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Invasive treatment of NSTEMI patients in German Chest Pain Units – Evidence for a treatment paradox

Frank P. Schmidt [a,k], Claus Schmitt [f], Matthias Hochadel [b], Evangelos Giannitsis [c], Harald Darius [d], Lars S. Maier [e], Claus Schmitt [f], Gerd Heusch [g], Thomas Voigtländer [h], Harald Mudra [i], Tommaso Gori [a,j], Jochen Senges [b], Thomas Münzel [a,*], for the German Chest Pain Unit Registry

[a] Zentrum für Kardiologie, Kardiologie 1, Johannes Gutenberg-University Mainz, Mainz, Germany
[b] Stiftung Institut für Herzinfarktforschung, Ludwigshafen, Germany
[c] 3rd Department of Medicine, University Hospital Heidelberg, Heidelberg, Germany
[d] Department of Cardiology, Angiology and Intensive Care Medicine, Vivantes-Klinikum Neukölln, Berlin, Germany
[e] 2nd Department of Medicine, University Hospital of Regensburg, Regensburg, Germany
[f] Clinic for Cardiology and Angiology, Municipal Hospital Karlsruhe, Karlsruhe, Germany
[g] Institute for Pathophysiology, West German Heart and Vascular Center University Duisburg-Essen, Essen, Germany
[h] CCB, Cardioangiologisches Centrum Bethanien, Frankfurt am Main, Germany
[i] Department of Cardiology, Pneumology and Internal Intensive Care Medicine, Klinikum Neuperlach, Städtisches Klinikum München GmbH, Munich, Germany
[j] Deutsches Zentrum für Herz- Und Kreislaufforschung, Standort Rhein-Mainz, Germany
[k] Klinikum Mutterhaus der Borromäerinnen, Trier, Germany

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ABSTRACT

Background: Patients with non ST-segment elevation myocardial infarction (NSTEMI) represent the largest fraction of patients with acute coronary syndrome in German Chest Pain units. Recent evidence on early vs. selective percutaneous coronary intervention (PCI) is ambiguous with respect to effects on mortality, myocardial infarction (MI) and recurrent angina. With the present study we sought to investigate the prognostic impact of PCI and its timing in German Chest Pain Unit (CPU) NSTEMI patients.

Methods and results: Data from 1549 patients whose leading diagnosis was NSTEMI were retrieved from the German CPU registry for the interval between 3/2010 and 3/2014. Follow-up was available at median of 167 days after discharge. The patients were grouped into a higher (Group A) and lower risk group (Group B) according to GRACE score and additional criteria on admission. Group A had higher Killip classes, higher BNP levels, reduced EF and significant more triple vessel disease ($p < 0.001$). Surprisingly, patients in group A less frequently received early diagnostic catheterization and PCI. While conservative management did not affect prognosis in Group B, higher-risk CPU-NSTEMI patients without PCI had a significantly worse survival.

Conclusions: The present results reveal a substantial treatment gap in higher-risk NSTEMI patients in German Chest Pain Units. This treatment paradox may worsen prognosis in patients who could derive the largest benefit from early revascularization.

1. Introduction

With a fraction of about 22% of the total, non-ST elevation myocardial infarctions (NSTEMIs) represent the largest cohort of patients evaluated for Acute Coronary Syndrome (ACS) in German Chest Pain Units (CPU). In recent years, the introduction of high-sensitivity troponin has lead to an increased diagnosis of NSTEMIs and changed the relative prevalence of NSTEMI and unstable angina [1], with a significant impact on the clinical characteristics and risk profile of NSTEMI patients. Further, resulting from this increased diagnosis rate, the NSTEMI population has become very homogeneous in terms of risk of death, further complicating the debate concerning the use of routine versus selective invasive strategy and early versus delayed revascularization therapy of this patient group. The decision for an invasive strategy has to outweigh the risk of an invasive diagnostics, while the decision for revascularization has to take into account morbidity and mortality associated with this strategy [2]. Randomized studies and subsequent meta-analyses have addressed the issue of optimal timing for coronary angiography and potential intervention in patients with NSTEMI, but produced surprisingly inconclusive and in part even contradicting results [3–7]. A patient-level meta-analysis of the FRISC II, RITA-3 and ICTUS trials showed a benefit of routine invasive strategy (vs. selective invasive),

