Original Research Article

Early or selective invasive strategy in patients with non-ST-segment elevation acute coronary syndrome according to the risk factors at presentation? An outcome study.

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ABSTRACT

Aims: Patients with acute coronary syndrome without ST segment elevation are a heterogeneous group with respect to the risk of having a major adverse cardiac event (MACE). History of diabetes mellitus (DM), chronic kidney disease (CKD) and elevated GRACE risk score are all factors defining a higher risk of MACE. We aimed to compare the outcome of patients with early vs selective invasive strategy according to the risk factors at presentation.

Methodology: We enrolled 178 patients with unstable angina or non-ST elevation myocardial infarction (UA/NSTEMI), 52 (29.2%) had DM, 32 (19.7%) - CKD, defined when MDRD measured glomerular filtration rate (GFR) was < 60 ml/min/1.73 m2 and 28 (15.7%) had GRACE ≥ 140. The study had two arms: an early invasive strategy one (coronary arteriography and percutaneous coronary intervention within 24 hours after admission), and a selective invasive strategy arm (medical stabilization, with coronary arteriography required only in case of angina recurrence and/or evidence of inducible myocardial ischemia). Follow-up was 22.8 ± 14 months.

Results: For the whole group MACE occurred less often and the event free period was longer in the early invasive strategy group compared to selective invasive one (p=0.001). Early invasive strategy in diabetic patients, those with CKD and with GRACE ≥ 140 was associated with a reduced MACE rate (p=0.008, 0.016 and 0.006, respectively) and longer time to MACE occurrence compared with the selective invasive strategy.

When we evaluated separately non-diabetics, patients with normal renal function and those with GRACE < 140 we found no significant difference in MACE rate between the patients allocated to early invasive strategy and those assigned to selective invasive strategy. Early invasive strategy, however, showed some advantage over the selective one also in the subgroup analysis - the time to occurrence of MACE was prolonged also patient with lower risk at presentation.

Conclusions: Early invasive strategy in UA/NSTEMI is associated with a reduced MACE rate and longer event-free period compared with selective invasive strategy. This benefit is clearly evident in higher risk subsets (patients with DM, CKD and GRACE ≥ 140).

Keywords: non-ST-segment elevation acute coronary syndrome (NSTE-ACS), unstable angina (UA), non-ST elevation myocardial infarction (NSTEMI), early invasive strategy, selective invasive strategy, diabetes mellitus, chronic kidney disease, GRACE risk score

1. INTRODUCTION

Cardiovascular diseases are currently the leading cause of death in developed countries, and by 2020 they are estimated to become number one cause of death in the developing countries [1].

Acute coronary syndromes (ACS) are considered as medical emergency but there are different subsets of patients in this larger group that require specific approach. Non-ST segment elevation acute myocardial infarction (NSTEMI) has a higher annual incidence than that of ST segment elevation myocardial infarction (STEMI) - approximately 3 per 1000 population [2]. Early hospital mortality of STEMI is higher than that of NSTEMI, although the mortality rates are comparable after six months; long-term follow up, however, showed that NSTEMI death rates were twice as high as those of STEMI at 4 years [3]. This can be most likely accounted for by the fact that NSTEMI patients tend to be older and with more co-morbidities, especially type 2 diabetes and chronic kidney disease (CKD) [4].

Optimal treatment strategy for ACS patients without ST segment elevation (unstable angina – UA and NSTEMI) is a subject of extensive debate. And while invasive strategy is adopted and recommended as the best therapeutic option for high-risk patients, the optimal time point for selective coronary arteriography (SCAG) and percutaneous coronary intervention (PCI) remains unspecified. Early revascularization of unstable plaque could prevent subsequent ischemic events while, on the other hand, intensive antiplatelet therapy has the potential to reduce thrombotic burden, to “soothe” the unstable plaque, thus ensuring safer percutaneous revascularization with less periprocedural ischemic complications.

Within the last years the results of several large clinical trials have been reported examining the effects of strategy choice on final outcome in patients with ACS. The results of Intracoronary Stenting with Antithrombotic Regimen Cooling Off strategy (ISAR-COOL) [5], Timing of Intervention in Patients with Acute Coronary Syndromes (TIMACS) [6] and Invasive versus Conservative Treatment in Unstable Coronary Syndromes (ICTUS) [7], comparing early versus delayed invasive strategy, are contradictory. ABOARD (Angioplasty to Blunt the Rise of Troponin in Acute Coronary Syndromes) [8] compares the effect of the aggressive strategy of very early intervention (similar to the approach for STEMI) with that of coronary arteriography and possible intervention on the next working day. The study did not find any clinical advantages that could be attributed to very early invasive strategy.

Among patients with NSTEMI, several subgroups at high risk of cardiovascular complications can be identified, and these are patients with diabetes mellitus (DM), CKD and those presenting with higher baseline risk (GRACE risk score ≥ 140). According to European Society of Cardiology guidelines for the management of NSTEMI from 2011 [4], the presence of DM, CKD or GRACE ≥ 140 in the setting of NSTEMI is a prerequisite for early invasive strategy.

In the present study we have tried to compare the effectiveness and prognostic significance of early compared to selective invasive strategy in UA/NSTEMI patients and to perform subgroup analysis for the prognostic role of strategy choice according to the presence or absence of DM, CKD and GRACE ≥ 140 at baseline.

2. MATERIAL AND METHODS

2.1 Study group

The present analysis included 178 prospectively enrolled (between April 2010 and January 2011) patients with UA/NSTEMI, at a mean age of 62.5±11.7 years, of whom 53 (29.8%) were female.

Inclusion criterions were symptoms of ACS, requiring hospital admission. NSTEMI was defined by the presence of 2 of the following criteria: 1) symptoms of myocardial ischemia; 2) electrocardiographic ST-segment abnormalities (horizontal or descendent ST depression of at least 0.1 mV); 3) an elevated cardiac troponin I value above the upper limit of the norm (0.022 ng/ml).

Unwillingness or inability to sign informed consent for coronary arteriography or PCI was considered as an exclusion criterion.

The study was conducted in two centers. In the first center there was no capability to perform on site PCI. All of the patients hospitalized in this center with UA/NSTEMI (102 subjects, or 57.3% of the study group) were managed conservatively which involved initial pharmacological treatment to stabilize the patient. If medical stabilization was successful – the patient had no recurrence of chest pain and no myocardial ischemia induced at stress test, he or she was not referred to SCAG and remained on conservative therapy. In case of recurrent angina (which was defined as angina pectoris despite pharmacological therapy used to stabilize the patient during hospitalization for acute coronary syndrome) and/or evidence for inducible myocardial ischemia the patient was transferred to the second study center, where we proceeded with invasive strategy. Patients hospitalized in the first center made up the selective invasive arm of the study.

