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ARTYKUŁ ORYGINALNY / *ORIGINAL ARTICLE*

Clinical characteristics, and in-hospital and long-term outcomes of stable angina treatment in patients below and over 40 years of age (from the PRESAGE registry)

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Abstract

Background: There is a paucity of data concerning young patients with stable angina (SA).

Aim: The study aimed to compare the characteristics, as well as in-hospital one-, two-, and five-year outcomes of patients aged ≤ 40 and > 40 years with SA.

Methods: The analysis involved 80 patients aged ≤ 40 years and 9299 patients aged > 40 years with SA treated in the 3rd Department of Cardiology in Zabrze between 2006 and 2014, and enrolled in the ongoing PRESAGE Registry. Propensity scores matching was used to adjust for differences in patients' baseline characteristics. The composite endpoint involved death, non-fatal myocardial infarction, and acute coronary syndrome (ACS) or ACS-driven unplanned revascularisation within one-, two-, and five-year follow-up periods.

Results: In comparison to older patients, the younger ones had a higher incidence of smoking (58.3% vs. 35.2%, $p < 0.0001$) and previous percutaneous angioplasty (45% vs. 33.7%, $p = 0.033$). There was no significant difference in in-hospital outcomes. The composite endpoint incidence did not differ significantly between the young and old group within one year (1.3% vs. 8.1%, $p = 0.068$), two years (5.8% vs. 12.9%, $p = 0.08$), and five years (23.1% vs. 25.7%, $p = 0.71$) after discharge. Young patients had a borderline lower mortality rate (0% vs. 4.5%, $p = 0.053$) after a one-year follow-up and a significantly lower mortality rate within two and five years after index hospitalisation (0% vs. 7.8%, $p = 0.02$ and 5.1% vs. 17.1%, $p = 0.04$, respectively). After propensity score matching analysis, a significantly lower two-year mortality was observed in the ≤ 40 age group (0% vs. 8.1%; $p = 0.016$), without significant difference during five-year follow-up (5.1% vs. 13.5%; $p = 0.21$).

Conclusions: The younger and older groups of patients with SA differed in clinical characteristics, with no significant difference in the in-hospital outcomes and composite endpoint incidence in the follow-up period. However, younger patients had a borderline lower mortality rate one year after discharge and a significantly lower mortality rate two and five years after the index hospitalisation.

Key words: young adults, stable angina, hospitalisation, registry, mortality

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INTRODUCTION

The incidence of stable angina (SA) increases with age, and so it is typical amongst older patients. By and large, the first manifestation of coronary artery disease (CAD) at a younger age is acute coronary syndrome (ACS) or sudden cardiac death (SCD) [1]. Patients under 40 years of age represent 2% to 10% of all patients with ACS [2–8]. The incidence of SA among young patients is an issue often neglected both in the registries and in the available literature [5, 9–11]. Moreover, there is a paucity of data concerning the clinical characteristics, management, and prognosis of SA in young patients [5, 9–11]. Due to the small number of patients with SA below 40 years of age noted in literature [5, 9–11], clinical investigations and results from registries are needed to determine the prognosis and the optimal management.

The aim of our study was to compare the characteristics, treatments, and in-hospital one-, two-, and five-year outcomes

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of patients aged ≤ 40 years and > 40 years with SA, who were enrolled in the Prospective Registry of Stable Angina Management and Treatment (PRESAGE).

METHODS

Registry design

The study was based on the data from the PRESAGE registry. In brief, the PRESAGE registry is an ongoing, single-centre, prospective observational study recruiting consecutive patients with SA, who were diagnosed and treated in the 3rd Chair and Department of Cardiology in the Silesian Centre for Heart Diseases in Zabrze, Poland. The Silesian Centre for Heart Disease is a highly-specialised cardiology centre with cardiac surgery facilities. To achieve complete follow-up data, only inhabitants of the Silesia Province, one of the 16 administrative regions of Poland, with 4.5 million residents, were selected for analysis. All admitted patients with suspected SA were screened for eligibility to enter the registry, and they were enrolled only after SA had been confirmed. The diagnosis of SA was based on the clinical symptoms, coronary angiography, and the current guidelines of the European Society of Cardiology (ESC) [1, 12, 13]. Patients with microvascular and/or vasospastic angina were also included in the study group. Pharmacological treatments, as well as all interventional strategies including the use of stents, periprocedural anti-thrombin and antiplatelet therapy, were used in accordance with the current recommendations of the ESC [1, 12, 13].