* Corresponding author at: Zentrum für Kardiologie, Kardiologie I, Universitätsmedizin der Johannes Gutenberg-Universität, Langenbeckstrasse 1, 55131 Mainz, Germany.
E-mail address: tmuenzel@uni-mainz.de (T. Münzel).

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which was more pronounced in the higher-risk groups [8]. Accordingly, the ESC guidelines recommend a timing of invasive strategy, which largely depends on risk criteria including the GRACE SCORE [2,9]. However, more recent meta-analyses on the timing of catheterization did not find a benefit of an early vs. delayed angiography [10,11].

As previously demonstrated, real-life experience in the CPU setting may deviate from guideline recommendations [12]. In addition, contemporary NSTEMI populations differ substantially from patients recruited in randomized controlled trials in terms of risk and background medical therapy. Recent registry data from Asian populations did not demonstrate a benefit of an immediate PCI in NSTEMI patients [13].

Thus we sought to determine whether patients with NSTEMI treated in German Chest Pain Units (CPU) may benefit from invasive versus conservative therapy guided by the recent (2015) recommendations from the ESC [14] and the GRACE Score.

2. Methods

1549 patients were prospectively enrolled in the German CPU registry with a primary diagnosis of NSTEMI between March 2010 and March 2014. NSTEMI was defined according to the ESC guidelines for acute coronary syndrome without ST-segment elevation [14].

The CPU registry was introduced during the CPU certification campaign and intended to include an all-comer population of CPU patients. On admission, electronic case report forms were filled by the admitting staff, follow-up was performed centrally. Details about the registry have been reported previously [12]. Informed consent was obtained from all patients, and the registry was approved by the central review board of the Landesaerztekammer Rheinland-Pfalz.

2.1. Definitions

Cardiovascular disease was defined as any history of myocardial infarction, coronary artery bypass surgery, PCI, implanted pacemaker, stroke, peripheral artery disease, aortic dissection, pulmonary embolism or cardiomyopathy. First medical contact was defined as the patient's first contact to medical staff either prehospital, in-hospital or in-office, respectively. An early invasive strategy was defined as performing PCI within 24 h after admission. MACCE was defined as death, myocardial infarction or stroke during or following the admission. Serum creatinine levels >1.5 mg/dl, CRP levels >12 mg/l, and BNP levels >400 pg/ml were considered abnormal.

Within the NSTEMI patients (generally considered high-risk according to guidelines) we distinguished a Group A at higher risk according to the GRACE score of hospital mortality and additional risk criteria from a lower-risk Group B, as suggested by the ESC guidelines [2]. Specifically, group A comprised all patients a) having very high-risk criteria (Killip 4, acutely developed Killip 3, resuscitation, systolic blood pressure ≤ 90 mm Hg), or b) a GRACE score > 140, or c) a GRACE score 109–140 plus at least one additional intermediate-risk criterion (diabetes, EF ≤ 40%, renal impairment, prior PCI/CABG).

2.2. Statistical analysis

Categorical data are presented as percentages, continuous measurements as median with quartiles. The distribution of binary variables was compared by Pearson chi-square test, that of ordinal or metrical variables by Wilcoxon rank-sum test.

Determinants for not performing PCI within 24 h after admission were analyzed by conditional multiple logistic regression stratified for centers. In addition to age ≥75 years and gender, the following potential predictors were included in a backward selection procedure (removing variables with $p > 0.05$): history of cardiovascular disease, diabetes, chronic kidney disease, peripheral arterial disease, Killip II + on admission, referral by emergency medical system, ST-segment changes in prehospital or first hospital ECG, atrial fibrillation, and known EF ≤ 40%.

