Risk is not flat. Comprehensive approach to multidimensional risk management in ST-elevation myocardial infarction treated with primary angioplasty (ANIN STEMI Registry)

Mariusz Kruk[1], Jakub Przyłuski[2], Łukasz Kalińczuk[1], Jerzy Pręgowski[2], Edyta Kaczmarska[1], Joanna Petryka[1], Cezary Kępka[1], Paweł Bekta[2], Zbigniew Chmielak[2], Marcin Demkow[1], Andrzej Ciszewski[2], Maciej Karcz[2], Mariusz Kłopotowski[2], Adam Witkowski[2], Witold Rużyłło[1]

[1]Coronary Disease and Structural Heart Diseases Department, Institute of Cardiology, Warsaw, Poland
[2]Department of Interventional Cardiology and Angiology, Institute of Cardiology, Warsaw, Poland

Abstract

Introduction: Current risk assessment concepts in ST-elevation myocardial infarction (STEMI) are suboptimal for guiding clinical management.

Aim: To elaborate a composite risk management concept for STEMI, enhancing clinical decision making.

Material and methods: 1995 unselected, registry patients with STEMI treated with primary percutaneous coronary intervention (pPCI) (mean age 60.1 years, 72.1% men) were included in the study. The independent risk markers were grouped by means of factor analysis, and the appropriate hazards were identified.

Results: In-hospital death was the primary outcome, observed in 95 (4.7%) patients. Independent predictors of mortality included age, leukocytosis, hyperglycemia, tachycardia, low blood pressure, impaired renal function, Killip > 1, anemia, and history of coronary disease. The factor analysis identified two significant clusters of risk markers: 1. age-anemia- impaired renal function, interpreted as the patient-related hazard; and 2. tachycardia-Killip > 1-hyperglycemia-leukocytosis, interpreted as the event-related (hemodynamic) hazard. The hazard levels (from low to high) were defined based on the number of respective risk markers. Patient-related hazard determined outcomes most significantly within the low hemodynamic hazard group.

Conclusions: The dissection of the global risk into the combination of patient- and event-related (hemodynamic) hazards allows comprehensive assessment and management of several, often contradictory sources of risk in STEMI. The cohort of high-risk STEMI patients despite hemodynamically trivial infarction face the most suboptimal outcomes under the current invasive management strategy.

Key words: acute coronary syndrome, ST-elevation acute coronary syndrome, primary angioplasty, risk assessment.

Introduction

The current management paradigm assumes acute ST-elevation myocardial infarction (STEMI) as an emergency medical condition with high risk of complications, justifying use of relatively aggressive anticoagulant/antiplatelet and reperfusion therapies in all patients [1, 2]. Such a uniform approach to all acute STEMI patients historically proved to be effective as the focus on timely and sustainable patency of the infarct-related artery led to significant reduction of mortality [3]. However, acute STEMI patients constitute a non-uniform group with regard to the risk of untoward outcomes, which can be aptly assessed by means of TIMI, GRACE or multiple other risk scores [4]. Moreover, there are also other predictors of death, including serum glucose, hemoglobin, leukocytosis, etc. [5, 6]. The multiplicity and vague pathophysiological significance of the individual components comprising the risk scores reflect a complex pathophysiological structure of risk. However, the current analytical approach, providing one-dimensional structure of risk (more risk markers = higher risk), is not capable of grasping the conundrum of contradictory risk sources in STEMI, those related to the disease and to the therapy. The solution is sought in more sophisticated endpoints, including the recent development of "net clinical benefit". However,

this endpoint is methodologically suboptimal and carries the risk of misinterpretation [7, 8]. The inadequacy of current risk scores for guiding acute clinical management is illustrated by the fact that none of them is adopted by the main STEMI guidelines [1, 2].

Analysis of the risk to benefit ratio comprises the basis of everyday clinical practice. However, neither the medical curriculum nor the literature provides appropriate tools for ordered risk management in the complex medical environment. According to mature risk management concepts applied in the U.S. Army, and the Federal Aviation Administration, composite risk management involves identification and assessment of hazards, followed by risk determination and further application of resources to minimize and control the probability or impact of untoward outcomes. The crucial concept shifts as compared to the traditional approach are: 1. introduction of the "hazard", defined as any condition that can potentially cause an injury, and 2. changed meaning of the "risk", defined as a derivative of the hazard severity and probability, which is assessed by means of "risk matrices" [9, 10]. The advantage of this mature conceptual risk management framework is its confirmed ability to identify targets for risk reduction in complex systems on both operational and general policy levels. According to the composite risk management rules, high risk indicates an unacceptable level of risk [9, 10].

Accordingly, we aimed to introduce a new risk management concept for acute STEMI treated with primary percutaneous coronary intervention (pPCI). It implied: 1) identification and assessment of hazards, 2) risk determination according to risk matrices, and 3) guidance for possible actions mitigating the risk. Given the novelty and complexity of the discussed issues, and possible multiple ways to approach the problem, the current paper should be regarded as a tentative approach to adapt mature risk management concepts to STEMI, and to find a conceptual basis for development of practical hazard assessment tools in the medical domain.

