Comparison of clinical profiles and associated factors for acute myocardial infarction among young and very young patients with coronary artery disease
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Background  This study aimed to compare the profiles of young and very young patients with coronary artery disease (CAD) and explore the factors associated with acute myocardial infarction (AMI) based on age.

Methods  Young CAD patients aged between 18 and 44 years diagnosed by angiography were enrolled retrospectively. They were divided into two groups according to age: young CAD was defined as patients aged between 36 and 44 years, and very young CAD was defined as patients aged between 18 and 35 years. Demographic and clinical characteristics of the patients were collected.

Results  In total, 9286 patients were included in the final database. Most were assigned to the young CAD group (86.5%), and 1250 (13.5%) had very young CAD. Most demographic and clinical characteristics of the young and very young patients with CAD differed significantly. The proportion of patients with CAD in the total population increased with age, whereas the incidence of AMI showed a decreasing trend. A previous percutaneous coronary intervention (PCI) was negatively associated with AMI. Dyslipidemia, current smoking, and hyperhomocysteinemia were positively associated with AMI in the overall and young population with CAD.

Conclusions  The clinical profiles and factors associated with AMI in CAD patients of different ages were significantly different. Lifestyle-related factors were significantly associated with AMI in young patients with CAD.

Keywords: age group, coronary artery disease, myocardial infarction, lifestyle

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Introduction
Coronary artery disease (CAD) remains the leading cause of death worldwide [1]. It is labeled a disease of senior citizens as the average age of first heart attack is around 65.0 years for men and 71.8 years for women. However, the prevalence of traditional cardiovascular risk factors and unhealthy lifestyles has increased with economic development, particularly among the younger population [2], resulting in an increasing trend of CAD in young adults. With an estimated prevalence of 2–10% of CAD cases in this age group, CAD in young adults is a growing medical, social, psychological and economic problem [3].

Previous studies have described the demographic and risk factor profiles of young CAD patients. However, data comparing the clinical features of young patients with CAD in different age brackets are insufficient. Moreover, the associated factors of acute myocardial infarction (AMI) in these patient populations are unclear. Therefore, this study aimed to assess clinical profiles based on age and identify AMI-related factors.

Methods

Study population
Young patients aged 18–44 years with suspected CAD, admitted to Beijing Anzhen Hospital between January 2007 and December 2017, were screened retrospectively. Patients with CAD who had undergone coronary angiography were included in the final analysis. Patients were excluded from the cohort if they had valvular heart disease, systemic inflammatory diseases, known immune system or connective tissue diseases, heart transplant recipients or had a life expectancy of fewer than 3 years. The study protocol was approved by the Institutional Review Board of Beijing Anzhen Hospital (2020070X) and was conducted in accordance with the principles of the Declaration of Helsinki. The requirement for informed consent was waived because of the study’s retrospective nature, and the analysis used anonymous clinical data.
Data collection
Each patient’s demographic and clinical characteristics were collected, including age, sex, smoking status and specific comorbidities. We also identified the most recently available information for specific clinical variables, including BMI, left ventricular ejection fraction (LVEF), hemoglobin A1c (HbA1c) and homocysteine. Procedural variables and prescriptions before discharge were collected retrospectively from a review of the cardiac catheterization database and medical records.

Definitions
Patients with a history of previous myocardial infarction (MI), previous percutaneous coronary intervention (PCI), previous coronary artery bypass grafting (CABG) or angiographically documented CAD as >50% stenosis of the left main stem, >70% stenosis in a major coronary vessel were identified as having CAD. Young CAD was defined as patients aged between 36 and 44 years, and patients aged ≤35 years were termed as very young CAD. In the first part, the demographic and clinical characteristics of the young and very young patients with CAD are compared. In the second part, we established three cohorts to explore the associated factors of AMI, including overall CAD population, young CAD population and very young CAD population. For each cohort, we compared characteristics between patients with AMI or not, respectively. To avoid potential bias, subanalysis was performed by excluding patients with previous MI, PCI and CABG to explore the associated factors of first AMI. ST-elevation myocardial infarction (STEMI) was diagnosed if patients had ongoing chest pain and ST-segment elevation >2 mm in two contiguous precordial leads, >1 mm in two contiguous limb leads or a new left bundle branch block on electrocardiogram (ECG). Non-ST-elevation myocardial infarction (NSTEMI) was an elevated cardiac troponin level without notable ECG changes. Traditional risk factors include hypertension, diabetes, dyslipidemia, obesity and smoking. Hypertension, diabetes and dyslipidemia were defined according to the American College of Cardiology’s key data elements and definitions for measuring the clinical management and outcomes of patients with acute coronary syndromes (ACS). Obesity was defined as BMI ≥30 kg/m². A family history of CAD is generally defined as having a first-degree male relative (i.e. father or brother) who had a heart attack by age 55 years or a first-degree female relative (i.e. mother or sister) by age 65 years. Multivessel disease (MVD) was defined as at least 50% stenosis in two major epicardial coronary arteries.