Data collection

Complete patient characteristics, treatments, and in-hospital data were obtained by reviewing the hospital records. The analysis encompassed the incidence of in-hospital events, including death, non-fatal myocardial infarction (MI), major bleeding, and contrast-induced nephropathy. A subsequent analysis included only data from the first hospitalisation due to SA. Five-year follow-up data were acquired from the National Health Fund. The vital status and follow-up information were available for all enrolled patients.

Endpoints and definitions

The composite endpoint involved death, non-fatal MI, and ACS or ACS-driven unplanned revascularisation within a one-, two-, and five-year observation period. Death was considered as an all-cause death. Non-fatal MI was defined as an ischaemic event that met the ESC/American College of Cardiology criteria for MI [14]. ACS-driven repeat revascularisation was defined as additional, unplanned percutaneous coronary angioplasty (PCI) or coronary artery bypass grafting (CABG), performed as an urgent procedure due to acute ischaemic symptoms [15]. Hypertension was defined as repeated systemic blood pressure measurements exceeding 140/90 mm Hg or treatment with antihypertensive drugs for a known diagnosis of hypertension. Diabetes mellitus was diagnosed by the fasting plasma glucose level > 125 mg/dL (7.0 mmol/L), a random plasma glucose level > 200 mg/dL (11.1 mmol/L), or a history of diabetes mellitus, including those treated with diet, oral medications, or insulin. Hypercholesterolaemia was defined as a baseline cholesterol level greater than 200 mg/dL (5.2 mmol/L) and/or a low-density lipoprotein level greater than 130 mg/dL (3.4 mmol/L), or previously diagnosed and treated hypercholesterolaemia. Obesity was diagnosed as a body mass index ≥ 30 kg/m^2. Positive family history (PFH) of premature CAD was recognised if CAD was revealed in a first-degree relative < 50 years of age in men and < 60 years in women. Significant CAD was defined as a haemodynamically significant stenosis in coronary arteries with a diameter ≥ 2.0 mm as determined by visual assessment. A ≥ 50% stenosis of the left main (LM) artery or the proximal segment of the left anterior descending (LAD) artery and a ≥ 70% stenosis in other segments was considered as haemodynamically significant. Non-significant CAD was defined as < 50% lesions in LM or proximal LAD and < 70% lesions in other segments of coronary arteries with a diameter ≥ 2.0 mm as determined by visual assessment. Smooth coronary arteries were defined as the lack of any atherosclerotic lesions in the coronary arteries. Major bleeding was defined as clinically overt bleeding: 1) with an ensuing decrease in haemoglobin to below 5 g/dL (3.1 mmol/L) or an absolute decrease of haematocrit by more than 15%; 2) resulting in haemodynamic disorders; or 3) requiring a blood transfusion. Contrast-induced nephropathy was defined as impaired renal function, based on relative (≥ 25%) or absolute (≥ 44 μmol/L) increase of creatinine concentration in the blood serum up to three days after the first or subsequent coronary angiography and the absence of an alternative explanation of renal dysfunction [6].

Study objectives

The study population was divided into two groups: (I) ≤ 40 years of age and (II) > 40 years of age. We compared the differences in the clinical presentation, characteristics, and cardiovascular risk factors of both groups. We also looked for any differences in angiographic characteristics and the treatment strategy, including PCI. Finally, we compared the in-hospital, one-, two-, and five-year outcomes, including the number of composite endpoints.

Statistical analysis

The statistical analysis included a comparison of baseline, angiographic, and in-hospital characteristics and the occurrence of the composite endpoint and its components in the 12-month follow-up period. Continuous variables were summarised using the arithmetic mean with standard deviation (SD) for data following normal distribution or the median with quartile 1 and 3 (Q1–Q3) for data demonstrating other-than-normal distribution. The t-student test was performed to compare continuous parameters with normal distribution, whereas the Mann-Whitney U test was used for parameters with

other-than-normal distribution. The normality of distribution was verified using the Shapiro-Wilk test. Categorical variables were summarised using frequency tables and were compared using the χ^2 test with Pearson's modification. To identify the independent predictors of long-term outcome, for all the patients both univariate and multivariate Cox regression analysis was performed using a stepwise backward logistic regression model. To minimise the impact of the missing data on the Cox regression analysis, a multiple imputation method was used to impute the missing data for several factors. The covariates used in the Cox regression included all significant factors influencing mortality in univariate analysis. Irrespectively of the Cox regression analysis, propensity score analysis to adjust for differences in patients' baseline characteristics was performed. A logistic regression model was used to generate a propensity score for individuals ≤ 40 years and > 40 years of age. Then, each subject from the ≤ 40 years group was matched to an individual from the > 40 years group using the derived propensity scoring. For all analyses, a two-tailed p-value ≤ 0.05 was considered as significant. STATISTICA 10 software (StarSoft Inc., Tulsa, Oklahoma) was used for all calculations.