Material and methods

Study design and patient population

Our study group was described elsewhere [5, 6]. Shortly, it is derived from 1995 unselected, Caucasian, consecutive, prospective registry patients with STEMI (ST-elevation of ≥ 0.1 mV in > 1 limb leads or of ≥ 0.2 mV in contiguous chest leads or new left bundle branch block (LBBB) at presentation) and with time from the pain onset to admission less than 12 h, enrolled between February 2001 and December 2004. The pre-defined set of data recorded in the hospital registry for consecutive patients with STEMI who were admitted to our institution for primary angioplasty included the following clinical and procedural data: gender, age, Killip class > 1, known diabetes mellitus, hypertension, hypercholesterolemia, anterior myocardial infarction (MI), history of prior coronary artery disease (CAD), current smoking, time

from onset to admission, systolic blood pressure, heart rate, culprit artery Thrombolysis in Myocardial Infarction (TIMI) flow above one prior to and after coronary intervention, multivessel disease (more than one coronary vessel with > 50% stenosis on coronary angiography), coronary stenting, and glycoprotein IIb/IIIa use at the time of the primary procedure. Patient's history data were obtained on admission from patient interview or available previous medical documentation. Also, a predefined set of hematological and biochemistry parameters was collected for each patient on admission and prior to any coronary procedures and contrast media, including blood glucose, morphology, and serum creatinine. Glomerular filtration rate (GFR) was calculated according to the Modification of Diet in Renal Disease formula: $186 \times (S_{cr})^{-1.154} \times (Age)^{-0.203} \times (0.742 \text{ if female})$, and anemia was defined as < 39% in men and < 36% in women [11]. In all the patients angioplasty of the culprit lesion was attempted in accordance with the standard techniques, following a loading dose of aspirin (300–500 mg) and clopidogrel (300–600 mg).

Study endpoints

In-hospital mortality was regarded as the primary study outcome. The mortality data were obtained for all subjects based on the hospital records. The analyzed safety outcome was bleeding, defined as intracranial or intraocular hemorrhage; bleeding at the access site, with a hematoma that required intervention; a decrease in the hemoglobin level of 4 g/dl or more without an overt bleeding source; reoperation for bleeding; or bleeding requiring blood transfusion [12].

From among the study patients in 55 (2.8%), 69 (3.5%), and 84 (4.2%) cases no pre-intervention blood count, serum creatinine and glucose levels, respectively, were available. However, incidence of the primary endpoint (mortality) in patients with the available risk markers vs. patients without did not differ significantly for any of these (92/1940 vs. 3/55 for blood count; 89/1926 vs. 6/69 for serum creatinine; 92/1911 vs. 3/84 for glycemia; *p* > 0.05 for all comparisons). The missing data were imputed as the lack of the factor after data categorization, so that all consecutive patients were analyzed in multivariable models.

The study complies with the Declaration of Helsinki. The locally appointed ethics committee (Terenowa Komisja Bioetyczna przy Instytucie Kardiologii) has approved the research protocol.

Statistical analysis

According to the composite risk management concept, the identification of hazards may be performed by expert judgment or may be assisted by use of additional analytical tools [9, 10]. Factor analysis emerged as a method helping to understand patterns underlying the co-occurrence of risk factors, and was successfully utilized to establish metabolic syndrome. Our approach involved factor analy-

sis which reduced the set of traditional STEMI risk markers to a smaller number of independent clusters called "factors", each of them containing within-factor correlated variables. Factor analysis itself comprises three main steps: 1) extraction of the initial components by means of principal component analysis; 2) elucidation of factors by orthogonal rotation of the components and 3) interpretation of results [13]. The interpretation of the factors analysis was based on the correlations, called loadings (range –1.0 to 1.0), between the factors and the original independent variables. Variables with loadings ≥ 0.4 are recommended for interpretation of the factor [13, 14].

The primary analysis was performed on all 1995 patients. Categorical variables were summarized as percentages and compared with the χ^2 test. Continuous variables were compared using Student's *t* test.

The 1st step of the analysis included exploratory analysis of univariable predictors of in-hospital mortality by means of regression analysis (non-normally distributed continuous variables were analyzed after log transformation). For the significant continuous risk markers, the 2nd step assured the choice of the best cut-off value with the most optimal sensitivity and specificity based on receiver operator characteristics (ROC). The 3rd step included multivariable analysis of the risk factors (all binary) to determine independent variables (including variables with $p < 0.10$ in univariable analysis). The 4th step comprised factor analysis based on the set of independent risk variables. Since the factor analysis assumes interpretation of the results, further analyses were dependent on the interpreted results and thus were not predefined. The 5th step included assessment of interaction between the major risk components with regard to the study outcomes. To assess the risk (the 6th step) the risk matrix was plotted as a product of the risk severity (based on the event rate) and probability for subsequent hazards groups.

