-ACS (Bassand JP et al., 2007).

2.1 GRACE score

The GRACE (Global Registry of acute coronary events) risk score takes into account age, heart rate, systolic blood pressure, serum creatinine level, Killip class on admission, need for resuscitation for cardiac arrest, presence of ST segment depression and increased values of of myocardial necrosis markers (Eagle KA et al., 2004; Fox KA et al., 2006). GRACE score is based on the analysis of a large unselected population from an international registry of all ACS (STEMI and NSTEMI). Evaluated risk factors show independent predictive value for both hospital and 6- month mortality (tab. 1).

2.2 TIMI score

The TIMI (Thrombolysis in myocardial infarction) risk score assesses anamnestic variables (age ≥ 65 years, ≥ 3 risk factors of ischemic heart disease, known coronary artery stenosis >

Risk score (Tertils)	GRACE risk score	Hospital mortality (%)	Mortality within 6 months (%)
low	< 108	<1	<3
mean	109-140	1-3	3-8
high	> 140	> 3	> 8

Table 1. Hospital and six month mortality rate depending on the GRACE risk score

TIMI RISK SCORE	
VARIABLE	**POINT**
age ≥ 65 years	1
≥ 3 risk factors for vascular disease	1
known coronary artery stenosis > 50%	1
use of aspirin in the last 7 days	1
severe angina within 24 hours	1
ST segment deviations > 0.5 mm	1
positive markers of necrosis	1
Risk score	**0-7**

Table 2. TIMI (Thrombolysis in myocardial infarction) risk score parameters

50%, aspirin therapy in the last 7 days and the actual presence of severe angina within 24 hours, ST segment deviations > 0.5 mm and increased laboratory markers of necrosis (Antman EM et al., 2000). TIMI score is then the sum of individual items (value 0-7) (tab. 2). Its advantage is simplicity, but has not so high predictive accuracy as a comprehensive GRACE score (Figure 1).

2.3 Correlation between coronary angiography findings and the TIMI risk score level

In a retrospective study, we investigated contribution of early risk stratification to the invasive management timing. Population consisted from 424 consecutive NSTE-ACS patients (264 men and 160 women), age 26-87 years (mean age 65,75 years, median 67 years), referred for coronary angiography to the Ist Department of Internal medicine University hospital Martin during the period from December 2009 to October 2010. Patients with NSTE-ACS were stratified according to the TIMI risk score and based on achieved risk score level subsequently divided into three risk groups (Figure 2 and 3):

1. low risk (0-2 points)
2. intermediate risk (3-4 points)
3. high risk (5-7 points)

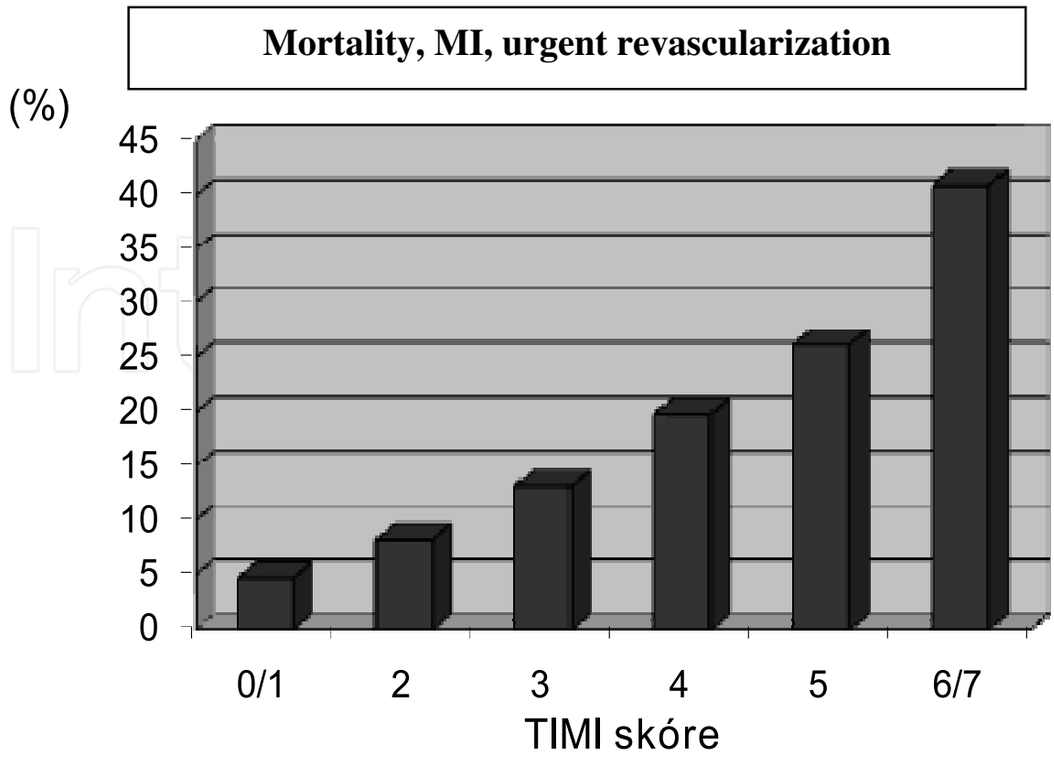


Fig. 1. Incidence of major cardiovascular events based on TIMI risk score level

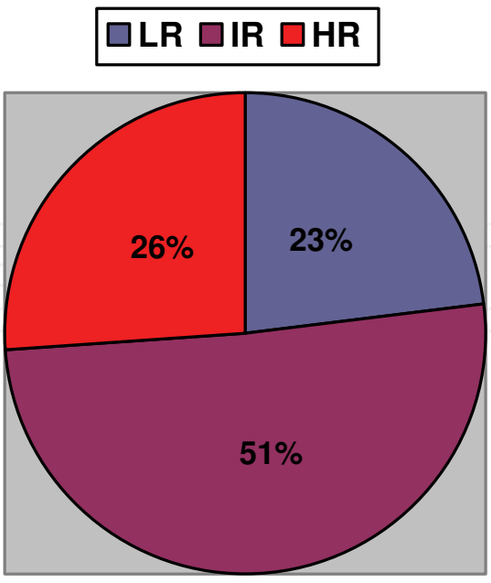


Fig. 2. Risk stratification according TIMI risk score
LR - low risk, IR - intermediate risk, HR - high risk

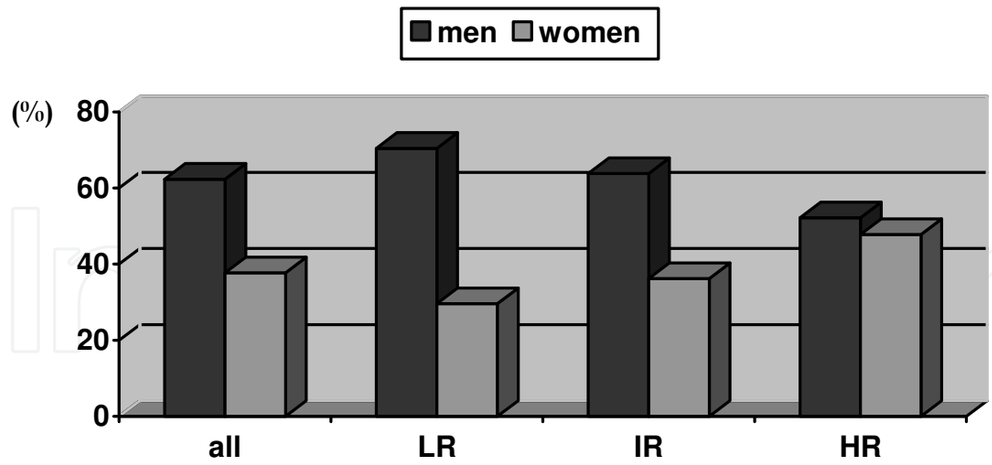


Fig. 3. Proportion of men and women in different risk groups
LR - low risk, IR - intermediate risk, HR - high risk

There were more men than women in the age range bellow 65 years in all risk groups, but this difference was no longer present in the age ≥ 65 years (Figure 4 and 5).

Fig. 4. Proportion of men and women in different risk groups in age below 65 year
LR - low risk, IR - intermediate risk, HR - high risk

Elevated cardiac troponin was identified as most frequent parameter of the TIMI risk score (in 81,8% of patients). Second often parameter occurred presence of ≥ 3 risk factors for coronary artery disease in 60,1% patients (Figure 6).
Frequency of risk factors for coronary artery disease rose with increasing TIMI risk score, so in high-risk group almost 90% of patients had ≥ 3 risk factors (Figure 7).
On coronary angiography was assessed stenosis of:

- main stem of left coronary artery – LMA > 50%
- ramus interventricular anterior - RIA > 75%
- ramus circumflexus – RCX > 75%

- arteria coronaria dextra – RCA > 75%
- multivessel coronary artery disease – stenosis ≥ 3 – coronary arteries

There were more coronary arteries stenoses identified with increasing TIMI risk score (Figure 8). In age range ≥ 65 years in comparison with age bellow 65 year, there were more coronary arteries stenoses among patients with intermediate risk. This relationship was even more pronounced in patients in high TIMI risk score group (Figure 9 and 10).

Fig. 5. Proportion of men and women in different risk groups in age ≥ 65 year
LR - low risk, IR - intermediate risk, HR - high risk

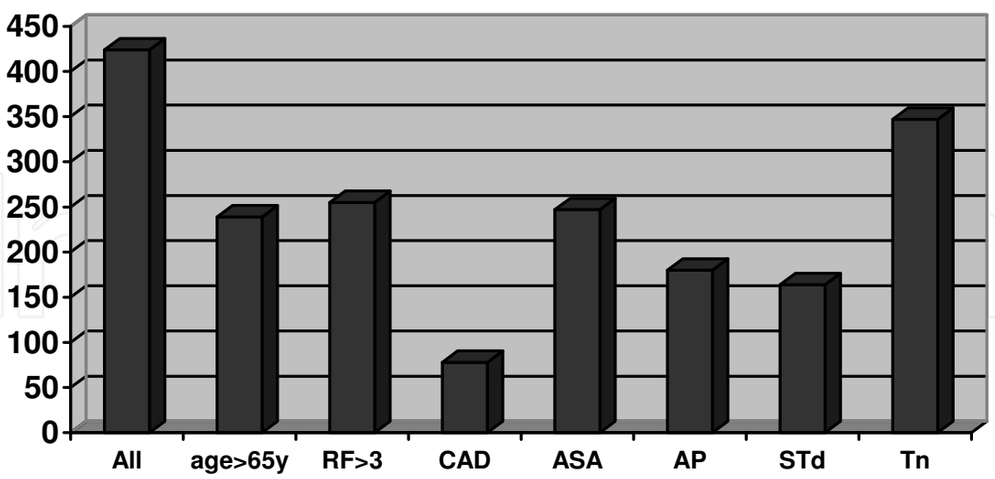


Fig. 6. Incidence of anamnestic, clinical and laboratory parameters of TIMI risk score
RF - risk factor for atherosclerosis, CAD - known coronary artery narrowing > 50%, ASA - acetylsalicylic acid, AP - angina pectoris, STd - ST segment depression ≥ 0.5 mm, Tn – troponin