RESULTS

Between January 2006 and December 2014, 9379 patients with SA were enrolled into the ongoing, prospective PRESAGE Registry. All patients were of Caucasian race. Only 80 (0.9%) patients were 40 years of age or younger. The baseline demographic and clinical characteristics of young patients compared to those older than 40 years of age, are shown in Table 1. Women accounted for 10.0% of the young patients, which was a significantly lower proportion ($p < 0.0001$) than in the older group (33.6%). Group I patients had a higher prevalence of PCI ($p = 0.03$) and a lower incidence of previous CABG ($p = 0.04$), in comparison to group II patients. Hypertension and diabetes mellitus were significantly more frequent in the older group than among younger patients ($p < 0.0001$). Compared to group II, group I had a higher incidence of smoking ($p < 0.0001$) and a PFH of premature CAD ($p = 0.0009$). Angiographic characteristics of both groups are presented in Table 1. Young patients had a higher prevalence of non-significant CAD ($p = 0.04$) and a lower incidence of multivessel CAD ($p = 0.0007$). There was no significant difference in the in-hospital outcomes and the treatment, apart from a higher frequency of PCI with bare stents in older patients ($p = 0.04$). The composite endpoint incidence did not differ significantly between the young and old group within one year ($p = 0.08$), two years ($p = 0.08$), and five years ($p = 0.71$) after discharge (Table 2). After propensity score matching of the study population group, 80 pairs were selected. The differences in baseline clinical characteristics and angiography were reduced with nonsignificant p values in all the analysed factors (Table 3). Propensity score matching analysis showed a significantly lower two-year mortality observed in the ≤ 40 years age group (0% vs. 8.1%, $p = 0.016$), without significant difference in one-year and five-year follow-up. The Kaplan-Meier curve comparing the mortality between the two groups during the five-year follow-up showed a better prognosis for the younger patients (Fig. 1). Univariate analysis of factors influencing five-year mortality is shown in Table 4. New York Heart Association (NYHA) class IV, chronic obstructive pulmonary disease, atrial fibrillation, and peripheral artery disease proved to be the strongest independent risk factors of death in multivariate analysis (Fig. 2). Other independent and significant factors increasing five-year mortality are listed in Figure 2.

DISCUSSION

Stable angina is a prevalent manifestation of CAD [16]. Notwithstanding, the number of studies regarding the management and treatment of patients with SA is limited [16–18]. Our study is a unique analysis involving patients under 40 years of age with SA and the longest five-year follow-up period. Additionally, for better evaluation of long-term outcomes, the propensity score matching technique was performed. In the available studies and registries, SA in young patients is a neglected issue [16–18]. It is probably a consequence of a lower incidence of angina symptoms in young adults. Although the percentage of young adults reaches as much as 10% in ACS registries [8], in our study only 0.9% of patients were 40 years of age or younger. This seems to be an underestimated problem. The occurrence of atherosclerosis in this population confirms autopsy examinations [19, 20]. Enos et al. [19] published the results of a pathologic investigation of 300 young American soldiers killed during the Korean War. Atherosclerotic lesions, from the luminal narrowing to a complete occlusion in at least one coronary artery, were noted in more than 77% of cases. Arzamendi et al. [20] assessed the occurrence of CAD in the autopsies of young individuals who died a sudden death. CAD was the main cause of SCD in 37% of adults aged 21–30 years and in 80% of adults aged 31–40 years. Among individuals who died of angina, three-vessel CAD was noted in 39.7% of cases.

The early occurrence of CAD is related to a higher prevalence of some cardiovascular risk factors. Due to the paucity of studies concerning young patients with SA, we have to extrapolate our data mainly to the ACS population. The most common risk factors for young adults with ACS or MI include smoking, hypercholesterolaemia, PFH of premature CAD, and hypertension [3, 4, 6, 21, 22]. In our study, hypercholesterolaemia, smoking, and hypertension (in that order) were the most frequent risk factors. The higher incidence of hypercholesterolaemia as compared to smoking is surprising. Khawaja et al. [10] observed a marked increase of hyperlipidaemia and hypertension over the last three decades among individuals ≤ 50 years of age having PCI. Chen et al. [23] noted

Table 1. Baseline clinical and angiographic characteristics, and invasive treatment of the study groups

