The atherosclerotic process starts in adolescence, but several decades are necessary for the development of plaques responsible for the onset of symptomatic coronary artery disease. Conventional risk factors such as hypertension, diabetes, hypercholesterolemia and smoking directly influence the dynamics and properties of atherosclerotic lesions. Hypertension, diabetes and hypercholesterolemia are more common in older patients, in women and patients with anterior acute myocardial infarction (AMI), while smoking is more frequent in younger patients, men and patients with inferior AMI. Furthermore, it has been suggested that Q-wave AMI is more frequent in men, and non-Q-wave AMI is more frequent in women. That suggests the possibility that the importance of pathophysiological mechanisms involved in onset of AMI differs according to age, gender, and risk profiles. However, diversity in triggering of cardiovascular events between such subgroups has been observed, in particular between men and women.

To investigate relationship between age, gender, risk profile and type and site of AMI we simultaneously analyzed the type and site of AMI categorizing AMI patients into four distinct subgroups: anterior Q-wave, anterior non-Q-wave, inferior Q-wave, inferior non-Q-wave AMI.

**BACKGROUND:** The importance of pathophysiological mechanisms involved in onset of acute myocardial infarction (AMI) differs with age, gender, and risk profiles. Diversity in the triggering of cardiovascular events has been observed, particularly between men and women. Therefore, we investigated the relationship between age, gender, and risk factors and location of AMI and the presence of Q waves in ECG.

**PATIENTS AND METHODS:** Data was obtained from a chart review of 2958 patients with first AMI: 770 (26%) patients with non-Q-wave AMI and 2188 (74%) patients with Q-wave AMI. Four clinical groups were formed by predetermined criteria (anterior Q-wave, anterior non-Q-wave, inferior Q-wave, inferior non-Q-wave). A logistic regression was performed to assess independent predictors of AMI type and site.

**RESULTS:** Key findings were: 1) inferior non-Q-wave AMI was more frequent in young women ($P<0.001$); 2) inferior Q-wave AMI was more common in young men ($P<0.001$); 3) anterior non-Q-wave AMI was more common in older men ($P<0.001$). Multivariate analysis revealed that independent predictors of anterior non-Q-wave AMI were age over 65 ($P=0.002$), male gender ($P=0.04$) and hypercholesterolemia ($P=0.0003$), and that predictors of inferior Q-wave AMI were male gender ($P=0.001$), smoking ($P=0.04$) and diabetes ($P=0.049$). In the gender-subgroup analyses, age <45 years ($P=0.02$), hypercholesterolemia ($P=0.02$) and smoking ($P=0.01$) were independent predictors of inferior Q-wave AMI whereas age >65 years ($P=0.0001$) and smoking ($P=0.0003$) were predictors of anterior non-Q-wave AMI in men. In women, age <45 years ($P=0.0001$) and smoking ($P=0.02$) were independent predictors of non-Q-wave AMI and hypercholesterolemia ($P=0.02$) was a predictor of inferior Q-wave AMI.

**CONCLUSION:** The link between particular types and the site of AMI and age, gender and risk factors suggest that the importance of pathophysiological mechanisms for onset of AMI differs according to sex and age subgroup.
Patients and Methods
We studied 3382 consecutive patients admitted for AMI to coronary care units at University Hospital Split in the period from January 1990 until December 1999. For inclusion, patients were required to meet the following criteria: 1) typical chest pain last more than 30 minutes; 2) characteristic ECG changes demonstrating significant evolution such as new pathologic Q-waves or 1 mm ST-segment elevation in two or more contiguous limb leads or new persistent ST-T wave changes diagnostic of a non-Q-wave AMI; 3) creatine kinase (CK) and/or its isoenzyme CK-MB level more than two times the upper limit of normal. Four hundred twenty-four patients were excluded from further analysis because of previous infarction, electrocardiographic uncategorized infarction (left bundle branch block, right ventricular stimulation, complete heart block with wide QRS, preexcitation) or missing data.