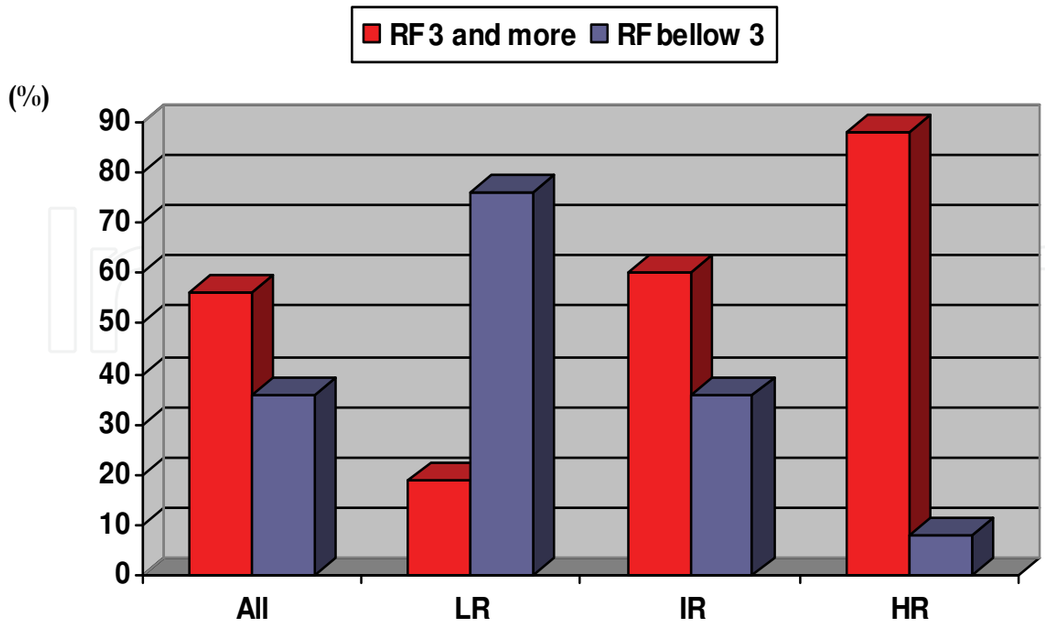


Fig. 7. Proportion of patients with ≥ 3 risk factors for coronary artery disease in different risk groups
LR - low risk, IR - intermediate risk, HR - high risk

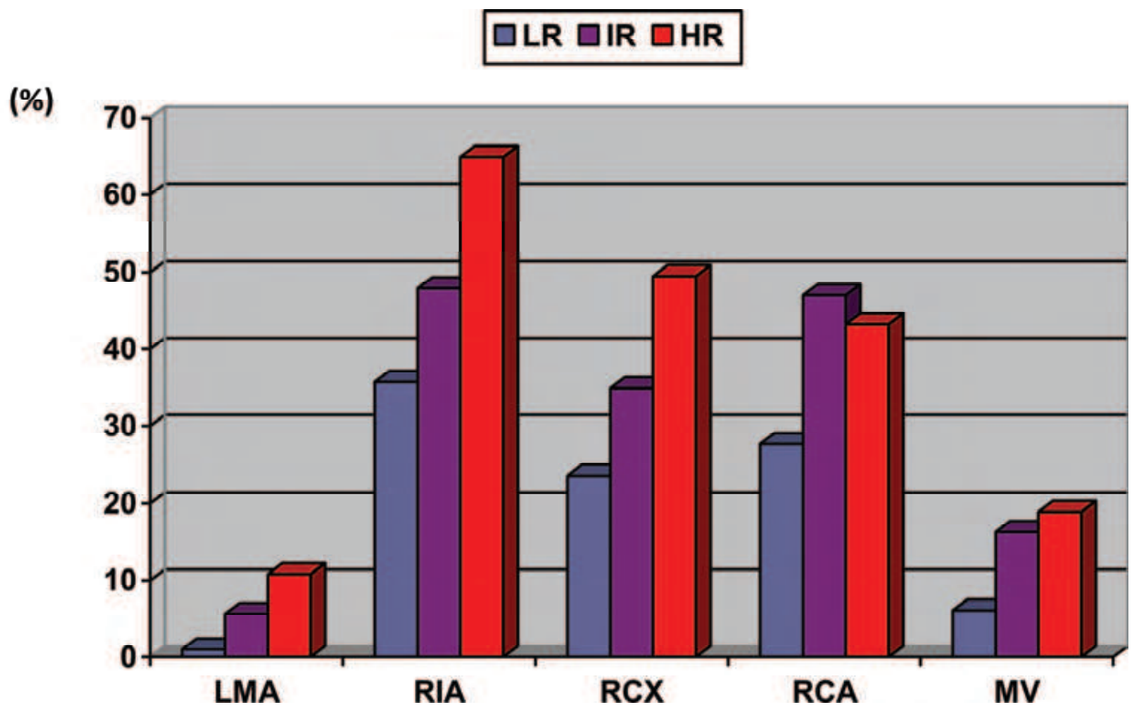


Fig. 8. Coronary arteries stenoses in different risk groups
LMA - left main coronary artery, RIA - ramus interventricularis anterior, RCX - ramus circumflexus, RCA - arteria coronaria dextra, MV - multivessel coronary artery disease

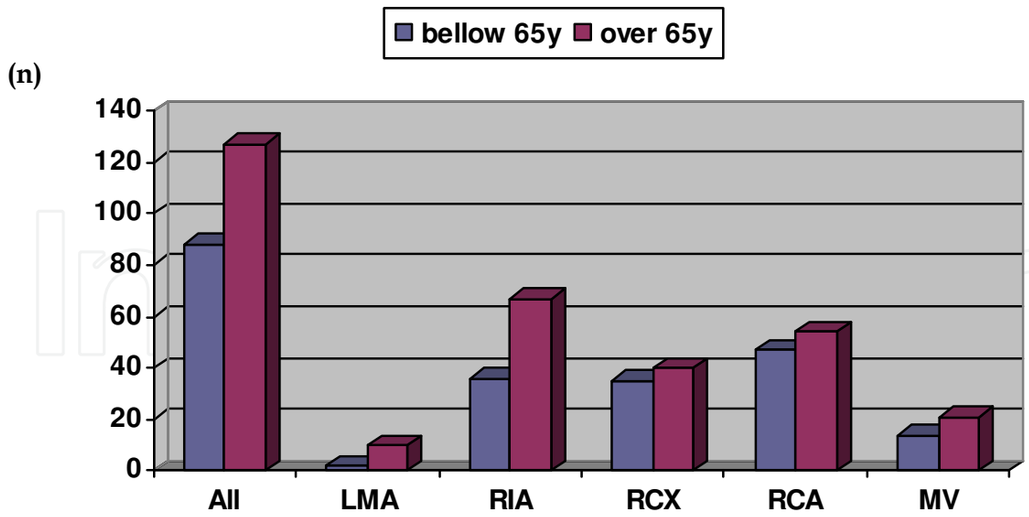


Fig. 9. Coronary arteries stenoses in patients with intermediate TIMI risk score in different age groups
LMA - left main coronary artery, RIA - ramus interventricularis anterior, RCX - ramus circumflexus, RCA - arteria coronaria dextra, MV - multivessel coronary artery disease

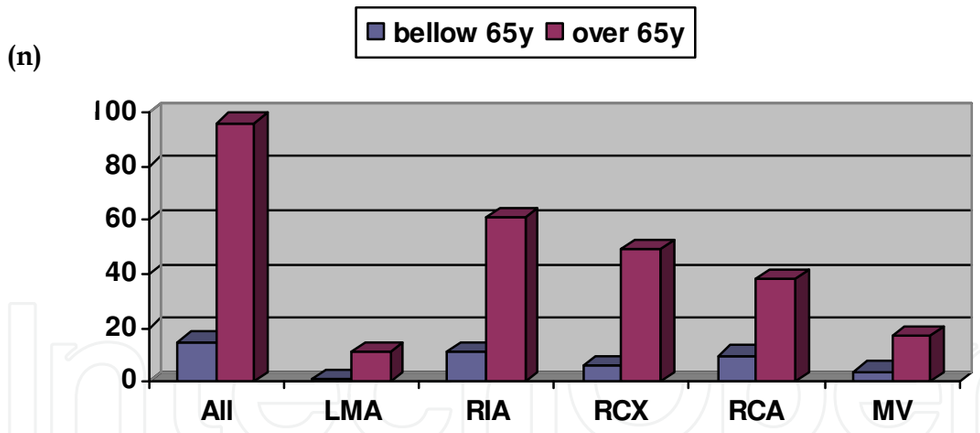


Fig. 10. Coronary arteries stenoses in patients with high TIMI risk score in different age groups
LMA - left main coronary artery, RIA - ramus interventricularis anterior, RCX - ramus circumflexus, RCA - arteria coronaria dextra, MV - multivessel coronary artery disease

Coronary angiography findings were negative in 25,7% of patients. While in the group with low risk, coronary angiography was without significant stenosis in 42,8% of patients, there was so in 25,5% in the intermediate risk group and in only 10,8% of patients in high risk group (Figure 11). Extensive involvement of coronary arteries was assessed by coronary angiography in intermediate and high risk groups.

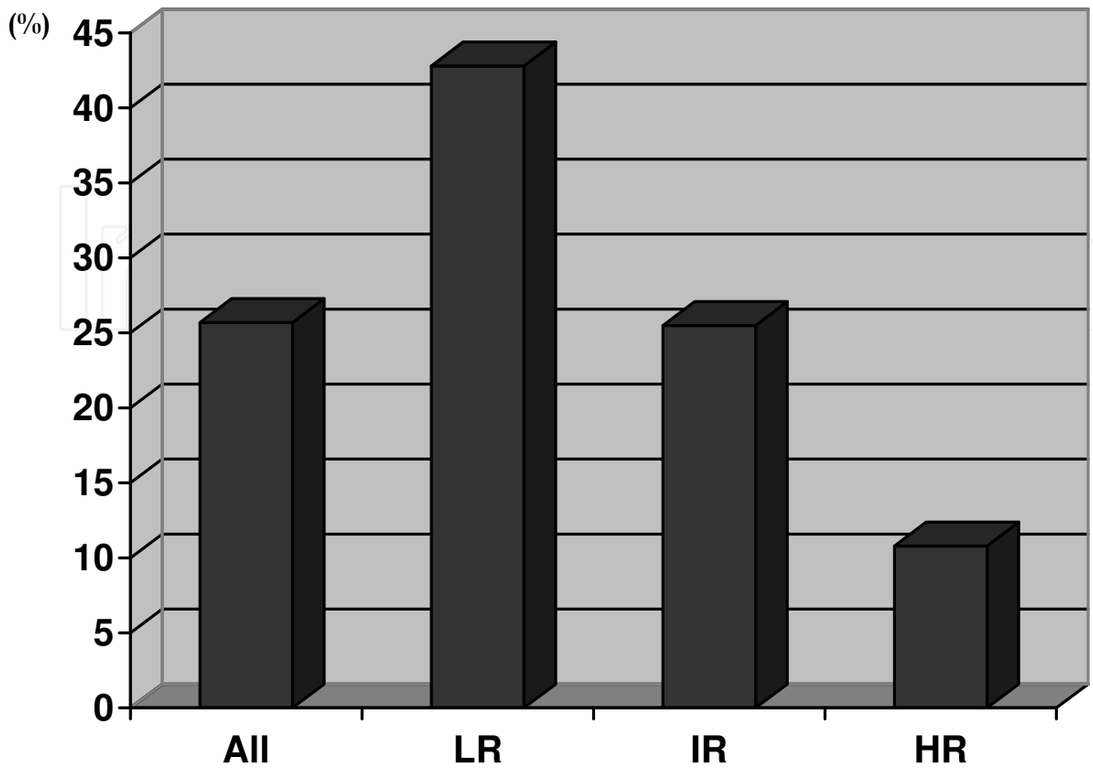


Fig. 11. Proportion of patients without significant coronary artery stenosis in different TIMI risk group
LR - low risk, IR - intermediate risk, HR - high risk

3. Indication and timing of invasive diagnostics

Depending on the risk score level, we can make decisions for the indication of invasive diagnostic and its timing in patients with NSTE-ACS in three modes (urgent, early invasively and elective) (Bassand JP et al., 2007):

3.1 Urgent invasive strategy

It is indicated within 2 hours in patients with high risk score. This strategy is taken in to account particularly in patients with:

a. Refractory angina
b. Recurrent angina despite intensive pharmacologic treatment with presence of deep (≥ 2 mm) ST segment depression or deep negatives T waves on ECG
c. Symptoms of heart failure or hemodynamic instability (incipient signs of shock)
d. Serious arrhythmias (ventricular fibrillation or ventricular tachycardia)

3.2 Early invasive strategy

This strategy is considered in NSTE-ACS patients with high risk of serious ischemic events. Coronary angiography should be performed within 72 hours in this group.

