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Risk-factors associated with extremely high cardiovascular risk of mid- and long-term mortality following myocardial infarction: Analysis of the Hyperlipidaemia Therapy in tERtiary Cardiological cEnTer (TERCET) registry

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ABSTRACT

Background and aims: Risk-factor identification and risk stratification are prerequisites to the effective primary and secondary prevention of cardiovascular disease (CVD). Patients at the highest risk benefit the most from the intensive risk-factor reduction. However, the high-risk patients' group is heterogeneous, and it is increasingly recognised that there is an 'extreme-risk' category of patients who may require particularly close attention and intensive therapeutic approach. The aim of this study was to identify subgroups of patients at the highest risk of death following myocardial infarction (MI) that might be considered as those at extremely high CVD risk.

Methods: We used data from 19,582 participants of the Hyperlipidaemia Therapy in tERtiary Cardiological cEnTer (TERCET) Registry (NCT03065543) of patients with ischaemic heart disease in Poland from 2006 to present. Characteristics of 13,052 patients with chronic coronary syndromes (CCS) were compared with those of 4295 patients with myocardial infarction (STEMI and NSTEMI). Multivariable logistic regression with stepwise backward elimination was used to identify risk factors associated with mortality in the 12–36 months following the index hospitalisation.

Results: The mortality rates were significantly higher in patients after MI than in patients with CCS. In the multivariable analysis, the risk factors most strongly associated with 12-month mortality in patients after MI were left ventricular ejection fraction (LVEF) lower than 35% (hazard ratio [HR] 3.83, 95% confidence interval [CI] 3.14–4.67), age >75 years (HR 1.91, 95%CI 1.55–2.35), multivessel coronary artery disease (HR 1.61, 95% CI 1.30–1.99), atrial fibrillation (HR 1.53, 95%CI 1.21–1.94) diabetes mellitus (HR 1.35, 95%CI 1.11–1.64) and increased LDL-C (HR per 1 mmol/l 1.09, 95%CI 1.01–1.19) or creatinine levels (HR per 10 μmol/L 1.04, 95% CI 1.04–1.05). The risk factors that influenced mortality after 24–36 months were consistent with those after 12 months, with additional low haemoglobin (20–25% risk increase per 1 mmol reduction) and chronic obstructive pulmonary disease (65% risk increase after 36 months).

Conclusions: In our large, single-center real-world analysis, we identified the patients with the highest risk of death who could probably benefit the most from the most intensive therapy, and hence should be considered to be an 'extreme risk' population.

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1. Introduction

Despite significant improvements in the quality of care, cardiovascular disease (CVD) remains the primary cause of death worldwide. In the European Union, CVD is responsible for 35% of deaths in women and men under the age of 75 years [1]. Moreover, it is predicted that in the coming decade, the number of disability-adjusted life years (DALY) lost due to CVD will increase from 169 million in 2020 to 187 million in 2030 [2].

Despite sustained efforts to reduce the global burden of CVD, the prevalence of CV risk factors along with cardiovascular and non-cardiovascular comorbidities has continued to rise [3–5]. In 2016, the European Society of Cardiology (ESC) published the guidelines on CV prevention [6], in which the authors stratify the population into patients with low, intermediate, high, and very high-risk of death or CV event in a 10-year follow-up. Patients with previously diagnosed CVD (including coronary artery disease (CAD), peripheral artery disease (PAD), and history of stroke) are all assigned to the very high-risk group, without the need for further risk scoring, because of the demonstrated high event-rate in this group [6].

However, it is important to consider that the subgroup of patients at very high risk of CVD is very heterogeneous, and one could speculate whether it should be further subdivided in order to identify the patients within this group who are most likely to experience adverse outcomes. These individuals could be offered the most intensive, individualised treatment, considering starting with combination therapy in order to reduce the risk as quickly as possible. The American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology approached this problem in 2017, identifying an additional group of patients with so-called 'extreme CV risk' [7]. This subgroup included patients with progressive atherosclerotic CVD despite the achievement of LDL-C <1.8 mmol/L (<70 mg/dL) or established CVD with concomitant: DM, stage 3/4 of CKD and/or familial heterozygous hypercholesterolaemia (HeFH) or a history of premature atherosclerotic CVD defined as <55 years of age for males and <65 years of age for females [7]. In these patients, the authors recommend a more aggressive approach to the management of lipid disorders, suggesting a new threshold for LDL-C of 1.4 mmol/L (55 mg/dL) [7]. However, these guidelines are based solely on the recommendation of experts, therefore they do not strictly comply with the principles of evidence-based medicine (EBM). Moreover, the recently (2019) published mutual guidelines of the ESC and European Atherosclerosis Society (EAS) for the management of dyslipidaemias modified the therapeutic LDL-C targets to <1.4 mmol/L (55 mg/dL) in the very high-risk subgroup, and also made the first step to specify a group of patients at 'extreme risk'. The authors of the guidelines recommend that reduction of LDL-C to <1 mmol/L (40 mg/dL) should be considered in patients who experience a second vascular event in the two years following the first [8]. The definition of the extremely high-risk patients' group has been next completed by the Polish experts in their most recent guidelines on laboratory diagnostics of lipid metabolism disorders, however, they based their definition mainly on the trials' results with proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors [9].