In the second center, with a PCI available on a 24/7 basis and surgical back-up, all patients initially hospitalized with UA/NSTEMI underwent coronary arteriography with the possibility for intervention within the first 24 hours after hospitalization. This group (76 patients or 42.7%) formed the early invasive strategy arm.

Hospitalization in one of the two study centers was determined by geographical factors and also self-referral preferences.

In DM patients specific diabetic treatment was administered at the discretion of the attending physician with or without a consultation with an endocrinologist. In general, the following tendencies can be outlined: 1. Metformin therapy was not suspended for the period around the invasive examination and intervention, which is in line with current guidelines for clinical behavior in this group [4]; 2. Infusion of glucose-insulin-potassium was not applied in any of the patients; 3. Poor glycemic control upon admission with existing diabetes or newly diagnosed diabetes with significantly elevated serum glucose levels necessitated insulin treatment in the early hospital and periprocedural period.

We used MDRD to estimate filtration rate (eGFR) and a cut-off of glomerular 60 ml/min/1.73 m^2 to define CKD (present in 20% of our group). For CKD patients we applied pre- and post-procedural hydration and kept intravenous contrast as minimal as possible. Serum creatinine value was controlled the day after the invasive procedure. With that approach we did not have contrast-induced nephropathy in our group.

We performed risk evaluation using the GRACE risk score, as recommended in the current ESC guidelines for NSTEMI management [4, 9, 10]. The calculation is based on baseline patient characteristics and determines in-hospital and 6-month probability for death and myocardial infarction combined with death.

In the present study we defined a group of high-risk patients with GRACE ≥ 140 (28 subjects – 16%) and a non-high-risk group (the rest of 150 patients named in this analysis as low-risk, but actually comprising intermediate risk (GRACE 109-140) and low-risk subjects GRACE ≤ 108).

2.2 Coronary arteriography and intervention

Femoral access was used for all patients. After artery cannulation, unfractionated heparin was administered at a dose of 10000 U with additional applications during the procedure as required.

Glycoprotein (GP) IIb/IIIa receptor inhibitor abciximab (0.25 mg/kg bolus, 0.125 mg/kg/min infusion) was administered at the discretion of PCI-performing physician. In cases of multivessel involvement, the target lesion only was treated during the primary intervention. In certain cases, upon judgment of the treating team, PCI was performed of > 1 affected vessel - this was the approach used for 10 patients (5.6% of the study group).

For PCI in this group we have used predominantly bare metal stents (BMS); drug-eluting stents were applied in only three of the patients. After stent implantation standard dual antiplatelet therapy with acetyl salicylic acid 100 mg and clopidogrel 75 mg daily was recommended for 12 months. At the time when the study was conducted newer antiplatelet agents (ticagrelor and prasugrel) were not available in Bulgaria.

2.3 Follow-up

The mean follow-up period was 22 months (difference between quartiles: 10-36), ranging from 5 to 51 months. Reported data refer to recurrent angina, re-hospitalization, coronary arteriography and intervention, development of MI, symptoms of heart failure, total mortality rate and combination of frequency of occurrence of MACE. Considering the present study, frequency of MACE refers to percentage of patients that have experienced any of the above-mentioned adverse events, and not the overall incidence of these events in the study group.

Follow-up methods included telephone interviews, discharge summaries from hospitals (if available) and death certificates.

2.4 Ethical considerations

All patients signed written informed consent for coronary arteriography and PCI and also an informed consent about personal data management and follow-up. The study was approved by the local institutional Ethics Committee and is in accordance with the Declaration of Helsinki.

2.5 Statistical analysis

The distribution of quantitative variables was studied with the Kolmogorov-Smirnov test. Data with normal distribution were expressed as mean ±SD, while the data with distribution different from normal - as median and interquartile range (difference between the 25th and 75th percentile). Qualitative variables were presented as a percentage. Parameters in the

two groups were compared using *t*-test for independent variables with a normal distribution of data, and Mann-Whitney U test in the absence of such a distribution. To search for a correlation between two qualitative variables we used the chi-square method (χ^2 test). The time to onset of MACE was evaluated using the Kaplan-Meier survival curves. We used Cox regression to evaluate the influence of confounding factors to the time of occurrence of MACE. Values of $P < .05$ were considered as statistically significant. All analyses were performed using SPSS version 13.0 for Windows.

3. RESULTS

3.1 Patients' characteristics

We implied early invasive strategy in 76 patients (42.7%) and selective invasive one in 102 (57.3%). In the latter group stress testing was performed in 65 subjects (63.7%) and was indicative of inducible myocardial ischemia in 32 of them (49.2%).

SCAG was done in 144 patients - 80.9% of the whole group and it proceeded with an intervention in 141 of the cases (97.9%). In the early invasive group all patients underwent SCAG and all but one (98.7%) - intervention. When the strategy was selective invasive one 68 of the patients proceeded to SCAG (66.7%) with an intervention performed in 66 of them (97.1%). The rest 34 subjects from this group were successfully stabilized medically and treated conservatively.

MACE occurrence during follow-up was relatively high – 44% of the patients had an untoward cardiac event and half of these events occur during the first month after hospital discharge. Six subjects died during follow-up and the reason was cardiovascular in all of the cases.

3.2 Comparison between early and selective invasive strategy in the whole group

Demographic characteristics, risk factors and medical history in the two groups according to invasive strategy are presented in table 1. Early invasive strategy patients have a higher rate of dyslipidemia and family history of coronary artery disease.

Table 1. Demographics, risk factors and medical history in studied groups

PARAMETER	**Whole group n = 178**	**Early invasive strategy n = 76**	**Selective invasive strategy n = 102**	**Statistical significance (*p*)***
Age – mean ± SD	62.5 (± 11.7)	61.7 (± 11.7)	63 (± 11.7)	.46
Female – number (%)	53 (29.8%	21 (27.6%)	32 (31.4%)	.62

AH – number (%)	162 (91%)	71 (93.4%)	91 (89.2%)	.43
DM – number (%)	52 (29.2%)	22 (28.9%)	30 (29.4%)	1
Dyslipidaemic – number (%)	144 (80.9%)	72 (94.7%)	72 (70.6%)	**< .001**
BMI – mean ± SD	29.2 (± 4.4)	28.6 (± 4.7)	29.5 (± 3.6)	.55
Smokers – number (%)	79 (44.4%)	39 (51.3%)	40 (39.2%)	.13
Family history of CAD – number (%)	69 (38.8%)	40 (52.6%)	29 (28.4%)	**.002**
History of MI – number (%)	77 (43.3%)	35 (46.1%)	42 (41.2%)	.54
PCI performed previously – number (%)	41 (23%)	23 (30.3%)	18 (17.6%)	.07
History of HF – number (%)	17 (9.6%)	9 (11.8%)	8 (7.8%)	.44
History of CVD – number (%)	18 (10.1%)	7 (9.2%)	11 (10.8%)	.81

Abbreviations: AH – arterial hypertension; BMI – body mass index; CAD – coronary artery disease; CVD – cerebro-vascular disease; DM – diabetes mellitus; HF – heart failure; MI – myocardial infarction; PCI – percutaneous coronary intervention; SD – standard deviation

** Between early invasive strategy and selective invasive strategy group*

Baseline clinical characteristics are presented in table 2 and medical therapy – in table 3. Patients allocated to early invasive strategy have higher creatinine-phospho kinase (CPK) and Troponin I values and are more often given beta blockers, ACE inhibitors or angiotensine receptor blockers and clopidogrel at presentation compared to those who underwent selective invasive strategy.