These are patients presenting with:
a. elevated troponin levels
b. dynamic ST segment or T waves changes (≥ 0.5 mm)
c. diabetes mellitus
d. reduced renal function (GFR <1 ml / s)
e. reduced left ventricular ejection fraction <40%
f. angina pectoris early after myocardial infarction
g. angina pectoris within 6 months after coronary intervention (PCI)
h. history of coronary artery bypass grafting (CABG)
i. medium or high risk GRACE score

3.3 Conservative (elective) strategy

It is indicated in those patients who meet all the following criteria:
Are free of:
a. Recurrence of angina pectoris
b. Symptoms of heart failure
c. Major arrhythmias
d. Changes in both initial and second ECG (after 6-12 hours)
e. Elevated troponin levels (at entrance examinations and even after 6-12 hours)

Low risk, as assessed by GRACE or TIMI scores, supports the decision making for a conservative treatment. These patients should undergo an exercise test before hospital discharge and coronary angiography in case of inducible ischemia.

Risk stratification of ACS patients (as recommended by the ESC) is now clearly recommended to identify patients with moderate to high risk of serious cardiovascular complications, who benefit most from both early invasive diagnosis and subsequent coronary arteries revascularization. In so selected risky ACS group coronary angiography has to be performed during index hospitalization.

4. Effect of early treatment strategy on long-term outcomes in NSTE-ACS

Because invasive diagnosis plays an important role in the management of NSTE-ACS, we decided to analyze the clinical course of patients who have been made coronary angiography at the beginning and by finding subsequently revascularization, and also in those patients who refused invasive testing (Kovar F et al., 2007).

4.1 Patients and methods

Prospective analysis of consecutive patients admitted to our clinic with a diagnosis of unstable angina or myocardial infarction without ST segment elevation. All patients received comprehensive standard (according to current recommendations) pharmacologic therapy. Within 48 hours was performed coronary angiography and further revascularization therapy if appropriate. Invasive diagnosis was not performed in patients who refused this procedure.

Initial coronary angiography record was analyzed according to location and type of coronary stenosis (A, B, C), closure of coronary artery was evaluated separately.

Lesion type A: a short concentric stenosis, easily accessible, less calcified, without thrombus, without side branch involving (success rate of intervention> 85%, low risk)

Lesion type B: tubular 10 to 20 mm long, eccentric, with the presence of calcifications, involving ostium of coronary artery, bifurcation stenosis, presence of thrombus (intervention success rate 60-85%, moderately high risk)
Lesion type C: diffuse stenosis> 20 mm, extremely coiled proximal segments, bifurcation lesions with the impossibility to access a lateral branches (success rate of intervention <60%, high risk) (Figure 12 a,b,c).
During the one-year follow-up period there were assessed mortality rate, need for repeated hospitalization for ACS or revascularization and left ventricular ejection fraction (LVEF). These endpoint variables were evaluated in four groups of patiens who: 1) underwent percutaneous coronary intervention (PCI) or 2) surgical revascularization (CABG), 3) after angiography were treated conservatively or 4) refused invasive diagnostics in the beginning.

4.2 Statistical analysis

Any analysis of the effectiveness of the treatment was made in four groups of patients: PCI, CABG, conservative treatment and conservative treatment without initial invasive diagnosis. Two-sided Fisher's exact test in the modification of 2 x 4 was used to test hypotheses about the same effect of therapies. χ^2 test were used for *a posteriori* analysis of categorical variables. As statistically significant we considered differences at significance level of $P < 0,05$.

4.3 Results

During the reporting period were for UA and NSTEMI admitted 183 patients, of which 109 were men aged 35-84 (mean ± SD: 55,9 ± 11,6) years and 74 women aged 44-86 (mean ± SD: 66; 5 ± 12.0) years. History and clinical variables are shown in table 3.

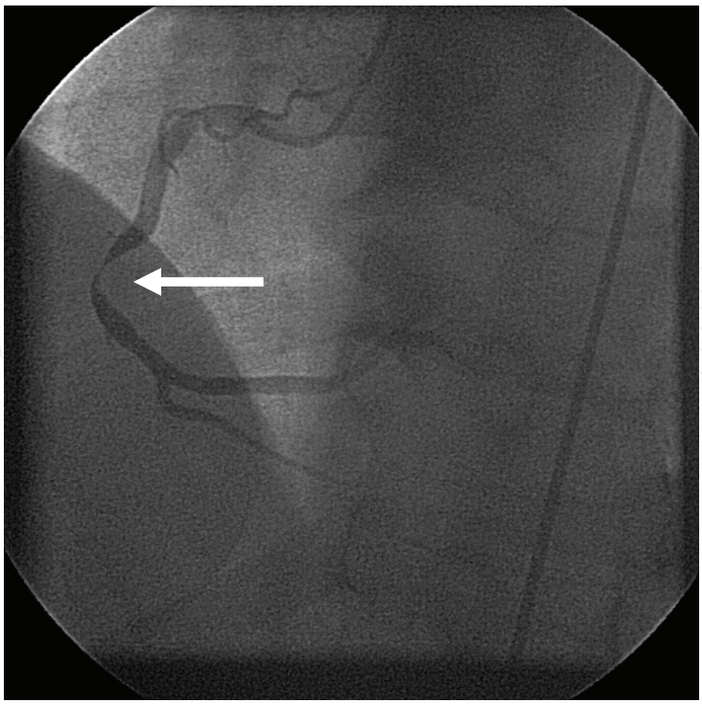


Fig. 12a. Lesion type A

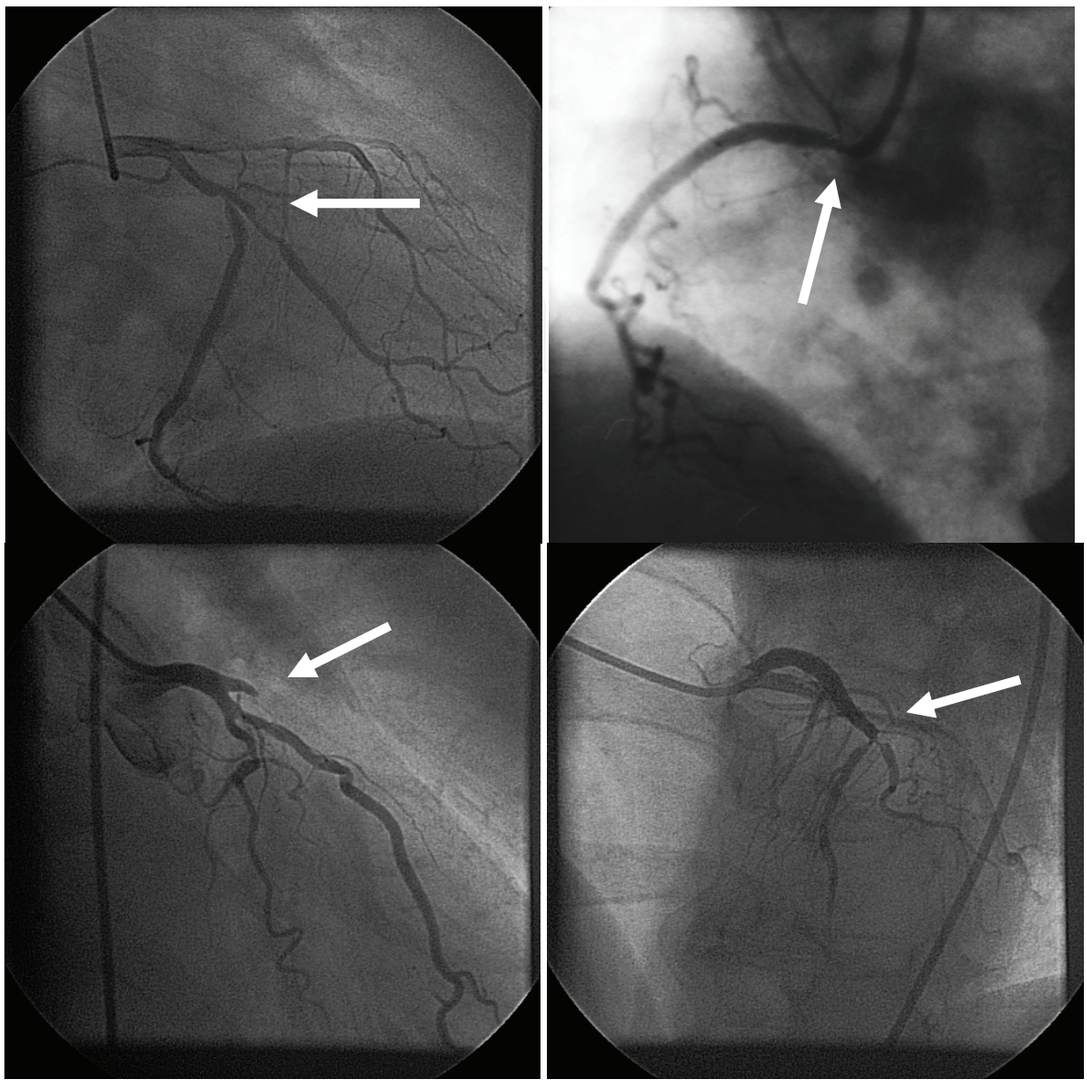


Fig. 12b. Lesions type B

Evaluated population of patients has been at high risk for the presence of cardiovascular risk factors and history of cardiovascular disease: more than 65% patients had hypertension, 37.7% had a myocardial infarction, in nearly 20% was already performed a revascularization of coronary arteries in the past, 9.8% had stroke, hypercholesterolemia was present in 77% and diabetes mellitus in 25.7% of all patients.

Early after hospital admission, 171 patients (93.4%) underwent coronary angiography and 12 (6.6%) patients refused invasive diagnostics (they were also treated conservatively).

There was found in 7.6% of patients closure of coronary arteries, advanced atherosclerotic coronary artery stenosis (stenosis B and C) were evaluated in 67.8% patients on the initial angiography. Frequency of significant coronary arteries stenosis (ramus interventricularis anterior, ramus circumflexus, right coronary artery) was similar (37.4%, 32.8%, respectively 22 %), significant impairment of left main coronary artery was present in 7% of patients.