In our opinion, the criteria for inclusion in the 'extreme-risk' definition of the abovementioned guidelines do not encompass all relevant patients, especially considering the fact that patients following a myocardial infarction (MI) are not automatically included in the 'extreme cardiovascular (CV) risk' group. The occurrence of MI is associated with substantially worse outcomes than other manifestations of CVD [10,11]. Based on the above, we aimed to identify subgroups of patients after myocardial infarction with the highest risk of death in a 3-year follow-up.

2. Patients and methods

The design, rationale, and primary results from the Hyperlipidaemia Therapy in tERtiary Cardiological cEnTer (TERCET) Registry, along with the patient recruitment scheme, the definitions and methods of the long-term follow-up data gathering have been described in detail elsewhere [12–14]. In brief, the registry includes consecutive patients with all types of ischemic heart disease, hospitalised in a specialist supraregional center from 2006 to the present time. The entire population of the registry, which consists almost solely of patients of Caucasian race, meets the criteria of 'very high' CV risk as defined by the ESC guidelines [8]. All patients received detailed information about the aim of the registry and gave informed consent to participate in the analysis. The study was prospectively registered (NCT03065543).

The aim of the registry is to evaluate the risk of adverse clinical events (death or recurrent cardiovascular events) as well as to assess the effectiveness of treatment, defined as achieving the therapeutic target of LDL-C level of <70 mg/dL (1.8 mmol/L) during the 12-month follow-up period (following the European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) 2016 guidelines for the treatment of lipid disorders) [15]. Data related to clinical events in the up to 36-month follow-up period were obtained from the National Health Fund and include: the date of death (cardiac/non-cardiac causes), non-fatal myocardial infarction, revascularization (either planned or following acute coronary syndrome - ACS) based on the following ICD-10 codes: I20.0, I21.0, I21.1, I21.2, I21.3, I21.4, I25.0, I25.2, I63.0 and I64.0.

Detailed information on the medical history of patients is gathered and supervised by the physician in charge. The data are regularly updated and archived both manually and digitally. The system requires the completion of all data (including demographic data and laboratory test results) by the end of the hospitalisation. Records of ambulatory patients, who are treated in the hospital outpatient clinic after discharge from the hospital, are gathered and stored in the same way.

Lipid profile parameters (concentrations of total cholesterol [TC], high-density lipoprotein cholesterol [HDL-C], LDL-C and triglycerides) were measured using the Cobas Integra 800 chemical auto-analyser (Roche Diagnostics, Switzerland). Triglyceride concentration was measured utilising the enzymatic-colourimetric method with glycerol-3-phosphate oxidase and 4-amino phenazone. TC, HDL-C, and LDL-C levels were measured directly using the homogenous colourimetric method based on a chain reaction between cholesterol esterase and oxidase, with the intensity of absorbance proportional to the change in colour of the specific pigment product concentration.

2.1. Statistical analysis

Basic parameters of descriptive statistics for the analysed continuous variables are presented as means and standard deviations (SD) if they are normally distributed, or otherwise as medians and the first and third quartiles (Q1-Q3). Normality of distribution was tested using the Shapiro-Wilk test. Between-group comparisons of continuous variables were conducted using Student's t-test (if normally distributed); otherwise, the Mann-Whitney *U* test was used.

The Pearson's chi-squared test was used to evaluate categorical variables. The interval of two-sided $p < 0.05$ was considered as statistically significant. Unifactorial and multifactorial analyses were performed to assess variables using the Cox proportional regression model or with the logistic regression ($p < 0.1$ for inclusion in the model, $p < 0.05$ for remaining in the model). All investigated clinical and angiographic parameters that were statistically significant were included in the unifactorial analysis after the exclusion of co-dependent variables in the correlation analysis and can be found in Supplementary Table. Estimated parameter values are presented as hazard ratios (HR) with a 95% confidence interval (CI). STATISTICA 10 (StarSoft Inc., Tulsa, OK, US) was used for all calculations.

3. Results

3.1. Patients' characteristics

At the time of the analysis, there were 19,582 patients included in the TERCET Registry. Among them, there were 4295 patients (21.9%, mean age 64.4 ± 11.5 years, women 32.0%) admitted due to acute myocardial infarction (2327 with ST-segment elevation myocardial infarction - STEMI, of whom women constituted 29.4% and 1968 patients with non-ST-segment elevation myocardial infarction - NSTEMI, of whom women constituted 34.7%). Patients with STEMI comprised 11.9% of the population and their mean age was 62.7 ± 11.6 years, whilst patients with NSTEMI comprised 10.0% of the population with a mean age of 66.2 ± 11.2 years. In 2325 patients, unstable angina (UA) was diagnosed (11.9% of the population, mean age 65.2 ± 10.5 years, with 35.5% percentage of women). The remaining 13,052 patients were admitted with the chronic coronary syndrome (CCS, 66.7% of the population, mean age 64.5 ± 9.5 years, of whom 36.0% were female). The full baseline clinical and therapeutic profile of the entire TERCET population is presented in Table 1.