Statistical analysis
Continuous variables are described as mean and SD or median with interquartile range (IQR). Student’s t-test or the Mann–Whitney U test was used to assess differences in continuous variables among groups. Categorical variables are expressed as absolute numbers and frequencies (%) and were compared using Pearson’s chi-square test or Fisher’s exact test. Logistic regression was used to explore the relationship between the variables and AMI. All analyses were performed using SPSS 21.0 (IBM Corp., Armonk, New York, USA). Differences obtained using a two-tailed test and \( P < 0.05 \) were deemed statistically significant.

Results
Baseline characteristics
A total of 9286 patients were enrolled in the final database, 1250 (13.5%) aged between 18 and 35 years old and 8036 (86.5%) aged between 36 and 44 years. The mean age of the overall cohort was 39.9 ± 4.0 years, with 93.9% men. The proportion of patients diagnosed with AMI accounted for 34.1%.

The demographic and clinical characteristics of the young and very young patients with CAD are compared in Table 1. Most of the variables were significantly different between the groups. Male sex characteristics were more significant in the very young CAD group. Most patients in both groups presented with ACS. It is worth noting that very young patients had higher rates of AMI (49.0 vs. 31.8%; \( P < 0.001 \)), including STEMI (37.0 vs. 24.1%; \( P < 0.001 \)) and NSTEMI (11.9 vs. 7.7%; \( P < 0.001 \)) and lower rates of unstable angina pectoris (40.5 vs. 59.4%; \( P < 0.001 \)).

We further illustrated the proportions of CAD and AMI incidence rates in different age ranges by dividing the overall cohort into nine groups. As indicated in Figs. 1 and 2, the proportion of CAD patients in the total population increased with age, whereas the incidence of AMI showed a decreasing trend. In addition, this phenomenon is particularly prominent in men.

The rates of hypertension and diabetes were significantly higher in patients of advanced age. The HbA1c levels were also significantly higher in these patients. However, cardiovascular risk factors, including dyslipidemia, current smoking and obesity, were much higher in very young patients with CAD. The homocysteine levels were also higher. These resulted the average total number of risk factors was comparable between the groups.

Regarding family history, patients aged ≥35 years were more likely to have familial CAD, and more patients have undergone a CABG procedure in this group.

Coronary angiographic characteristics
The most commonly infarcted coronary artery was the left anterior descending (LAD) artery for the overall (67.2%), very young (64.2%) and young (67.7%) CAD populations. For patients with very young CAD, left main disease was more common, and LAD, left circumflex and right coronary artery were less likely to have stenosis compared...
The prescription rate of each optimal medical therapy medication was reasonably high (48.0–90.4%) for the overall population. Aspirin prescription was comparable between the groups. However, the utility of P2Y12 inhibitors, statins, beta-blockers and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers was much higher in very young patients with CAD.

Associated factors of acute myocardial infarction

Demographic, clinical and procedural characteristics were compared between the AMI and non-AMI groups (Table 2). In addition, we explored factors associated with AMI (Table 3). Age negatively correlated with AMI in the overall population. Conversely, dyslipidemia, current smoking and hyperhomocysteinemia were positively associated with AMI in the overall and young CAD populations. Surprisingly, the previous revascularization by PCI was negatively associated with AMI in all populations.