Table 2. Clinical characteristics in studied groups

PARAMETER	Whole group n = 178	Early invasive strategy n = 76	Selective invasive strategy n = 102	Statistical significance (*p*)*
Angina pectoris 24 hours before hospitalization – number (%)	67 (37.6%)	26 (34.2%)	41 (40.2%)	.44
Previous antiplatelet therapy – number (%)	122 (68.5%)	45 (59.2%)	77 (75.5%)	**.02**
CPK – median (25-75 percentile)	115.5 (72.8-199)	91.5 (53.3-152.3)	132 (86.8-236.3)	**< .001**
MB – median (25-75 percentile)	15 (11-25)	14 (11-22)	17 (10.8-26)	.32
Trop I – median (25-75 percentile)	0.02 (0.09-0.128)	0.039 (0.014-0.38)	0.018 (0.006-0.08)	**.003**
CKD – number (%)	35 (19.7%)	20 (26.3%)	15 (14.7%)	.06
Creatinine (µmol/l) – median (25-75 percentile)	89.5 (76.8-101)	87.5 (72.5-106)	91 (78-100.3)	.39
GRACE – mean ± SD	113.7 (± 32.6)	116.6 (± 38.4)	111.6 (± 27.6)	.34
TIMI Risk Score – median (25-75 percentile)	3 (2-4)	3 (2-4)	2.5 (2-3)	**.002**
ECG:				.81

No changes – number (%)	20 (11.2%)	7 (9.2%)	13 (12.8%)	
T wave changes – number (%)	89 (50%)	37 (48.7%)	52 (51%)	
ST depression – number (%)	63 (35.4%)	29 (38.2%)	34 (33.3%)	
Uninterpretable – number (%)	6 (3.4%)	3 (4%)	3 (2.9%)	
ACS:	102 (57.3%)			
UA – number (%)		41 (53.9%)	61 (59.2%)	.45
NSTEMI – number (%)	76 (42.7%)	35 (46.1%)	41 (40.2%)	
Time to intervention (hours) – mean ± SD		6.8 ± 7.2	52.5 ± 31.6	**< .001**

Abbreviations: CKD – chronic kidney disease; CPK – creatinine phospho-kinase; NSTEMI – non ST elevation myocardial infarction; SD – standard deviation; UA – unstable angina

** Between early invasive strategy and selective invasive strategy group*

Table 3. Baseline pharmacological therapy in studied groups

AGENT	**Whole group n = 178**	**Early invasive strategy n = 76**	**Selective invasive strategy n = 102**	**Statistical significance (p)***
Beta blocker – number (%)	154 (86.5%)	71 (93.4%)	83 (81.4%)	**.03**
ACE inhibitor – number (%)	146 (82%)	68 (89.5%)	78 (76.5%)	**.03**
ARB – number (%)	14 (7.9%)	2 (2.6%)	12 (11.8%)	**.03**

CCB – number (%)	43 (24.2%)	17 (22.4%)	26 (25.5%)	.72
Nitrate – number (%)	78 (43.8%)	19 (25%)	59 (57.8%)	**< .001**
Acetyl salicylic acid – number (%)	169 (94.9%)	71 (93.4%)	98 (96.1%)	.5
Clopidogrel – number (%)	137 (77%)	68 (89.5%)	69 (67.6%)	**.001**
GP IIbIIIa – number (%)	16 (9%)	9 (11.8%)	7 (6.9%)	.3
Statin – number (%)	154 (86.5%)	68 (89.5%)	86 (84.3%)	.38

Abbreviations: ACE – angiotensine-converting enzyme; ARB – angiotensine-receptor blockers; CCB – calcium channel blocker; GP – glycoprotein

** Between early invasive strategy and selective invasive strategy group*

During follow-up patients allocated to an early invasive strategy had significantly lower incidence of angina recurrence, MI, SCAG and PCI compared to the rest of the group – table 4. Kalan-Mayer survival curves showed that the time to occurrence of MACE was also significantly longer in the former group compared to selective invasive one – figure 1.

Table 4. MACE occurrence with early and selective invasive strategy

MACE	**Whole group n = 178** **Occurrence** number (%)	**Early invasive strategy n = 76** **Occurrence** number (%)	**Selective invasive strategy n = 102** **Occurrence** number (%)	**Statistical significance (*p*)***
Angina pectoris recurrence	65 (36.5%)	20 (26.3%)	45 (44.1%)	**.02**

MI	14 (7.9%)	2 (2.6%)	12 (11.8%)	**.03**
Re-hospitalization	63 (35.4%)	22 (28.9%)	41 (40.2%)	.15
SCAG	55 (30.9%)	16 (21.1%)	39 (38.2%)	**.02**
PCI	52 (29.2%)	15 (19.7%)	37 (36.3%)	**.02**
HF	22 (12.4%)	11 (14.5%)	11 (10.8%)	.5
Stroke	10 (5.6%)	6 (7.9%)	6 (5.9%)	.33
Mortality	6 (3.4%)	3 (4%)	3 (2.9%)	.7
Patients with MACE	78 (43.8%)	29 (38.2%)	49 (48%)	.22

213 *Abbreviations: MACE – major adverse cardiac events; MI – myocardial infarction; PCI – percutaneous*
214 *coronary intervention; SCAG – selective coronary angiography*