In order to establish factors potentially associated with extreme risk of death in the 12–36 months following the index event, all patients with STEMI and NSTEMI diagnosis were included in the analysis. Therefore, the group constituted 4295 patients (54.2% with STEMI and 45.8% with NSTEMI). The clinical characteristics of the combined subgroup of TERCET patients with STEMI/NSTEMI are presented in Table 1.

Patients admitted with MI differed significantly from those with CCS. There was a higher proportion of males in the MI group (68.0% *vs* 64.0%, $p < 0.001$) and less prolific history of prior myocardial infarction or either type of revascularization procedure (26.7% *vs* 34.2% for MI, 22.8% *vs* 32.1% for PCI and 7.4% *vs* 11.6% for coronary artery bypass graft surgery - CABG in respective groups, all $p < 0.001$). Furthermore, in patients with MI, the occurrence of PAD, hypertension, diabetes, hyperlipidaemia, atrial fibrillation (AF), and chronic obstructive pulmonary disease (COPD) was significantly lower. Left ventricular ejection fraction (LVEF) was significantly lower (42,7 ± 10,2%) in patients with MI than in patients with CCS (46.5 ± 11.5%, $p < 0.0001$), and the percentage of patients with LVEF lower than 35% was 22.6% in patients after MI *versus* 17.9% in patients with CCS.

Patients admitted due to MI had a higher prevalence (52.7% *vs* 34.2%, $p < 0.001$) of multivessel coronary artery disease (MVD) on admission. The groups also differed with respect to treatments provided. A significantly higher proportion of patients admitted due to MI were treated with percutaneous coronary intervention (PCI), and the frequency of coronary artery bypass graft surgery (CABG) performed in this population was significantly lower (89.4% *vs* 38.5% when PCI and 5.5% *vs* 9.2% when CABG were concerned, both $p < 0.001$).

3.2. Extremely high-risk patients

The patients with an acute MI had a significantly worse prognosis than those with CCS. The rates of all-cause mortality, recurrent MI, or repeat revascularization were approximately 3-fold higher, whilst the stroke occurred almost 2-fold higher in MI patients, as presented in Table 2.

In order to assess the risk factors associated with worse outcomes in patients after MI, multivariate analysis with a stepwise backward regression model was performed. The all-cause mortality of MI patients

Table 1
Baseline clinical characteristics of the study population.

