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Impact of age on short- and long-term mortality of patients with ST-elevation myocardial infarction in the VIENNA STEMI network

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Summary
Background and aim Our senescent society includes a growing number of elderly people suffering from ST-elevation myocardial infarction (STEMI); however, exactly this population is often underrepresented in randomized trials. Hence, our aim was to investigate the influence of age on patient characteristics, as well as short- and long-term outcome in the Vienna STEMI registry.
Methods We included all patients of the Vienna STEMI registry (2003–2009). Patients were stratified into age cohorts (≤45, 46–59, 60–79 and ≥80 years, respectively). Differences between cohorts were investigated by descriptive statistics and regression models. Crude and adjusted mortality rates were investigated using log rank test and Cox regression models, respectively. The influence of treatment on mortality was further investigated using propensity score matching.
Results A total of 4579 patients fulfilled the criteria for further investigation. With rising age of cohorts, the number of females, diabetes mellitus (DM), hypertension (HTN), previous myocardial infarction (MI), shock, no reperfusion therapy and anterior wall infarction significantly increased. In contrast, the number of patients with a positive family history, smoking and hyperlipidemia (HLP) significantly declined. Log rank analysis showed significant differences between age cohorts for short- and long-term mortality. Cox regression analysis for short-term mortality revealed an independent association for age at the event, HTN and shock, while age, smoking, DM, HTN, HLP, previous MI and shock independently influenced long-term mortality after correction for confounders. Also, we found a significant association of age and total ischemic time (TIT), which however had no influence on long-term mortality (interaction term $p = 0.236$). Propensity score matching revealed reduced mortality rates for patients who received reperfusion therapy

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compared to conservative management, irrespective of age.
Conclusions Increasing age independently influenced short- and long-term mortality in patients with STEMI in the Vienna STEMI network. The TIT significantly increased with baseline age, but had no impact on mortality. Furthermore, reperfusion therapy exerted beneficial effects irrespective of the patients' age.

Keywords STEMI · Age · Mortality · Total ischemic time

Introduction

Cardiovascular diseases are the number one cause of mortality in Europe and the USA with ST-elevation myocardial infarction (STEMI) being a major contributor [1, 2]. In particular, this applies to people with advanced age, who are known to suffer more often from cardiovascular risk factors and comorbidities compared to their younger counterparts [3–7]. They often present with advanced angiographic risk profiles [8] and more frequently bear the risk of complicated clinical courses, including stroke, heart failure and death, in cases of STEMI [3, 6, 9]. In light of our senescent society [1], this group of patients represents a rapidly growing group of high-risk patients; however, these patients are commonly underrepresented or even excluded in randomized clinical trials [10, 11], which in turn might have contributed to a high number of elderly patients not receiving evidence-based reperfusion therapy for STEMI on hospital admission. This resulted in an increased rate of in-hospital mortality for patients not receiving reperfusion therapy [12]. Both European and American guidelines suggest primary percutaneous coronary intervention (pPCI) as the preferred treatment for STEMI, regardless of patient age [13, 14]; however, some authors doubt the positive effect of reperfusion strategies for this patient cohort [5]. Hence, we were interested in this specific situation in the VIENNA STEMI network and moreover in the long-term influence of such treatment. In contrast to patients of advanced age, juvenile patients suffering from STEMI often exhibit very good long-term outcomes [15]. Furthermore, data are not fully conclusive on a possible age-related influence on treatment delay [16, 17]. In this respect, the patient-related delay (time from onset of symptoms, which is assumed to be the time of vessel occlusion, until first medical contact; FMC) is commonly distinguished from the system-related delay (time from FMC to start of reperfusion therapy) [13]. Summed up they represent the total ischemic time (TIT, period from symptom onset until restoration of blood flow), which was associated with worse outcome in previous investigations [18, 19].

The aim of this study was to investigate the pattern of patient characteristics within different age cohorts, age-related confounders of time delays, and 30-day as well as 3-year all-cause mortality, including a landmark analysis of hospital survivors after 30 days of patients included in the VIENNA STEMI registry between 2003 and 2009.

Methods

Patient enrollment

Since 2003, the Vienna STEMI network, composed of the Vienna Ambulance Service and 6 interventional cardiology departments (including 5 non-academic hospitals and the Medical University of Vienna), has provided a 24-h pPCI service for the whole metropolitan area of Vienna, which includes roughly 2 million inhabitants [20]. The VIENNA STEMI registry gathers information in an all-comer fashion of all patients treated for STEMI within this network. The study population investigated consists of patients enrolled in the registry between January 2003 and December 2009. All patients with documented age at admission and a known status for short and long-term mortality were eligible for further analysis and were stratified into different cohorts according to their age at admission (≤45, 46–59, 60–79 and ≥80 years). The diagnosis of STEMI was made according to the European Society of Cardiology (ESC) guidelines valid during the enrollment period [21, 22]. In brief, ST-segment elevation of 1 mm or more in 2 or more contiguous leads was considered a STEMI. In cases of clinical signs of reduced cardiac output with low systolic blood pressure (<90 mm Hg) or the need for vasopressor treatment, cardiogenic shock was diagnosed. According to the electrocardiogram (ECG) and angiographic findings, infarct location was categorized as anterior wall infarction (AWI) or non-anterior wall infarction (non-AWI). Medical history and risk factors were extracted from the medical charts of the patients and were documented by trained study personnel in the registry data set. Delay times were investigated by contact with the patients, their relatives or the ambulance personnel on admission at the PCI center and further controlled by ambulance protocols. Recognition of symptoms leading to the first contact of the STEMI network was defined as onset of pain and FMC was considered as the time of the first ECG recorded in the ambulance or the emergency room (in self-presenters), which confirmed the diagnosis of STEMI. The TIT is given in minutes and was defined as the period from symptom onset until initiation of reperfusion, i.e. balloon inflation in cases of pPCI or administration of fibrinolytic drugs in cases of fibrinolysis. As there is no end of ischemia in conservatively managed patients, these patients have been excluded in calculations including the TIT. All patients received contemporary therapy including acetylsalicylic acid, $P2Y_{12}$-receptor inhibitor, and unfractionated heparin pre-hospital or in the emergency room, as well as angiotenisn-convertinc enzyme inhibitors/angiotensin

Table 1 Patient characteristics and comorbidities evaluated at admission. Values show number and percentage of patient characteristics and median and interquartile range (IQR) for the total ischemic time of the different age cohorts