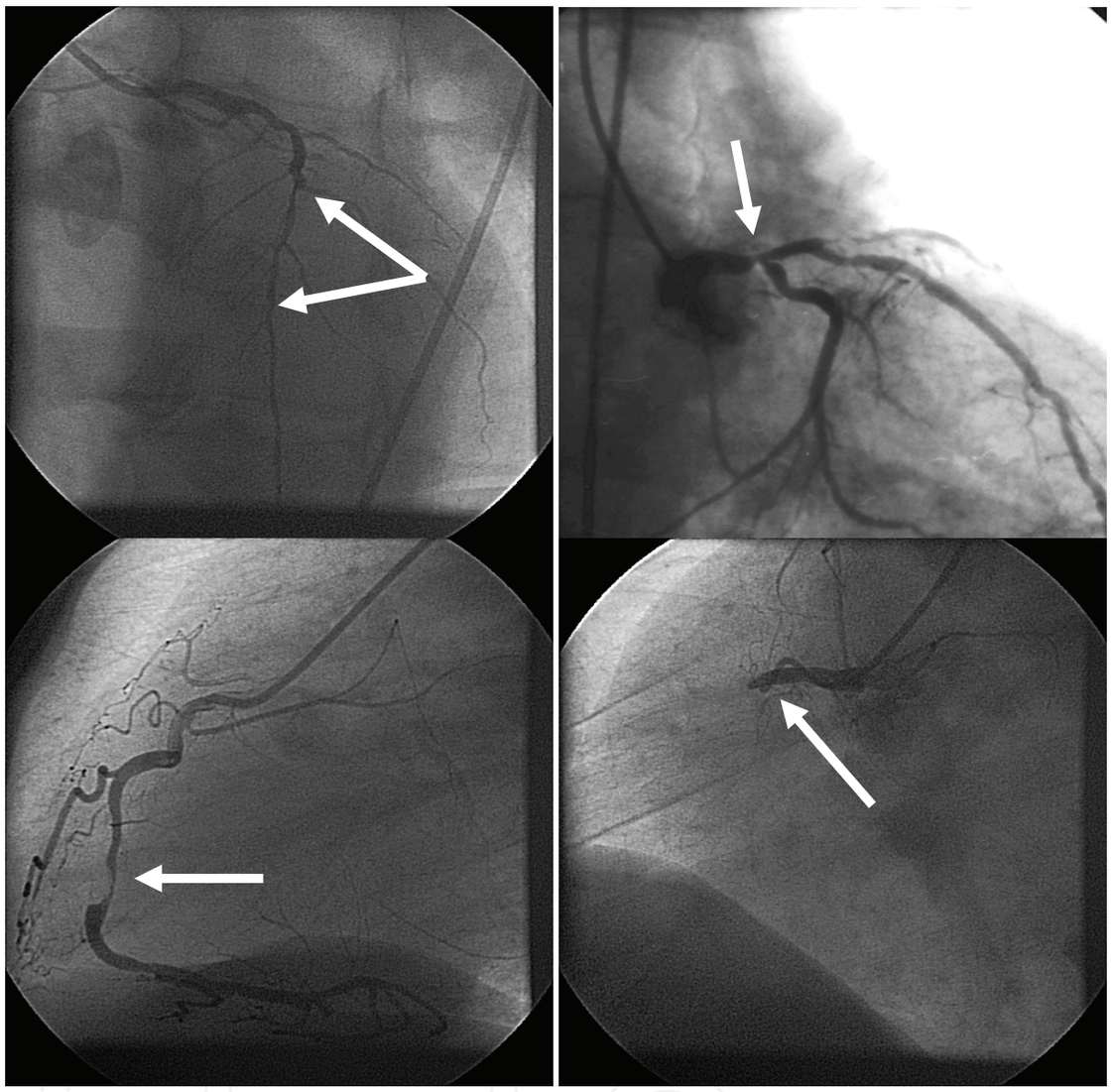


Fig. 12c. Lesions type C

Subsequent coronary revascularization underwent 72.1% of patients (mostly PCI was performed), 21.3% were treated conservatively after angiography and in 6.6% patients was not coronary angiography performed in the beginning.

Table 4. shows the presence of analyzed clinical parameters in different groups during a one-year follow-up, their comparison is in table 5.

There was a trend to higher mortality rate and more frequent need for both repeat hospitalization or revascularization for ACS among patients treated conservatively without angiography at the beginning in comparison with invasive strategy group. LVEF> 50% occurred significantly more in patients treated according angiographic findings compared with patients without initial coronary angiography. The different incidence reached the highest statistical significance when compared group of patients without coronary angiography with patients treated with PCI (a posteriori analysis).

	n	%
No. of patients	183	100,0
men	109	56,3
hypertension	120	65,6
hypercholesterolemia	141	77,0
History of MI	69	37,7
History of PCI	23	12,6
History of CABG	13	7,1
LV insufficiency	39	21,3
history of CVD +	56	30,6
DM	47	25,7
History of ictus	18	9,8
Cigarette smoking	41	22,4
Obesity (BMI ≥ 30)	63	34,4

Table 3. History and clinical variables
MI – myocardial infarction, PCI – percutaneous coronary intervention, CABG – bypass grafting, LV – left ventricle, DM – diabetes mellitus, CVD – cardiovascular disease

1 – year follow up								
	PCI (n = 84)		CABG (n =48)		Without revascularization (n = 39)		Without angiography (n = 12)	
Parameter	**n**	%	**n**	%	**n**	%	**n**	%
Mortality rate	4	4,8	2	4,2	4	10,3	3	25,0
Rehospitalization for UA / PCI / MI	11	13,1	5	10,4	6	15,4	5	41,7
LVEF ≥ 50%	71	84,5	31	64,6	22	56,4	4	33,3
LVEF <50%	13	15,5	17	35,4	17	43,6	8	66,7

Table 4. 1-year follow up
UA – unstable angina, PCI – percutaneous coronary intervention, MI – myocardial infarction, LVEF – left ventricle ejection fraction

	PCI (N = 84)	CABG (N = 48)	Without Revasc. (N = 39)	Without angiography (N = 12)	P value
mortality rate	4 (4,8)	2 (4,2)	4 (10,3)	2 (16,7)	0,2047
repeat hospitalization	11 (13,1)	5 (10,4)	6 (15,4)	5 (41,7)	0,0811
LVEF ≥ 50%	71 (84,5)	31 (64,6)	22 (56,4)	4 (33,3)	0,0001

Table 5. Comparison of applied therapeutic strategies during 1 year follow up
PCI – percutaneous coronary intervention, LVEF – left ventricle ejection fraction, CABG – bypass grafting

5. SLOVACS registry of acute coronary syndromes

Slovak registry of acute coronary syndromes (SLOVACS) deals with data collection and evaluation of patients hospitalized for ACS since 2007 year. Sheets with information about of ACS patients hospitalization are sent by physicians from various hospital departments (coronary units, intensive care units, cardiology or internal departments).

5.1 Objective

The aim of this analysis is to provide an assessment of management of patients with NSTE-ACS in Slovakia in 2008 year and to assess compliance of fair practice and official recommended guidelines for diagnosis and treatment of ACS without ST segment elevations. The source data for analysis were drawn from the registry of acute coronary syndromes SLOVACS (Kovar F et al., 2010).

5.2 Methods

SLOVACS registry is dedicated to both systematic data collection and subsequent analysis of ACS in Slovakia since 2007 year. This registry is organizationally arranged by Slovak Society of Cardiology (SKS) and National Health Information Centre (NHIC) (Studencan M et al., 2008).
Data on patients with acute coronary syndrome are recruited from sheets of ACS, which are completed and electronically transmitted to the NHIC by physicians from different departments (internal, cardiology, intensive care units, coronary units), where is the patient hospitalized with a diagnosis of ACS. This activity is supervised by the special regional coordinators.
In this particular analysis we evaluated data results in patients with NSTE-ACS and non-specified ACS. If the detailed and clear ECG diagnosis and accurate categorization of ACS at admission was not possible, this ACS was marked like non-specified ACS (presence of left bundle branch block, after repeated myocardial infarction, repolarization changes in left ventricular hypertrophy).
In NSTE-ACS population were assessed selected history variables, age and gender of patients. There was made an analysis of given therapy, with special attention to invasive diagnosis of ACS and revascularization therapy (PCI or surgical). It was also evaluated hospital mortality and subsequent analysis of the causes of death.

5.3 Statistical analysis

Descriptive statistics were calculated for patient groups of men and women in the categories of UA / NSTEMI-ACS and non-specified ACS. Averages and standard deviations (SD) were calculated for continuous variables and for categorical variables were calculated frequency distribution or percentage was used respectively. To estimate the statistical significance of differences, Student's *t-test* for continuous variables and Fisher's exact test for categorical variables were used. For statistically significant differences the significance level of $P < 0,05$ was determined. Statistical analysis was performed in SPSS, Windows version 13.0 (SPSS Inc., Chicago, IL, USA).

5.4 Results

There were reported to NHIC 3047 hospitalization for NSTE-ACS and 799 hospitalizations for non-specified ACS during period 1.1.2008 - 31.12.2008. For all subtypes of ACS, women were on average older than men and men diagnosed with NSTE-ACS were significantly older compared with a group of men in the STEMI-ACS (66 ± 12 vs. 61 ± 12, P < 0,001). Tab. 6 shows the proportion of patients in different types of ACS, taking into account age and sex.

	Number of cases			**Mean age (years± SD)**		
	Total	Men	Women	Total	Men	Women
ACS	6 241	3816 (61.1%)	2425 (38.9%)	67 ± 12	64 ± 12	71 ± 11 a
STEMI	2415 (38.7%)	1593 (66.0%)	822 (34.0%)	64 ± 13	61 ± 12 b	71 ± 12 a
UP / NSTEMI	3047 (48.8%)	1799 (59.0%)	1268 (41.0%)	68 ± 12	66 ± 12	71 ± 11 a
Non-spec. ACS	799 (12.5%)	444 (55.6%)	355 (44.4%)	68 ± 12	65 ± 13	71 ± 11 a

Table 6. Distribution of ACS by type, age and sex

[a] P < 0,001 men vs women, [b] P < 0,001 men with STEMI vs men with NAP/NSTEMI, ACS - acute coronary syndrome, STEMI - acute coronary syndrome with ST segment elevation, UA / NSTEMI - Unstable angina pectoris / myocardial infarction without ST segment elevations

5.5 Anamnestic data

Each patient was systematically assessed with respect to the evidence of hypertension, diabetes mellitus type I or II, history of stroke. As is apparent from the graphs 12 and 13, in both types of ACS was significantly often present arterial hypertension (80.1% respectively 78.3%) and diabetes mellitus type II (30.3% respectively 27.1%) and 12.1% of patients has history of stroke (Figures 13 and 14).

Occurence of concominat diseases in patinens with non-STE-ACS was similar in both SLOVACS registries 2007 and 2008 years (Figure 15).

5.6 Revascularization therapy

Among 3047 patients with NSTE-ACS coronary angiography was performed in 943 patients (30.9%) during index hospitalization, 799 patients (26.2%) were sent to catheterization laboratory from other institutions. Of the 799 patients with non-specified ACS was performed coronary angiography in 284 patients (35.5%). To invasive diagnosis were referred 187 patients (23.4%) from other hospitals (without catheterization facilities).

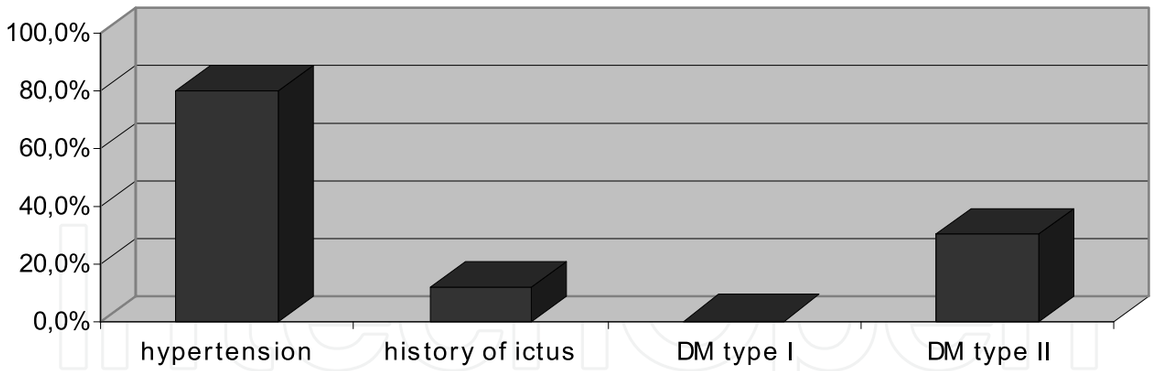


Fig. 13. Occurrence of major diseases observed in patients with UA / NSTEMI
DM - diabetes mellitus, UA / NSTEMI - Unstable angina pectoris / myocardial infarction without ST segment elevations