For the predefined set of analyses including derivation of independent risk factors α was set at 0.05. Given the exploratory nature of the factor analysis, and its unexpected results, to avoid the risk of spurious findings, we defined a significant α level as $p < 0.01$ for all analyses secondary to the factor analysis (steps 5 and 6).

Statistical analyses were performed with SPSS (version 9.0) and SAS (SAS Institute, Cary, North Carolina) statistical packages.

Results

Baseline characteristics

All 1995 study patients were included in the analysis. Overall in-hospital death was observed in 95 (4.8%) patients, and bleeding occurred in 141 (7.1%) patients. Cardiogenic shock on admission was reported for 76 (3.8%) patients, of whom 35 (46.1%) died. The study group characteristics are provided in Table 1. According to univariable analysis the following variables were predictive of in-hospital mor-

tality: male gender, smoking, multivessel disease, post-procedure culprit artery TIMI flow < 2, Killip > 1, anemia, age, leukocytosis, glucose, heart rate, blood pressure, GFR; the numerical values are provided in Table 1. For continuous variables the thresholds with best specificity/sensitivity characteristics were found according to ROC curves, and their numerical values and the outcome of multivariable analysis are provided in Table 2.

Hazard identification and assessment – factor analysis

Results of factor analysis with rotated components are presented in Table 3. The first significant component revealed by a factor analysis comprised chronic conditions independent of the index event: older age, anemia and low GFR. The second component comprised parameters directly related to the index event reflecting the individual's hemodynamic compromise and neurohormonal activation including higher heart rate and Killip class coupled with (acute) hyperglycemia and leukocytosis. The third, least significant component comprised low blood pressure and anemia.

On the pathophysiological background, it was assumed that at least two clinically meaningful and independent risk components further referred to as the hazards may be identified based on the factor analysis, namely the "patient-related (chronic) hazard", independent of the index event, and the "event-related (hemodynamic) hazard" directly related to the markers of hemodynamic compromise (Figure 1). Accordingly, the constitutive individual risk markers were summarized for each of the hazards for each patient (i.e. 0–3 factors for patient-related hazard and 0–4 for event-related (hemodynamic) hazard). Patients with cardiogenic shock were categorized as having high event-related (hemodynamic) hazard irrespective of the other hemodynamic markers. Respective numbers of patients with from low to high patient-related hazard were: 1047 (52.5%), 600 (30.1%), 348 (17.4%) for 0, 1, and > 1 risk markers. For the event-related (hemodynamic) hazard the numbers were: 1096 (54.9%), 571 (28.6%), 206 (10.3%), 122 (6.1%) respectively for 0, 1, 2 and > 2 risk markers.

The interaction term between the event- and patient-related hazards and the main outcome was significant ($p = 0.001$). The patient-related (chronic) hazard had a different impact on mortality depending on the event-related (hemodynamic) hazard: the highest impact in patients with low event-related (hemodynamic) hazard, moderate impact in patients within mid event-related (hemodynamic) hazard groups and no impact in patients within the high event-related (hemodynamic) hazard group (Figure 2).

Risk determination – combining hazard severity and probability

The death rate increased with increasing number of risk markers for each of the individual hazards. However, due

Table 1. Baseline and procedural characteristics and the hazard ratio (95% confidence intervals) with regard to mortality

Variable	Overall (*N* = 1995), *n* (%)	Hazard ratio (95% CI) univariable
Men [%]	1443 (72.3)	0.64 (0.42–0.98)
Age [years]	60 (51–69)	1.06 (1.04–1.08)
Heart rate [beats/min]	80 (69–91)	1.04 (1.03–1.05)
Systolic blood pressure [mm Hg]	132 (114–152)	0.98 (0.97–0.99)
Killip class > 1 [%]	200 (10.0)	13.62 (8.80–21.07)
Time from onset [h]	3.9 (2.8–5.7)	1.06 (0.96–1.17)
Hyperlipidemia [%]	531 (26.6)	1.09 (0.66–1.81)
Diabetes [%]	204 (10.2)	1.20 (0.59–2.42)
Hypertension [%]	888 (44.5)	1.17 (0.77–1.79)
Previous coronary disease [%]	540 (27.1)	1.54 (0.997–2.36)
Anterior MI	775 (38.8)	1.10 (0.72–1.68)
Smoking [%]	638 (32.0)	0.47 (0.26–0.83)
Glycemia [mg/dl]	7.9 (6.6–10.1)	142.48 (45.29–448.17)*
Anemia [%]	383 (19.2)	2.47 (1.58–3.87)
GFR	69.2 (56.8–82.9)	0.96 (0.95–0.97)
WBC count [K/μl]	11.3 (9.3–13.7)	36.37 (7.29–181.50)*
Angiography, intervention		
Multivessel disease [%]	1065 (53.4)	2.70 (1.68–4.32)
TIMI flow > 1 pre-PCI [%]	309 (15.5)	0.49 (0.23–1.02)
TIMI flow > 1 post-PCI [%]	1684 (84.4)	0.30 (0.19–0.47)
Stent [%]	1696 (85.0)	0.59 (0.30–1.15)
IABP [%]	33 (1.7)	37.62 (18.01–78.57)
Abciximab [%]	909 (45.5)	1.12 (0.73–1.73)