The cumulative incidence of MACCE (death, myocardial infarction, or stroke) within 120 days from index discharge was estimated by the Kaplan-Meier method, and compared by log-rank test. Unadjusted and adjusted hazard ratios were calculated in Cox regression models.

All *P*-values are results of two-tailed tests. P-values < 0.05 were considered statistically significant. The statistical analysis was performed at the biometrics department of the Stiftung IHF using SAS software package version 9.3 (SAS Inc., Cary, NC, US).

3. Results

3.1. Baseline characteristics

The baseline characteristics of Group A and Group B patients are summarized in Table 1. The prevalence of risk characteristics was almost balanced (higher-risk: 764 patients, lower-risk 785 patients). Group A patients were older, more men, and were more likely to have cardiovascular disease (CVD) including previous MI, PCI or CABG. In addition, these patients were more frequently diagnosed for heart failure, cardiomyopathy and were more likely to be equipped with an ICD or pacemaker. Higher-risk patients had a significantly higher percentage of cardiovascular risk factors such as diabetes and arterial hypertension and more chronic kidney disease (Table 1). Likewise, they were more on CVD medication including aspirin, dual antiplatelet therapy and were treated with anticoagulants reflecting the increased presence of atrial fibrillation (online Table 3).

Table 1
Baseline characteristics of NSTEMI-CPU patients (I).

Parameters	Group A	Group B	*P* value
Number of patients	764	785	
Age (years)	75.2 (69.4; 80.6)	60.9 (52.9;70.2)	< 0.001
Age > 75 y	388 (50.9%)	103(13.1%)	<0.001
Women	246 (32.2%)	201(25.6%)	0.004
Men	518 (67.8%)	584 (74.4%)	0.004
History of CVD	567 (74.4%)	273 (34.7%)	<0.001
Previous MI	248(32.5%)	105(13.4%)	<0.001
Previous PCI	331(43.3%)	108(13.8%)	<0.001
Previous bypass	180 (23.6%)	35(4.5%)	<0.001
Previous stroke	58 (7.6%)	24 (3.1%)	<0.001
Heart failure	92(12.0%)	12 (1.5%)	<0.001
Cardiomyopathy	47 (6.2%)	6 (0.8%)	<0.001
Implanted ICD or pacemaker	51 (6.7%)	17 (2.2%)	<0.001
Cardiovascular risk factors			
Diabetes mellitus	317 (41.5%)	92(11.7%)	<0.001
Chronic kidney disease	163 (21.3%)	10 (1.3%)	<0.001
Arterial hypertension	678 (88.7%)	573 (73.0%)	<0.001
Hyperlipidemia	468 (61.3%)	390 (49.7%)	<0.001
Smoking	184 (24.1%)	358 (45.6%)	<0.001
Family history of CVD	156 (20.4%)	240 (30.6%)	<0.001
Medication			
ASA	311 (40.7%)	153 (19.5%)	<0.001
Clopidogrel	27/395 (6.8%)	14/425 (3.3%)	0.020
Ticagrelor	9/395 (2.3%)	2/425 (0.5%)	0.025
Prasugrel	3/395 (0.8%)	2/425 (0.5%)	0.60
Dual antiplatelet therapy	32/395 (8.1%)	13/425 (3.1%)	0.002
Anticoagulation	38/395 (9.6%)	12/425 (2.8%)	<0.001

Data are presented as absolute number and percentages of patients in brackets, age as median with quartiles. CVD = cardiovascular disease; MI = myocardial infarction, PCI = percutaneous coronary intervention; ICD = implantable cardioverter defibrillator; ASA = acetylsalicylic acid.