215 ** Between early invasive strategy and selective invasive strategy group*

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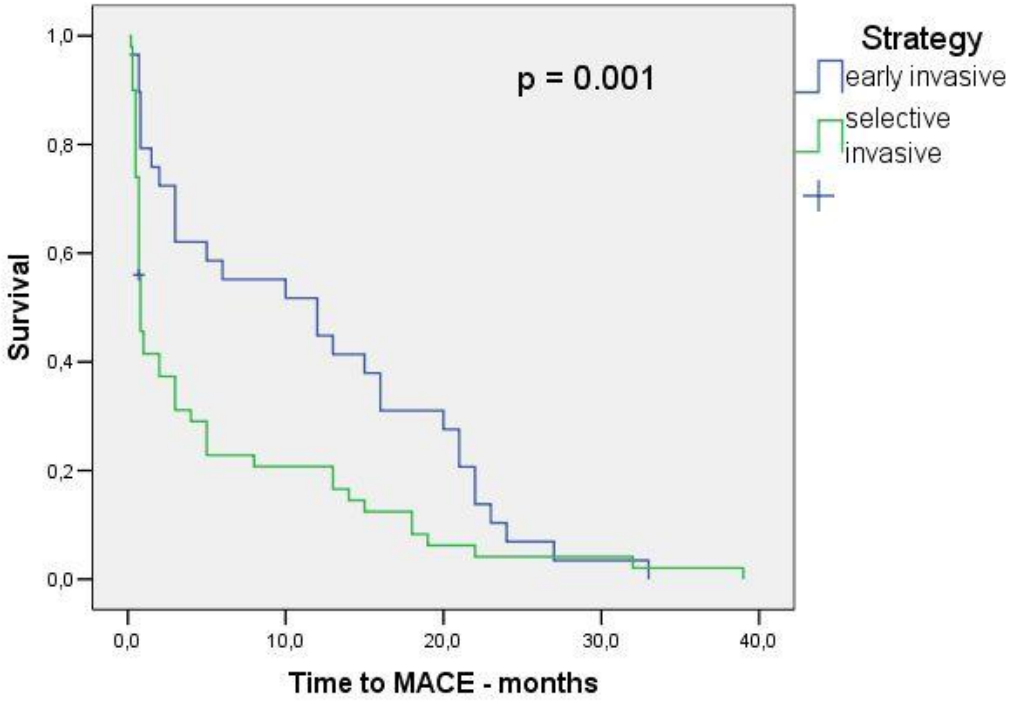

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Figure 1. Kaplan-Meier survival curves for the occurrence of MACE in the whole group according to strategy choice.

3.3 Significance of strategy selection according to the presence or absence of DM

Fifty-two (29%) patients had DM. In this subgroup there was not a significant difference in baseline patient characteristics and therapy between those allocated to early or selective invasive strategy, with the only exception – higher prevalence of women in the early invasive group: 10 (45.5%) vs 5 (16.7%), *P* = .03.

During follow-up MACE occurred less often in diabetics allocated to early as compared to selective invasive strategy: angina recurrence – 36 vs 77%, *P* = .01; re-hospitalization – 23 vs 73%, *P* = .001; SCAG – 23 vs 73%, *P* = .001; PCI – 18 vs 67%, *P* = .001. Mortality did not differ significantly between groups. As a whole MACE occurred in 80% of diabetics with selective invasive strategy and in 41% of those with an early invasive one (*P* = .01). Event-free survival was also significantly longer when early instead of selective invasive strategy was applied – figure 2.

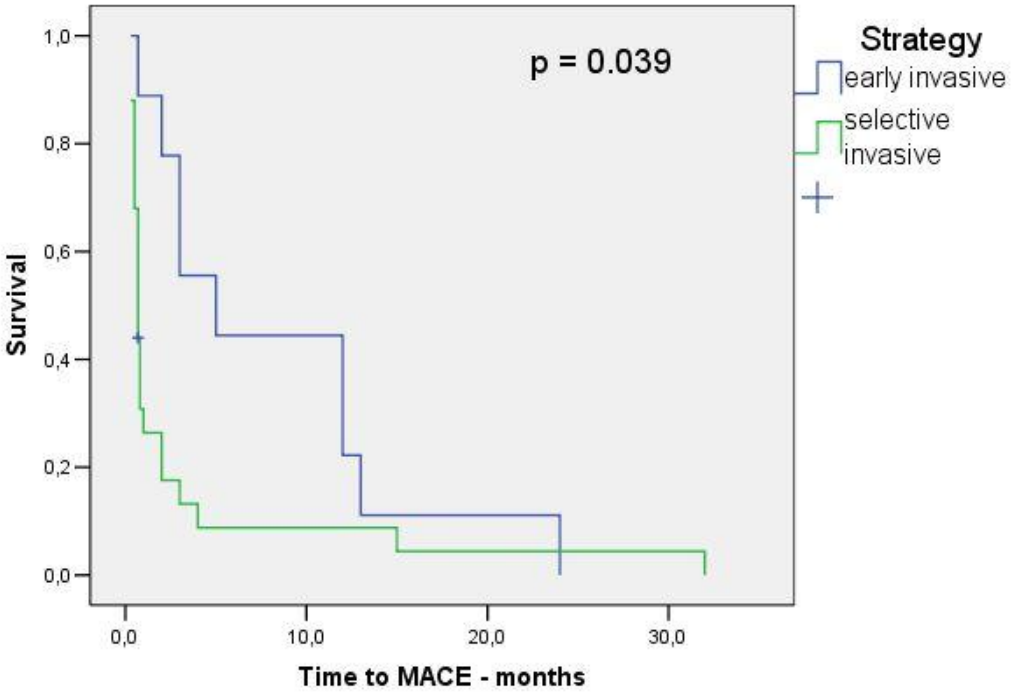

Figure 2. Kaplan-Meier survival curves for the occurrence of MACE in patients with DM according to strategy choice.

The 126 non-diabetics represented 71% of the study group. In this subgroup there were more males allocated to an early invasive strategy (79.6% vs 63.5%, *P* = .05) and the prevalence of dyslipidemia (94.4% vs 63.9%, *P* < .001) and family history of CAD (55.6% vs 26.4%, *P* = .002) was higher as compared to the selective invasive strategy group. Early invasive strategy patients were more likely to receive a beta-blocker (94.4% vs 80.6%, *P* = .03) and clopidogrel (92.6% vs 59.7%, *P* < .001) and less likely to be treated with nitrates (25.9% vs 62.5%, *P* < .001), compared to selective invasive strategy ones.

Non-diabetics assigned to early and selective invasive strategy did not differ significantly in terms of frequency of observed adverse cardiovascular events during follow-up. Kaplan-Mayer survival analysis, however, showed that early invasive strategy had some advantage in this subgroup – MACE occurred significantly later in time when the strategy was early instead of selective invasive one – figure 3.