Trained research assistants abstracted the information from the medical record of hospitalization and entered data into an electronic database. The data included demographic variables, prior cardiac history, and clinical course during hospitalization, laboratory data and ECG. The clinical variables analyzed were age, gender, hypertension, hypercholesterolemia, diabetes, cigarette smoking, type (Q-wave, non-Q-wave) and site (anterior, inferior) of AMI, and peak CK level.

AMI was classified as Q-wave or non-Q-wave (based on review of all hospital ECG) if ST-segment and T-wave abnormalities were observed with or without progression to pathologic Q-waves. With regard to ECG location, all AMI were classified as anterior (septal, anterolateral, high lateral, extensive location-alteration in one or more of the following lead groups: V1-V3; V4-V6; D1 and AVL) or inferior (inferior, inferolateral, inferoanterior, lateral, lateral, inferolateromesial location-alteration in one or more of the following lead groups: D2, D3, AVF; D1, AVL; V5 and V6; V7 and V8).

The presence of risk factors (hypertension, hypercholesterolemia, diabetes, smoking) in three age subgroups (<45, 45-64, >65 years) were analyzed according to type and site of AMI (anterior Q-wave, anterior non-Q-wave, inferior Q-wave, inferior non-Q-wave). Continuous variables were presented as mean±standard deviation, and dichotomous variables as percentage of presence in a particular subgroup. Group differences in continuous variables were compared by two tailed t-test and Mann-Whitney U test. Dichotomous variables were compared by the Chi-square test with Yates’ continuity correction. The unconditional logistic regression was used to assess which variables were independent predictors of type of AMI within AMI site. Since in both AMI site multivariate models gender was an independent predictor, we further performed the same multivariate models separately for men and women. Three age subgroups were included in the models as dummy variables. These results were expressed as odds ratio (OR) estimates, 95% confidence interval (CI) and P value. The level of statistical significance was defined as P<0.05. All statistical analyses were performed by using the SPSS statistical software package (version 8.0, SPSS Inc, Chicago, USA).

Results
A total of 2958 patients were enrolled in the study: 770 (26%) patients with non-Q-wave AMI and 2188 (74%) patients with Q-wave AMI. Baseline clinical data are presented in Table 1. Patients with Q-wave AMI were younger, more likely to have hypercholesterolemia, and more likely to be smokers than patients with non-Q-wave AMI. Systolic blood pressure at admission were significantly lower in patients with Q-wave AMI, while mean peak CK level and mortality were higher in patients with Q-wave AMI.

Significantly higher number of inferior non-Q-wave AMI was found in women under 45 than in women over 45 (Table 2). Inferior Q-wave AMI was significantly more frequent in men under 45 than in women over 45 (Table 2).

Table 1. Baseline clinical characteristics of the study population by type of acute myocardial infarction (AMI).

|                        | Non-Q-AMI | Q-wave AMI | P   |
|------------------------|-----------|------------|-----|
| Patients in cohort     | 770 (26)  | 2188 (74)  |     |
| Age (y ±SD)            | 67.8±11.1 | 64.8±12.1  | <0.001 |
| Hypertension           | 315 (41)  | 968 (44)   | 0.12  |
| Hypercholesterolemia   | 149 (19)  | 750 (34)   | <0.001 |
| Smoking                | 185 (24)  | 656 (30)   | 0.002  |
| Systolic BP (mmHg)     | 145.4±25.4| 141.0±25.5 | <0.001 |
| Diastolic BP (mmHg)    | 85.2±14.9 | 84.6±11.8  | 0.31  |
| Mean peak CK level (IU)| 608.1±659.2| 1015.5±888.2| <0.001 |
| Mortality              | 107 (14)  | 410 (19)   | 0.003  |

Number (%) of patients
men over 45, while anterior non-Q-wave AMI was significantly more frequent in men over 65 than in men under 65.