After excluding patients with previous MI, PCI and CABG, age was negatively correlated with AMI, current smoking and hyperhomocysteinemia were positively associated with AMI in the overall population. Current smoking, hyperhomocysteinemia, dyslipidemia and HbA1c were positively associated with AMI in the young population. Current smoking is the only associated factor with AMI in the very young population (Table 4).

To young CAD. In addition, patients in the very young group were more likely to have a single-vessel disease (55.0%), and patients in the young group commonly had MVD (53.3%); the difference was significant between the groups.

With regard to revascularization strategy, 78.9% of the patients received PCI or CABG. The PCI rates were comparable between the groups. However, patients aged ≥35 years underwent more CABG procedures than very young patients did.

Medicine therapy

The prescription rate of each optimal medical therapy medication was reasonably high (48.0–90.4%) for the overall population. Aspirin prescription was comparable between the groups. However, the utility of P2Y12 inhibitors, statins, beta-blockers and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers was much higher in very young patients with CAD.
Incidence of acute myocardial infarction (AMI) in each group (Group 1, 18–20 years; Group 2, 21–23 years; Group 3, 24–26 years; Group 4, 27–29 years; Group 5, 30–32 years; Group 6, 33–35 years; Group 7, 36–38 years; Group 8, 39–41 years and Group 9, 42–44 years).

Table 2  Demographic, clinical and procedural characteristics

| Age, years | Overall (n=9288) | AMI (n=3171) | non-AMI (n=6115) | P value |
|------------|------------------|--------------|-----------------|---------|
| Male, n (%)| 39.9±4.0         | 39.1±4.6     | 39.2±4.3        | <0.001  |
| Hospital length, days | 6.4±5.4 | 6.6±5.2 | 6.3±5.6 | 0.025   |

Type of CAD

STEMI, n (%) | 2402 (25.9) | 2402 (75.7) | 0 (3.1) | <0.001 |
NSTEMI, n (%) | 769 (8.3) | 769 (24.3) | 0 (0.0) | <0.001 |
Unstable angina, n (%) | 5283 (56.9) | 0 (0.0) | 5283 (86.4) | <0.001 |
Stable angina pectoris, n (%) | 64 (0.7) | 10 (0.3) | 54 (0.9) | 0.015 |

Number of risk factor, n (%) | 2.3±1.1 | 2.4±1.0 | 2.3±1.1 | <0.001 |

Hypertension, n (%) | 4300 (46.3) | 1356 (42.8) | 2944 (48.1) | <0.001 |
Diabetes, n (%) | 1698 (18.3) | 513 (16.2) | 1185 (19.4) | <0.001 |
Dyslipidemia, n (%) | 7071 (73.0) | 2515 (81.7) | 4556 (72.6) | <0.001 |

Current smoking, n (%) | 5871 (63.2) | 2321 (73.2) | 3550 (58.1) | <0.001 |

Obesity, n (%) | 1829 (21.1) | 433 (13.5) | 1396 (22.4) | <0.001 |

Previous PCI, n (%) | 1487 (16.0) | 326 (10.3) | 1161 (19.0) | <0.001 |

Previous CAGB, n (%) | 123 (1.3) | 4 (0.1) | 119 (1.9) | <0.001 |

Family history, n (%) | 1079 (25.7) | 439 (22.8) | 640 (22.4) | <0.001 |

LVEF, % | 60.4±9.1 | 57.7±9.0 | 61.7±8.9 | <0.001 |

Hcy, μmol/L | 18.1±11.8 | 19.2±12.8 | 17.6±11.3 | <0.001 |

HbA1c, % | 6.2±1.4 | 6.3±1.5 | 6.2±1.3 | 0.004 |

Infarcted artery

LM, n (%) | 383 (4.1) | 91 (2.9) | 292 (4.8) | <0.001 |
LAD, n (%) | 6240 (67.2) | 2174 (68.6) | 4066 (66.5) | 0.044 |
LCx, n (%) | 3485 (37.5) | 1237 (40.1) | 2212 (36.2) | <0.001 |
RCA, n (%) | 3921 (42.2) | 1488 (46.3) | 2433 (40.1) | <0.001 |