	≤ 40 years (n = 80)	> 40 years (n = 9299)	p
Age [years]	37 ± 3	65 ± 9	< 0.0001
Males	90.0 (72/80)	66.4 (6177/9299)	< 0.0001
Prior MI	51.4 (37/72)	42.0 (3634/8650)	0.11
Prior PCI	45.0 (36/80)	33.7 (3127/9281)	0.03
Prior CABG	5.0 (4/80)	12.6 (1166/9272)	0.04
Prior stroke	2.8 (2/72)	4.9 (428/8650)	0.40
Smoking	58.3 (42/72)	35.2 (3050/8664)	< 0.0001
Hypertension	53.3 (40/75)	77.2 (6828/8844)	< 0.0001
Diabetes mellitus	12.5 (9/72)	34.5 (3011/9729)	< 0.0001
Hypercholesterolaemia	75.7 (56/74)	71.0 (6314/8894)	0.38
Obesity	32.1 (18/56)	34.2 (2337/6824)	0.74
PFH of premature CAD	34.7 (25/72)	19.2 (1663/8647)	0.0009
Atrial fibrillation	5.6 (4/72)	18.4 (1606/8720)	0.0049
Peripheral artery disease	6.3 (5/80)	11.3 (1055/9299)	0.15
COPD	1.4 (1/72)	5.0 (431/8664)	0.16
CCS	1.61 ± 0.75	1.91 ± 0.82	0.01
Duration of disease [years]	2.21 ± 2.08	4.81 ± 6.07	< 0.0001
NYHA	1.47 ± 0.67	1.62 ± 0.81	0.07
NYHA IV	0.0 (0/72)	1.9 (164/8650)	0.24
LVEF [%]	44 ± 14	47 ± 11	0.21
LVEF ≤ 35%	28.4 (19/67)	15.6 (1206/7706)	0.0045
BMI [kg/m^2]	27 (24–31)	28 (26–31)	0.21
WBC [1000/μL]	7.7 (6.4–8.7)	7.0 (5.8–8.3)	0.05
Haemoglobin [mmol/L]	9.1 ± 0.9	8.7 ± 0.9	< 0.0001
Glucose [mmol/L]	5.5 (4.9–6.1)	5.7 (5.1–6.8)	0.53
Serum creatinine [μmol/L]	77 (69–87)	80 (67–94)	0.42
GFR [mL/min/1.73 m^2]	102 (89–116)	83 (68–98)	< 0.0001
Total cholesterol [mmol/L]	4.8 (3.9–5.8)	4.5 (3.8–5.4)	0.07
LDL cholesterol [mmol/L]	3.1 (2.3–3.9)	2.6 (1.9–3.3)	0.003
HDL cholesterol [mmol/L]	1.1 (0.8–1.4)	1.3 (1.1–1.6)	< 0.0001
Triglycerides [mmol/L]	1.7 (1.3–2.7)	1.4 (1.0–1.8)	< 0.0001
No stenosis in coronary arteries	6.3 (5/80)	5.0 (461/9271)	0.60
Non-significant CAD	31.2 (25/80)	21.9 (2037/9271)	0.04
Significant CAD	62.5 (50/80)	73.1 (6773/9271)	0.21
Single-vessel CAD	46.3 (37/80)	38.7 (3581/9271)	0.16
Multivessel CAD:	16.2 (13/80)	34.3 (3192/9271)	0.0007
2-vessel CAD	11.2 (9/80)	22.1 (2045/9271)	0.02
≥ 3-vessel CAD	5.0 (4/80)	12.4 (1147/9271)	0.04
Chronic total occlusion	26.3 (21/80)	32.1 (2986/9299)	< 0.0001
PCI:	40.0 (32/80)	44.5 (4123/9271)	0.42
Stent	84.3 (27/32)	90.0 (3749/4123)	0.25
Drug eluting stent	71.9 (23/32)	59.8 (2466/4123)	0.15
Bare metal stent	15.6 (5/32)	32.8 (1351/4123)	0.04
Drug eluting balloon	3.1 (1/32)	1.5 (62/4123)	0.45
CABG performed during or after hospitalisation	9.7 (7/80)	10.0 (842/8433)	0.94

Values presented as means ± standard deviation (SD), number and percentage or the median with interquartile range (Q1–Q3); BMI — body mass index; CABG — coronary artery bypass grafting; CAD — coronary artery disease; CCS — Canadian Cardiovascular Society; COPD — chronic obstructive pulmonary disease; CTO — chronic total occlusion; GFR — glomerular filtration rate; HDL — high-density lipoprotein; LDL — low-density lipoprotein; LVEF — left ventricular ejection fraction; MI — myocardial infarction; NYHA — New York Heart Association; PCI — percutaneous coronary intervention; PFH — positive family history; WBC — white blood cell