*Frequency (%) for categorical variables, median (25th, 75th percentiles) for continuous variables; *continuous data after log transformation. CI – confidence interval, IABP – intra-aortic balloon pump, GFR – glomerular filtration rate, HR – hazard ratio, PCI – index event percutaneous coronary intervention, TIMI – thrombolysis in myocardial infarction, WBC – white blood cell*

to the significant interaction between the two hazards, we illustrated the impact of combinations of the distinct hazards on the individual's outcomes (death and bleeding) according to a 3 × 4 table (Figure 3). The contribution of successive patient subgroups to total mortality was plotted in Figure 4. Given the varying significance of the chronic hazard depending on the hemodynamic hazard, based on the rate of death (severity) and the proportion (probability), the chronic hazard was plotted in separate risk matrices for each of the hemodynamic hazard groups (Figure 4) [15].

Discussion

Our study introduces a novel concept for risk management in STEMI treated with pPCI based on 1. identification of hazards and 2. redefinition of the risk as a product of the outcome severity and probability. The dissection of the global risk into the combination of the patient- and the event-related (hemodynamic) hazards allows more comprehensive assessment and management of several, often contradictory sources of risk for STEMI patients, and subsequently balancing the risk/benefit ratio for a given ther-

apy on an individual level. The risk matrices indicate the high-risk subgroup of patients for whom current invasive management seems to provide the least optimal outcomes. On

Table 2. Independent predictors of the primary outcome according to multivariable analysis (hazard ratio and 95% confidence intervals)

Risk factor	Coefficient	Hazard ratio (95% confidence interval)
Age above 67 [years]	0.31	1.36 (1.15–1.62)
GFR (< 54.3) [ml/min/1.73 m²]	0.29	1.34 (1.03–1.74)
Leukocytosis (> 15.0) [k/μl]	0.33	1.39 (1.16–1.66)
Glucose (> 12.0) [mmol/l]	0.35	1.42 (1.19–1.68)
Heart rate (> 89/minute)	0.37	1.45 (1.24–1.71)
Systolic blood pressure (< 108) [mm Hg]	0.36	1.44 (1.11–1.87)
Killip class > 1	1.70	5.47 (3.30–9.07)
Anemia	0.72	2.06 (1.23–3.46)
Previous coronary disease	0.58	1.79 (1.09–2.96)

Table 3. Results of factor analysis showing the clusters of individual risk markers

Variable	Factor 1	Factor 2	Factor 3
Age above 67 [years]	**0.700**	−0.119	−0.105
Leukocytosis (> 15.0) [k/μl]	−0.159	**0.666**	7.113×10^{-2}
Glucose (> 12.0) [mmol/l]	0.359	**0.559**	1.785×10^{-2}
Heart rate (> 89/minute)	-2.570×10^{-2}	**0.583**	-1.545×10^{-2}
Systolic blood pressure (< 108) [mm Hg]	6.582×10^{-3}	4.922×10^{-2}	0.826
Glomerular filtration rate (< 54.3) [ml/min/1.73 m²]	**0.647**	0.255	9.228×10^{-2}
Killip class > 1	0.367	**0.402**	0.338
Anemia	**0.449**	−0.300	**0.411**
Previous coronary disease	0.356	-8.785×10^{-2}	−0.370

Extraction method: principal component analysis. Rotation method: Varimax with Kaiser normalization. Factor loadings represent the correlation between the individual variable and each factor
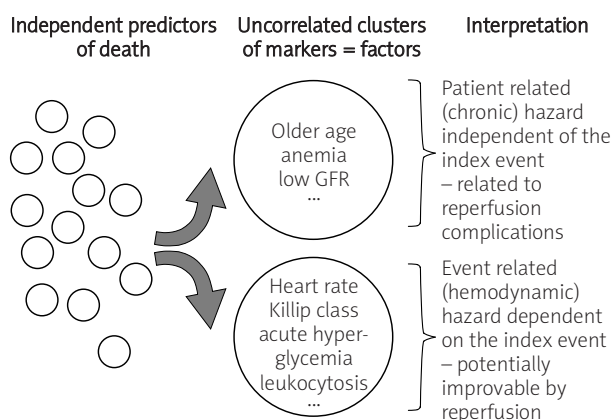

Fig. 1. Graphic description of the novel concept of hazards. Identification of the hazards is made by means of factor analysis. The small circles represent the independent variables included in the analysis; the large circles represent the two newly defined factors. As noted in "Methods," only factor loadings greater than 0.40 were used for the factor interpretation

Fig. 2. The interaction between the event-related (hemodynamic) and patient-related (chronic) hazards and the main outcome (in-hospital death) ($p = 0.001$ for the interaction). Hazard ratio and 99% confidence intervals for the patient-related (chronic) hazard
Event – event-related (hemodynamic) hazard, Patient – patient-related (chronic) hazard

an individual level, the current work provides the conceptual foundation for development of new, practical risk assessment tools enhancing risk management – hazard scores.