In the univariate analysis, patients with anterior non-Q-wave AMI were more likely to be male, diabetic and over 65 years of age. Those with inferior Q-wave AMI were more likely to be hypercholesterolemic, smokers and those with inferior non-Q-wave more likely to be diabetic. In multivariate analysis, age over 65 and male gender, in addition to hypercholesterolemia, remained independent predictors of anterior non-Q-wave AMI. Male gender, smoking and diabetes were independently associated with inferior Q-wave AMI (Table 3). In further gender-subgroup analyses, age <45 years, hypercholesterolemia and smoking were independent predictors of inferior Q-wave AMI whereas age >65 years and smoking were predictors of anterior non-Q-wave AMI in men. In women, age <45 years and smoking were independent predictors of non-Q-wave AMI and hypercholesterolemia was a predictor of inferior Q-wave AMI. (Table 4)

Table 2. Type and site of acute myocardial infarction by age groups.

|                | Non-Q-wave AMI | Q-wave AMI |
|----------------|---------------|------------|
|                | Anterior      | Inferior   |                | Anterior      | Inferior   |
|                | 442 (57)      | 328 (43)   | P             | 1043 (48)     | 1145 (52)  | P             |
| <45 y Men      | 6 (46)        | 7 (54)     | 0.59          | 26 (25)       | 76 (75)†   | <0.0001       |
| Women          | 0 (0)         | 9 (100)*   | 0.002         | 7 (64)        | 4 (36)     | 0.45          |
| 45-64 y Men    | 105 (57)      | 78 (43)    | 0.34          | 326 (47)      | 363 (53)   | 0.86          |
| Women          | 32 (52)       | 29 (48)    | 0.49          | 96 (50)       | 97 (50)    | 0.60          |
| >65 y Men      | 173 (67)‡     | 86 (33)    | 0.0002        | 345 (50)      | 349 (50)   | 0.21          |
| Women          | 126 (51)      | 119 (49)   | 0.03          | 243 (49)      | 256 (51)   | 0.64          |

Number (% of patients)
*P<0.001 inferior non-Q-wave in women <45 y vs. >45 y; †P< 0.001 inferior Q-wave AMI in men <45 y vs. >45 y; ‡P< 0.01 anterior non-Q-wave in men >65 y vs. <65 y

Table 3. Predictors of AMI type according to AMI site.

|                | Univariate analysis | Multivariate analysis |
|----------------|---------------------|-----------------------|
|                | OR ( 95% CI )       | P                     | OR ( 95% CI )       | P                     |
| Anterior (non-Q-wave vs. Q-wave) |                     |                       |                       |                       |
| Male gender    | 0.43 (0.33-0.56)    | <0.0001               | 0.74 (0.73-1.21)     | 0.04                  |
| Hypertension   | 0.90 (0.73-1.12)    | 0.35                  | 0.86 (0.65-1.14)     | 0.30                  |
| Hypercholesterolemia | 1.18 (0.93-1.49) | 0.18                  | 0.53 (0.37-0.75)     | 0.0003                |
| Smoking        | 1.24 (0.96-1.60)    | 0.11                  | 0.73 (0.52-1.04)     | 0.08                  |
| Diabetes       | 0.73 (0.57-0.93)    | 0.01                  | 0.23 (0.19-0.69)     | 0.19                  |
| Age >65 y      | 0.50 (0.40-0.63)    | <0.0001               | 0.60 (0.44-0.82)     | 0.002                 |
| Inferior (non-Q-wave vs. Q-wave) |                     |                       |                       |                       |
| Male gender    | 0.99 (0.79-1.24)    | 0.91                  | 2.51 (1.87-3.37)     | <0.0001               |
| Hypertension   | 0.96 (0.74-1.26)    | 0.79                  | 0.98 (0.78-1.23)     | 0.84                  |
| Hypercholesterolemia | 2.03 (1.46-2.81) | <0.0001               | 0.86 (0.66-1.12)     | 0.27                  |
| Smoking        | 1.45 (1.08-1.94)    | 0.01                  | 1.28 (1.03-1.77)     | 0.04                  |
| Diabetes       | 0.72 (0.53-0.97)    | 0.03                  | 1.30 (1.01-1.69)     | 0.049                 |
| Age >65 y      | 1.00 (0.77-1.30)    | 0.99                  | 0.82 (0.62-1.09)     | 0.18                  |
Discussion
This study investigated the relationship between age, risk factors and type and site of AMI in men and women by simultaneously analyzing the location of AMI and presence or absence of Q waves. To our knowledge, this is the first study categorizing AMI patients into four distinct subgroups (anterior Q-wave, anterior non-Q-wave, inferior Q-wave, inferior non-Q-wave) according to location of AMI and presence or absence of Q waves. Observations that inferior Q-wave AMI was more frequent in men under 45, while inferior non-Q-wave AMI was more frequent in younger women, as well as that anterior non-Q-wave AMI was more frequent in men over 65 and had a different distribution of coronary risk factors, suggest that the importance of pathophysiological mechanisms involved in onset of AMI differ in particular sex and age subgroups.