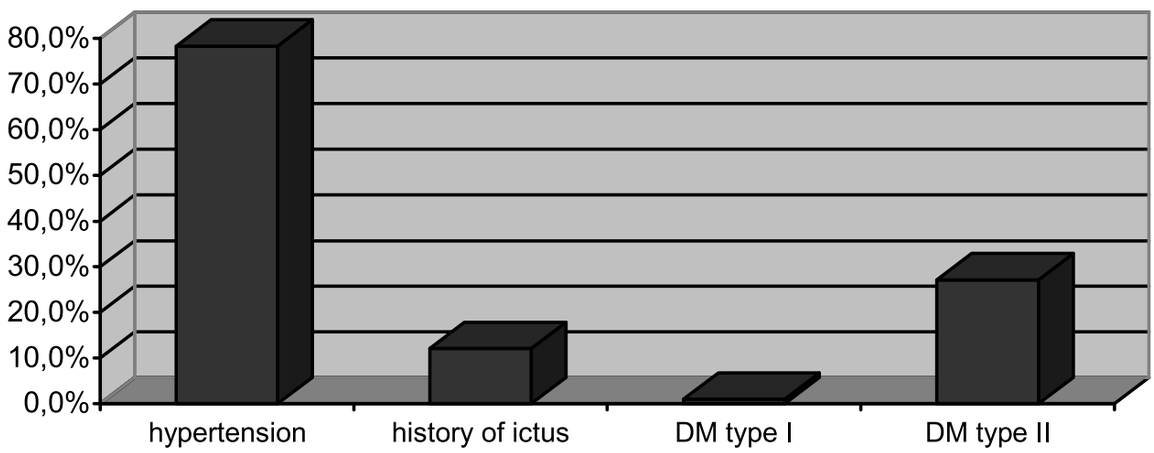


Fig. 14. Occurrence of major diseases observed in patients with non-specified ACS
DM - diabetes mellitus, ACS - acute coronary syndrome

Percutaneous coronary intervention (PCI) was performed in 409 patients (13.4%) with NSTE-ACS and 50 patients (6.3%) with non-specified ACS. During PCI was in NSTE-ACS implanted 370 intracoronary bar metal stents and 76 (20.5%) drug eluting stents. In non-specific ACS patients were during intervention procedures implanted 111 stents, including 17 (15.3%) drug eluting stents.
Surgical revascularization (CABG) was performed during hospitalization for NSTE-ACS in 165 patients (5.4%) or was scheduled electively for additional 128 patients (4.2%). Together was cardiac therapy planned for 293 patients (9.6%). In case of non-specific ACS were performed CABG immediately in 27 patients (3.5%), and planned later in 30 pts. (3.8%), together was cardiac revascularization indicated in 57 patients (7.3%).

5.7 Pharmacological treatment

SLOVACS registry systematically monitor the use of antiplatelet therapy (aspirin, clopidogrel), platelet glycoprotein IIb / IIIa receptor blockers, unfractionated and low molecular weight heparin, beta blockers, angiotensin converting enzyme inhibitors and statins. Use of individual drug groups shows table 7 and 8.

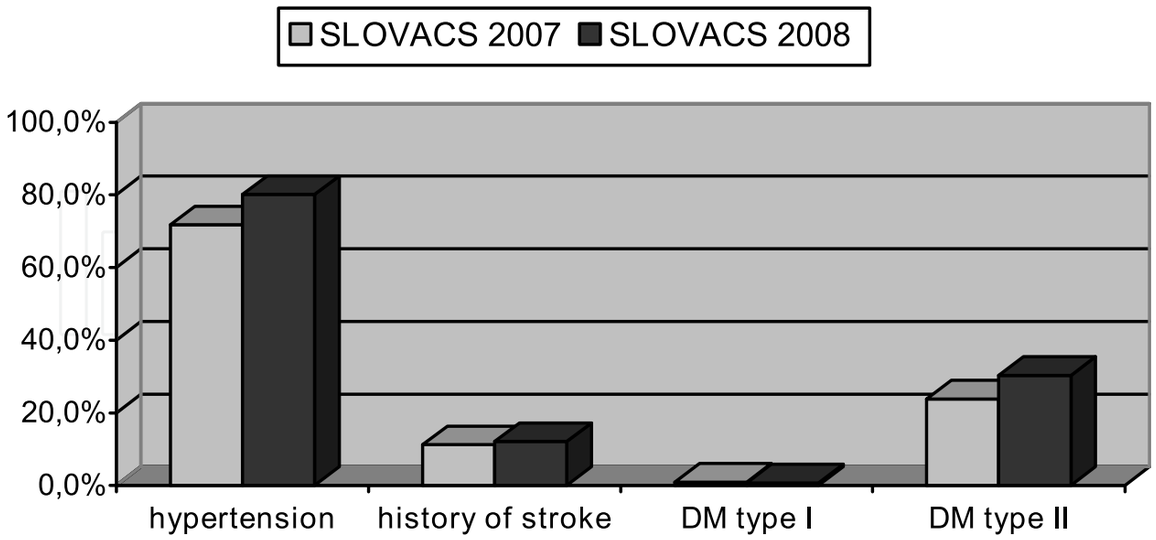


Fig. 15. Comparison of incidence of major diseases in patients with NSTE-ACS in both SLOVACS registry 2007 and 2008 year

Pharmacological treatment	N (%)
Aspirin	2753 (90.4%)
GP IIb / IIIa	70 (2.3%)
Clopidogrel	2636 (86.5%)
Beta-blocker	2471 (81.1%)
Heparin (UFH)	729 (23.9%)
Heparin (LMWH)	2267 (74.4%)
ACE inhibitor	2410 (79.1%)
Statin	2403 (78.9%)

Table 7. Concomitant treatment studied in patients with UA / NSTEMI
GP - platelet glycoprotein IIb / IIIa receptor blockers, UFH - unfractionated heparin, LMWH - low molecular weight heparin, ACE - angiotensin converting enzyme, UA / NSTEMI - Unstable angina pectoris / myocardial infarction without ST segment elevation

5.8 Hospital mortality analysis and causes of death

In group of patients hospitalized with a diagnosis of NSTE-ACS, 109 patients died (3.6%). Analysis of causes of death during hospitalization for men and women in the group with NSTE-ACS is shown in table 9 and 10.

Pharmacological treatment	N (%)
Aspirin	690 (88.6%)
GP IIb / IIIa	19 (2.4%)
Clopidogrel	625 (80.2%)
Beta-blocker	615(79.2%)
Heparin (UFH)	207 (26.6%)
Heparin (LMWH)	507 (65.1%)
ACE inhibitor	619 (79.5%)
Statin	598 (76.9%)

Table 8. Concomitant treatment studied in patients with non-specified ACS
GP - platelet glycoprotein IIb / IIIa receptor blockers, UFH - unfractionated heparin, LMWH - low molecular weight heparin, ACE - angiotensin converting enzyme, UA / NSTEMI - Unstable angina pectoris / myocardial infarction without ST segment elevation

Immediate cause of death	men	women	P
	N (%)	N (%)	
Proportion of all deaths	47 (2.6%)	62 (4.9%)	<0.001
Rupture of interventricular septum	0 (0%)	1 (1.6%)	0,413
Higher degree AV block	0 (0%)	1 (1.6%)	0,413
Cardiogenic shock	15 (31.9%)	22 (35.5%)	0,011
Pulmonary edema	5 (10.6%)	8 (12.9%)	0,076
Ventricular fibrillation	3 (6.4%)	4 (6.5%)	0,206
Other cardiac events	19 (40.4%)	18 (29.0%)	0,087
Stroke	2 (4.3%)	1 (1.6%)	0,426
Other non-cardiac cause	3 (6.4%)	7 (11.3%)	0,049

Table 9. The immediate cause of death in patients with UA / NSTEMI during the hospitalization phase
UA / NSTEMI - Unstable angina pectoris / myocardial infarction without ST segment elevation, AV - atrioventricular

Immediate cause of death	men	women	P
	N (%)	N (%)	
Proportion of all deaths	20 (4.5%)	28 (8.4%)	0.017
Rupture of interventricular septum	0 (0%)	0 (0%)	-
Higher degree AV block	1 (5.0%)	1 (3.4%)	0,494
Cardiogenic shock	7 (35.0%)	14 (50.0%)	0,021
Pulmonary edema	4 (20.0%)	2 (7.1%)	0,283
Ventricular fibrillation	2 (10.0%)	3 (10.7%)	0,271
Other cardiac events	4 (20.0%)	4 (14.3%)	0,261
Stroke	1 (5.0%)	1 (3.4%)	0,494
Other non-cardiac cause	1 (5.0%)	3 (10.7%)	0,195

Table 10. The immediate cause of death in patients non-specified ACS during the hospitalization phase
UA / NSTEMI - Unstable angina pectoris / myocardial infarction without ST segment elevation, AV - atrioventricular

Comparison of hospital mortality data from the register SLOVACS per year 2007 and 2008 and the Euro Heart Survey II provides figure 16.

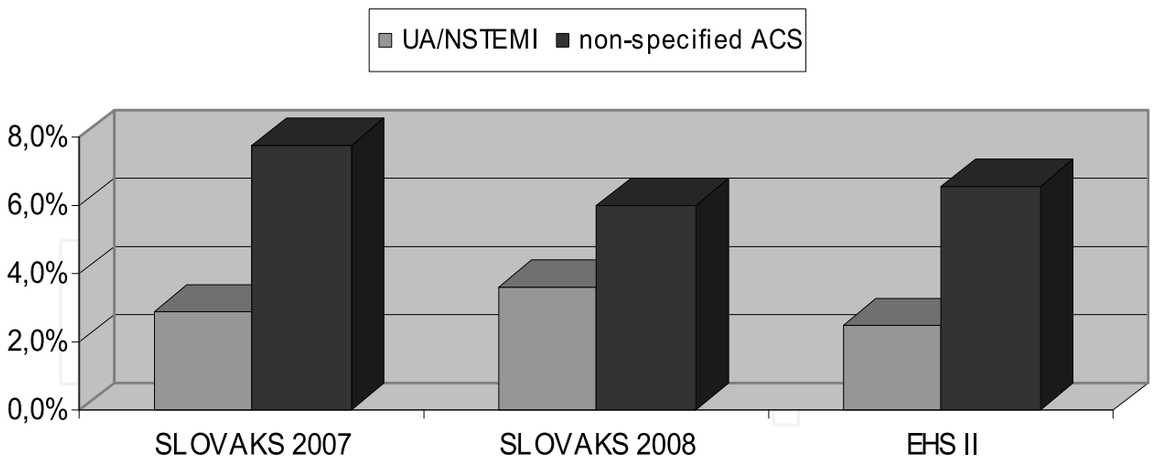


Fig. 16. Hospital mortality rate in patients with UA / NSTEMI ACS and non-specified ACS in SLOVACS registry per year 2007 and 2008 and EHS II
UA / NSTEMI - Unstable angina pectoris / myocardial infarction without ST elevation, ACS - acute coronary syndrome, EHS - Euro Herat survey

As apparent, pharmacologic treatment is administered sufficiently according guidelines. Few, however, were indicated glycoprotein IIb / IIIa platelet receptors blockers, which are applied mainly in patients during coronary intervention. Comparison with data from the register SLOVACS in 2007 and 2008 and Euro Heart Survey I and II is given in figure 17.

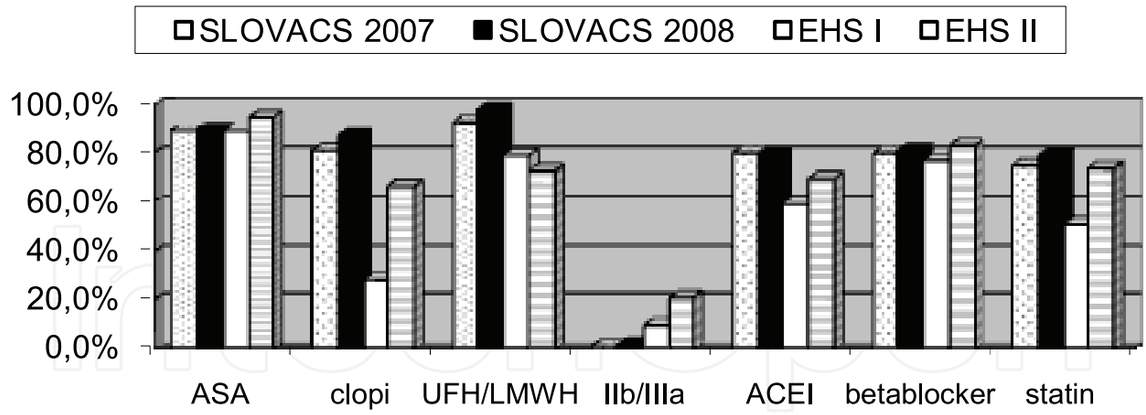


Fig. 17. Comparison of applied concomitant therapy for patients with UA / NSTEMI in the register SLOVACS 2007 and 2008 and EHS I and II
ASA - acetylsalicylic acid, clopi – clopidogrel, IIb/IIIa - platelet glycoprotein receptor blocker, UFH - unfractionated heparin, LMWH - low molecular weight heparin, ACEI - angiotensin converting enzyme inhibitor, EHC - Euro Herat survey

However, disappointing is the low proportion of patients with NSTE-ACS who are indicated for invasive diagnosis and possible subsequent coronary vessels revascularization. Comparison of data from the SLOVAKS registry 2007 and Euro Heart Survey II in terms of indications of coronary angiography and percutaneous coronary intervention in patients with NSTE-ACS shows figure 18.