Risk markers

The mortality rate of our cohort was similar to that of other non-randomized studies of patients treated with pPCI [16]. Our study group was relatively unique, as it comprised real life patients with an ample set of baseline (sampled prior to the intervention) biochemical data, allowing us to analyze hard endpoints (total mortality) within the acute phase (in-hospital) of a uniform condition (STEMI) treated with pPCI. This rendered the set of independent baseline variables related to in-hospital mortality, including elderly age, higher heart rate, lower systolic blood pressure, Killip > 1, and previous history of CAD, decreased GFR, leuko-
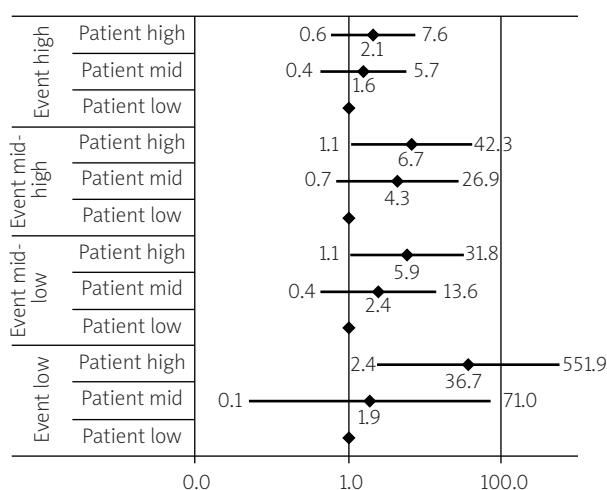
cytosis, hyperglycemia, and anemia which were unique yet not contradictory to previous similar analyses [17, 18]. It has been shown that the risk markers for a specific cohort like ours may differ from: randomized studies due to selection bias, studies using different reperfusion strategies (including sole medical management), studies assessing different biomarkers or markers sampled after the reperfusion, studies of non-uniform conditions (including non-ST elevation acute coronary syndrome), studies employing composite ("softer") endpoints, and finally, those assessing longer term follow-up, where disease progression and other late complications may override the markers of acute complications [19–22]. Our cohort was the first previously showing the independent significance of leukocytosis and anemia in unselected patients treated with pPCI [5, 23, 24] and the detailed discussion regarding our independent risk markers in re-
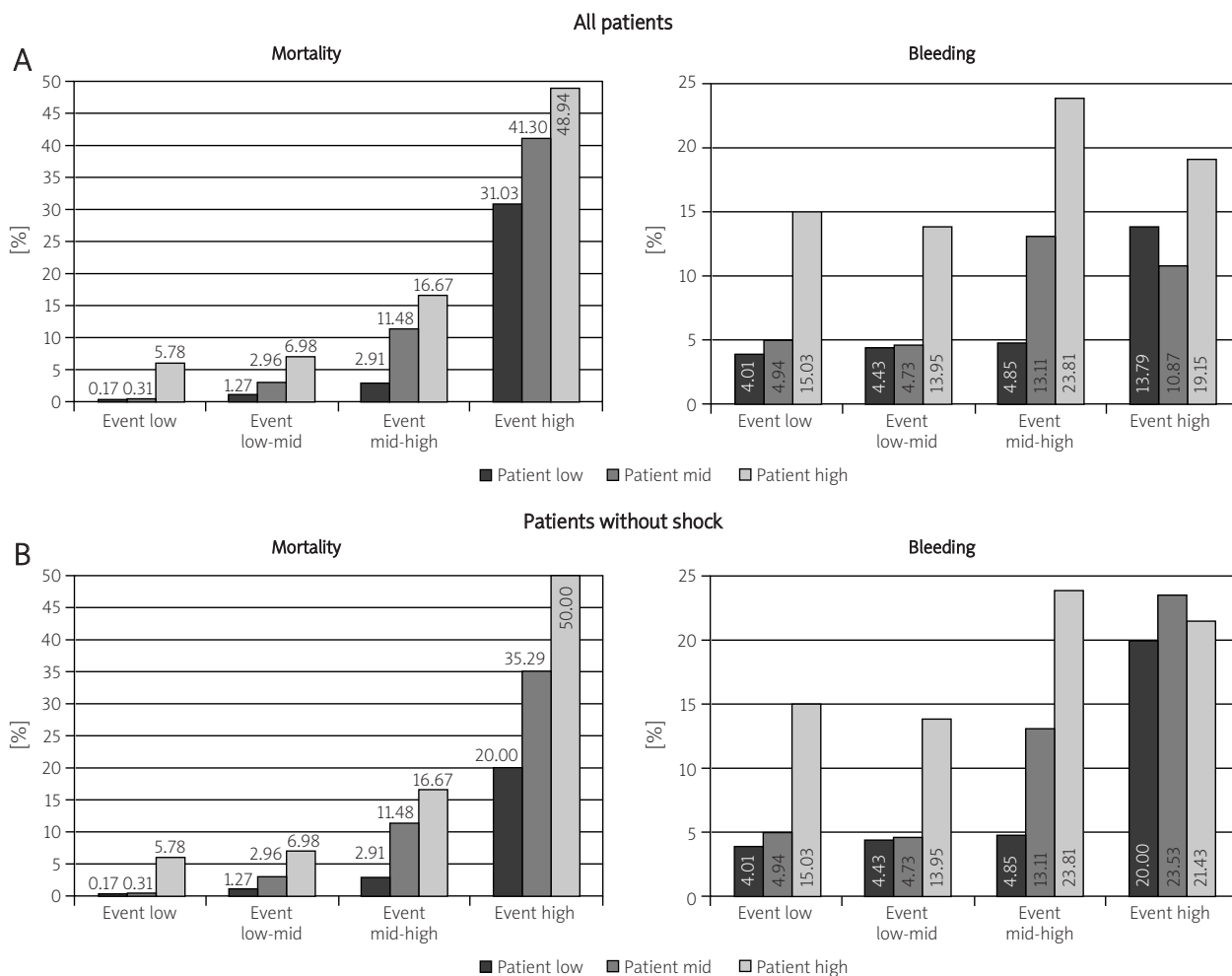
Fig. 3. Mortality and bleeding rates according to the patient- and event-related (hemodynamic) hazards for all patients (**A**) and for patients without cardiogenic shock (**B**)
Event – event-related (hemodynamic) hazard, Patient – patient-related (chronic) hazard