	Age cohorts (in years)				
Patient characteristics *n* (%)	≤45	46–59	60–79	≥80	*p*-value
Females	93 (16.2%)	310 (19.6%)	622 (32.7%)	295 (57.3%)	<0.0001
Anterior wall infarction	270 (51.0%)	670 (45.4%)	864 (48.8%)	264 (54.3%)	=0.003
Known diabetes mellitus	47 (9.0%)	269 (18.7%)	436 (25.3%)	111 (24.0%)	<0.0001
Smoking	295 (72.0%)	654 (58.5%)	374 (28.4%)	16 (4.7%)	<0.0001
Hypertension	173 (33.1%)	684 (47.6%)	1003 (58.3%)	291 (62.6%)	<0.0001
Hyperlipidemia	213 (41.2%)	631 (44.2%)	664 (39.0%)	113 (24.8%)	<0.0001
Positive family history	164 (32.5%)	281 (20.9%)	200 (12.6%)	19 (4.5%)	<0.0001
Previous infarction	43 (11.0%)	167 (15.3%)	259 (19.8%)	85 (24.1%)	<0.0001
Admission in shock	23 (4.0%)	92 (5.9%)	195 (10.4%)	82 (16.2%)	<0.0001
No reperfusion	10 (2.1%)	34 (2.5%)	80 (5.0%)	54 (13.3%)	<0.0001
Primary PCI	398 (82.1%)	1157 (84.5%)	1309 (82.0%)	313 (77.3%)	
Thrombolytic therapy	77 (15.9%)	178 (13.0%)	208 (13.0%)	38 (9.4%)	
Total ischemic time (in minutes)	203 (140–345)	214 (139–356)	235 (157–384)	249 (170–352)	<0.0001

PCI percutaneous coronary intervention

receptor blockers, beta-blockers and statins for secondary prevention thereafter according to the guideline recommendations valid between 2003 and 2009 [23].

Outcome measurement

In Austria, all deaths are registered by Statistics Austria and are centrally recorded in the Death Statistics Austria, representing a non-profit federal institution. Data are provided for authorized institutions on request. For long-term all-cause mortality, names, birthdates and gender of patients were matched with the centrally registered death statistics to identify cases of death.

Statistical analysis

For all patient characteristics at hospital admission (baseline) descriptive statistical analysis was performed stratified according to the age cohorts. Discrete characteristics are expressed as frequencies and percentages, differences between groups were determined by the χ^2-test and linear trends between age cohorts were calculated with the linear-by-linear association test. Continuous characteristics are expressed as means with standard deviations or medians and quartiles, where appropriate. The TIT between cohorts was examined using the Kruskal-Wallis test and the correlation with age using Spearman's test. Linear regression models were used to investigate independent confounders of TIT and predictors of age. Logarithm-transformed values of TIT (ln(TIT)) were entered in the regression models to counteract the unbalanced distribution. Log rank testing was used for unadjusted comparison of mortality. Cox regression models treating age as a continuous variable were set up for adjusted impact on short- and long-term mortality. The following variables were entered in the model: sex, age, diabetes mellitus (DM), current smoking status, hypertension (HTN), hyperlipidemia (HLP), shock, location of myocardial infarction (MI), i.e. non-AWI or AWI, previous MI and family history. Cox regression was also done in a landmark analysis for 30-day survivors. Propensity score matching was used to investigate mortality between conservatively managed and reperfused patients (treatment variable: no reperfusion vs. any reperfusion). Patients were matched depending on their age (nearest neighborhood matching: < or ≥75 years) and the following covariates were used for adjustment: sex, shock, location of infarction and the patient-related delay. All calculations were performed using IBM SPSS 23 or higher and R 3.2.2 for Mac.

Funding, conflicts of interest and ethics

The study was supported by the Ludwig Boltzmann Cluster for Cardiovascular Research, Vienna, and the Association for the Promotion of Research in Arteriosclerosis, Thrombosis and Vascular Biology (ATVB), Vienna. None of the authors report conflicts of interest with this investigation. The authors had full access to the data and take responsibility for its integrity. All authors have read and agreed to the manuscript. The study was performed according to the Helsinki declaration and approved by the local ethics committee.

Results

Baseline patient characteristics

In this study 4579 patients presenting with STEMI between 2003 and 2009 fulfilled the criteria for further analysis and were stratified in age cohorts as follows: ≤45 years (n = 575, 12.6%), 46–59 years (1585, 34.6%)

Table 2 Independent association of patient characteristics with age at admission. Backward multiple linear regression model treating age as a continuous variable. Adjusted for gender, location of infarction, diabetes mellitus, smoking, hypertension, hyperlipidemia, positive family history, previous myocardial infarction and cardiogenic shock

	Unstandardized regression coefficient	95% confidence interval (CI)	*p*-value
Females	4.907	3.882–5.933	<0.0001
Diabetes mellitus	1.238	0.064–2.412	0.039
Smoking	−10.360	−11.308– −9.413	<0.0001
Hypertension	3.452	2.517–4.388	<0.0001
Hyperlipidemia	−1.554	−2.562– −0.547	0.003
Positive family history	−3.970	−5.259– −2.681	<0.0001
Admission in shock	3.538	1.881–5.195	<0.0001
Reperfusion	−7.618	−10.341– −4.895	<0.0001

60–79 years (1903, 41.6%) and ≥80 years (516, 11.3%). Table 1 shows baseline demographic patient characteristics on admission. With rising age, the percentage of females ($p < 0.0001$), patients with known HTN ($p < 0.0001$) and previous MI ($p < 0.0001$), as well as patients admitted in shock ($p < 0.0001$) significantly increased within the given age cohorts. On the contrary, a current smoking habit ($p < 0.0001$), a known history of HLP ($p < 0.0001$) or a positive family history ($p < 0.0001$) at admission were found more frequently in younger age cohorts. Despite a significant difference between age cohorts concerning anterior wall infarction ($p = 0.003$), we found no significant linear association with age ($p = 0.086$).

A multiple linear regression analysis was calculated to predict patient age at admission adjusted for baseline characteristics. Estimated regression coefficients are provided in Table 2. In this model, female gender ($p < 0.0001$), DM ($p = 0.008$), a smoking habit ($p < 0.0001$), HTN ($p < 0.0001$), HLP ($p < 0.0001$), a positive family history ($p < 0.0001$) and admission in shock ($p < 0.0001$) were independently associated with baseline age.