Factor	The TERCET registry N = 19,582					
	CCS n = 13,052	UA n = 2235	NSTEMI n = 1968	STEMI n = 2327	Total MI n = 4295	*p*
Age, years; mean (SD)	64.5 (9.6)	65.2 (10.5)	66.2 (11.2)	62.7 (11.6)	64.4 (11.5)	<0.0001
Males, % (n)	64 (8357)	64.5 (1269)	65.3 (1278)	70.6 (1642)	68.0 (2920)	<0.0001
Prior MI, % (n)	34.2 (4372)	46 (887)	36.2 (801)	17.6 (407)	26.7 (1208)	<0.0001
Prior PCI, % (n)	32.1 (4100)	49.1 (948)	34.6 (766)	11.6 (269)	22.8 (1035)	<0.0001
Prior CABG, % (n)	11.6 (1481)	17.3 (340)	12.6 (282)	2.5 (57)	7.4 (339)	<0.0001
Prior stroke, % (n)	5.6 (724)	5.7 (112)	6.5 (145)	1.5 (34)	3.9 (179)	<0.0001
Peripheral artery disease, % (n)	14.9 (1904)	12.8 (246)	13 (288)	1.5 (34)	7.1 (34)	<0.0001
Atrial fibrillation, % (n)	20.3 (2592)	14.6 (285)	14.6 (326)	7.8 (182)	11.1 (508)	<0.0001
Arterial hypertension, % (n)	80.0 (10,360)	84.7 (1644)	78.3 (1738)	53.7 (1249)	65.7 (2987)	<0.0001
Diabetes mellitus, % (n)	34.1 (4360)	39.7 (767)	39.5 (876)	21.2 (493)	30.1 (1369)	<0.0001
LVEF ≤35%, % (n)	17.9 (1610)	13.5 (246)	22.2 (483)	23.1 (514)	22.6 (514)	<0.0001
LDL-C, mmol/L (Q1-Q3)	2.44 (1.93–3.08)	2.50 (1.80–3.25)	2.71 (1.96–3.58)	3.00 (2.13–3.82)	2.85 (2.01–3.74)	<0.0001
HDL-C, mmol/L (Q1-Q3)	1.21 (1.00–1.50)	1.14 (0.98–1.40)	1.19 (0.93–1.45)	1.19 (0.98–1.47)	1.19 (0.96–1.46)	<0.0001
TG, mmol/L (Q1-Q3)	1.30 (0.97–1.79)	1.34 (0.95–1.88)	1.28 (0.88–1.81)	1.74 (0.82–1.66)	1.51 (0.85–1.72)	<0.0001
Cardiac arrest, % (n)	0.0 (0)	0.5 (9)	2.0 (44)	4.5 (105)	3.3 (149)	<0.0001
Killip III class, % (n)	0.6 (75)	0.6 (12)	2.4 (53)	2.9 (64)	2.7 (117)	<0.0001
Killip IV class, % (n)	0.0 (0)	0.2 (4)	1.3 (28)	8.0 (176)	4.6 (204)	<0.0001
LVEF, %; mean (SD)	46.5 (11.5)	47.1 (10.4)	43.2 (11.0)	42.1 (9.4)	42.7 (10.2)	<0.0001
Serum creatinine, μmol/L; median (Q1-Q3)	81 (68–96)	83 (70–100)	84 (70–103)	81 (68–98)	83 (69–100)	<0.0001
GFR <60 ml/min/1.73 m^2, % (n)	17.4 (2260)	25.9 (574)	21.8 (423)	14.4 (336)	17.6 (759)	<0.0001
Multi-vessel CAD, % (n)	34.2 (4463)	40.8 (774)	57.1 (1231)	48.5 (1113)	52.7 (2344)	<0.0001
PCI, % (n)	38.5 (5026)	70.7 (1391)	80.6 (1802)	97.8 (2257)	89.4 (4059)	<0.0001
CABG, % (n)	9.2 (1200)	5.7 (113)	5.2 (117)	5.7 (132)	5.5 (249)	<0.0001
Acetylsalicylic acid, % (n)*	84.1 (9880)	89.3 (1742)	87.6 (1928)	98.3 (2149)	92.9 (4077)	<0.0001
P2Y12 receptor inhibitor, % (n)*	42.2 (4954)	74.1 (1445)	87.1 (1918)	95.9 (2096)	91.5 (4014)	<0.0001
Oral anticoagulant, % (n)*	20.7 (2435)	12.2 (237)	10.3 (226)	5.8 (132)	8.2 (358)	<0.0001
Beta-blocker, % (n)*	92.7 (10,888)	85.2 (1661)	83.5 (1838)	94.9 (2075)	89.2 (3913)	<0.0001
ACE inhibitor/ARB, % (n)*	84.6 (9935)	80.4 (1567)	77.4 (1705)	89.7 (1961)	83.5 (3666)	<0.0001
Statin, % (n)*	85.5 (9919)	92.9 (1754)	93.6 (1973)	94.8 (1619)	94.1 (3592)	<0.0001
Diuretic, % (n)*	51.6 (6054)	35.1 (684)	38.3 (844)	26.6 (619)	33.3 (1463)	<0.0001

Values presented as percentage (frequency) or means and standard deviation (SD) or median and inter-quartile range (Q1-Q3). ACE - angiotensin converting enzyme; ACS - acute coronary syndrome; ARB - angiotensin receptor blocker; CABG - coronary artery bypass grafting; CAD - coronary artery disease; CCS - chronic coronary syndrome; COPD - chronic obstructive pulmonary disease; GFR - glomerular filtration rate; HDL-C - high-density lipoprotein cholesterol; LDL-C - low-density lipoprotein cholesterol; LVEF - left ventricular ejection fraction; NSTEMI - non-ST-segment elevation myocardial infarction; PCI - percutaneous coronary intervention;; STEMI - ST-segment elevation myocardial infarction; TG - triglycerides; UA – unstable angina.

* Pharmacotherapy administered at discharge during the baseline hospital admission.

Table 2
One-year outcomes of the study population.

Factor	The TERCET registry N = 19,582					
	CCS n = 13,052	UA n = 2235	NSTEMI n = 1968	STEMI n = 2327	Total MI n = 4295	*p*
Death, % (n)	4.8 (628)	5.5 (108)	12.3 (274)	12.0 (279)	12.1 (553)	<0.0001
MI, % (n)	2.1 (269)	5.2 (103)	9 (202)	5.5 (129)	7.3 (331)	<0.0001
ACS-driven revascularization, % (n)	2.2 (290)	8.7 (171)	9.3 (208)	4.3 (101)	6.8 (309)	<0.0001
Stroke, % (n)	1.0 (127)	1.1 (21)	2.0 (45)	1.5 (36)	1.8 (81)	0.0001

ACS - acute coronary syndrome; CCS - chronic coronary syndrome; MI - myocardial infarction; NSTEMI - non-ST-segment elevation myocardial infarction; STEMI - ST-segment elevation myocardial infarction; UA – unstable angina.