lation to other studies may be found elsewhere [5, 6, 23]. Given our methodology (blood sampling in patients within 0–12 h of STEMI onset and prior to the attempted reperfusion), it may be assumed that the baseline values of hematocrit and GFR closely represent their chronic levels and are not yet significantly affected by the course of the disease or its acute treatment. Given the dynamic nature of parameters like Killip class, heart rate, blood pressure, glycemia or leukocytosis under acute stress, these variables likely reflect the acute neurohormonal activation closely associated with the hemodynamic compromise. Importantly, all the parameters are readily assessable on admission during patient examination and point of care blood testing, which enables their incorporation in future routine risk assessment tools.

State of the art – the risk is flat

The cumulative risk associated with STEMI treated with pPCI is a derivative of hemodynamic consequences of the cardiac ischemic event, combined with the risks and ben-

efits of the reperfusion treatment. The current risk assessment paradigm links directly the individual risk markers to the outcomes, providing a flat risk structure, i.e. indicating the level of cumulative risk (more risk markers = higher risk). Importantly, the risk markers of overall mortality in STEMI, including renal dysfunction, anemia, worse Killip class, older age, or leukocytosis, interfere with those of the treatment complications (bleeding and contrast-induced nephropathy) and are unable to discriminate between the risks associated with the disease and with treatment complications [25, 26]. The cumulative risk structure may also lead to "attribution error" resting upon the confusion of mortality associated with STEMI (sometimes aggravated by pharmaco-mechanical reperfusion), with mortality due to STEMI (potentially preventable by reperfusion). The "attribution error" leads to a uniform therapeutic response to the higher risk conditions irrespective of their pathophysiological significance. This refers in particular to patients with renal disease and the elderly, for whom equally aggressive treatment is reinforced by STEMI guidelines despite the following facts: 1. revascu-
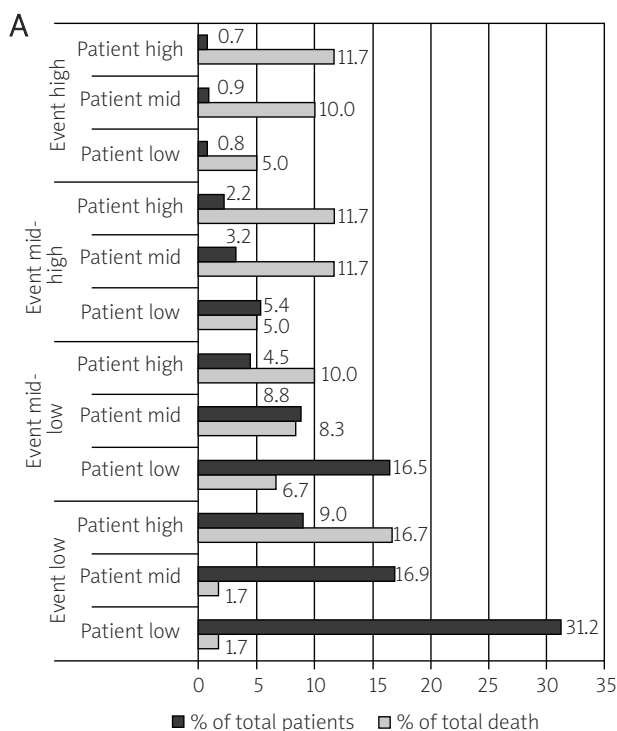