Delay times

In a previous study, we have already analyzed the patient-related delay [17], while in the current investigation we were interested in the impact of age on TIT. For this purpose, we had sufficient information from 2532 patients. Table 1 provides the median delay times with 25th and 75th percentile for all age cohorts. We found a significant correlation between age and TIT if treated as continuous variables (correlation coefficient = 0.079, $p < 0.001$), as well as if comparing the median values of the given age cohorts ($p < 0.0001$). In addition, a multiple linear regression model was calculated to predict ln(TIT) based on baseline patient characteristics. Significant predictors for ln(TIT) were age, increase of ln(TIT) by 0.004 with every year (95%CI 0.001–0.008, $p = 0.008$), DM, increase of ln(TIT) by 0.119 (95%CI 0.013–0.226, $p = 0.028$) and shock, increase of ln(TIT) by 0.256 (95%CI 0.094–0.418, $p = 0.002$).

Reperfusion therapy

Most patients were treated with pPCI (82.4%), followed by thrombolytic therapy (TT) (13.0%) and conservative treatment (4.6%). Table 1 shows the change of reperfusion therapy between age cohorts. With rising age at admission, the number of patients treated with pPCI and TT decreased. Consequently, the percentage of patients with conservative treatment increased ($p < 0.0001$). If reperfusion was treated as a categorical variable (no reperfusion vs. any reperfusion) we found an independent association for age at admission (odds ratio OR 0.933, 95%CI 0.912–0.955, $p < 0.0001$) and DM (OR 0.439, 95%CI 0.263–0.732, $p = 0.002$) after adjusting for the risk factors HTN, HLP, smoking, previous MI, infarct location, family history and shock.

Short and long-term mortality

The 30-day and 3-year all-cause mortality for the entire analyzed study cohort were 7.5% and 12.5%, respectively. When patients were stratified in age cohorts, there was a significant difference in mortality between the cohorts in terms of short- and long-term mortality rates as shown in Fig. 1a, b (30-day mortality: log-rank <0.0001, ≤45 = 1.6%, 46–59 = 3%, 60–79 = 9.2% and ≥80 = 21.9%; 3-year mortality: log-rank <0.0001, ≤45 = 3.1%, 46–59 = 5.4%, 60–79 = 15.2% and ≥80 years= 34.9%). Long-term mortality in survivors of the index event (landmark analysis) is shown in Fig. 1c (3-year mortality; log-rank <0.0001; ≤45 = 1.6%, 46–59 = 2.5%, 60–79 = 6.3% and ≥80 years= 15.6%). In a multivariable Cox regression model, we found the following variables to be independently associated with 3-year all-cause mortality: age at admission (hazard ratio HR 1.052, 95%CI 1.036–1.067, $p < 0.0001$), smoking (HR 0.465, 95%CI 0.283–0.765, $p = 0.003$), HTN (HR 0.711, 95%CI 0.505–1.000, $p = 0.05$), HLP (HR 0.625, 95%CI 0.410–0.953, $p = 0.029$), positive family history (HR 0.343, 95%CI 0.139–0.851, $p = 0.021$), previous MI (HR 1.677, 95%CI 1.141–2.463, $p = 0.008$), and shock (HR 5.512, 95%CI 3.838–7.916, $p < 0.0001$). The TIT showed borderline significance (HR 1.225, 95%CI 0.989–1.518, $p = 0.063$). Furthermore, the interaction term of age and TIT on mortality was

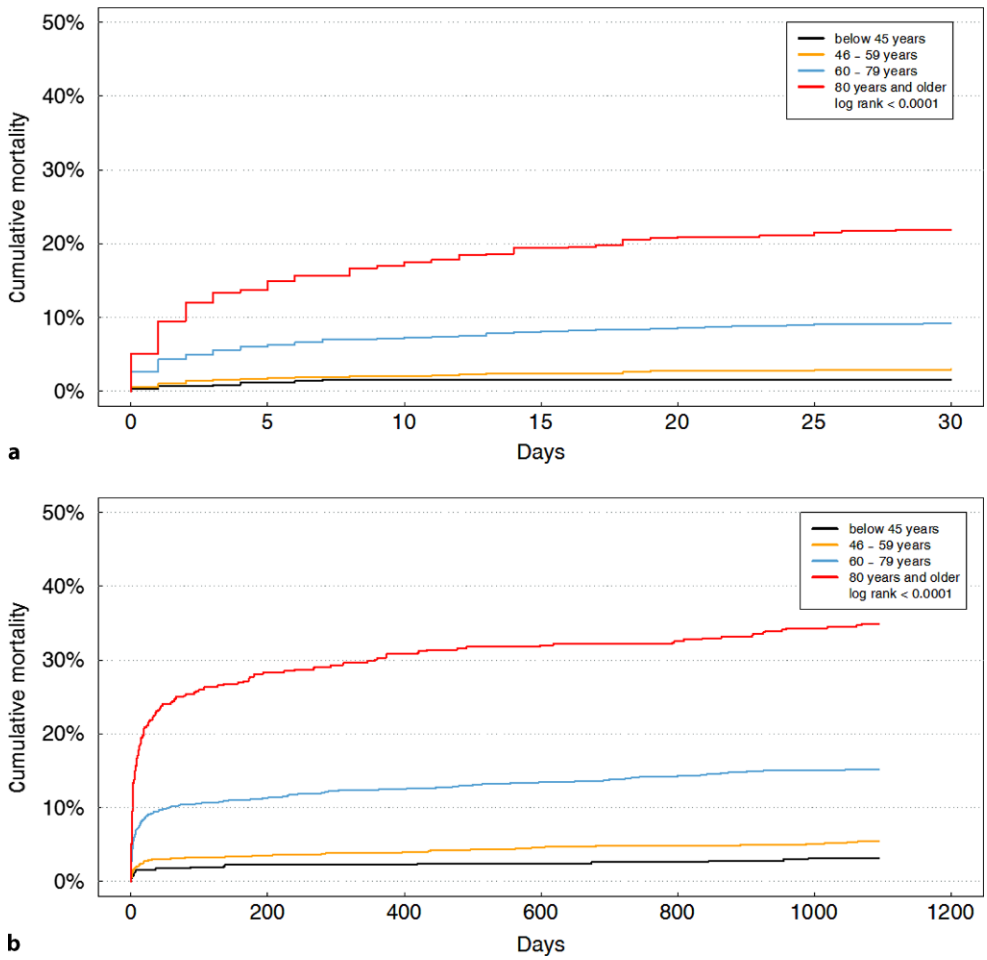

Fig. 1 **a** Kaplan-Meier plot of 30-day mortality. Log-rank <0.0001; **b** Kaplan Meier plot of 3-year all-cause mortality. Log-rank <0.0001

not significant ($p = 0.236$). Variables with independent association for 3-year all-cause mortality of the landmark population surviving the first month are shown in Fig. 2.