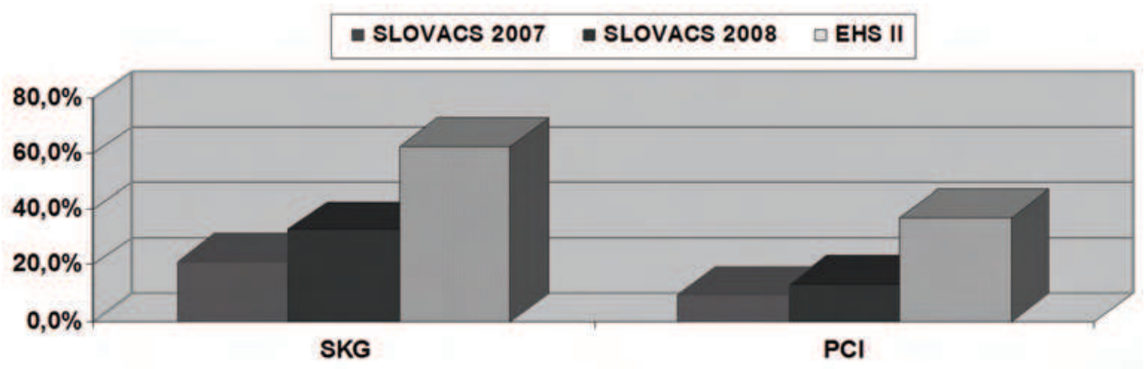


Fig. 18. Consumption of coronary angiography and PCI in patients with UA / NSTEMI according to the data from SLOVACS registry 2007 and 2008 and the EHS II
SKG - selective coronary angiography, PCI - percutaneous coronary intervention, EHS - Euro Heart Survey

Of patients who were not admitted to departments with the option for invasive diagnosis, were transferred to catheterization only 799 of 2405 patients (33.2%). Of the total number of admissions for NSTE-ACS, diagnostic catheterization underwent 943 (30.9%) patients, interventional treatment was performed in 409 patients (13.4%). These data are similar to data from other registries ACS (Polonski L et al., 2007).
There is even more serious situation in the indication of patients for invasive diagnosis among non-specified ACS group, which has highest hospital lethality (6%) in comparison

with various types of ACS. These patients are often elderly, with more significant co morbidity, renal insufficiency (Lev EI et al., 2003). From invasive diagnostic benefit most patients with high risk of cardiovascular complications.

Patients with UA / NSTEMI represent a heterogeneous group of diseases with potentially serious both in-hospital course and long-term prognosis. As was found by the results of SLOVACS registry 2008, there is frequent co morbidity with high presence of hypertension and diabetes mellitus type II in patients with NSTE-ACS. Hospital mortality was 3.6%, in patients with NSTE-ACS and 6% in non-specified ACS, respectively. SLOVACS registry data confirm excellent acceptance of recommendations, relating to the combined pharmacological treatment of NSTE-ACS with a high administeration rate of dual antiplatelet therapy, beta blockers, angiotensin converting enzyme inhibitors, anticoagulant therapy (UFH and LMWH) and statins. In the management of NSTE-ACS would be desirable more frequent application of platelet glycoprotein IIb / IIIa inhibitors, especially in high-risk patients. Unsatisfactory low is the indication rate for invasive diagnostic procedures and revascularization treatment. Only 30.9% of patients with UA / NSTEMI and 23.4% with non-specified ACS have performed selective angiography during the initial hospitalization. PCI was performed in 13.4% patients with NSTE-ACS and only 6.3% patients with non-specified ACS. SLOVACS registry results suggest the need for increased concentration of attention on a consistent risk stratification of patients with NSTE-ACS. In the case of medium or high risk of cardiovascular complications and unfavorable course, patients should be indicated for selective angiography and depend on finding, further coronary artery revascularization. Invasive diagnosis in these patients has to be conducted during the index hospitalization for NSTE-ACS.

6. Impact of bleeding complications on the prognosis of NSTE-ACS

In most cases a vulnerable plaque (with rupture or erosion) in the coronary artery with the presence of intracoronary platelets rich thrombus represents pathophysiologic basis of ACS. The key basic treatment regimen for NSTE-ACS is, therefore, antiplatelet therapy (mostly dual) and application anticoagulants agents (unfractionated heparin, low molecular weight heparin, fondaparinux, and direct thrombin inhibitors). In patients treated with PCI are often administered platelet IIb / IIIa receptor blocker. These combined and effective antithrombotic approaches significantly reduce the incidence of thrombotic complications in NSTE-ACS, but are often associated with an increased risk of bleeding. Recently, systematic attention is paid to the impact of bleeding on prognosis in patients with NSTE-ACS.

6.1 Occurrence

Bleeding complications can achieve varying degrees of severity. The most frequently used assessment is according to the TIMI (Thrombolysis in myocardial infarction) and GUSTO (Global utilization of streptokinase and t-PA for occluded coronary arteries) criteria (Table 11) (Antman EM et al., 2005; GUSTO investigators, 1993).

The incidence of major bleeding complications in the treatment of NSTE-ACS is in the range 2-15% (OASIS-2 investigators, 1999; Ferguso JJ et al., 2004; Bhat DL et al., 2004). Frequency of bleeding is influenced by excessive dose antithrombotic medications, antithrombotic agents alternation (switching), presence of renal dysfunction, higher age of the patient and female gender (Alexander KP et al., 2005; Collet JP et al., 2005). European register GRACE (Global

registry of acute coronary events) has identified additional independent predictors of major bleeding complications in NSTE-ACS patients (Table 12) (Moscucci M et al., 2003).

Hemorrhage	Characteristics of bleeding
TIMI classification	
Large	intracranial, decreased Hb ≥ 50 g / l
Small	decrease in Hb 30-50 g / l
Minimum	decrease in Hb <30 g / l
GUSTO classification	
Severe / life -threatening	intracranial or hemodynamically significant or requiring intervention
Medium	requiring transfusion but without hemodynamic disability
Slightly	does not meets the criteria for severe or moderate major bleeding

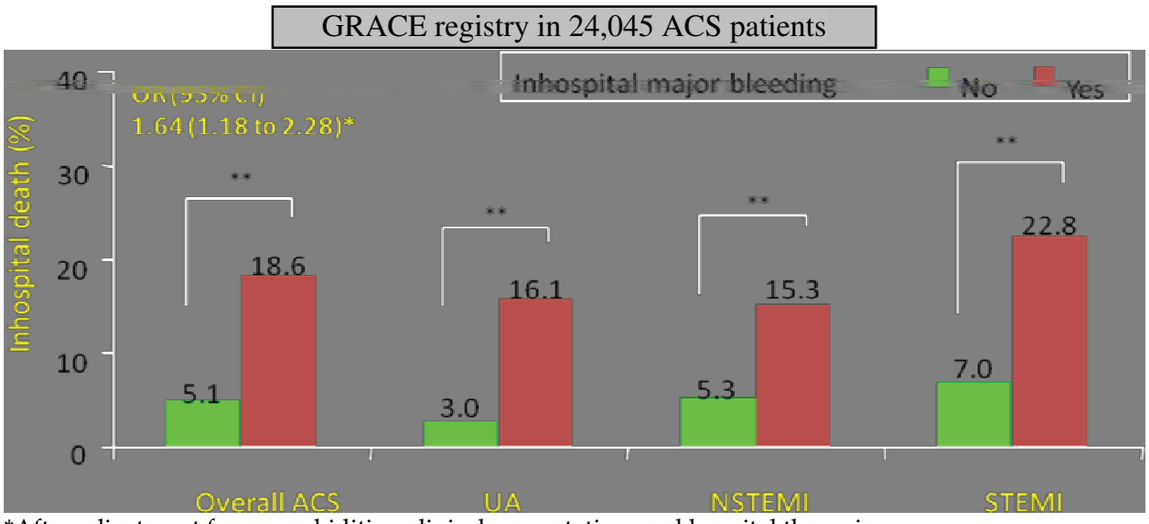
Table 11. Assessment of severity of bleeding in acute coronary syndrome
TIMI = Thrombolysis in myocardial infarction, GUSTO = Global utilization of streptokinase and t-PA for occluded coronary arteries

Parameter	Adjusted OR	95% CI	P
age (increase per 10year)	1,22	1,10-1,35	0,0002
female sex	1,36	1,07-1,73	0,0116
renal insufficiency	1,53	1,13-2,08	0,0062
history of bleeding	2,18	1,14-4,08	0,014
mean BP (per 20mmHg decrease)	1,14	1,02-1,27	0,019
diuretic therapy	1,91	1,46-2,49	<0.0001
IIb / IIIa receptor blocker therapy	1,86	1,43-2,43	<0.0001
fibrinolysis receptor blocker + IIb / IIIa	4,19	1,68-10,4	0,002
administration of inotropic agents	1,88	1,35-2,62	0,0002
right-sided catheterization	2,01	1,38-2,91	0,0003

Table 12. Independent predictors of major bleeding in NSTE-ACS
NSTE ACS = acute coronary syndrome without ST segment elevation, BP = mean blood pressure

6.2 The prognosis in patients with severe bleeding

Significant increase of hospital mortality rate in patients with ACS and bleeding (OR 1.64, p <0.0001) highlighted the results from the GRACE registry, which collects data of patients with NSTE ACS already since 1999 year (Moscucci M et al., 2003) (Figure 19).



*After adjustment for comorbidities, clinical presentation, and hospital therapies
**p<0.001 for differences in unadjusted death rates

Fig. 19. Association of major bleeding and an increased risk of hospital death in ACS patients

In REPLACE (Randomized Evaluation of PCI linking angiomax to reduced clinical events) - 2 study, patients with major bleeding had 30 times higher risk of death during the 30-day monitoring in comparison with patients without such bleeding complications (5.2% vs. 0.2%; p <0.001). Moreover, the multivariate analysis identified a major bleeding as the third strongest predictor (with renal dysfunction and heart failure) of 1-year mortality (OR 3.53, 95% CI 1.91 to 6.53, p <0.0001) (Stone GW, 2004).

Analysis of more than 26 000 patients from ACS studies GUSTO (Global utilization of streptokinase and t-PA for occluded coronary arteries) IIb, PURSUIT (Platelet glycoprotein IIb / IIIa in unstable angina: receptor suppression using INTEGRILIN therapy) and PARAGON (Platelet IIb / IIIa antagonist for the reduction of acute coronary syndrome events in a global organization network) shows a link between 30-day mortality and severity of bleeding, irrespectively of invasive procedures (Figure 20) (Rao SW et al., 2005).

Another meta-analysis (34 000 patients) from OASIS (Organization to ASSESS strategies in acute ischemic syndromes) registry, OASIS-2 study and CURE (Clopidogrel in unstable angina to Prevent Recurrent Events) study confirmed that serious bleeding is a strong independent predictor of mortality, myocardial infarction and stroke (Table 13) (Eikelboom JE et al., 2006).

Interesting results were shown by a 10-year retrospective analysis of 11 000 patients treated with PCI (Kinnaird TO et al., 2003). Major bleeding was confirmed as an independent risk factor for hospital mortality (OR 3.5, 95% CI 1.9 to 6.7, p = 0.001). Patients with bleeding complications had significantly higher incidence of Q-wave myocardial infarction (1.2% vs. 0.2%, p <0.001), non Q-wave myocardial infarction (30.7% vs. 11.8%, p <0.001) and needs for repeat revascularization (1.9% vs. 0.3%, p <0.001) compared with the group without bleeding. Significantly increased risk of death was associate with bleeding by TIMI criteria rated as small as well (1.8% vs. 0.6%, p <0.001) (Figure 21).