AMI is the consequence of an interruption of coronary flow caused by interaction of an atherothrombotic occlusion, vasospasm and spontaneous fibrinolytic activity of the plasma. Atherothrombotic occlusion is the most common mechanism in the onset of AMI. In patients with normal or minimally stenotic arteries AMI is often accompanied by coronary spasm. Even minimal atherosclerotic changes, commonly found in younger patients, may be associated with endothelial dysfunction and an exaggerated response to spastic stimuli. It has been already noted that inferior AMI was more often subject to circadian rhythm and was more frequently preceded by smoking, mental and meteorological stress, while anterior AMI was more likely to occur at rest or during increased physical exertion. A hypothesis was set that the spasm of the right coronary artery participated more significantly in the onset of inferior AMI, while atherothrombotic process of the left anterior descending (LAD) coronary artery played a more significant role in the onset of anterior AMI. It is now accepted that Q-wave AMI is associated with sustained coronary occlusion and that non-Q-wave AMI often results from a nonsustained occlusion. Accordingly, we reported that Q-wave AMI follows typical circadian variation in incidence and is more likely to be associated with possible external triggers while non-Q-wave AMI may be more often precipitated by mental stress. In earlier investigations, including our previous reports, the site of AMI was analyzed regardless of type of infarction. A higher rate of inferior AMI was noticed only in men under 45, and that was explained by the spastic reaction of the right coronary artery to smoking. In the present study, a higher rate of inferior AMI has been noticed in patients under 45, in non-Q-wave AMI in women, and in Q-wave AMI in men.

The effect of estrogen on relaxation of the smooth muscles of the arterial wall and fibrinolytic activity

| Table 4. Independent predictors of AMI type according to AMI site in men and women. |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
|                                | Women           | P               | Men             | P               |
|                                | OR (95% CI)     |                 | OR (95% CI)     |                 |
| Anterior (non-Q-wave vs. Q-wave)|                 |                 |                 |
| Hypertension                   | 1.05 (0.79-1.38) | 0.76            | 0.94 (0.64-1.39) | 0.78            |
| Hypercholesterolemia           | 1.26 (0.88-1.79) | 0.21            | 0.90 (0.59-1.37) | 0.41            |
| Smoking                        | 1.22 (0.87-1.70) | 0.24            | 0.38 (0.20-0.71) | 0.0003          |
| Diabetes                       | 0.76 (0.54-1.07) | 0.11            | 0.78 (0.51-1.18) | 0.26            |
| Age >65 y                      | 1.01 (0.87-1.27) | 0.34            | 0.81 (0.68-0.98) | <0.0001         |
| Inferior (non-Q-wave vs. Q-wave)|                 |                 |                 |
| Hypertension                   | 1.14 (0.77-1.69) | 0.51            | 1.25 (0.82-1.90) | 0.30            |
| Hypercholesterolemia           | 1.81 (1.12-2.93) | 0.02            | 1.90 (1.13-3.18) | 0.02            |
| Smoking                        | 0.58 (0.37-0.90) | 0.02            | 2.68 (1.23-5.81) | 0.01            |
| Diabetes                       | 1.01 (0.67-1.53) | 0.96            | 1.18 (0.75-1.84) | 0.48            |
| Age <45 y                      | 0.88 (0.80-0.99) | <0.0001         | 1.12 (1.01-1.31) | 0.04            |
of plasma might represent the possible mechanism of partial occlusion or rapid spontaneous recanalization of the coronary artery with restoration of flow in younger women. It can be hypothesized that in men the androgen effect is not sufficient for the protection of coronary spasm, whose duration and intensity are sufficient for the onset of inferior Q-wave AMI. Furthermore, physiologic levels of testosterone impair relaxation and augment the endothelial dysfunction associated with environmental tobacco smoke and hypercholesterolemia. However, in younger age groups smoking was significantly more often present as a risk factor, which suggests that in both sexes coronary spasm could be the crucial mechanism in the onset of AMI in younger age.