The effect of reperfusion therapy in the very elderly (defined by the age of ≥75 years at admission) and their younger counterparts on 3-year all-cause mortality is depicted in Fig. 1d (log rank test <0.0001 and <0.0001, respectively). To account for differences between these two patient cohorts with respect to comorbidities and a possible influence on the decision of therapy, a 1:1 nearest neighbourhood propensity score matching was calculated. Patients were matched on being younger or ≥75 years at admission, treatment was defined as receiving conservative management or reperfusion therapy (pPCI or fibrinolysis) and covariates used for adjustment included sex, location of infarction (AWI vs. non-AWI), presentation in shock and patient-related delay. The 3-year all-cause mortality was further investigated in the matched population ($n = 284$) using a Cox regression model including age as a categorical variable (< and ≥75 years, respectively) and reperfusion therapy (none vs. any). Both age (HR 2.579, 95%CI 1.584–4.199; $p < 0.001$) and reperfusion therapy (HR 0.574, 95%CI 0.347–0.950; $p = 0.031$) had an independent influence on survival.

Discussion

Our study represents the analysis of a multicenter metropolitan STEMI registry investigating the impact of age on short- and long-term mortality. We could underline the importance of age as an independent risk factor and predictor for short- and long-term outcome of STEMI patients, demonstrate the relationship of age classes with certain cardiovascular risk factors, but did not find an independent age-related influence of TIT on long-term mortality, all after correcting for confounders.

The importance of this study is based on its all-comers design therefore providing real-life data of STEMI treatment within a specific system of care in a metropolitan area of roughly 2 million inhabitants. Compared to many clinical trials, in which elderly, female, and hemodynamically compromised patients are frequently excluded [10, 11], this investigation also contained data of such subgroups of STEMI patients, which are usually associated with a higher mortality [6, 24, 25].

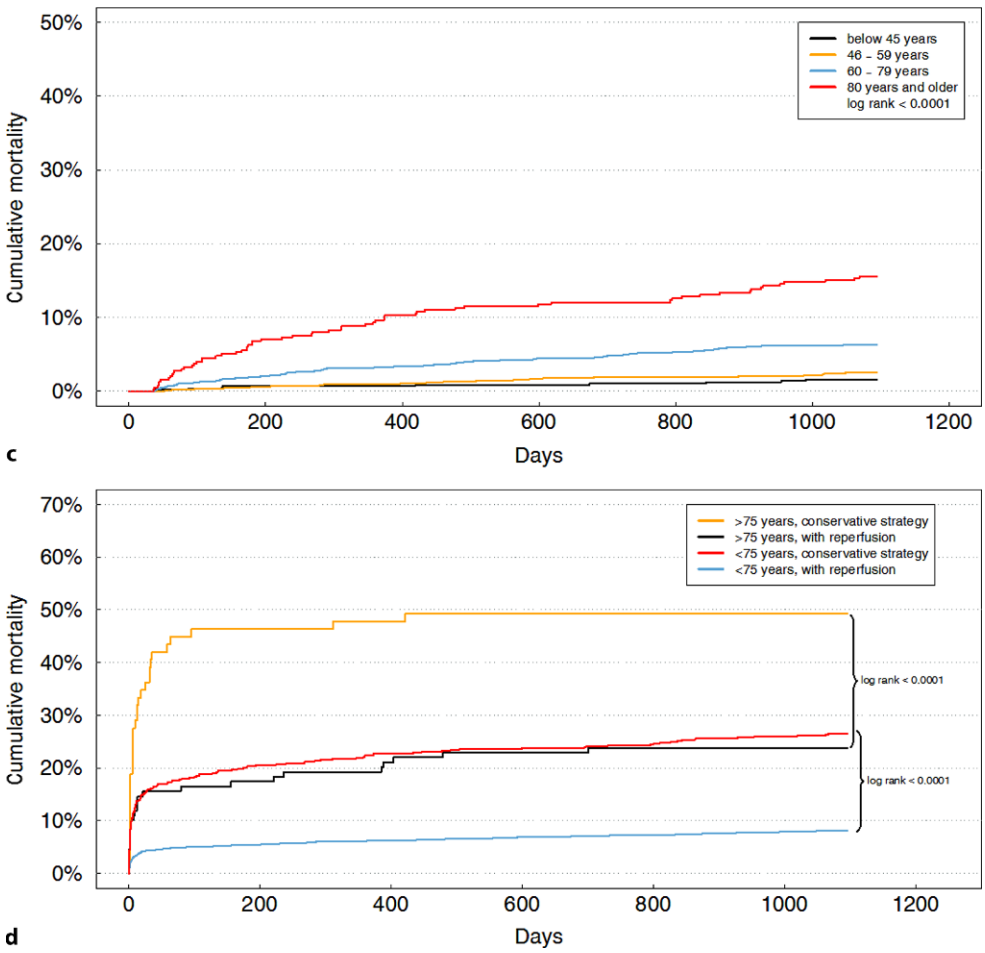

Fig. 1 (continued) **c** Depicts a landmark analysis including survivors of the index event. Log-rank <0.001 between ≥80 years and 60–79 years, <0.001 between 60–79 and 46–59 years and 0.199 between 46–59 years and ≤45 years. **d** Comparison of 3-year all-cause mortality between very elderly patients (>75 years) and their younger counterparts grouped according to therapy (reperfusion therapy vs. conservative strategy)

Patient characteristics

The evaluation of patient characteristics at admission revealed an increased percentage of females, of patients with histories of HTN or previous MI, as well as of DM with advanced age. Also, the number of patients admitted in cardiogenic shock was highest in the oldest age cohort. In contrast, a positive family history, the current smoking habit and the presence of HLP was more common in the younger age cohorts. Our findings are in accordance with other analyses of STEMI patients [5, 15, 18, 26] and underline the high-risk profile of elderly patients, as they usually present with more risk factors and comorbidities than younger patients. As expected, this was further confirmed in multivariable regression analysis, where we could demonstrate an independent association of age and the presence of cardiovascular risk factors gender, DM, smoking habit, HTN, HLP, a positive family history and shock (Table 2).