was respectively 12.1%, 16.1%, and 19.6% in the 12-month, 24-month, and 36-month follow-up. The following factors were most strongly associated with higher 12-month mortality in patients after MI (in order of decreasing hazard ratio): LVEF <35%, age >75 years, multivessel CAD, atrial fibrillation, diabetes mellitus, and increased LDL-C or creatinine levels (Fig. 1). In the 24-month analysis, the aforementioned risk factors remained significantly associated with mortality, while the reduction of haemoglobin levels at baseline was an additional independent predictor of all-cause death (Fig. 2). Finally, at 36 months, the presence of chronic obstructive pulmonary disease (COPD) was next additional independent risk factor of all-cause mortality (Fig. 3). The sole factor independently improving survival in any analysed follow-up period (by 40%) was PCI performed in an acute phase of MI. The aggregate summary of risk factors, associated with extremely high risk, and hazard ratios for the 12-month, along with 24-month and 36-month all-cause death are presented in Figs. 1–3.

Based on the definitions of extremely high-risk patients from the AACE and Polish Society of Laboratory Diagnostics (PSLD) and Polish Lipid Association (PoLA) guidelines, we analysed the risk of these specified populations and summarized the results in Table 3 [7–9]. The 1-year mortality of patients with MI was 12.1%. The highest risk of all-cause death was observed in the subgroup with established CVD and concomitant: DM or stage 3/4 of chronic kidney disease (CKD) and/or heterozygous familial hypercholesterolaemia (18.3%) and in patients with progressive atherosclerotic CVD despite the achievement of LDL-C <70 mg/dL (16.0%). The 1-year mortality of the remaining subgroups was lower than in the overall MI cohort.

4. Discussion

In the large, single-center real-world registry encompassing almost 20,000 patients with various manifestations of coronary artery disease, we showed that the mid- and long-term mortality rate was significantly higher in patients after MI, than in patients with CCS. The risk factors most strongly associated with higher 36-month mortality in patients after an MI were LVEF lower than 35%, age older than 75 years, atrial fibrillation, multi-vessel CAD, diabetes mellitus, increased LDL-C or creatinine, and decreased haemoglobin levels. The group of patients with these risk factors constitutes the population of the highest risk of death that should be considered to be the 'extreme risk' population.

In 2016, in the USA alone, 550,000 'first in life' and 200,000 recurrent MIs were reported [16]. In Poland, the annual incidence of MI is approximately 85,000–90,000 [17]. Data from the national Polish PL-ACS registry, one of the largest registries in Europe, which encompasses patients with acute coronary syndromes, suggests that in-hospital mortality in patients with MI is 8.5%, and one-year mortality is 19.4% [17]. This overall dismal prognosis may be partially explained by the suboptimal organisation of post-MI care in Poland in the past. However, the prognosis for each individual depends on the presence of risk factors, comorbidities, and the method and intensity of their treatment [10–14].

We believe that an identification of patients at the highest risk could result in a more appropriate selection of the individuals requiring the most intensive pharmacological treatment. In the recent years, new evidence emerged indicating that therapy with new groups of drugs acting on various pathological pathways of cardiovascular disease, significantly reduced CV risk. The present analysis identified the CV risk factors independently increasing the risk of death after MI. Among those factors identified on admission to hospitalisation, those modifiable with the long-term secondary prevention strategies, included elevated levels of LDL-C, diabetes, hyperglycaemia, and atrial fibrillation.

Two recent, large, randomized trials with PCSK9 inhibitors demonstrated that in specific subgroups of patients, the treatment with those potent drugs resulted in a lower incidence of hard clinical endpoints [18,19]. More specifically, the absolute risk reduction of the composite endpoint (death from coronary artery disease, nonfatal MI, fatal or non-fatal ischaemic stroke, or unstable angina requiring hospitalisation) was 2% in the overall population studied in the ODYSSEY-Outcomes trial (number needed to treat - NNT of 49) [19,20]. However, based