Corresponding to our results, earlier studies have shown that women who undergo their first AMI are on average eight years older than men, have a higher rate of hypertension, diabetes and hyperlipidemia but are significantly less frequently smokers. A decrease in prevalence of smoking and increase in the prevalence of hypertension and diabetes with age in both sexes suggest the greater importance of the atherothrombotic process, which may be more pronounced in the LAD artery, and explains the higher frequency of anterior AMI in elderly patients.

Invasive studies have not confirmed sex differences in the distribution and severity of coronary lesions, which in both sexes are most frequently in the LAD, then in the right coronary artery, and most rarely in the circumflex artery. However, the postmenopausal increase in the prevalence of the most common risk factors and AMI in women, suggests a sex difference in the dynamics of the atherosclerotic process and a possible difference in plaque stability. The process of atherogenesis, intensified in women after the loss of estrogen-mediated protection, results in a faster growth of plaques, which might be softer and more likely to rupture. A slower and more gradual atherosclerotic process, as can be supposed in men, is characterized by a strengthening of plaque’s protective fibrous cap, stabilizing the plaque, reducing the possibility of rupture. Liu et al. have showed that the atherosclerotic process in women accelerates during interpause, a period that begins approximately two years before and lasts five years after the last menstrual cycle. A sudden reduction of estrogen level, with equal or even increased testosterone production results in relative hyperandrogenism, considered to be the key element in progression of atherosclerosis in women. This suggests that, before the menopause, women are protected from the development of atherosclerosis, its progression being delayed or modified so that acute and complete coronary occlusion is less likely. In men, the level of androgens gradually decreases from the 35 years of age, with a proportional increase in risk of coronary disease.

Investigating influence of age and gender on the presence of coronary calcium by ultrafast computed tomography, Devries et al. found that for the same degree of luminal narrowing of coronary arteries the plaques contained less calcium in women, pointing indirectly to a longer preclinical phase of atherosclerotic disease in men. Corroborating our results, Burke et al. describe that out of all women who die of coronary artery thrombosis, the younger ones are often smokers with plaque erosions with relatively little coronary narrowing, whereas older women are often hypercholesterolemic and have plaque ruptures with relatively severe coronary narrowing. A protracted course of subclinical coronary disease accompanied by repeated periods of ischemia stimulates the development of a collateral circulation. It is therefore plausible to presume that collateral circulation is better developed in elderly men, and the most severe atherosclerotic lesions of the LAD artery and supply of the endangered area by collateral flow can explain the higher incidence of anterior non-Q-wave AMI in men over 65.

A limitation of our study is the lack angiographic data providing information on the level of stenosis related to AMI and development of collateral circulation. Furthermore, information on the properties of the atherosclerotic lesion responsible for the AMI might link some lesion types to Q-wave and others to non-Q-wave AMI. Finally, the significant influence of some uncontrolled risk factors (e.g. hyperhomocysteinemia, sedentary lifestyle, hormone replacement and other medication therapy) cannot be excluded. In conclusion, our results suggest that different types and sites of AMI, in particular sex and age subgroups, could reflect differences in the dynamics of atherogenesis and the importance of the pathophysiological processes that are involved in AMI development.
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