The inverse correlation between age and smoking, HLP and a positive family history in our analysis has been already previously described and is most likely due to a more rapid progression of coronary artery disease and, hence, an earlier presentation of related sequelae, including STEMI [5, 15].

Delay times

The TIT, defined as the time period starting with the onset of pain until the initiation of reperfusion, is known to be a substantial determinant of infarct size and influences morbidity and mortality in STEMI patients [18, 27]. Some authors also described a prolonged TIT in elderly patients [18, 24], which might contribute to the worse clinical outcome in the elderly. A prolongation of TIT might be explained by the frequently atypical symptoms of elderly patients, i. e. by a prolonged patient-related delay, but also by a prolongation of the system delay, as necessary diagnostic measures are frequently provided too late in the elderly [25]. With respect to the patient-related delay in the VIENNA STEMI network, we were able to demonstrate an age-dependant prolongation only by univariate analysis in a previous investigation, which diminished after adjustment for confounders [17]. As shown in Table 1 and by the correlation described, in the present analysis TIT significantly increased with higher age cohorts by crude evaluation; however, besides reaching statistical significance, the correlation coefficient is relatively small (=0.079). To further analyze the unbalanced distribution of TIT we used logarithmic transformed values. In the linear regression

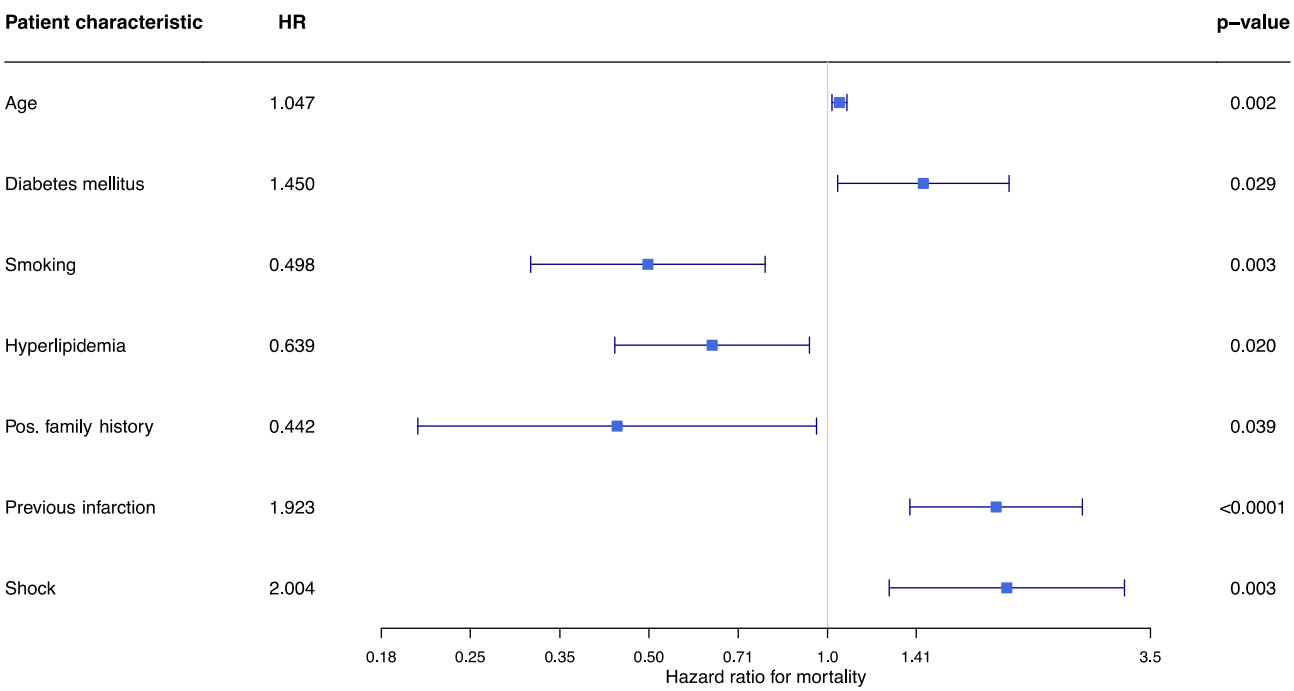

Fig. 2 Results of a backward eliminating Cox regression model of the landmark population (surviving 30 days and the index hospital stay)

model, we also saw an independent influence of age on ln(TIT). In addition, this effect was further seen for DM and shock. This might be explained by an underlying diabetic neuropathy, which has influenced the symptomatic burden and obscured the acuity of the situation. Consequently, this could have led to a prolongation in the patient-related delay, which in turn also affected the TIT [17]. In contrast, patients in shock usually have very short patient-related delay times [17, 28]. The fact that shock was a major factor for prolonged TIT in our registry can be explained by the need for specific diagnostic and/or therapeutic strategies in STEMI patients in shock, which consequently delayed reperfusion therapy. Despite the missing significance in our Cox regression model for ln(TIT), age remained a highly significant predictor of 3-year all-cause mortality. Moreover, the interaction term of age and ln(TIT) in the Cox regression model investigating long-term mortality did not reach statistical significance, suggesting that the influence of ln(TIT) on mortality was not affected by age and vice versa. For visualization of these findings we plotted median values of TIT for each age cohort together with the outcome status (Fig. 3).

Reperfusion therapy

Most STEMI patients were treated with pPCI, but with rising baseline age the number of conservatively treated patients increased. Potential reasons for this include more contraindications for reperfusion therapy in the elderly, especially for fibrinolytic agents, based on their advanced profile of comorbidities, a generally higher bleeding risk, more patients refusing any reperfusion therapy and an increased rate of expected procedural complications [5–7, 29] All those reasons for not providing any reperfusion strategy were also present in our conservatively treated patient cohort. In addition, some authors have also questioned the benefit of reperfusion therapy in higher aged patients in principle [5]. This point is of great importance as De Luca et al. reported reduced rates of successful PCI and myocardial blush grades in the elderly, an effect that was associated with worse clinical outcome at 1 year [30]. A possible increase in procedural complications on reperfusion in the very elderly as discussed by others [5, 31] was not specifically collected in our data file, but had obviously no or only minor impact on clinical outcome in patients receiving primary PCI. To counteract such potential confounders that might have an influence on the decision of therapy, we made use of a nearest neighborhood propensity score matching. We can show that the benefits of reperfusion therapy are still present in the very elderly compared to a younger group of patients. As we used the endpoint of all-cause mortality 3 years after the index event for this investigation, a potential harm by an increased amount of complications in the elderly due to reperfusion therapy is certainly outweighed by the benefits of reperfusion for survival. These data should encourage reperfusion therapy not to be withheld to the elderly.