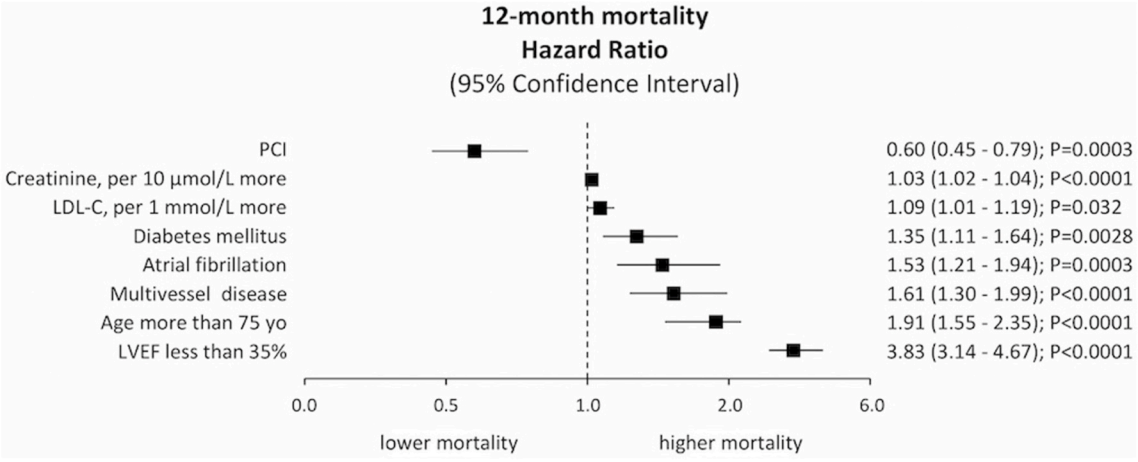

Fig. 1. Multivariate analysis of risk factors associated with 12-month mortality in patients with myocardial infarction.
LDL-C, low-density lipoprotein cholesterol; LVEF – left ventricular ejection fraction; PCI – percutaneous coronary intervention, YO – years of age.

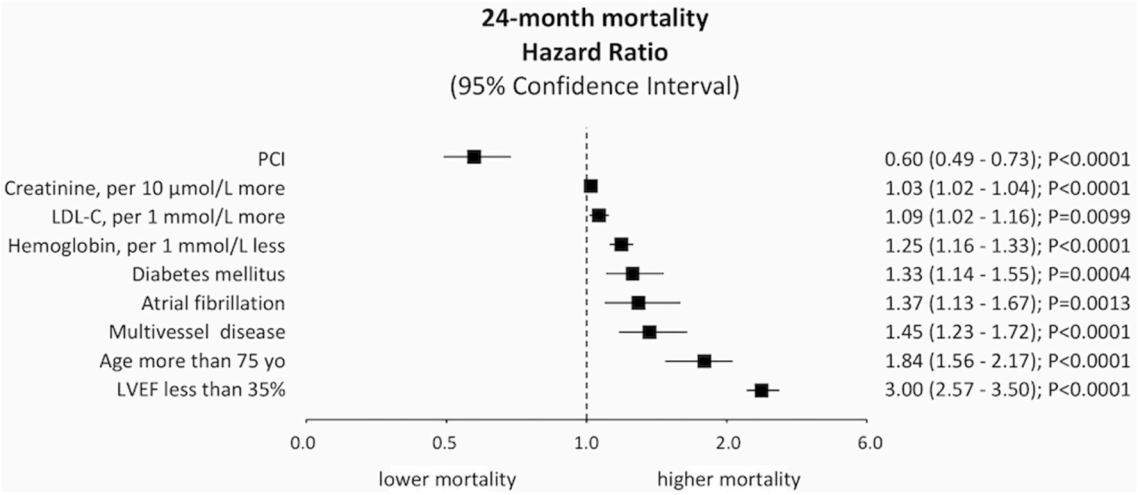

Fig. 2. Multivariate analysis of risk factors associated with 24-month mortality in patients with myocardial infarction.
LDL-C, low-density lipoprotein cholesterol; LVEF – left ventricular ejection fraction; PCI – percutaneous coronary intervention, YO – years of age.

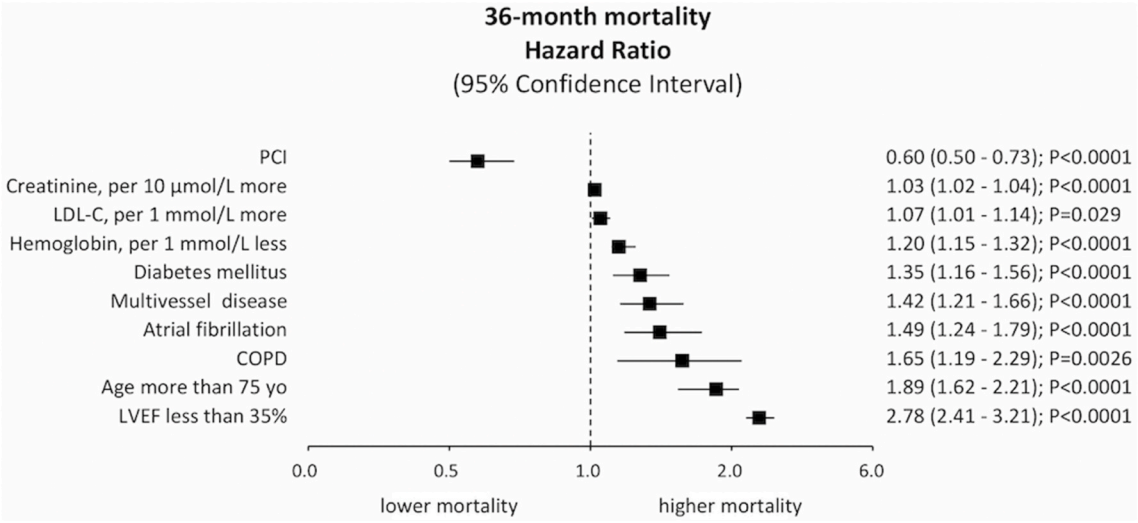

Fig. 3. Multivariate analysis of risk factors associated with 36-month mortality in patients with myocardial infarction.
COPD – chronic obstructive pulmonary disease; LDL-C, low-density lipoprotein cholesterol; LVEF – left ventricular ejection fraction; PCI – percutaneous coronary intervention, YO – years of age.