Table 2. In-hospital, 12-month, two-, and five-year outcomes

	≤ 40 years (n = 80)	> 40 years (n = 9299)	p
In-hospital outcomes			
Death	0.0 (0/80)	0.2 (17/9299)	0.70
Non-fatal MI	0.0 (0/80)	0.2 (18/9299)	0.70
TVR	0.0 (0/80)	0.1 (10/9299)	0.77
Major bleeding	0.0 (0/80)	0.8 (70/9299)	0.44
CIN	6.9 (5/73)	4.6 (379/8189)	0.37
After-discharge outcomes			
12-month composite endpoint:	1.3 (1/80)	8.1 (750/9299)	0.08
Death	0.0 (0/80)	4.5 (416/9299)	0.05
MI	1.3 (1/80)	2.4 (221/9299)	0.51
ACS-driven revascularisation	1.2 (1/80)	2.7 (247/9299)	0.4
Two-year composite endpoint:	5.8 (4/69)	12.9 (897/6960)	0.08
Death	0 (0/69)	7.8 (544/6960)	0.02
MI	4.3 (3/69)	3.5 (244/6960)	0.71
ACS-driven revascularisation	2.9 (2/69)	4.1 (286/6960)	0.61
Five-year composite endpoint):	23.1 (9/39)	25.7 (900/3507)	0.71
Death	5.1 (2/39)	17.1 (599/3507)	0.04
MI	7.7 (3/39)	6.9 (242/3507)	0.85
ACS-driven revascularisation	12.8 (5/39)	8.1 (283/3507)	0.28

Values presented as number and percentage of subjects; ACS — acute coronary syndrome; CIN — contrast-induced nephropathy; MI — myocardial infarction; TVR — target vessel revascularisation

Table 3. Baseline clinical, angiographic characteristics, invasive treatment, in-hospital, 12-month, two-, and five-year outcomes of the study groups after propensity score-matching

	≤ 40 years (n = 80)	> 40 years (n = 80)	p
Age [years]	37 ± 3	60 ± 8	< 0.0001
Males	90.0 (72/80)	90.0 (72/80)	0.99
Prior MI	51.4 (37/72)	57.1 (44/77)	0.51
Prior PCI	45.0 (36/80)	43.7 (35/80)	0.87
Prior CABG	5.0 (4/80)	11.2 (9/80)	0.15
Prior stroke	2.8 (2/72)	3.9 (3/77)	0.71
Smoking	58.3 (42/72)	53.2 (41/77)	0.53
Hypertension	53.3 (40/75)	60.8 (48/79)	0.42
Diabetes mellitus	12.5 (9/72)	18.2 (14/77)	0.34
Hypercholesterolaemia	75.7 (56/74)	84.8 (67/79)	0.16
Obesity	32.1 (18/56)	38.2 (26/68)	0.57
PFH of premature CAD	34.7 (25/72)	32.5 (24/77)	0.65
Atrial fibrillation	5.6 (4/72)	3.9 (3/77)	0.63
Peripheral artery disease	6.3 (5/80)	13.7 (11/80)	0.19
COPD	1.4 (1/72)	6.5 (5/77)	0.11
CCS	1.61 ± 0.75	1.64 ± 0.78	0.58
Duration of disease [years]	2.21 ± 2.08	5.47 ± 6.40	0.0072
NYHA	1.47 ± 0.67	1.54 ± 0.74	0.21
NYHA IV	0.0 (0/72)	2.6 (2/77)	0.17
LVEF [%]	44 ± 14	42 ± 13	0.22
LVEF ≤ 35%	28.4 (19/67)	32.4 (22/68)	0.61

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Table 3 (cont.). Baseline clinical, angiographic characteristics, invasive treatment, in-hospital, 12-month, two-, and five-year outcomes of the study groups after propensity score-matching