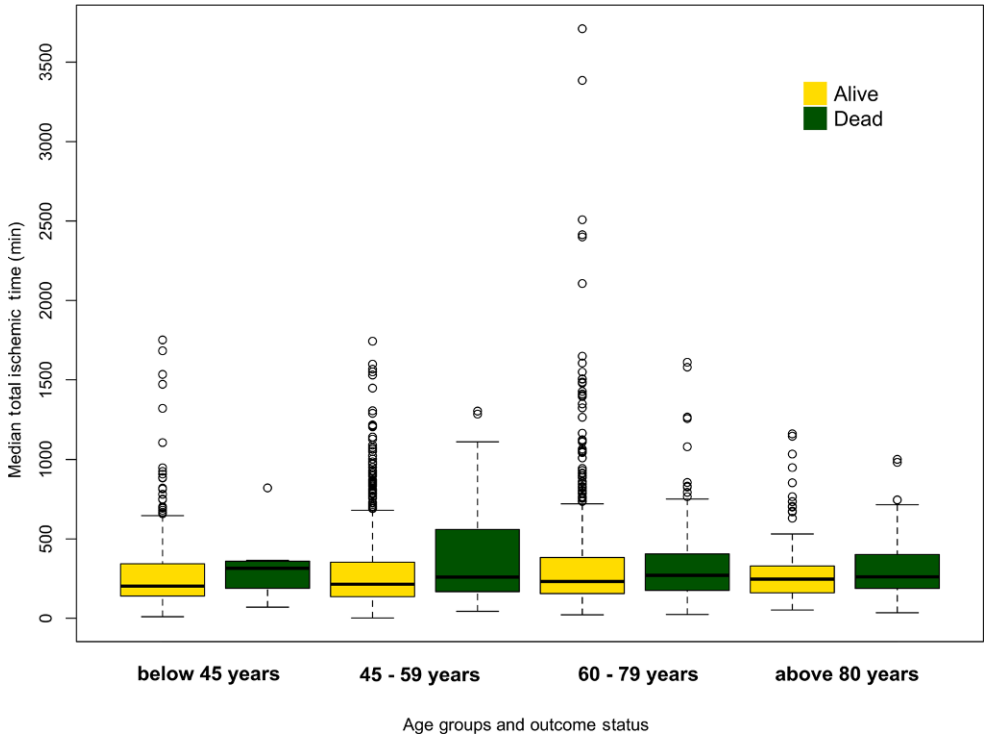

Fig. 3 Median values of the total ischemic time for each age cohort at admission, with further stratification based on the status of 3-year all-cause mortality

Mortality

In accordance with other authors [6, 7, 24, 32], we also found increased mortality rates with rising age. Many other predictors for worse clinical outcome are associated with age and the influence of age at the event was consistent with several kinds of mortality measurements (30-day, 3 years, long-term in survivors of the index event). More importantly and in line with prior reports [12], elderly patients in the VIENNA STEMI network often did not receive a guideline-recommended reperfusion strategy, but were treated conservatively instead. Consequently, this also led to an increased all-cause mortality rate not only in short-term, but also in long-term clinical outcomes. Interestingly, we also found some inverse correlations of cardiovascular risk factors and long-term mortality, i. e. with smoking, positive family history and HLP. The phenomenon of inverse correlation in retrospective analysis of registries has been described previously and deserves explanation. In our hands, most STEMI patients in the Vienna STEMI network are immediately treated with high-dose highly effective statins and anti-hypertensive agents and are offered pharmacologic or psychosomatic support for stopping smoking, measures that might influence clinical outcome in a positive way [33].

Strengths and limitations

A potential limitation is the retrospective analysis of this work. Despite prospective data entry, the data quality of registries is considered to be lower compared to prospective trials; however, we performed a thorough data acquisition by direct double control of ambulance, emergency room and catheter laboratory protocols and thus avoiding missing variables. A potential problem is the fact that exact time delays could only be obtained from 2532 patients, since patients frequently cannot define the exact onset of pain. The number of patients included in this analysis seems, however, sufficient for the conclusions drawn. Moreover, we could follow all patients for short and long-term mortality data at 30 days and 3 years after the index event. As data were only recorded in patients admitted to one of the PCI hospitals participating in the Vienna STEMI network, data of patients who died at home or on the way to hospital were not recorded. Further strengths of this study are its all-comer design, the inclusion of specific subgroups of patients regardless of the therapeutic approach as for example females, very elderly, or patients in cardiogenic shock, who are frequently excluded from clinical trials.

Conclusion

With increasing age STEMI patients consist of more females and suffer more frequently from comorbidities, which in part might explain the worse short- and long-term mortality rates in the elderly. Cardiovascular risk factors, such as smoking, positive family history and HLP were found more frequently in younger age groups thus indicating a faster progression of coronary artery disease in these patient cohorts. As described elsewhere, in the Vienna STEMI network age exhibited an independent predictor of

short- and long-term mortality. Despite a weak correlation of TIT and age at the event that reached statistical significance after correction of confounders, this association of age and TIT had no independent influence on long-term mortality. This might reflect a well-organized system of care for STEMI with short system delays. Most importantly, reperfusion therapy, mainly the mechanical reperfusion strategy that is provided to the clear majority of STEMI patients in the Vienna STEMI network, is associated with improved clinical outcomes irrespective of the patient age at the event and should not be withheld from the elderly, unless severe comorbidities with short life expectancy or the wish of the patient prevent such strategies.

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Compliance with ethical guidelines

Conflict of interest P.M. Haller, B. Jäger, S. Farhan, G. Christ, W. Schreiber, F. Weidinger, T. Stefenelli, G. Delle-Karth, A. Kaff, G. Maurer, and K. Huber declare that they have no competing interests.

Ethical standards The study was performed according to the 1964 Helsinki declaration and its later amendments and was approved by the local ethics committee.