on the subgroup analyses of the trials with both evolocumab and alirocumab, it was shown that for individuals with MVD, peripheral artery disease, or the history of multiple MIs, or statin intolerance, the clinical efficacy of the treatment with PCSK9 inhibitors were significantly higher, resulting in an NNT lower than 30 [21,22]. Therefore, the stratification of patients with the highest risk allows to determine those individuals who are most likely to benefit from more intensive lipid-lowering therapy [21,22].

It has been consistently demonstrated that the reduction of LDL-C levels is associated with a reduced risk of CVD [23]. The results of the available studies, in which either angiographic or clinical endpoints were assessed, demonstrate that the reduction of LDL-C should be one of the primary goals of CVD prevention [23,24]. A large meta-analysis of randomized-controlled trials of statin therapy demonstrated a dose-dependent reduction of relative CV risk. A reduction of LDL-C by 1 mmol/L (38.6 mg/dl) is associated with an annual 20–25% reduced risk of CV death and non-fatal MI for every year, after the first year of treatment [25]. Furthermore, a recent meta-analysis supports further LDL-C reduction even in patients with very low LDL-C levels. It was demonstrated that the linear association between LDL-C and CV risk persists with a similar magnitude beyond <70 mg/dL [26].

Unfortunately, despite the presence of more effective lipid-lowering drugs and increasing numbers of patients being on more potent statins, the percentage of patients, who reach therapeutic target remains low (only 1/3 of patients in the Da Vinci Study) [27]. It is worth noting that in two large international European surveys conducted in patients who had undergone acute coronary syndrome or coronary revascularization, the percentage of patients who reached the therapeutic target of 1.8 mmol/L did not exceed 30% [28,29].

Data from multiple studies indicate that patients with diabetes who experience MI have a more advanced coronary atherosclerosis and worse short- and long-term outcomes, than the non-diabetic MI patients [30–33]. The pooled results of the randomized trials, as well as from the Global Registry of Acute Coronary Events (GRACE) registry, indicate that in patients with either non-ST segment acute coronary syndrome (NSTE-ACS) or STEMI, risk of death at short- and medium-term follow-up, is significantly higher in the presence of diabetes [32,34]. In the recent years, the results of the large, randomized trials have been published, which demonstrated that the sodium-glucose co-transporter-2 (SGLT-2) inhibitors, the new group of drugs for the treatment of

Table 3
One-year mortality of patients defined as of extreme-risk in the AACE guidelines in the population of patients from the TERCET registry.

Group	Number of patients	All-cause mortality in 12 months
Progressive atherosclerotic CVD despite the achievement of LDL-C <1.8 mmol/L (<70 mg/dL)	638	**16.0%**
Established CVD with concomitant: DM, stage 3/4 of CKD and/or HeFH	1832	**18.3%**
History of premature atherosclerotic CVD defined as <55 years of age for males and <65 years of age for females	225	**5.9%**
Status post-ACS and the presence of peripheral artery disease or polyvascular disease (despite optimal treatment with maximum tolerated statin doses)	103	**10.7%**
Status post-ACS and coexistent multivessel coronary artery disease (despite optimal treatment with maximum tolerated statin doses)	893	**7.1%**
Status post-ACS and familial hypercholesterolaemia (FH) – despite optimal treatment with maximum tolerated statin doses	30	**6.7%**

ACS - acute coronary syndrome CKD - chronic kidney disease; CVD - cardiovascular disease; DM - diabetes mellitus; FH - familial hypercholesterolaemia; HeFH - heterozygous familial hypercholesterolaemia; LDL-C – low-density lipoprotein cholesterol.
The remaining groups of "extreme CV risk" patients are those, who "experience a second vascular event in the two years following the first event" - due to the character of our registry allowing us to determine the outcomes after the baseline hospitalisation, not before the event, the quantification of the risk in this subgroup was not possible.

diabetes, reduced the CV risk in patients of either high- or very-high CV risk, both with and without diabetes [35,36]. It should be noted that there are ongoing randomized trials evaluating the efficacy of SGLT-2 inhibitors in patients after MI, but the preclinical studies and already published analyses from the other populations of patients suggest that these drugs might significantly improve outcomes in patients after MI. However, one should note that the SGLT-2 inhibitors were not widely available in Poland during the analysed period (due to lack of reimbursement) and almost none of the patients included in the study was treated with these drugs.