Fig. 4. Risk determination. The contribution of successive patient subgroups to total mortality and the corresponding risk matrices. Hazards are ranked according to the severity (= mortality rate) and the likelihood, which is illustrated by where they fall on the risk matrix. Hazards with high risk receive higher priority for treatment and mitigation [15]
Event – event-related (hemodynamic) (acute) hazard, Patient – patient-related (chronic) hazard
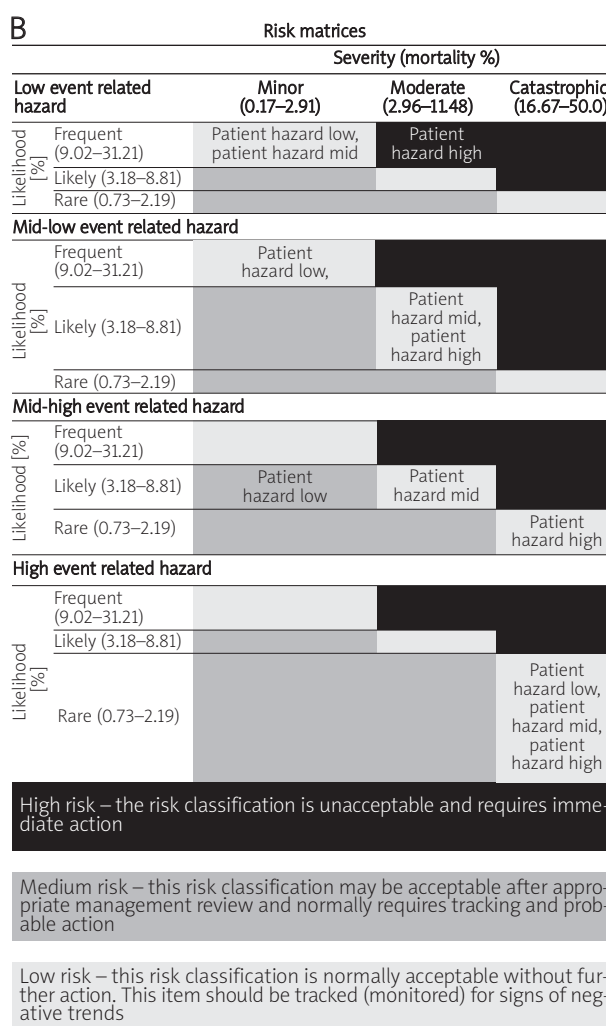
larization has no positive impact on renal dysfunction or age, 2. renal dysfunction and age comprise the most important markers of global risk by increasing the rate of treatment complications [27, 28], 3. renal dysfunction and elderly patients are severely underrepresented in most clinical trials, resulting in an uncertain risk/benefit ratio for a given treatment, and 4. renal disease patients may experience an unfavorable risk/benefit ratio for reperfusion [28–30].

The above conceptual problems with one-dimensional risk assessment effectively impede use of the existing risk scores for guiding clinical management in STEMI and limit their practical significance to actuarial purposes. The confusion regarding risk management in STEMI is further perpetuated by multiply defined and often unclear use of the term "high risk" in the American guidelines, and its lack (except for secondary prevention) in the European ones [1, 2].

New risk assessment and management concept

Pharmaco-mechanical reperfusion offers a decreasing benefit for patients with a smaller ischemic area and delayed reperfusion up to the point of no benefit, or pos-

sibly harm (aptly shown in the Occluded Artery Trial) [31], while the complication rate of reperfusion therapy (catheterization, anticoagulants, antiplatelets, contrast) seems constant irrespective of its benefit for a given patient. The factor analysis used in the current study allowed segregation of the cluster of individual risk markers into hazards, which can be understood as "sources" of risk [9, 10, 15]. The hazards set the distinction between the portion of the total risk that can be targeted and in many cases improved by pharmaco-mechanical reperfusion (event-related (hemodynamic) hazard) and its counterpart, refractory or even aggravated by the reperfusion and anticoagulants (patient-related hazard). This distinction allows one to better define at which point the treatment benefit may be offset by its complications, and subsequently guide the therapeutic choices.