3.2. Symptoms and findings on admission

Group A had a higher percentage of dyspnea and syncope or presyncope. Higher-risk patients had higher Killip classes, and a heart rate >90 bpm was more frequent in Group A. An ECG was recorded within 10 min in 70 and 71% of the patients respectively. The higher-risk group had more ST segment depression and T-wave inversion and significantly more atrial fibrillation (Table 2).

The BNP levels were higher in Group A as was creatinine and the prevalence of anemia. Higher-risk patients were more likely to have a moderately or severely impaired left ventricular function than the lower risk patients (EF < 40%; Table 2). The GRACE score in Group A versus Group B was higher for in-hospital mortality (144.2 vs. 98.7; $p < 0.001$) and in-hospital endpoint death/MI (171.8 vs 112.2; $p < 0.001$) (Table 2). Likewise, the GRACE Score was markedly higher in Group A with respect to post-hospital mortality (123.4 vs. 81.4; $p < 0.001$) and post-hospital death/MI (131.8 vs. 97.3; $p < 0.001$) (Table 2).

3.3. Results of invasive diagnostic and therapy of NSTEMI patients

With respect to critical time intervals, Group A patients had a substantially longer symptom to first medical contact time and a longer symptom to chest pain unit admission time. Interestingly, lower-risk patients had significantly more angina than higher-risk patients, while dyspnea was more frequent in high-risk ones (Table 3, online only).

Table 2
Symptoms and findings at admission.

Parameters	Group A	Group B	P value
Number of patients	764	785	
GRACE score			
Hospital mortality	144.2 (127.3; 160.9)	98.7 (82.8; 112.4)	<0.001
Post-hospital mortality	123.4 (108.5; 138.7)	81.4 (65.2; 95.9)	<0.001
Syncope/presyncope	4.6	3.6	<0.001
Heart failure (Killip Class II+)	141 (18.5%)	11 (1.4%)	<0.001
Killip II	107 (14.0%)	11 (1.4%)	<0.001
Killip III	30 (3.9%)	0	<0.001
Killip IV	4 (0.4%)	0	<0.001
ECG			0.31
First ECG < 10 min	70.1%	71.4%	0.65
Heart Rate < 60/min	79 (10.3%)	112 (14.3%)	0.019
Heart Rate > 90/min	192 (25.1%)	83 (10.6%)	<0.001
ST segment depression/T-inversion	359 (47.0%)	161 (20.6%)	<0.001
Atrial fibrillation	73 (9.6%)	12 (1.5%)	<0.001
Laboratory findings			
First Troponin available <45 min	88.2%	87.8%	0.86
First Troponin elevated	80.3%	64.3%	<0.001
BNP abnormal	60.0%	17.0%	<0.001
Creatinine abnormal	22.5%	3.2%	<0.001
Anemia (WHO definition)	30.5%	9.6%	<0.001
CRP abnormal	30.1%	16.9%	<0.001
LV function (EF) documented	82.2%	81.7%	0.78
Normal (>55%)	44.2%	76.0%	<0.001
Mildly impaired (41–55%)	23.1%	20.4	<0.001
Moderately → severe impairment (31–40%)	19.6%	2.8%	<0.001
Severely impaired (<30%)	13.1%	0.8%	<0.001

Presenting symptoms, signs and findings from diagnostic testing according to risk group. For biomarkers the percentage of abnormal values is given based on the normal ranges in participating centers. Data are presented as n (%) or percentages of patients were appropriate, values of GRACE score as median with quartiles. ECG = electrocardiogram; CRP = C-reactive protein; BNP = brain natriuretic peptide; LV = left ventricular; EF = ejection fraction.

More patients of group B received an immediate heart catheterization while higher-risk patients were more likely to have an elective procedure.

Higher-risk patients were more frequently diagnosed with triple vessel disease but were less revascularized by means of PCI or CABG. The door-to-needle time was markedly longer in Group A than B patients.