	≤ 40 years (n = 80)	> 40 years (n = 80)	p
BMI [kg/m^2]	27 (24–31)	28 (24–31)	0.68
WBC [1000/μL]	7.7 (6.4–8.7)	6.6 (5.9–7.4)	0.0003
Haemoglobin [mmol/L]	9.1 ± 0.9	9.2 ± 0.8	0.46
Glucose [mmol/L]	5.5 (4.9–6.1)	5.6 (5.0–6.9)	0.11
Serum creatinine [μmol/L]	77 (69–87)	71 (62–84)	0.019
GFR [mL/min/1.73 m^2]	102 (89–116)	104 (87–121)	0.94
Total cholesterol [mmol/L]	4.8 (3.9–5.8)	4.5 (3.9–5.4)	0.30
LDL cholesterol [mmol/L]	3.1 (2.3–3.9)	2.5 (2.1–3.4)	0.038
HDL cholesterol [mmol/L]	1.1 (0.8–1.4)	1.3 (1.1–1.6)	0.010
Triglycerides [mmol/L]	1.7 (1.3–2.7)	1.6 (1.2–2.3)	0.27
No stenosis in coronary arteries	6.3 (5/80)	3.8 (3/80)	0.47
Non-significant CAD	31.2 (25/80)	21.2 (17/80)	0.32
Significant CAD	62.5 (50/80)	75.0 (60/80)	0.088
Single-vessel CAD	46.3 (37/80)	50.0 (40/80)	0.63
Multivessel CAD:	16.2 (13/80)	25.0 (20/80)	0.17
2-vessel CAD	11.2 (9/80)	15.0 (12/80)	0.48
≥ 3-vessel CAD	5.0 (4/80)	10.0 (8/80)	0.23
Chronic total occlusion	26.3 (21/80)	27.5 (22/80)	0.86
PCI:	40.0 (32/80)	47.5 (38/80)	0.34
Stent	84.3 (27/32)	92.1 (35/38)	0.31
Drug eluting stent	71.9 (23/32)	63.2 (24/38)	0.44
Bare metal stent	15.6 (5/32)	28.9 (11/38)	0.19
Drug eluting balloon	3.1 (1/32)	0.0 (0/38)	0.27
CABG performed during or after hospitalisation	9.7 (7/80)	4.0 (3/76)	0.32
In-hospital outcomes:			
Death	0.0 (0/80)	0.0 (0/80)	–
Non-fatal MI	0.0 (0/80)	0.0 (0/80)	–
TVR	0.0 (0/80)	0.0 (0/80)	–
Major bleeding	0.0 (0/80)	0.0 (0/80)	–
CIN	6.9 (5/73)	8.0 (6/76)	0.81
After-discharge outcomes:			
12-month composite endpoint:	1.3 (1/80)	5.0 (4/80)	0.17
Death	0.0 (0/80)	3.7 (3/80)	0.080
MI	1.3 (1/80)	1.3 (1/80)	0.99
ACS-driven revascularisation	1.2 (1/80)	0.0 (0/80)	0.32
Two-year composite endpoint:	5.8 (4/69)	11.3 (7/62)	0.26
Death	0 (0/69)	8.1 (5/62)	0.016
MI	4.3 (3/69)	3.2 (2/62)	0.74
ACS-driven revascularisation	2.9 (2/69)	1.6 (1/62)	0.62
Five-year composite endpoint:	23.1 (9/39)	24.3 (9/37)	0.90
Death	5.1 (2/39)	13.5 (5/37)	0.21
MI	7.7 (3/39)	8.1 (3/37)	0.95
ACS-driven revascularisation	12.8 (5/39)	8.1 (3/37)	0.50

Values presented as means ± standard deviation (SD) or number and percentage of subjects or the median with interquartile range (Q1–Q3); ACS — acute coronary syndrome; BMI — body mass index; CABG — coronary artery bypass grafting; CAD — coronary artery disease; CIN — contrast-induced nephropathy; CCS — Canadian Cardiovascular Society; COPD — chronic obstructive pulmonary disease; CTO — chronic total occlusion; GFR — glomerular filtration rate; HDL — high-density lipoprotein; LDL — low-density lipoprotein; LVEF — left ventricular ejection fraction; MI — myocardial infarction; NYHA — New York Heart Association; PCI — percutaneous coronary intervention; PFH — positive family history; TVR — target vessel revascularisation WBC — white blood cell

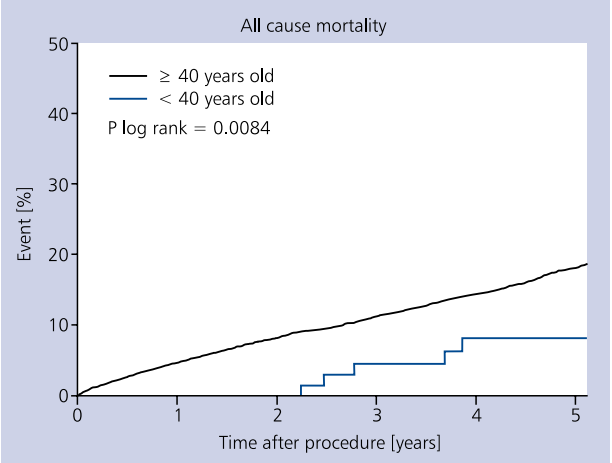

Figure 1. Kaplan-Meier analysis of the long-term survival in patients with stable angina stratified by age

significantly higher levels of total cholesterol and low-density lipoprotein cholesterol in patients with CAD under 40 years of age, as compared to those who develop the disease after the age of 60 years. This is contradictory to our study, where the incidence of hypercholesterolaemia was not significantly different in both groups.