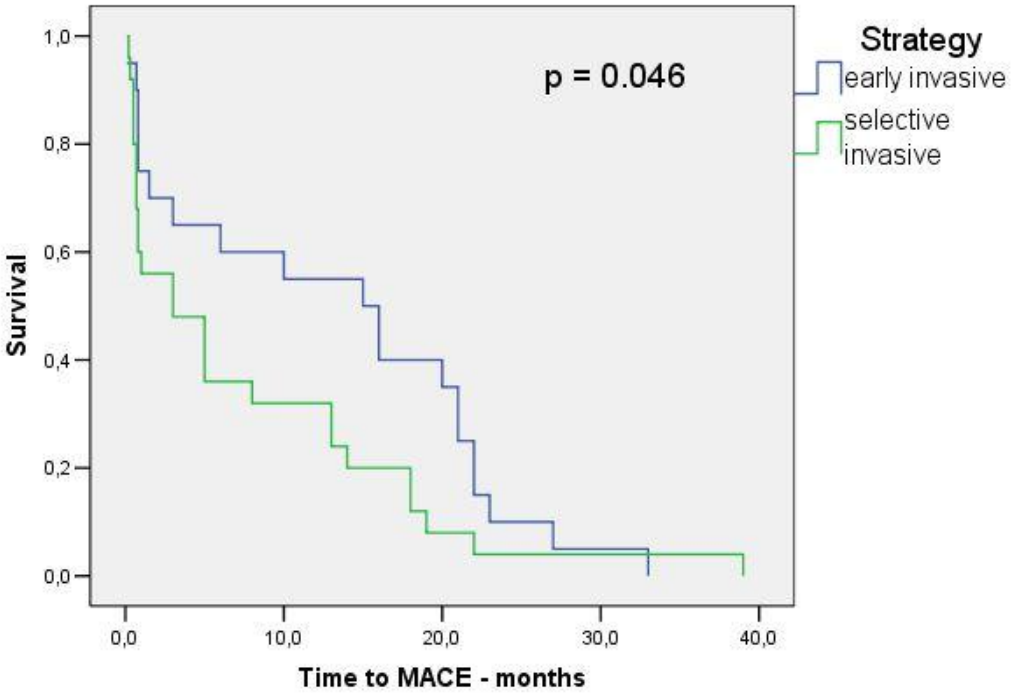

Figure 3. Kaplan-Meier survival curves for the occurrence of MACE in patients without DM according to strategy choice.

3.4 Significance of strategy selection according to the presence or absence of CKD

CKD (eGFR < 60 ml/min/1.73 m^2) was present in 32 patients – 20% of the study group. Demographic characteristics, risk factors, medical history and pharmacological therapy were similar between those of them allocated to early or selective invasive strategy. Serum creatinine levels were elevated in all of these patients, but more so in the selective invasive strategy subgroup (140.1 ± 25.5 vs 124.1 ± 15.8 μmol/l, *P* = .04).

During follow-up MACE were less likely to occur in CKD patients assigned to early as compared to selective invasive strategy: angina recurrence – 20 vs 80%, *P* = .001; re-hospitalization – 25 vs 73%, *P* = .01; SCAG and PCI – 20 vs 73%, *P* = .002. Once again mortality did not differ significantly between groups. 35% of the patients in the early invasive strategy group experienced any kind of MACE compared to 80% of those with selective invasive strategy (*P* = .02). Occurrence of MACE was also significantly delayed in time in CKD subgroup when these patients had an early intervention compared to a selective one – figure 4.

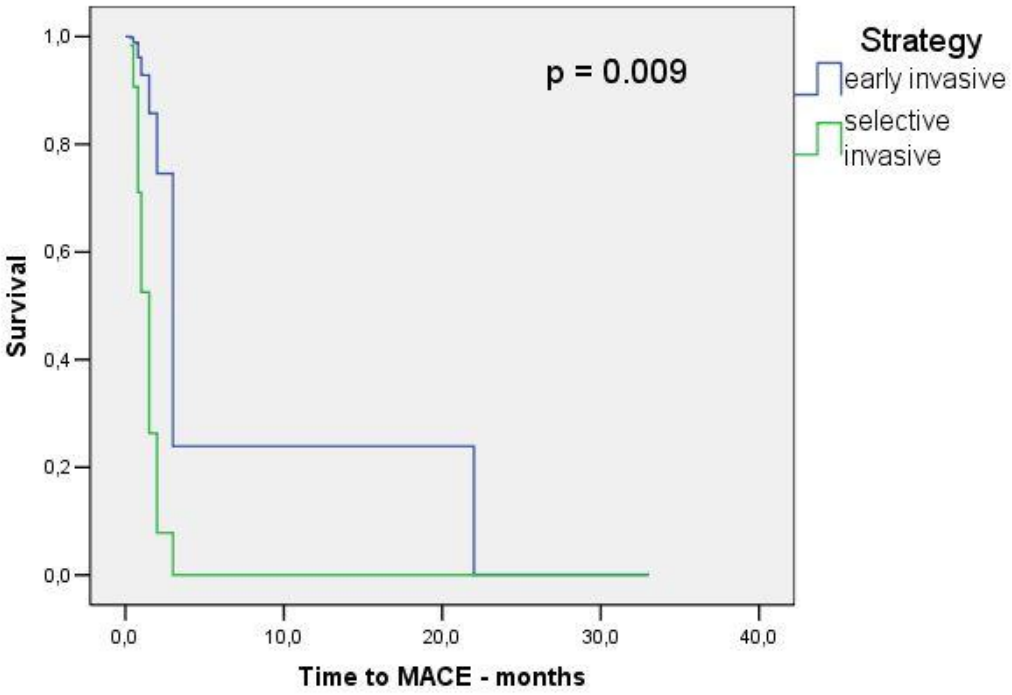

Figure 4. Kaplan-Meier survival curves for the occurrence of MACE in patients with CKD according to strategy choice.

Patients with preserved renal function (146, 80% of the whole group) were significantly younger (58.8 ± 9.7 vs 62.7 ± 11.7, *P* = .04), but with a higher prevalence of dyslipidemia (95% vs 70%, *P* < .001) and family history of CAD (55% vs 26%, *P* = .001) when allocated to the early invasive strategy group as compared to the selective invasive group. Although in the normal range, serum creatinine levels were significantly lower in early as compared to selective invasive strategy group (79.4 ± 13.9 vs 85.8 ± 13 μmol/l, *P* = .01), and the former patient group was more likely to be treated with clopidogrel (89% vs 64%, *P* = .001) and less likely to receive a nitrate (20% vs 58%, *P* < .001) compared to the latter.

During follow-up the occurrence of MACE was evenly distributed between patients without CKD who were allocated to an early or a selective invasive strategy. Survival free of MACE,

however, was significantly longer in this subgroup when the strategy was early invasive one – figure 5.