Logistic regression analysis revealed that higher age, female gender, a history of cardiovascular disease, presentation in Killip class II+, lack of ST-segment changes, the delay from symptom onset to CPU admission, chronic kidney disease, a documented EF < 40% and the diagnosis of a diabetes mellitus (online only: Table 4) were mainly responsible for a delay in performing intervention.

3.4. Effects of coronary intervention in higher and lower-risk NSTEMI-CPU patients on prognosis

Follow-up data at a median of 167 days post discharge were available for 92.9% of patients discharged alive in Group A and for 92.7% of Group B, respectively.

In Group A, 42.4% of patients underwent an early intervention (<24 h) compared to 65.1% in Group B. Kaplan-Meier survival analysis revealed that PCI had no impact on the 3-months prognosis of group B patients, whereas survival was markedly reduced in Group A patients without coronary intervention (Fig. 1A and B). After adjustment in Cox regression models for 120 days post discharge the association of early PCI with better prognosis was preserved in Group A (HR: 1.91 (CI 1.10–3.32), $p = 0.02$), but still no significant association emerged in Group B (HR: 1.15 (CI 0.45–2.92), $p = 0.77$) (Fig. 2).

4. Discussion

The clinical spectrum of non-ST-elevation myocardial infarction patients may range from patients free of symptoms at presentation to individuals with ongoing ischemia, electrical or hemodynamic instability or cardiac arrest. Given this highly variable clinical spectrum, the expected benefit of early versus delayed therapeutic intervention is highly inhomogeneous with this large cohort of patients.

The main finding of the present investigation is that higher-risk NSTEMI-CPU patients receive less early invasive coronary diagnostics and less coronary interventions despite the expected potentially larger benefit. In theory, this group should, according to the ESC-NSTEMI guidelines, be considered for early coronary interventions. Not undergoing a PCI in the higher-risk group was clearly associated with a higher in-hospital mortality and a higher mortality within 4 months after discharge from the hospital. In contrast, withholding a coronary intervention in the lower-risk group had, from the prognosis point of view, no impact at all. In both groups the timing (<24 vs. >24 h after presentation) of PCI was not associated with differences in outcome.

Whether or not patients with NSTEMI may benefit from an acute intervention has been a long matter of debate. While some RCTs demonstrated that early angiography and revascularization may improve clinical outcome [15,16] others showed an increase in infarct size or mortality [17,18]. Several other trials also showed no significant effect in cardiovascular outcome [19–21]. Importantly, one of the largest of these trials [20] established a significant reduction in the combined endpoint of death MI and stroke at 6 months for patients with the highest risk defined as having a GRACE score > 140, an effect that was lost at 10-year follow-up [22].

In addition, a meta-analysis of several randomized controlled trials and a more recently published meta-analysis including also observational studies [3,4] showed little or no benefit with an early intervention. The authors concluded that the currently available evidence does not allow firm conclusions to be drawn in favor of or against an early invasive approach in the NSTEMI-ACS population [4].

The different results of randomized trials may largely be explained by differences in their inclusion criteria. While studies with low rates of angiography and revascularization in the selective groups (FRISC II, RITA-3) report early benefits, those benefits are not seen in a setting were the selective groups after further testing eventually also undergo coronary angiography in >60%, like in the ICTUS trial. A recent Cochrane analysis found no mortality benefit of a routine invasive strategy at 12 months; however, patients in the routine invasive group had less recurrent MI, refractory angina and re-hospitalisations [23]. The benefit of a routine invasive strategy appears to be more doubtful for women compared to men [24] [25] Women also are treated less invasively [26]; however, the prognosis after intervention is not consistently different for women [27, 28]. The timing of the intervention is still an unsettled issue and probably cannot be uniformly answered for all NSTEMI patients. However, when it comes to who is most likely to derive benefit from early intervention, the current evidence is more congruent and favors patients with higher mortality and risk of complications.