MVD, n (%) | 4849 (52.2) | 1710 (53.9) | 3139 (51.3) | 0.018 |
PCI, n (%) | 6222 (67.0) | 2497 (78.7) | 3725 (60.9) | <0.001 |
CABG, n (%) | 1113 (12.0) | 187 (5.9) | 926 (15.1) | <0.001 |
Revascularization, n (%) | 7327 (78.9) | 2680 (87.4) | 4647 (76.0) | <0.001 |

Prescription before discharge

Aspirin, n (%) | 8398 (90.4) | 2884 (90.0) | 5514 (90.2) | 0.227 |
P2Y12 inhibitor, n (%) | 7588 (81.7) | 2781 (87.7) | 4807 (78.6) | <0.001 |
Statin, n (%) | 7899 (85.1) | 2721 (85.8) | 5178 (84.7) | 0.147 |
Beta-blocker, n (%) | 6833 (73.6) | 2469 (77.9) | 4364 (71.4) | <0.001 |
ACEI/ARB, n (%) | 4458 (48.0) | 1910 (60.2) | 2548 (41.7) | <0.001 |

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CABG, coronary artery bypass grafting; CAD, coronary artery disease; HbA1c, hemoglobin A1c; Hcy, homocysteine; LAD, left anterior descending; LCx, left circumflex; LM, left main; LVEF, left ventricular ejection fraction; MVD, multivessel disease; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; RCA, right coronary artery; STEMI, ST-elevation myocardial infarction.

Despite significant progress in primary and secondary prevention, the AMI rate continues to increase in young adults. We found that patients who received prior PCI were less likely to have AMI when they had coronary disease. First ACS and recurrent ACS without prior PCI were more likely to present with AMI. The benefits of PCI in patients with STEMI are clear. In unstable scenarios, including unvascularized post-AMI, MVD following STEMI and non-ST-elevation ACS, PCI was associated with a significant reduction in MI, cardiac death and mortality [4]. A revascularization procedure was the only protective factor at both 1- and 3-year time points [5]. We confirmed these advantages over AMI in young and very young patients with CAD.

A previous study showed that dyslipidemia, smoking and overweight/obesity in young patients with CAD were the most important risk factors [3]. According to our study, in young patients with CAD, risk factors, including dyslipidemia, smoking and hyperhomocysteinemia, were significantly associated with AMI. However, the factors associated with very young patients were unclear.

In 2008, the US Preventive Services Task Force (USPSTF) strongly recommended lipid screening in all men aged ≥35 years and in women aged ≥45 years at increased risk for coronary heart disease (CHD) (A recommendation) based on evidence that lipid-lowering drug therapy decreases the incidence of CHD events in persons with abnormal lipid levels, resulting in substantial absolute benefits. We demonstrated the association of dyslipidemia with young patients, especially those aged between 35 and 45 years.

Smoking is another independent risk factor for AMI in young patients. Tobacco product use is primarily established during adolescence. Nearly nine out of 10 adults who smoke cigarettes daily first try smoking by age 18 years, and 99% first try smoking by age 26 years in the USA [6]. The number of smokers in China exceeds 300 million, and the smoking rate of people aged 15 years and
over is 26.6%, of which the smoking rate of men is as high as 50.5%.

Smoking can accelerate atherosclerosis progression. A combination of endothelial dysfunction increased myocardial oxygen demand, and increased risk of thrombosis are believed to contribute to this pathophysiology [7,8]. Current smokers experienced their first AMI more than a decade earlier than nonsmokers, and younger smokers had a higher mortality rate [9]. Moreover, the greater the amount of smoking and the longer the duration, the higher the risk of cardiovascular events. In the Partners YOUNG-MI registry, approximately half of the individuals who experienced MI at age 50 years or younger were active smokers [10]. In our study, 73.2% of the AMI patients were current smokers. Most smokers who received antismoking advice during their hospitalization for AMI quit smoking in the year following the acute event. Smoking cessation before and after AMI is associated with improved survival. Smoking cessation within 1 year after MI was associated with more than 50% lower all-cause and cardiovascular mortality. Among persistent smokers, reducing intensity after AMI appears to be beneficial [11].