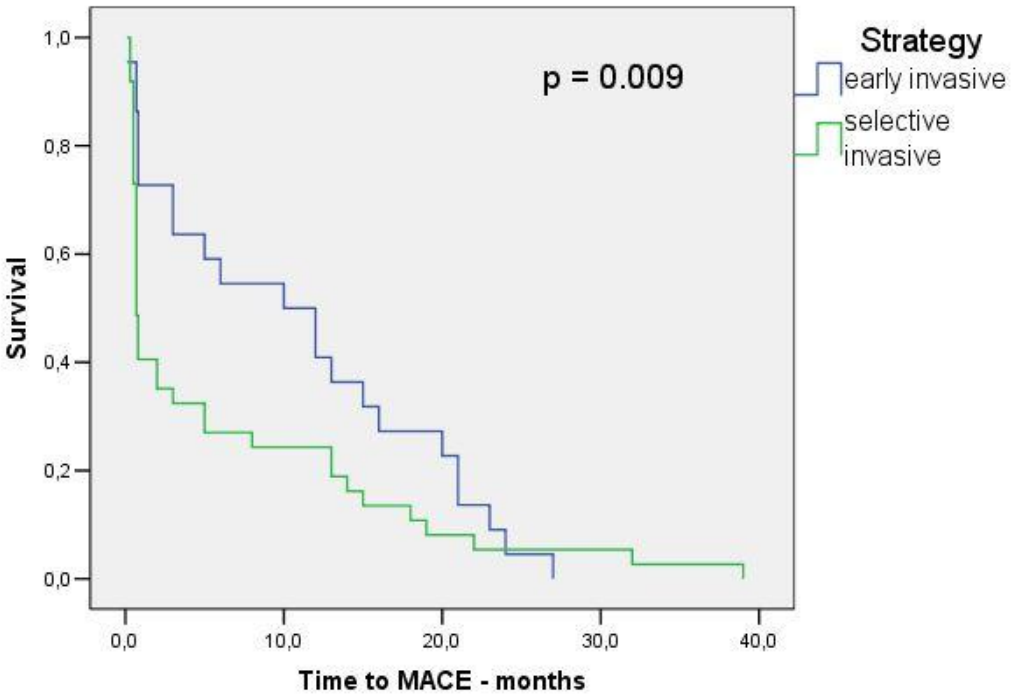

Figure 5. Kaplan-Meier survival curves for the occurrence of MACE in patients without CKD according to strategy choice.

3.5 Significance of strategy selection according to the GRACE risk score

High-risk group (GRACE ≥ 140) comprised of 28 subjects (16%). Demographic characteristics, risk factors, medical history, clinical presentation did not differ significantly between those of them allocated to early or selective invasive strategy, except for dyslipidemia which was more prevalent in the early invasive group (100% vs 67%, *P* = .02).

All high-risk patients in the selective invasive group experienced some kind of MACE during follow-up, compared to only 38% of those assigned to an early invasive strategy, *P* = .01. Occurrence of individual end-point in the early and selective invasive group were as follows: angina recurrence – 25 vs 100%, *P* < .001; re-hospitalization – 31 vs 100%, *P* < .001; SCAG and PCI – 25 vs 92%, *P* = .001. Mortality, myocardial infarction, stroke and heart failure signs and symptoms did not differ between groups. Kaplan-Mayer survival analysis showed that the time to occurrence of MACE was significantly prolonged when selected strategy was early as compared to selective invasive one – figure 6.

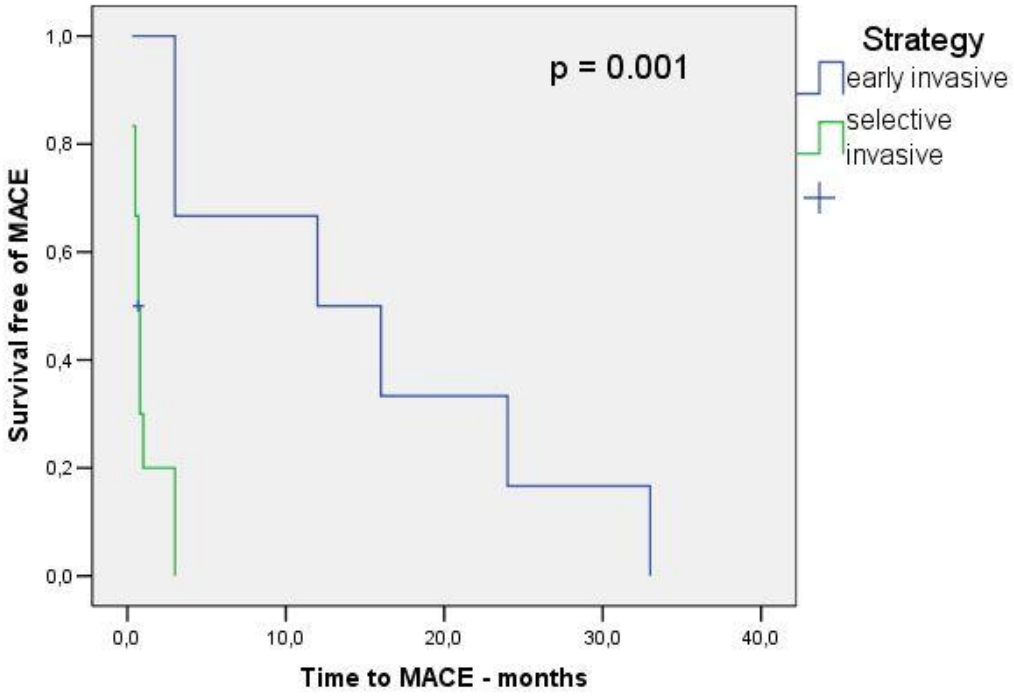

Figure 6. Kaplan-Meier survival curves for the occurrence of MACE in high-risk patients.

Low-risk group (defined as GRACE < 140) consisted of 150 patients (84%). Those of them allocated to early invasive strategy had a higher prevalence of dyslipidemia (93 vs 71%, *P* = .001), family history of CAD (60 vs 29%, *P* < .001) and CKD (22 vs 9%, *P* = .03), higher troponin I values (0.035 IQR: 0.01-0.36 vs 0.012 IQR: 0.05-0.067, *P* = .003) and were more likely to be treated with clopidogrel (92 vs 63%, *P* < .001) and less likely to receive nitrates (23 vs 60%, *P* < .001) than patients in the selective invasive strategy group.

We did not find a significant difference in the occurrence of MACE in the low-risk subgroup in accordance to the allocation to early or selective invasive strategy. The only exception was the rate of myocardial infarction during follow-up which was significantly lower in the group of patients assigned to early invasive strategy (0 vs 10%, *P* = .01). Survival free of MACE, however, was significantly longer in the early as compared to selective invasive group – figure 7.