The ESC guidelines recommend an intervention based on risk criteria [14]. Among those the GRACE risk score, used to predict in hospital and 6 months mortality [9,29], (http://www.gracescore.org/website/webversion.aspx) which includes parameters like age, heart rate, systolic blood pressure, serum creatinine levels, cardiac arrest at admission, elevated cardiac markers and ST-segment deviations has recently been shown to provide a superior risk discrimination than the TIMI score in patients with UA/NSTEMI to predict in hospital and 6 months mortality [30]. The GRACE score was derived from a cohort of roughly 11.000 patients recruited in the global registry of acute coronary events between 1999 and 2001. Thus, we employed the ESC recommendations including the GRACE-SCORE to group our patients in a higher and lower-risk group as described (see Methods section).

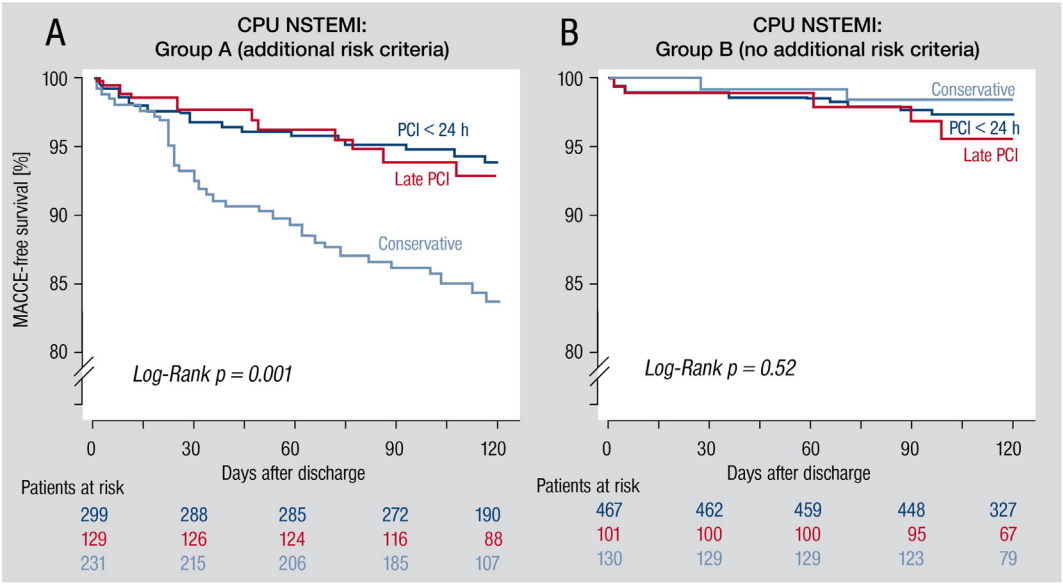

Fig. 1. Kaplan-Meier survival curves for patients who had early coronary intervention (<24 h), delayed intervention and those patients who were treated conservatively. 2A depicts the high-risk groups with a significant difference between early PCI and conservative management (log-rank < 0.001) 2B showing survival of Group B with no significant difference whether PCI was performed or not p (0.52).

The results of the present study indicate that critical time intervals (from symptom onset to first medical contact and from symptom onset to PCI) were markedly longer in the higher-risk than the lower-risk patient group. In addition, lower-risk patients were more likely to receive immediate heart catheterization (<2 h) than higher-risk patients. The same was true for invasive procedures <24 h. In contrast, elective invasive procedures were more frequent in higher-risk than lower-risk NSTEMI patients.

Thus, these results identified an obvious treatment paradox in German Chest Pain Units for NSTEMI patients being less aggressively catheterized despite having a higher risk.