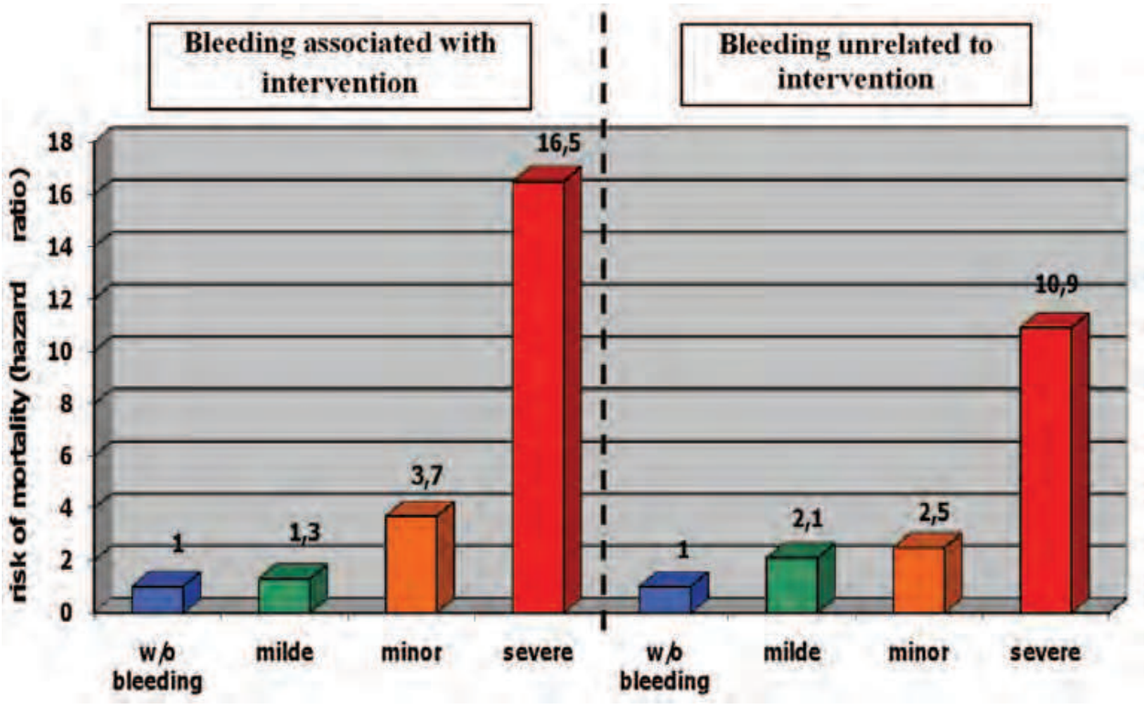


Fig. 20. Effect of bleeding severity by GUSTO criteria on 30-day mortality in patients with NSTE-ACS
GUSTO = Global utilization of streptokinase and t-PA for occluded coronary arteries, NSTE-ACS = acute coronary syndrome without ST segment elevation

OASIS registry, OASIS-2 and CURE (N = 34 126)				
Parameter	**Severe bleeding**	**No major bleeding**	**Adjusted HR (95% CI)**	**P**
Mortality	12.8%	2.5%	5.37 (3,97-7,26)	<0.0001
Myocardial infarction	10.6%	4.1%	4.44 (3,16-6,24)	<0.0001
Stroke	2.6%	0.6%	6.46 (3,54-11,79)	<0.0001

Table 13. Effect of bleeding on the clinical course
OASIS = Organization to assess strategies in acute ischemic syndromes, CURE = Clopidogrel in unstable angina to prevent recurrent events

Unambiguous confirmation of the negative impact of bleeding on the both early and long-term prognosis of patients with NSTE-ACS was brought by randomized trial OASIS-5 (Yusuf S et al., 2006). This clinical study compared the effect of fondaparinux and enoxaparin in the treatment of more than 20 000 patients with NSTE-ACS. Although the primary efficacy endpoint (incidence of death, myocardial infarction or refractory ischemia to day 9) was similar in both groups (5.8% vs. 5.7%, p = ns), treatment with fondaparinux was associated with significantly lower incidence of bleeding complications (2.2% vs. 4.1%, p <0.001). Net clinical benefit, expressed the occurrence of death, myocardial infarction,

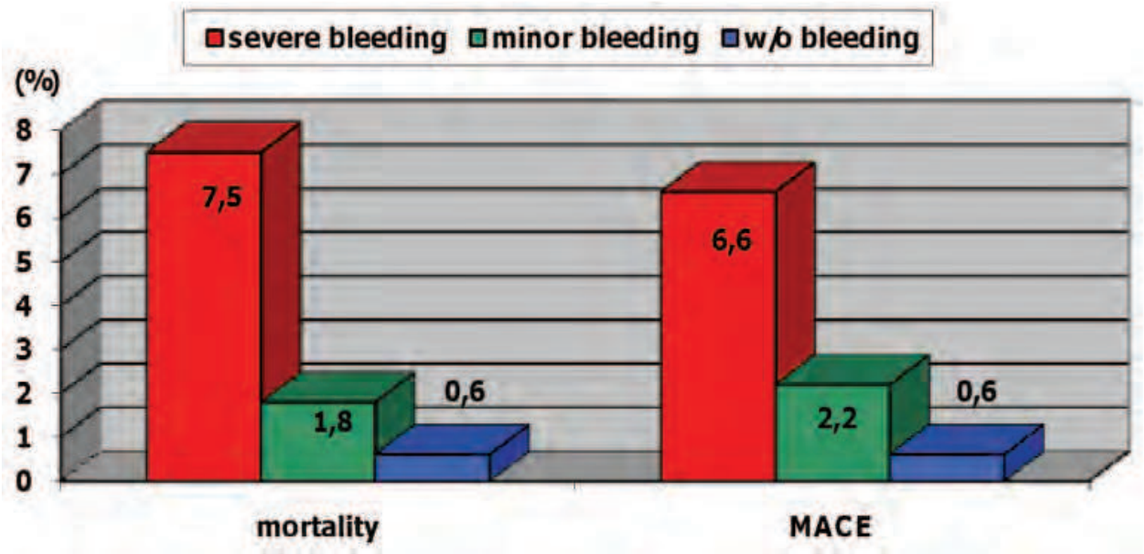
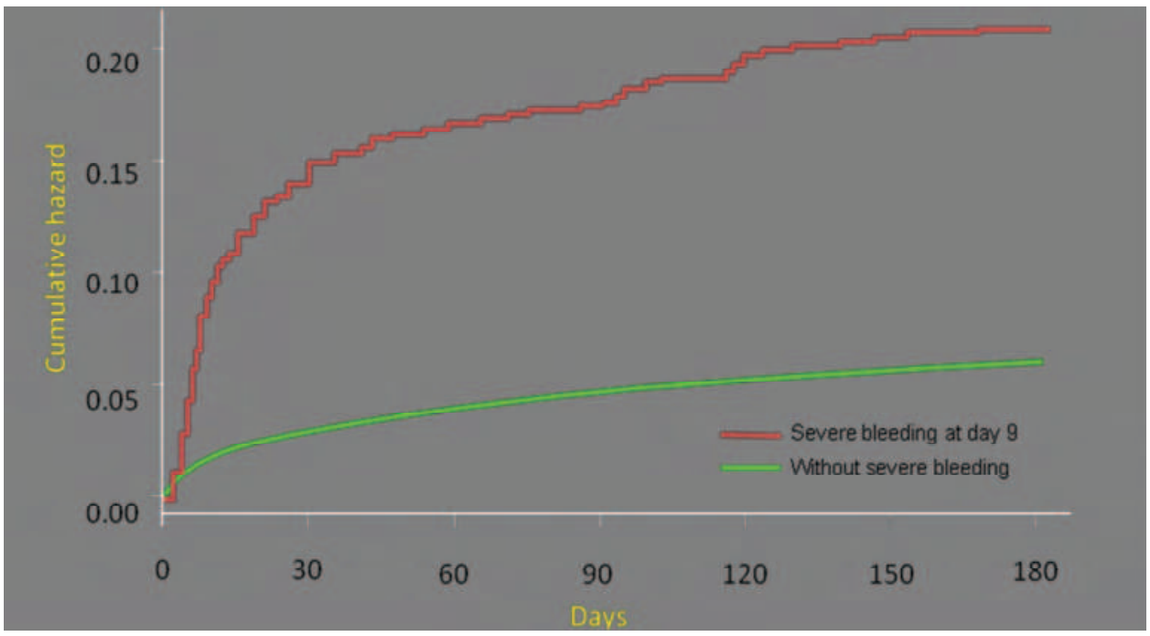


Fig. 21. Effect of bleeding on the hospital course in patients treated with PCI
PCI = percutaneous coronary intervention, MACE = major cardiac events

OASIS-5 (n = 20,078)		
	30 days	**180 days**
Major bleeding	**HR (95% CI)**	**HR (95% CI)**
Death	5.06 (4,59-5,62)	3.16 (2,92-3,44)
Myocardial infarction	5.01 (4,56-5,57)	2.99 (2,75-3,28)
CMP	4.77 (3,95-6,00)	3,30 (2,82-3,97)
Minor bleeding	**HR (95% CI)**	**HR (95% CI)**
Death	2.42 (2,03-2,97)	1.76 (1,31-2,37)
Myocardial infarction	1.48 (1,28-1,78)	1,29 (1,15-1,48)
CMP	1.54 (1,06-2,67)	1.48 (0,76-2,89)

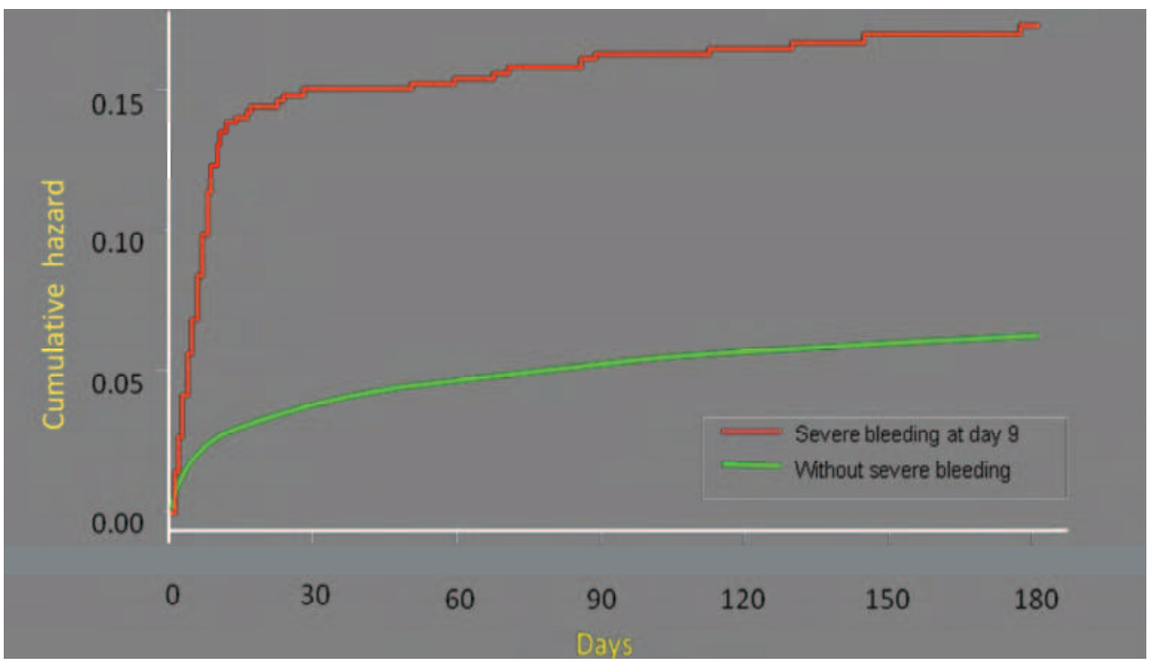
Table 14. Effect of bleeding to day 9 at 30 and 180-day course of patients with NSTE-ACS
OASIS = Organization to ASSESS strategies in acute ischemic syndromes, stroke = stroke, NSTE-ACS = acute coronary syndrome without ST segment elevation

refractory ischemia or major bleeding was more favorable in fondaparinux group (7.3% vs. 9.0%, p <0.001). Patients with significant bleeding to 9 day, had during a long-term (30 and 180 days) follow-up in the OASIS-5 study higher cumulative risk of mortality, myocardial infarction and stroke. This increased cumulative risk was present even in group of patients with a small bleeding (Table 14, Figure 22, 23, 24) (Budaj A et al., 2006).