References

1. Nichols M, Townsend N. et al. European cardiovascular disease statistics 2012. Brussels, Sophia Antipolis: European Heart Network, European Society of Cardiology; 2012.
2. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Blaha MJ, Dai S, Ford ES, Fox CS, Franco S, Fullerton HJ, Gillespie C, Hailpern SM, Heit JA, Howard VJ, Huffman MD, Judd SE, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Mackey RH, Magid DJ, Marcus GM, Marelli A, Matchar DB, McGuire DK, Mohler ER 3rd, Moy CS, Mussolino ME, Neumar RW, Nichol G, Pandey DK, Paynter NP, Reeves MJ, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Wong ND, Woo D, Turner MB. Executive summary: heart disease and stroke statistics – 2014 update: a report from the American Heart Association. Circulation. 2014;129(3):399–410.
3. Avezum A, Makdisse M, Spencer F, Gore JM, Fox KA, Montalescot G, Eagle KA, White K, Mehta RH, Knobel E, Collet JP, Investigators G. Impact of age on management and outcome of acute coronary syndrome: observations from the Global Registry of Acute Coronary Events (GRACE). Am Heart J. 2005;149(1):67–73.
4. Halon DA, Adawi S, Dobrecky-Mery I, Lewis BS. Importance of increasing age on the presentation and outcome of acute coronary syndromes in elderly patients. J Am Coll Cardiol. 2004;43(3):346–52.
5. Forman DE, Chen AY, Wiviott SD, Wang TY, Magid DJ, Alexander KP. Comparison of outcomes in patients aged ⟨75, 75 to 84, and ⟩/= 85 years with ST-elevation myocardial infarction (from the ACTION Registry-GWTG). Am J Cardiol. 2010;106(10):1382–8.
6. Fach A, Bunger S, Zabrocki R, Schmucker J, Conradi P, Garstka D, Fiehn E, Hambrecht R, Wienbergen H. Comparison of outcomes of patients with ST-segment elevation myocardial infarction treated by primary percutaneous coronary intervention analyzed by age groups (⟨75, 75 to 85, and ⟩85 years); (results from the Bremen STEMI registry). Am J Cardiol. 2015;116(12):1802–9.
7. Christiansen EC, Wickstrom KK, Henry TD, Garberich RF, Rutten-Ramos SC, Larson DM, Grey EZ, Thiessen NL, Hauser RG, Newell MC. Comparison of functional recovery following percutaneous coronary intervention for ST elevation myocardial infarction in three age groups (⟨70, 70 to 79, and ⟩/=80 years). Am J Cardiol. 2013;112(3):330–5.
8. White HD, Barbash GI, Califf RM, Simes RJ, Granger CB, Weaver WD, Kleiman NS, Aylward PE, Gore JM, Vahanian A, Lee KL, Ross AM, Topol EJ. Age and outcome with contemporary thrombolytic therapy. Results from the GUSTO-I trial. Global utilization of streptokinase and TPA for occluded coronary arteries trial. Circulation. 1996;94(8):1826–33.
9. Guagliumi G, Stone GW, Cox DA, Stuckey T, Tcheng JE, Turco M, Musumeci G, Griffin JJ, Lansky AJ, Mehran R, Grines CL, Garcia E. Outcome in elderly patients undergoing primary coronary intervention for acute myocardial infarction: results from the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) trial. Circulation. 2004;110(12):1598–604.
10. Dodd KS, Saczynski JS, Zhao Y, Goldberg RJ, Gurwitz JH. Exclusion of older adults and women from recent trials of acute coronary syndromes. J Am Geriatr Soc. 2011;59(3):506–11.
11. Lee PY, Alexander KP, Hammill BG, Pasquali SK, Peterson ED. Representation of elderly persons and women in published randomized trials of acute coronary syndromes. JAMA. 2001;286(6):708–13.
12. Medina HM, Cannon CP, Fonarow GC, Grau-Sepulveda MV, Hernandez AF, Peacock FW, Laskey W, Peterson ED, Schwamm L, Bhatt DL, Committee GS Investigators. Reperfusion strategies and quality of care in 5339 patients age 80 years or older presenting with ST-elevation myocardial infarction: analysis from get with the guidelines-coronary artery disease. Clin Cardiol. 2012;35(10):632–40.
13. Steg PG, James SK, Atar D, Badano LP, Blomstrom-Lundqvist C, Borger MA, Di Mario C, Dickstein K, Ducrocq G, Fernandez-Aviles F, Gershlick AH, Giannuzzi P, Halvorsen S, Huber K, Juni P, Kastrati A, Knuuti J, Lenzen MJ, Mahaffey KW, Valgimigli M, van 't Hof A, Widimsky P, Zahger D. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J. 2012;33(20):2569–619.
14. American College of Emergency P, Society for Cardiovascular A Interventions, O'Gara PT, Kushner FG, Ascheim DD, Casey DE Jr., Chung MK, de Lemos JA, Ettinger SM, Fang JC, Fesmire FM, Franklin BA, Granger CB, Krumholz HM, Linderbaum JA, Morrow DA, Newby LK, Ornato JP, Ou N, Radford MJ, Tamis-Holland JE, Tommaso CL, Tracy CM, Woo YJ, Zhao DX, Anderson JL, Jacobs AK, Halperin JL, Albert NM, Brindis RG, Creager MA, DeMets D, Guyton RA, Hochman JS, Kovacs RJ, Kushner FG, Ohman EM, Stevenson WG, Yancy CW. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2013;61(4):e78–e140.
15. Rathod KS, Jones DA, Gallagher S, Rathod VS, Weerackody R, Jain AK, Mathur A, Mohiddin SA, Archbold RA, Wragg A, Knight CJ. Atypical risk factor profile and excellent long-term outcomes of young patients treated with primary