The treatment paradox has apparently prognostic implications. The results of the present study clearly demonstrate that the high-risk NSTEMI patients from German Chest Pain Units benefit from a PCI resulting in a better survival. Patients categorized as being higher-risk were older, had a worse ejection fraction (<40%), higher Killip-class and had more chronic kidney disease. Actually all these points were identified as determinants for not performing a PCI (Table 4, online only). It is interesting to note that patients with a reduced ejection fraction and coronary artery disease in particular will have prognostic benefit from a coronary intervention. A recent meta-analysis indicated that revascularization strategies are clearly superior to medical treatment in improving survival in patients with coronary artery disease and reduced ejection fraction [31]. Thus, the fact that in higher-risk patients the intervention was delayed or even performed as an elective procedure may reflect that interventional cardiologists are hesitant to perform rapid interventions in patients promising trouble during the procedure because of their high age, female gender, impaired left ventricular function and kidney insufficiency. This more conservative approach in higher risk or older individual is in obvious contradiction with data reporting benefits also in octogenarians [32]. On the other hand coronary angiography may be delayed due to clinical instability or because of a clinical picture considered to be acutely decompensated heart failure with concomitant troponin elevation rather than ACS.

In contrast to the higher-risk patients in Group A, NSTEMI patients in Group B did not derive any benefit in terms of MACCE-free survival by undergoing PCI. Event rates in Group B were almost identical between conservative and invasive treatments, numerically even favoring conservative management. While the high-risk patients may receive too little invasive treatment, the higher rates of angiography and PCI in the low-risk patients has no apparent benefit in our study population. A risk-adapted allocation of invasive management therefore has the potential of benefiting patients and saving resources at the same time. The results suggest that there is no need to do more PCI but rather to provide it to the right patients.

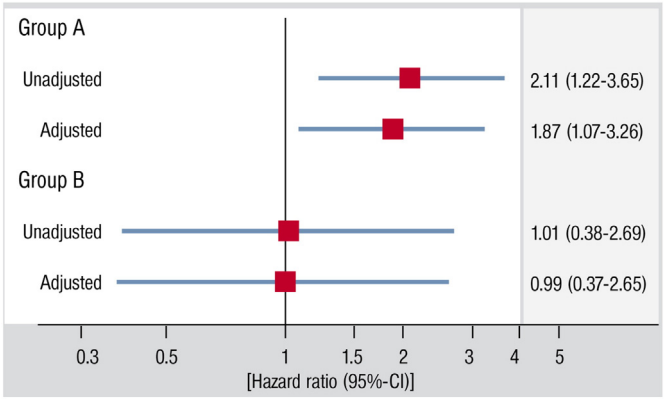

Fig. 2. Adjusted effects of factors on MACCE in a Cox-Regression model for 3 months follow-up after discharge from the CPU *adjusted for age, sex, cardiovascular disease, chronic kidney disease, diabetes, and Killip II+ on admission

5. Limitations of the present studies

Since the cohort was not randomized to different treatment strategies in our registry, it remains unclear how much of the observed differences depend on confounding rather than treatment effects of PCI. Differences in outcome can therefore not necessarily be attributed to the intervention but may result from unaccounted baseline differences. The reasons for not performing a coronary angiography or PCI in patients at higher-risk were not defined on an individual basis and therefore it remains speculative, if absence of treatment represents under-treatment or lack of veritable treatment options. The follow-up period of only 3 months may influence results, since some complications of treatment like restenosis or stent-thrombosis may occur later.

6. Conclusions

The present study shows that, contrary to guideline recommendation, lower-risk rather than higher-risk NSTEMI patients undergo early coronary intervention in German CPUs. This treatment paradox is associated with lower survival rates within a 3-month period after CPU discharge. Thus, like in CPU STEMI patients, we demonstrated a gap between recommendations and practice in the treatment of this patient population in Germany. Whether this reflects ability or willingness to treat remains unclear. To address the clinically important question whether more aggressive treatment in an all-comers high-risk group is of benefit, a prospective trial with a large sample size and extended clinical follow-up would be needed. Until then, clinicians should – based on study data and guideline recommendations – not withhold treatment in higher risk patients.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2017.11.018.

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