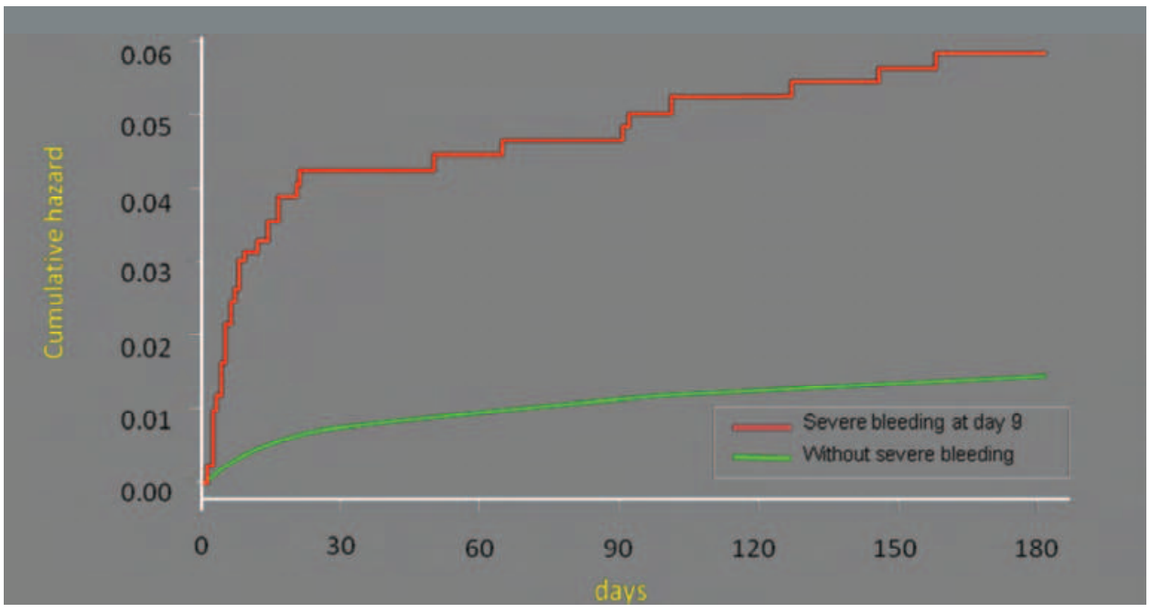
Adjusted HR (95% CI) at day 30: 5.06 (4.59-5.62); at day 180: 3.16 (2.92-3.44)

Fig. 22. Increase mortality rate in patients with severe bleeding at day 9 (all pts at day 30 resp. day 180)



Adjusted HR (95% CI) at day 30: 5.01 (4.56-5.57); at day 180: 2.99 (2.75-3.28)

Fig. 23. Increase risk of myocardial infarction in patients with severe bleeding at day 9 (all pts at day 30 resp. day 180)



Adjusted HR (95% CI) at day 30: 4.77 (3.95-6.00); at day 180: 3.30 (2.82-3.97)

Fig. 24. Increase risk of stroke in patients with severe bleeding at day 9
(all pts at day 30 resp. day 180)

6.3 The mechanisms for worsening clinical course

There are postulated several mechanisms in connection with bleeding that could worse clinical course in NSTE-ACS (Table 15).

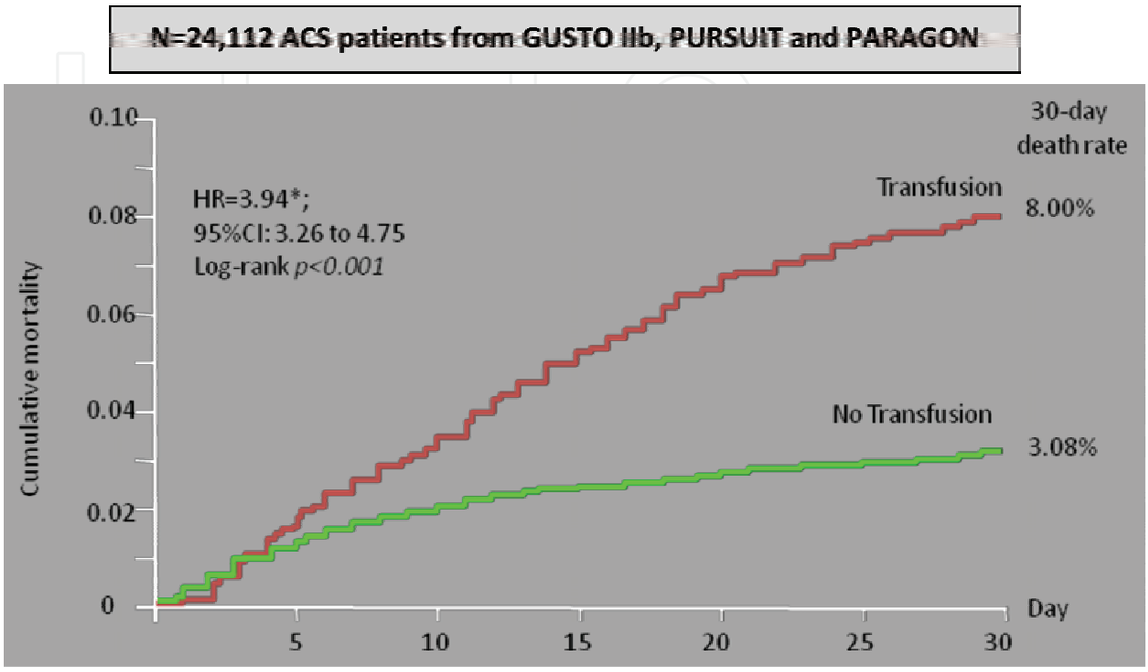
hemodynamic consequences
renal failure
effect of transfusion
prothrombotic and proinflammatory state triggered by bleeding
need to discontinue antiplatelet and anticoagulant therapy

Table 15. Postulated mechanisms of worse course during bleeding

Serious consequence of bleeding is interruption of antithrombotic therapy. Clinically significant bleeding actually required discontinuation of anticoagulant and antiplatelet therapy until resolution. In the case of small transition bleeding is often possible to continue this therapy (Bassand JP et al., 2007).

Application of blood transfusion improves the prognosis of elderly patients with acute myocardial infarction and hematocrit <30% (Wu WC et al., 2001). However, in the hematocrit values > 33% there was not demonstrated the usefulness of a blood transfusion.

By contrast, in several clinical trials and meta-analysis, the administration of blood transfusion was associated with increased mortality, higher incidence of myocardial infarction and refractory ischemia (Sabatine MS et al., 2005; Rao SW et al., 2004) (Figure 25).



Adjusted for baseline characteristics, bleeding and transfusion propensity and nadir hematocrit

Fig. 25. Association of blood transfusion with an increased 30-day mortality in UA/NSTEMI patients

On the worsening clinical course in patients with NSTE-ACS after transfusion administration may participate:

a. erythrocyte damage
b. influence the metabolism of NO in blood storage
c. impaired release of oxygen from hemoglobin in the reduction content of 2,3 - difosfoglycerate in erythrocytes
d. increase inflammatory mediators (Fransen SV et al., 2008)

Accurate cut-off level of hemoglobin and hematocrit for indication of blood transfusion in patients with NSTE-ACS are not provided. According to current recommendations of the European Society of Cardiology transfusion is not indicated for hemoglobin> 80g / 1 or hematocrit> 25%, provided that anemia is a hemodynamically well tolerated (Bassand JP et al., 2007).

6.4 Prevention of bleeding complications

Given the demonstrated risk of severe clinical events associated with bleeding and administration of blood transfusions, it is extremely important to use in patients with NSTE-ACS all available measures in bleeding prevention. It is necessary to focus particularly on:

- choice of safe drug (fondaparinux in OASIS-5 study)
- appropriate dosage (taking into account age, gender, creatinine clearance)
- duration of antithrombotic therapy
- timing of early invasive treatment
- choice of arterial access
- combination of anticoagulant and antiplatelet therapy to choose only by certified indications

Prevention of bleeding complications is also important in terms of reducing hospital costs for treatment of NSTE-ACS. As shown by economic analysis of the GUSTO IIb study, with an increase in severity of bleeding, there is prolonged hospitalization and rising financial costs. Length of hospitalization for NSTE-ACS without bleeding was 5.4 days, with slight bleeding 6.9, with moderate 15.0 days, and severe bleeding 16.4 days ($p < 0.01$). Financial cost of hospitalization in each group significantly increased as follows: 14 282 USD vs. 21 674 USD vs. 45 798 USD vs. 66 564 USD ($p < 0.01$) (Rao SV et al., 2008).

7. Conclusion

In addition to a comprehensive pharmacologic treatment of NSTE-ACS, which includes the combined antiplatelet regimens (aspirin, clopidogrel, platelet receptor IIb / IIIa blockers) and effective anticoagulant therapy, plays an important role early invasive diagnosis and by finding subsequent coronary artery revascularization. From invasive procedures benefit most high risk patients with NSTE-ACS, who undergoing PCI. Early invasive strategy is for this risk group of patients safe and is associated with long-term favorable clinical course and substantially influence prognosis.

There is very important in NSTE-ACS patients risk stratification at the beginning and according to the assessed risk scores subsequent decision for urgent or early invasive strategy. In low-risk NSTE-ACS is indicated stress test and in case of inducible ischemia is than followed by coronary angiography before hospital discharge.

Patients with NSTE-ACS represent a risk population with an increased incidence of ischemic and bleeding complications. Bleeding events significantly affect both short and long-term prognosis of patients with NSTE-ACS. This is why it is necessary in the global risk stratification of NSTE-ACS a careful assessment of the risk of bleeding. Balanced assessment of the risk for both thrombotic and bleeding complications allows then to select optimal diagnostic and therapeutic management of patients with NSTE-ACS.

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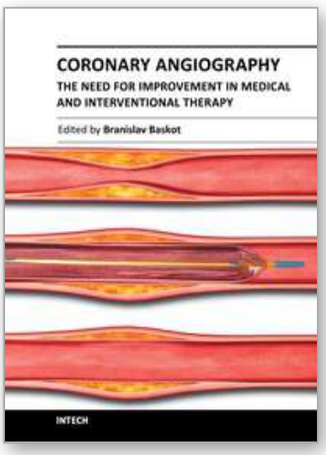

Coronary Angiography - The Need for Improvement in Medical and Interventional Therapy

Edited by Prof. Baskot Branislav

ISBN 978-953-307-641-6
Hard cover, 206 pages
Publisher InTech
Published online 06, September, 2011
Published in print edition September, 2011

In this book we examined a periprocedural complication of coronary angiography, and coronary intervention. That includes related to cardiac catheterization and diagnostic coronary angiography, and those that occur as a consequence of the specific equipment. However, improvements in devices, the use of stents, and aggressive antiplatelet therapy have significantly reduced the incident of major periprocedural complications. This book giving knowledge and experiences many of interventional cardiologists from all over the world, and provide possibility to recognize new approach in this domain. Book gives lecture on how we image and how we decide on what to treat, how to treat it, and then results of that treatment. They offer many answers to what we have today and what we will have tomorrow.

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