What is noteworthy, the lipid profile was less favourable among the young patients in our study. On the other hand, the proportion of patients with hypercholesterolaemia was not significantly different in both groups, probably due to previous diagnosis and the implementation of a lipid-lowering therapy in patients > 40 years of age.

The strongest risk factor associated with CAD in young patients seems to be tobacco use [5, 24, 25]. In their investigation of patients < 45 years of age, Oliveira et al. [25] showed that patients smoking more than 25 cigarettes a day had an eightfold increased risk of MI, compared with those who had never smoked. Smoking and PFH of premature CAD were the only risk factors significantly more frequent in the younger group. Although smoking was more prevalent in the younger group (58.3%), its incidence was lower than in other studies regarding the ACS population. Tobacco use among young patients with ACS ranges from 65.9% to 94.5% [3–8, 21, 22]. It is noteworthy that only about two-thirds of our young patients had a significant atherosclerotic lesion as compared to the ACS population, where the dominant majority had a critical or total coronary artery occlusion [2–4, 6–8, 21, 22]. Similar to other studies, both hypertension and diabetes mellitus were prevalent in the older group [4, 6, 9–11]. In one study, the incidence of diabetes mellitus among young individuals increased by 100% — from 10% in 1980–1989 to 20% in 2000–2007 [10].

Similar to other studies [5, 10, 11], the majority of our individuals were men. Our study confirms the results obtained by other authors, namely that only 5–15% of young CAD

Table 4. Univariate analysis of factors influencing five-year mortality

	Hazard ratio	95% CI	p
Age (per 5 years more)	1.21	1.18–1.25	< 0.0001
Males	1.32	1.17–1.47	< 0.0001
Prior MI	1.56	1.41–1.72	< 0.0001
Prior PCI	1.02	0.92–1.13	0.73
Prior CABG	1.26	1.10–1.45	0.0011
Prior stroke	1.83	1.54–2.18	< 0.0001
Smoking	1.18	1.07–1.31	0.0010
Hypertension	0.85	0.75–0,95	0.0047
Diabetes mellitus	1.58	1.43–1.75	< 0.0001
Hypercholesterolaemia	0.73	0.65–0.81	< 0.0001
Obesity	0.86	0.77–0.97	0.011
PFH of premature CAD	0.86	0.76–0.98	0.25
Atrial fibrillation	2.03	1.82–2.27	< 0.0001
Peripheral artery disease	1.94	1.73–2.17	< 0.0001
COPD	2.52	2.17–2.92	< 0.0001
Duration of disease	1.03	1.02–1.04	< 0.0001
NYHA IV	4.81	3.86–6.00	< 0.0001
LVEF [%]	1.31	1.28–1.33	< 0.0001
LVEF ≤ 35%	3.64	3.26–4.07	< 0.0001
BMI [kg/m^2]	0.98	0.97–0.99	0.0061
WBC [1000/uL]	1.07	1.05–1.08	< 0.0001
Haemoglobin [mmol/L]	1.41	1.33–1.48	< 0.0001
Glucose [mmol/L]	1.00	0.99–1.01	0.20
Serum creatinine [μmol/L]	1.04	1.03–1.05	< 0.0001
GFR [mL/min/1.73 m^2]	1.15	1.13–1.17	< 0.0001
Total cholesterol [mmol/L]	0.88	0.84–0.92	< 0.0001
LDL cholesterol [mmol/L]	0.92	0.87–0.97	0.0023
HDL cholesterol [mmol/L]	0.65	0.60–0.76	< 0.0001
Triglycerides [mmol/L]	0.91	0.85–0.97	0.0061
No stenosis in coronary arteries	0.62	0.48–0.81	0.0005
Non-significant CAD	0.72	0.63–0.83	< 0.0001
Significant CAD	1.48	1.30–1.68	< 0.0001
Single-vessel CAD	1.06	0.96–1.18	0.22
Multivessel CAD	1.11	0.99–1.24	0.072
Chronic total occlusion	1.67	1.52–1.84	< 0.0001
PCI	0.96	0.87–1.06	0.39
CABG performed during or after hospitalisation	0.97	0.92–1.02	0.30

BMI — body mass index; CABG — coronary artery bypass grafting; CAD — coronary artery disease; CCS — Canadian Cardiovascular Society; CI — confidence interval; COPD — chronic obstructive pulmonary disease; CTO — chronic total occlusion; GFR — glomerular filtration rate; HDL — high-density lipoprotein; LDL — low-density lipoprotein; LVEF — left ventricular ejection fraction; MI — myocardial infarction; NYHA — New York Heart Association; PCI — percutaneous coronary intervention; PFH — positive family history; WBC — white blood cell