Hyperhomocysteinemia is an independent risk factor for atherosclerotic disease in the young, middle-aged and elderly populations [12]. High levels of homocysteine are not only associated with the severity of vascular disease but are also associated with an increased risk of sudden events, such as MI and stroke [13,14]. A recent study that included 1103 young participants (18–35 years of age) demonstrated that hyperhomocysteinemia was an independent predictor of ACS after adjusting for traditional confounders [15]. Moreover, young ACS patients with hyperhomocysteinemia had an increased prevalence of STEMI, MVD, decreased LVEF and higher Gensini Scores in ACS patients. Previous prospective studies have observed weaker associations with increasing age. In this study, we demonstrated that hyperhomocysteinemia is strongly associated with AMI in young patients with CAD.

Other risk factors, such as sleep loss, which is prominent in the young population, should be assessed in the future. Sleep loss is a common condition in modern society, with evidence showing that people sleep on average only 6.8 h per night, 1.5 h less than a century ago. Sleep deprivation has been associated with hypertension, CHD and diabetes by increasing sympathetic nervous system activity [16].

In addition, psychiatric conditions, including anxiety and depression, have been linked to an increased risk of CAD. Physiologic (autonomic dysfunction, inflammation, endothelial dysfunction and changes in platelet aggregation) and health behavior (less healthy diet, low physical activity, reduced treatment adherence and smoking) mechanisms may help explain the relationships between anxiety disorders and cardiovascular disease [17].

### Table 3 Independent risk factors of acute myocardial infarction in young patients

| Variables      | Overall | Very young CAD | Young CAD |
|----------------|---------|----------------|-----------|
|                | HR      | 95% CI         | P value   | HR      | 95% CI         | P value   | HR      | 95% CI         | P value   |
| Agea           | 0.887   | 0.811–0.970    | 0.009     | 1.786   | 1.272–2.537    | 0.001     | 1.539   | 1.181–2.006    | 0.001     |
| Dyslipidemia   | 1.652   | 1.202–2.270    | 0.002     | 1.539   | 1.181–2.006    | 0.001     |        |                |           |
| Current smoking| 1.533   | 1.199–1.960    | 0.001     | 0.265   | 0.120–0.582    | 0.001     | 0.453   | 0.335–0.611    | <0.001    |
| Previous PCI   | 0.419   | 0.316–0.555    | <0.001    | 0.419   | 0.316–0.555    | <0.001    |        |                |           |
| HHCYb          | 1.287   | 1.020–1.624    | 0.034     | 1.287   | 1.020–1.624    | 0.034     | 1.298   | 1.010–1.667    | 0.042     |

Data were analyzed by use of a Logistic regression model.
CAD, coronary artery disease; CI, confidence interval; HHCY, hyperhomocysteinemia; HR, hazard ratio; PCI, percutaneous coronary intervention.

| Variables      | Overall | Very young CAD | Young CAD |
|----------------|---------|----------------|-----------|
|                | HR      | 95% CI         | P value   | HR      | 95% CI         | P value   | HR      | 95% CI         | P value   |
| Agea           | 0.820   | 0.734–0.916    | <0.001    | 1.501   | 1.089–2.068    | 0.013     |        |                |           |
| Current smoking| 1.574   | 1.170–2.119    | 0.003     | 1.442   | 1.067–1.947    | 0.017     | 1.563   | 1.028–2.376    | 0.037     |
| HHCYb          | 1.359   | 1.029–1.769    | 0.031     | 1.520   | 1.023–2.568    | 0.048     |        |                |           |

Data were analyzed by use of a Logistic regression model.
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Data were analyzed by use of a Logistic regression model.
CAD, coronary artery disease; CI, confidence interval; HbA1c, hemoglobin A1c; HHCY, hyperhomocysteinemia; HR, hazard ratio; PCI, percutaneous coronary intervention.

aAge was divided into 9 intervals.
bHHCY for ≥15 μmol/L.
Fortunately, most factors associated with AMI can be corrected by lifestyle changes. For example, avoiding tobacco use, eating a healthy diet, exercising regularly and managing blood cholesterol would postpone the development of severe heart disease.

Limitations
First, the retrospective nature of the study may have resulted in bias. Second, the follow-up information was not available. Therefore, further large-scale studies are needed to confirm our findings.

Conclusion
The clinical profiles and factors associated with AMI in CAD patients from different age groups differ. Lifestyle-related factors were significantly associated with AMI in young patients with CAD.

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Conflicts of interest
There are no conflicts of interest.

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