Nonetheless, one has to acknowledge that the excessive CV risk is often a result of concomitant activity of atherosclerosis- and non-atherosclerosis related pathways, such as atrial fibrillation. Thus, the patients constituting this group might obtain a larger benefit from the more potent secondary prevention of recurrent ischemic events. According to the available data, AF is present in 5–23% of patients after MI [37]. In our population of patients with MI, the prevalence of AF was 11%. It has previously been demonstrated that the subpopulation of patients with MI and AF has a significantly worse clinical profile and more comorbidities than other patients [38]. A recent subanalysis of the RE-DUAL PCI trial demonstrated that there was a significant overall benefit of dual antithrombotic therapy with dabigatran and either ticagrelor or clopidogrel over triple antiplatelet therapy with warfarin, aspirin and either ticagrelor or clopidogrel, in patients with atrial fibrillation and STEMI, which was similar to patients with NSTEMI, UA or CCS [39]. Similarly, as with SGLT-2 inhibitors, due to various reasons, including uncertainties with the reimbursement and high expensiveness of novel oral anticoagulants, only a small percentage of patients in our registry was treated with one of these drugs in the analysed period.

Nevertheless, the factor most strongly associated with 1-year mortality after MI was LVEF <35%. According to the literature, even more than 40% of patients discharged following MI have LVEF <35% [40]. In our analysis, reduced LVEF was associated with nearly 4-fold higher 1-year mortality than in patients with normal LV contractility following an MI, and despite reduction in the hazard ratio over time, lower LVEF remained the most significant risk factor of higher mortality at 24 and 36 months.

In our opinion, patients with concurrent HF and CAD are substantially underrepresented in the largest randomized clinical trials, such as The Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) and Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk (FOURIER) trials, where the symptoms of CHF were present in respectively 4.5% and 13.5% of patients [18,19,23]. Moreover, the majority of patients included in the FOURIER trial had experienced MI more than three years before they were recruited into the study. This approach can lead to 'survivor bias' resulting in a stable group of patients with relatively low residual risk compared to the overall population of post-MI patients. Because patients with low LVEF following MI are at such a high risk of mortality, they may derive more benefit from intensive secondary prevention therapy than the general population of high-risk patients [41].

4.1. Limitations

Our analysis is the retrospective assessment of the prospective registry and thereby cannot demonstrate causal relationships owing to residual confounding. Because the study included patients with only up to 36-month follow-up, it was not possible to directly compare the outcomes derived from our analysis with their risk predicted using the SCORE calculator, which predicts a 10-year mortality risk. Similarly, in our opinion the results of the present analysis are not comparable to the previously published risk scores such as TIMI, or SMART scores [42,43], which were performed in the different populations of patients, predict the CV risk in the different follow-up periods, and are not focused specifically on patients with an acute MI, who as demonstrated in our analysis, are at higher risk of death, than the overall cohort of patients with CVD. Moreover, the analysed population consists of inhabitants of a highly urbanized and polluted region. Although such environmental factors are not included in the major calculators of CV risk, they may significantly influence both short- and long-term outcomes [44–46]. It is worth mentioning that the population included in the study consists of patients burdened with multiple comorbidities and CV risk factors, who were treated in the single tertiary cardiovascular center, therefore the generalisability of the results to the more diverse populations might be limited. Moreover, despite being already established as an important CV risk factor significantly worsening prognosis in patients with CVD, almost none of the patients included in the present analysis had level of lipoprotein(a) measured, which therefore prohibits from analysing its association with outcomes of the studied population [47,48]. Furthermore, although our analysis included the assessment of various "extreme CV risk" subgroups defined previously, the single subgroup of patients, namely those who „experience a second vascular event in the two years following the first event" – was not available for analysis, due to the retrospective character of our registry and no information on the exact timing of the prior CV event. Finally, the retrospective character of our study allows one to observe the associations the analysed variables but prohibits from drawing the straightforward conclusions on the causality of the effects.

4.2. Conclusions

Patients with a history of MI have the highest risk of death in the whole spectrum of atherosclerotic coronary artery disease. This explains the inclusion of these patients in the 'very-high CV risk' subgroup as defined in the ESC guidelines. However, even within this group, there is a range of risk, with some patients more susceptible to recurrent events

than others. In our large, single-center, real-world analysis we identified factors that aggravated the mid- and long-term survival of patients initially stratified into 'very-high CV risk' population. These patients are expected to derive the most benefit from intensive secondary-prevention therapy, and hence should be considered to be an "extreme risk" population.

Declaration of competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Krzysztof Dyrbuś: Conceptualization, Writing – original draft. **Mariusz Gąsior:** Conceptualization, Writing – original draft. **Piotr Desperak:** Formal analysis, interpreted. **Przemysław Trzeciak:** Writing – review & editing. **Jolanta Nowak:** Writing – review & editing. **Peter E. Penson:** Writing – original draft, critically revised. **Tadeusz Osadnik:** Writing – review & editing. **Maciej Banach:** Conceptualization, Writing – original draft.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2021.08.024.

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