The redefinition of risk involves the use of risk matrices, which define risk based on both hazard severity and probability (Figure 4). This results in attribution of high risk not necessarily to hazards with worst outcomes, unless they are relatively frequent. According to our analysis, the only

subgroup with high (= unacceptable) risk comprised patients combining high patient with low hemodynamic hazards. Despite the intermediate mortality rate (severity), however, the prevalence of these patients is high (Figure 4). The identified high-risk group merits particular attention for several reasons; 1. the potential benefit of primary PCI in these patients is dubious and therefore may not be counterbalanced by the high complication rate, 2. despite being a common (and likely expanding due to society aging) group of real life patients (9%), it is also the most underrepresented one in clinical trials, and literally ignored in clinical guidelines and literature [19, 28, 29]. The latter fact may contribute to the high risk of the group, since "evidence-based therapies" have not been tested in these patients.

Implications

The implications of our findings have both a general context, indicating the direction of further STEMI management improvement, and an individual context, suggesting tailored modification of management based on the individual patients' hazards.

Our evidence necessitates specific customization of management in high-risk patients with low hemodynamic hazard (trivial infarction). As shown by significant interaction of the patient and hemodynamic hazards and the outcome, the patient-related hazard seems to determine prognosis solely in patients with hemodynamically trivial MIs (low hemodynamic hazard). Given the high rate of bleeding within the high patient hazard group (Figure 3), it may be speculated that the treatment complications may significantly contribute to the mortality in the high-risk patients with trivial infarctions [8]. Many already applicable management options offer a lower complication rate, including transradial access, lower sheath size, safer anticoagulant and antiplatelet therapies, lower quantity and better quality of contrast, other kidney protection measures, gastrointestinal bleeding prevention with proton pump inhibitors, minimizing intracoronary manipulation, or even opting out of pPCI [2, 32].

At the policy level, it is important to recognize the group of STEMI patients with high risk despite hemodynamically trivial infarction as possibly requiring a non-routine approach, and incorporate the above management options in the updated STEMI guidelines. The general implications also refer to clinical trials of reperfusion or antiplatelet/anticoagulant interventions in acute coronary syndromes. For clinical trials in acute coronary syndromes, usually the higher risk subsets are selected in order to lower the number of participants, and sometimes increase chances for the desired study result. Consequently, the higher hemodynamic and lower patient-related hazard traits are usually preselected [19, 29]. The results of these trials may be less relevant to aging western populations than assumed, and our analysis allows more conscious assessment of the study entry criteria by both study designers and the regulatory agencies. Our data also support appropriately pre-defined interaction analyses to assess the safety of a given treatment within the hazard subgroups, instead of creating complex endpoints (net benefit). The clinical guidelines pertaining to STEMI (in particular European) should also more critically refer to the results of randomized trials indicating more precisely the populations which were tested, and those which were not (excluded).

On the individual level, our data enhance identification of patients who may require modification of the routine STEMI management due to expected high risk of complications and lower benefit of revascularization. This may improve the patients' outcomes and the treatment cost effectiveness. Proliferation of point-of-care testing may further facilitate early assessment of the individual hazards based on clinical signs and biochemistry data. Our findings also pertain to the problem of lower rates of revascularization in patients with high-risk non-cardiac conditions, partially explainable by the intuitive (= prone to error) judgment of the physician on the unfavorable treatment risk/benefit ratio in some patient subsets. Current data and further elaboration of our tentative concept should provide more evidence-based support and guidance for clinical decision making in these clinically equivocal situations.

Limitations

The current study is based on a prospective registry and should be viewed as generating hypotheses, and not identifying causal relationships. To limit the possibility of spurious findings we restricted the α value for the secondary analyses and respectively provided the results with a 99% confidence interval. At the current stage our data may be helpful in some management decisions, but it may be only hypothesized that the specific therapeutic interventions based on acknowledgement of our findings may translate into clinical benefit.

The hazards identified in our analysis are both intuitively and pathophysiologically consistent. However, they should be viewed as one of the multiple possible hazard combinations, since there are multiple ways to establish the hazards [9, 10]. Importantly, also the hazard components may be different, including left ventricle ejection fraction and brain natriuretic peptides for hemodynamic hazard, but we did not perform these measurements prior to the reperfusion and therefore they were not included in our analysis.

Our analysis provides a tentative tool for clinical decision making, and also for development of the hazards' scores, which should be validated on an external dataset, and optimally tested in a randomized clinical trial.

Our results are based on a group of patients with STEMI on admission, who were treated with primary PCI. Therefore, extrapolating our results to other types of acute coronary syndromes should be done with caution.

Conclusions

We propose a new risk management concept in STEMI resting upon assessment of separate hazards, easily identified in the clinical setting. Splitting the global risk into hazards allows early comprehension and adequate management of several, often contradictory sources of risk for STEMI patients. The group of high-risk patients with hemodynamically trivial infarction may comprise the optimal target for the most significant reduction of mortality in STEMI.

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