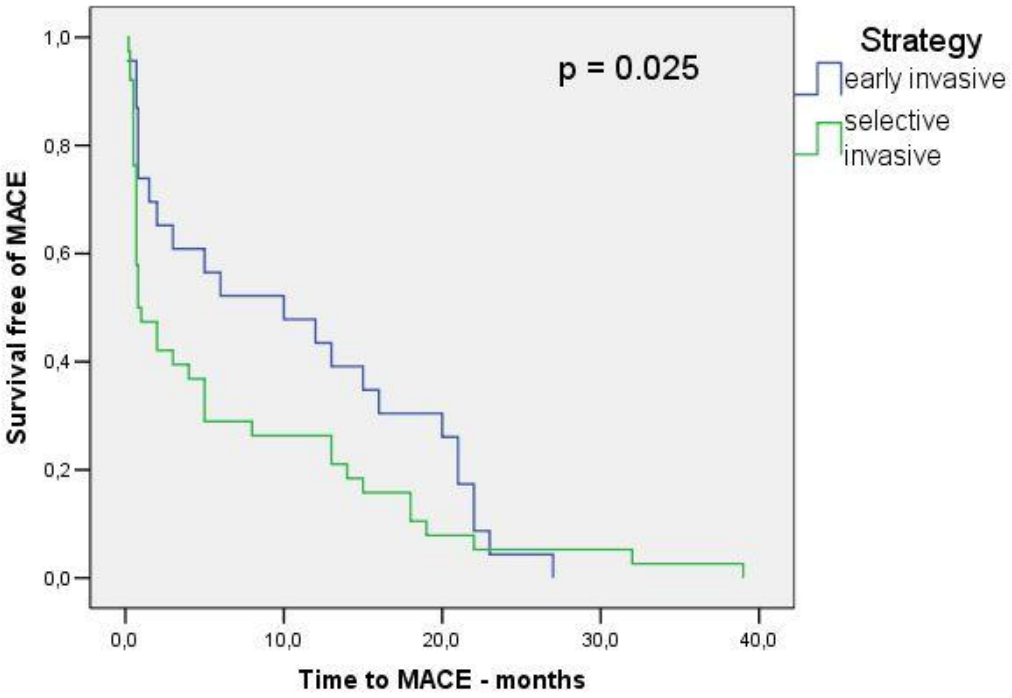

Figure 7. Kaplan-Meier survival curves for the occurrence of MACE in low-risk patients.

4. DISCUSSION

The present study investigates the impact of treatment strategy (early invasive vs selective invasive) on the frequency of adverse cardiovascular events in patients with NSTE-ACS in subgroups of different cardiovascular risk, determined by the presence or absence of DM, CKD and GRACE score value.

We have found that in the whole group of 178 NSTE-ACS patients the adoption of early invasive strategy is associated with a significantly reduced rate of MACE and longer MACE-free period as compared to selective invasive strategy. The subgroup analysis revealed that the reduction in the number of MACE could be attributed mainly to benefits of early invasive strategy in higher risk subgroups: diabetic patients, those with CKD and with GRACE ≥ 140 had a significantly lower rate of MACE after early intervention as compared to a selective one. On the contrary, in groups without DM, CKD or with GRACE < 140 the choice of invasive strategy did not have any significant influence (with small exceptions) on the number of MACE during follow-up.

The time to the occurrence of MACE, however, was significantly longer with early as opposed to selective invasive strategy in the higher as well as in the lower risk subgroups. In other words: early invasive strategy has the potential to increase the event-free survival in different NSTEMI-ACS populations according to their cardiovascular risk.

According to literature data approximately 20% to 30% of hospitalized patients diagnosed with UA/NSTEMI have a history of DM [11] and the combined incidence of known and newly diagnosed DM is as high as 37% according to data from registries [12]. The observed incidence of DM in our study group (29%) is relatively similar to previously published data.

Presence of DM is an independent predictor of MACE and mortality in ACS patients without ST segment elevation [13]. Despite of this, diabetic patients with ACS are less likely to receive any form of revascularization and to be prescribed thienopyridines or GP IIb/IIIa inhibitors [13, 14]. According to European Society of Cardiology guidelines for the management of NSTEMI presence of DM is a prerequisite for SCAG with possible revascularization within the first 72 hours after presentation even in the absence ST segment changes or positive markers of myocardial necrosis [4]. Early invasive strategy has proven its benefits in terms of MACE reduction in the diabetic subgroup [15-18].

Renal dysfunction in ACS patients without ST segment elevation is also considered as an independent mortality predictor. Serum creatinine values are used in GRACE risk score calculation [4]. Although accepted as a high risk category, CKD patients often do not receive optimal medical therapy, including early invasive strategy and recommended protective pharmacological therapy, such as double antiplatelet therapy, optimal anticoagulation, statins, and inhibitors of rennin-angiotensin-aldosterone system [19-24]. A possible explanation for this conservative behaviour could be the increased bleeding risk in this subgroup.

Prospective randomized data for the role of invasive strategy in MACE reduction in ACS-NSTEMI patients with CKD are lacking. In registries, substudies of clinical trials and observational studies invasive management and early invasive strategy has been shown to improve the outcome but the benefit decreased with worsening renal function [4].

According to the GRACE subgroups the results from our study are in accordance with that of TIMACS [6], showing a reduction in MACE incidence in the group with GRACE score > 140 when early instead of delayed invasive strategy was applied, and absence of such a benefit in the lower risk patients. Based on the results of TIMACS [6], TACTICS-TIMI 18 [17] and meta-analysis [25] early invasive strategy is now recommended in every patient with a GRACE score > 140. In the lower risk subgroup in the present study (comprising 150 patients), however, we have found a certain benefit of applying an early instead of selective invasive strategy – time to the occurrence of MACE was significantly prolonged in lower-risk patients with an earlier coronary intervention. This finding requires further confirmation, preferably in a randomized clinical study.

Considering previous work in the field, the merits of the present study could be defined in the confirmation of the benefits of early as opposed to selective invasive strategy in categories of patients with higher risk during a follow-up of nearly two years, as well as in providing evidence of some benefit (not in the incidence but in the time to the occurrence of MACE) even in lower risk subgroups when an early invasive intervention is adopted.

The study has several limitations: this is not a randomized study; having two different population in different centres would have created a bias in the treatment management (e.g. there is a likelihood for the cardiology team in the hospital to pursue conservative management in the absence of PCI-facility until complications develop); the number of patients in some of the subgroups is relatively small, which could have underpowered the results; frequency of DES implantation was very low.

5. CONCLUSION

Early invasive strategy in UA/NSTEMI patients is associated with a reduced MACE rate and longer event-free survival compared with selective invasive strategy. This benefit is clearly evident in higher risk subsets (patients with DM, CKD and GRACE ≥ 140). In lower risk subgroups the rate of MACE is not influenced by the choice of strategy but early intervention leads to a significant prolongation of the time to occurrence of MACE as opposed to a selective invasive approach.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

AUTHORS' CONTRIBUTIONS

All authors took participation in the design of the study. ND, IS and HM wrote the protocol. Data management was performed by ND, IS, BB and HM. IS, HM and ND managed the analyses of the study. IS performed the statistical analysis. IS wrote the first draft of the manuscript. ND and IS managed the literature searches. All authors read and approved the final manuscript.