percutaneous coronary intervention for ST-elevation myocardial infarction. Eur Heart J Acute Cardiovasc Care. 2016;5(1):23–32.
16. Nielsen CG, Laut KG, Jensen LO, Ravkilde J, Terkelsen CJ, Kristensen SD. Patient delay in patients with ST-elevation myocardial infarction: time patterns and predictors for a prolonged delay. Eur Heart J Acute Cardiovasc Care. 2016. doi:10.1177/2048872616676570
17. Jager B, Farhan S, Rohla M, Christ G, Podczeck-Schweighofer A, Schreiber W, Laggner AN, Weidinger F, Stefenelli T, Delle-Karth G, Kaff A, Maurer G, Huber K, Vienna SRG. Clinical predictors of patient related delay in the VIENNA ST-elevation myocardial infarction network and impact on long-term mortality. Eur Heart J Acute Cardiovasc Care. 2017;Apr;6(3):254–261. doi:10.1177/2048872616633882. Epub 2016 Feb 17.
18. Fokkema ML, Wieringa WG, van der Horst IC, Boersma E, Zijlstra F, de Smet BJ. Quantitative analysis of the impact of total ischemic time on myocardial perfusion and clinical outcome in patients with ST-elevation myocardial infarction. Am J Cardiol. 2011;108(11):1536–41.
19. Terkelsen CJ, Sorensen JT, Maeng M, Jensen LO, Tilsted HH, Trautner S, Vach W, Johnsen SP, Thuesen L, Lassen JF. System delay and mortality among patients with STEMI treated with primary percutaneous coronary intervention. JAMA. 2010;304(7):763–71.
20. Jager B, Farhan S, Kalla K, Glogar HD, Christ G, Karnik R, Norman G, Prachar H, Schreiber W, Kaff A, Podczeck-Schweighofer A, Weidinger F, Stefenelli T, Delle-Karth G, Laggner AN, Maurer G, Huber K, Vienna SRG. One-year mortality in patients with acute ST-elevation myocardial infarction in the Vienna STEMI registry. Wien Klin Wochenschr. 2015;127(13–14):535–42.
21. Van de Werf F, Ardissino D, Betriu A, Cokkinos DV, Falk E, Fox KA, Julian D, Lengyel M, Neumann FJ, Ruzyllo W, Thygesen C, Underwood SR, Vahanian A, Verheugt FW, Wijns W. Task force on the management of acute myocardial infarction of the European Society of C. management of acute myocardial infarction in patients presenting with ST-segment elevation. The task force on the Management of acute myocardial infarction of the European Society of Cardiology. Eur Heart J. 2003;24(1):28–66.
22. Van de Werf F, Bax J, Betriu A, Blomstrom-Lundqvist C, Crea F, Falk V, Filippatos G, Fox K, Huber K, Kastrati A, Rosengren A, Steg PG, Tubaro M, Verheugt F, Weidinger F, Weis M, Guidelines ESCCfP. Management of acute myocardial infarction in patients presenting with persistent ST-segment elevation: the Task Force on the Management of ST-Segment Elevation Acute Myocardial Infarction of the European Society of Cardiology. Eur Heart J. 2008;29(23):2909–45.
23. Van de Werf F. Management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J. 2003;24(1):28–66.
24. Otten AM, Maas AH, Ottervanger JP, Kloosterman A, van 't Hof AW, Dambrink JH, Gosselink AT, Hoorntje JC, Suryapranata H, de Boer MJ. Zwolle Myocardial Infarction study G. Is the difference in outcome between men and women treated by primary percutaneous coronary intervention age dependent? Gender difference in STEMI stratified on age. Eur Heart J Acute Cardiovasc Care. 2013;2(4):334–41.
25. Brieger D, Eagle KA, Goodman SG, Steg PG, Budaj A, White K, Montalescot G. Acute coronary syndromes without chest pain, an underdiagnosed and undertreated high-risk group: insights from the Global Registry of Acute Coronary Events. Chest. 2004;126(2):461–9.
26. Dziewierz A, Siudak Z, Rakowski T, Dubiel JS, Dudek D. Age-related differences in treatment strategies and clinical outcomes in unselected cohort of patients with ST-segment elevation myocardial infarction transferred for primary angioplasty. J Thromb Thrombolysis. 2012;34(2):214–21.
27. Solhpour A, Chang KW, Arain SA, Balan P, Loghin C, McCarthy JJ, Vernon Anderson H, Smalling RW. Ischemic time is a better predictor than door-to-balloon time for mortality and infarct size in ST-elevation myocardial infarction. Catheter Cardiovasc Interv. 2016;87(7):1194. doi:10.1002/ccd.26230.
28. Saczynski JS, Yarzebski J, Lessard D, Spencer FA, Gurwitz JH, Gore JM, Goldberg RJ. Trends in prehospital delay in patients with acute myocardial infarction (from the Worcester Heart Attack Study). Am J Cardiol. 2008;102(12):1589–94.
29. Farshid A, Brieger D, Hyun K, Hammett C, Ellis C, Rankin J, Lefkovits J, Chew D, French J. Characteristics and Clinical Course of STEMI Patients who Received no Reperfusion in the Australia and New Zealand SNAPSHOT ACS Registry. Heart Lung Circ. 2016;25(2):132–9.
30. De Luca G, van 't Hof AW, Ottervanger JP, Hoorntje JC, Gosselink AT, Dambrink JH, de Boer MJ, Suryapranata H. Ageing, impaired myocardial perfusion, and mortality in patients with ST-segment elevation myocardial infarction treated by primary angioplasty. Eur Heart J. 2005;26(7):662–6.
31. Dudek D, Mehran R, Dziewierz A, Witzenbichler B, Brodie BR, Kornowski R, Fahy M, Lansky AJ, Rakowski T, Legutko J, Bryniarski L, Stone GW. Impact of advanced age on the safety and effectiveness of paclitaxel-eluting stent implantation in patients with ST-segment elevation myocardial infarction undergoing primary angioplasty: the HORIZONS-AMI trial. Catheter Cardiovasc Interv. 2013;82(6):869–77.
32. De Luca G, Dirksen MT, Spaulding C, Kelbaek H, Schalij M, Thuesen L, van der Hoeven B, Vink MA, Kaiser C, Musto C, Chechi T, Spaziani G, Diaz de la Lera LS, Pasceri V, Di Lorenzo E, Violini R, Suryapranata H, Stone GW. Impact of age on long-term outcome after primary angioplasty with bare-metal or drug-eluting stent (from the DESERT cooperation). Am J Cardiol. 2013;112(2):181–6.
33. Tentzeris I, Rohla M, Jarai R, Farhan S, Freynhofer MK, Unger G, Nurnberg M, Geppert A, Wessely E, Wojta J, Huber K. Influence of high-dose highly efficient statins on short-term mortality in patients undergoing percutaneous coronary intervention with stenting for acute coronary syndromes. Am J Cardiol. 2014;113(7):1099–104.