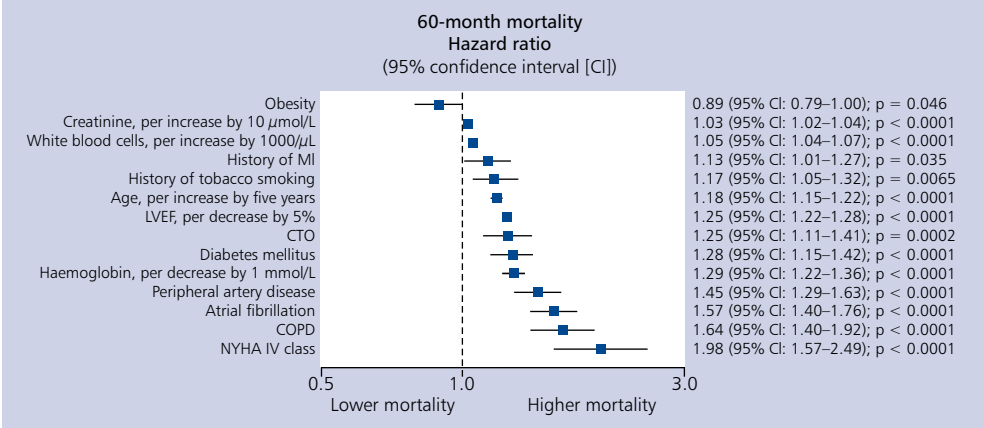

Figure 2. Independent predictors of five-year mortality; COPD — chronic obstructive pulmonary disease; CTO — chronic total occlusion; LVEF — left ventricular ejection fraction; MI — myocardial infarction; NYHA — New York Heart Association

patients are women, compared with 40–50% in older populations [5, 11, 24]. Other studies comparing younger and older patients with MI showed that young adults are discharged with a higher left ventricular ejection fraction (LVEF) and have fewer co-morbidities [4, 5]. In our analysis, in spite of a nearly 30-year difference in the median age, older patients had only a higher prevalence of atrial fibrillation and multivessel CAD. The confirmation of aggressive atherosclerosis in young patients is found in a higher percentage of previous PCI, as well as in individuals with an LVEF of 35% or less. A higher percentage of young adults with low LVEF is probably the consequence of previous MI recorded in 51.4% of cases.

Our in-hospital outcomes are in concordance with other studies reporting low mortality and complication rate among young patients with ACS [4, 7, 8] or undergoing PCI [9, 10]. We did not note any significant difference in the in-hospital outcomes or in the incidence of composite endpoint between both groups during the follow-up period. Although older patients had a higher mortality rate within two and five years after index hospitalisation, it is worth mentioning that there was nearly a 30-year difference in the median age between the two groups. A comparison of long-term prognosis remains controversial. Initial studies suggested more favourable results in young CAD patients [5]. Later studies challenged previous results and indicated that sudden death may be higher in the younger population [11]. Another analysis showed that the long-term mortality among young CAD individuals has not changed over time, despite a decreased in-hospital mortality [5, 10]. In their meta-analysis of five PCI trials, Mukherjee et al. [9] showed that patients ≤ 40 years of age — as compared to their older counterparts — had a lower mortality six months after the procedure (0.4% vs. 1.6%, p = 0.04) without any significant difference one and 12 months after PCI: 0.4% vs. 0.7%, p = 0.77; 0.8% vs. 2.3%, p = 0.77, respectively. In the Cole et al. [11] study, lower LVEF and prior MI were some of the predictors of cardiovascular mortality in patients under 40 years of age followed for the subsequent 15 years. In our study NYHA class IV, chronic obstructive pulmonary disease, atrial fibrillation, and peripheral artery disease were revealed to be the strongest independent risk factors of death in multivariate analysis in a five-year follow-up period.

Limitations of the study

There are some limitations in our analysis. The main limitation is the small number of patients aged ≤ 40 years compared with the older population. The retrospective design of the study was associated with selection bias and other consequences. One such weakness is the failure to register familial hypercholesterolaemia, autoimmune diseases, and connective tissue disorders. Our study did not involve malignancy and hypercoagulable states as factors predisposing for premature acute coronary syndrome.

CONCLUSIONS

Young patients with SA differ from their older counterparts in clinical and angiographic characteristics. In spite of that, we did not note any significant difference in the in-hospital outcomes and the composite endpoint incidence in the long-term follow-up period. Young patients had a borderline lower mortality rate one year after discharge and a significantly lower mortality rate two and five years after the index hospitalisation.

Conflict of interest: *none declared*

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