REFERENCES

1. Murray CL, Lopez AD. Alternative projections of mortality and disability by cause 1990-2020: Global burden of disease study. Lancet 1997;349:1498-504.

2. Fox KA, Eagle KA, Gore JM, Steg PG, Anderson FA. The Global Registry of Acute Coronary Events, 1999 to 2009 – GRACE. Heart 2010;96:1095-101.

3. Yeh RW, Sidney S, Chandra M, Sorel M, Selby JV, Go AS. Population trends in the incidence and outcomes of acute myocardial infarction. N Engl J Med 2010;362:2155-65.

4. Hamm C, Bassand JP, Agewall S, Bax J, Boersma E, Bueno H, et al. ESC Guidelines for the management of acute coronary syndrome in patients presenting without persistent ST segment elevation. The Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J 2011;32:2999-3054.

5. Neumann FJ, Kastrati A, Pogatsa-Murray G, Mehilli J, Bollwein H, Bestehorn HP, et al. Evaluation of prolonged antithrombotic pretreatment ("cooling-off" strategy) before intervention in patients with unstable coronary syndromes: a randomized controlled trial. JAMA 2003;290(12):1593–9.

6. Mehta SR, Granger CB, Boden WE, Steg PG, Bassand JP, Faxon DP, et al., TIMACS Investigators. Early versus delayed invasive intervention in acute coronary syndromes. N Engl J Med 2009;360(21):2165-75.

7. de Winter R., Windhausen F., Cornel JH., Dunselman P., Janus CL., Bendermacher P. et al for the Invasive versus Conservative Treatment in Unstable Coronary Syndromes (ICTUS)

Investigators. Early Invasive versus Selectively Invasive Management for Acute Coronary Syndromes. N Engl J Med 2005; 353:1095-1104

8. Montalescot G, Cayla G, Collet JP, Elhadad S, Beygui F, Le Breton H, et al. Immediate vs delayed intervention for acute coronary syndromes: a randomized clinical trial. JAMA 2009;302(9):947-54.

9. Fox KA, Dabbous OH, Goldberg RJ, Pieper KS, Eagle KA, Van de Werf F, et al. Prediction of risk of death and myocardial infarction in the six months after presentation with acute coronary syndrome: prospective multinational observational study (GRACE). BMJ 2006;333:1091.

10. Fox KA, SG Goodman, W Klein, Brieger D, Steg PG, Dabbous O, et al. Management of acute coronary syndromes. Variations in practice and outcome; findings from the Global Registry of Acute Coronary Events (GRACE). Eur Heart J 2002;23:1177–1189.

11. Granger CB, Goldberg RJ, Dabbous O, Pieper KS, Eagle KA, Cannon CP, et al. Predictors of hospital mortality in the global registry of acute coronary events. Arch Intern Med 2003;163:2345–2353.

12. Hasdai D, Behar S, Boyko V, Danchin N, Bassand JP, Battler A. Cardiac biomarkers and acute coronary syndromes – the Euro Heart Survey of Acute Coronary Syndromes Experience. Eur Heart J 2003;24:1189–1194.

13. Bartnik M, Malmberg K, Norhammar A, Tenerz A, Ohrvik J, Rydén L. Newly detected abnormal glucose tolerance: an important predictor of long-term outcome after myocardial infarction. Eur Heart J 2004; 25:1990-7.

14. Hasdai D, Behar S, Wallentin L, Gitt AK, Boersma E, Fioretti PM, et al. A prospective survey of the characteristics, treatments and outcomes of patients with acute coronary syndromes in Europe and the Mediterranean basin; the Euro Heart Survey of Acute Coronary Syndromes (Euro Heart Survey ACS). Eur Heart J 2002;23:1190-201.

15. Hasin T, Hochadel M, Gitt AK, Behar S, Bueno H, Hasin Y. Comparison of treatment and outcome of acute coronary syndrome in patients with compared to patients without diabetes mellitus. Am J Cardiol 2009;103:772-8.

16. Dotevall A, Hasdai D, Wallentin L, et al. Diabetes mellitus: clinical presentation and outcome in men and women with acute coronary syndromes. Data from the Euro Heart Survey ACS. Diabet Med 2005;22:1542-50.

17. Cannon CP, Weintraub WS, Demopoulos LA, Vicari R, Frey MJ, Lakkis N, et al. Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb/IIIa inhibitor tirofiban. N Engl J Med 2001;344:1879-87.

18. Lourenço C, António N, Teixeira R, Saraiva F, Jorge E, Baptista R, et al. Predictors of adverse outcome in a diabetic population following acute coronary syndromes. Rev Port Cardiol 2011;30(3):263-75.

19. Cardinal H, Bogaty P, Madore F, Boyer L, Joseph L, Brophy JM. Therapeutic Management in Patients with Renal Failure who Experience an Acute Coronary Syndrome. CJASN 2010;5 (1):87-94.

480 20. Han JH, Chandra A, Mulgund J, Roe MT, Peterson ED, Szczech LA, et al. Chronic
481 kidney disease in patients with non-ST-segment elevation acute coronary syndromes. Am J
482 Med 2006;119:248–254.

483 21. Shlipak MG, Heidenreich PA, Noguchi H, Chertow GM, Browner WS, McClellan MB.
484 Association of renal insufficiency with treatment and outcomes after myocardial infarction in
485 elderly patients. Ann Intern Med 2002;137:555–562.

486 22. Wright RS, Reeder GS, Herzog CA, Albright RC, Williams BA, Dvorak DL, et al. Acute
487 myocardial infarction and renal dysfunction: a high risk combination. Ann Intern Med
488 2002;137:563–570.

489 23. Chertow GM, Normand SL, McNeil BJ. "Renalism": Inappropriately low rates of coronary
490 angiography in elderly individuals with renal insufficiency. J Am Soc Nephrol 2004;15:2462–
491 2468.

492 24. Keough-Ryan TM, Kiberd BA, Dipchand CS, Cox JL, Rose CL, Thompson KJ, et al.
493 Outcomes of acute coronary syndrome in a large Canadian cohort: Impact of chronic renal
494 insufficiency, cardiac interventions, and anemia. Am J Kidney Dis 2005;46:845–855.

495 25. Bavry AA, DJ Kumbhani, R Quiroz, Ramchandani SR, Kenchaiah S, Antman EM.
496 Invasive therapy along with glycoprotein IIb/IIIa inhibitors and intra-coronary stents improves
497 survival in non-ST segment elevation acute coronary syndromes: a meta-analysis and
498 review of the literature. Am J Cardiol 2004;93:830-5.

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