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ACUTE CORONARY SYNDROMES IN THE YOUNG
THE ISACS-TC EXPERIENCE

Presentata da:
Dott.ssa Beatrice Ricci

Coordinatore Dottorato:
Chiar.ma Prof.ssa Annalisa Patrizi

Relatore:
Chiar.mo Prof. Raffaele Bugiardini

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ABBREVIATIONS LIST

ACS: Acute coronary syndrome

ACE: Angiotensin-converting-enzyme

BMI: Body mass index

CVD: Cardiovascular disease

CHD: Coronary heart disease

CI: Confidence intervals

CABG: Coronary artery bypass grafting

CAD: Coronary artery disease

ISACS-TC: International Survey of Acute Coronary Syndromes in Transitional Countries

MI: Myocardial infarction

NSTE-ACS: Non ST-segment elevation acute coronary syndrome

OR: Odd ratios

PCI: Percutaneous coronary intervention

SD: Standard deviation

STEMI: ST-segment elevation myocardial infarction

TIMI: Thrombolysis In Myocardial Infarction

UFH: Unfractioned heparin

SUMMARY

Background: Although coronary heart disease (CHD) mainly occurs in patients over the age of 50, younger patients can be affected as well. Most studies have used an age cut-off of 45 years to define "young" patients with CHD or acute coronary syndrome (ACS). We used this definition to investigate clinical characteristics and outcomes of ACS young patients in a large international cohort.

Methods: Between October 2010 and April 2016, 14, 931 ACS patients were enrolled in the ISACS-TC registry (ClinicalTrials.gov NCT01218776). Of these patients, 1,182 (8%) were aged ≤ 45 years old **(**mean age 40.3 years, 15.8% female). The primary end-point was ST segment elevation myocardial infarction (STEMI) as index event and 30-day all-cause mortality. Percent diameter stenosis of 50% or less was defined as insignificant coronary disease.

Results: STEMI is the most common clinical manifestation of ACS in the younger cases (68% versus 59.6%). Younger patients had a higher incidence of insignificant coronary artery disease (7.6% versus 5.4%) and single vessel disease (66.9% versus

52.5%). Conversely, three-vessel disease was less common (7.7% versus 16.3%) in the younger patients . Smoking was the most important risk factor in this population (61.2% versus 33.7%). Predictors of ACS in the young population included male sex (OR: 2.21; 95% CI 1.86-2.62), smoking habit (OR: 1.10; 95% CI 1.06-1.16), and higher Body Mass Index (OR: 1.04; 95% CI 1.01-1.06). Thirty-day unadjusted survival rates were 98.7% versus 93.1% for young and older patients respectively. After adjusting for baseline characteristics, medications at admission and reperfusion therapy, age ≤ 45 years old was a predictor of survival in men (OR 0.25, 95% CI 0.10-0.64) , but not in women (OR 1.51, 95% CI 0.55-4.18). Moreover, younger women had worse outcomes than men of a similar age (OR 6.84, 95% CI 2.23-20.97).

Conclusion: ACS at a young age is characterized by less severe coronary disease and worse clinical presentation. Women have higher mortality than men. Factors underlying ACS in young patients and higher mortality rates in female sex warrant further investigation

CHAPTER 1

INTRODUCTION

1.1BACKGROUND

Although coronary heart disease (CHD) mainly occurs in patients over the age of 45, younger patients can be affected as well. Nowadays our knowledge about acute coronary syndrome (ACS) derives from studies in older cohort of patients. Most studies on patients with chest pain have excluded individuals under 40 years of age [1-3]. Comparatively few studies have focused on the clinical presentation, treatment and outcome of ACS in young patients [4-9].

Coronary artery disease in young age represents an issue of increasing clinical interest considering the years of potential life lost, long-term disability [1,6,10-12], significant morbidity, psychological effects, and financial constraints for the family of those people [13]. The actual incidence of the ACS in young depends upon the cut-off age used in the investigations. It was found to range from 0.4% to19% [14-18]. The

prevalence of the disease was found to be greater in men than women. Women represents approximately from 5% to 25% of all myocardial infarction in young patients [9,14,19-23].

The causes for ACS among patients aged less than 45 are still largely unknown. Among young patients with reported atherosclerosis, cigarette smoking was found to be common in up to 92%. As well, obesity and lack of physical activity were found to be more common in patients who had their ACS aged less than 45 years [13,14,24]. Much more importantly, it is unknown whether having an ACS at a younger age carries a worse prognosis, or requires a different management from that commonly used in the older patients. [5] [25-32].

1.2 AIM OF THE STUDY

The purpose of this study was to investigate the clinical presentation and outcome of patients aged 45 years or younger hospitalized for ACS in a large international cohort. In order to analyse specific differences, findings of young patients were compared with those of the older population (aged 45 years or more)

1.3 WHY 45 YEARS OR YOUNGER?

The comparison among studies about young ACS patients is difficult because of the lack of uniformity concerning the definition for "youth". In addition there are a limited number of articles published on the topic. The range between 35 to 55 years was used by several studies to identify a population of ACS patients relatively young as compared with the old cohorts that usually are affected by it. The majority of these

studies used the age cut-off at 45 years [9, 17, 23]. The same age will be used in the current study. The main reason supporting this choice is excluding the influence of hormonal disorders on the course of coronary artery disease during menopause in women [22]. Early menopause is associated with an increased risk for CHD[33], [34].

CHAPTER 2

MATERIAL AND METHODS

2.1 SETTING AND DESIGN

The International Survey of Acute Coronary Syndromes in Transitional Countries (ISACS-TC [ClinicalTrials.gov NCT01218776]) is a large observational and multinational registry [35-39]. ISACS-TC is both a retrospective and prospective study, aiming to collect data of patients with ACS, and herewith control and optimize internationally guideline recommended therapies in countries with economy in transition. Data were collected from 41 centres in 12 countries in Europe(including Bosnia and Herzegovina, Croatia, Italy, Kosovo, Lithuania, Macedonia, Hungary, Moldova, Montenegro, Romania, Russian Federation, Serbia). Among these, there were 22 tertiary healthcare services providing advanced medical investigation and treatment including PCI and/or cardiac surgery, and 19 secondary healthcare services providing intensive care in critical coronary care units.

Patients enrolled in the ISACS-TC were eligible for inclusion if they met the following criteria: age ≥ 18 years, symptoms consistent with acute cardiac ischemia, documented evidence of new or presumed new significant ST-segment-T wave (ST–T) changes or new left bundle branch block on serial electrocardiograms and/or elevated biomarkers of myocardial necrosis according to universal standardized criteria [40]. Approximately 200 baseline variables were collected for each patient. The data coordinating centre has been established at the University of Bologna. The study was approved by the local research ethics committee from each hospital.

2.2 STUDY POPULATION

The study population consisted of 14,931 eligible patients with ACS enrolled between October 2010 and April 2016. Appropriateness of inclusion was adjudicated by a specialist cardiology considering clinical history, physical exam, ECG, cardiac biomarkers, angiography, and/or postmortem findings [40]. Patients included in the analysis were categorized into two groups: younger patients, aged ≤ 45 years old, and older patients, aged > 45 years old. They were followed-up for30 days.

2.3 ENDPOINTS AND MEASUREMENTS

The primary end-point was ST segment elevation myocardial infarction (STEMI) as index event and 30-day all-cause mortality. We also evaluated length of hospital stay, and the extent and severity of angiographic-defined coronary artery disease.

Baseline risk was estimated using the Thrombolysis In Myocardial Infarction (TIMI) risk index score, which was calculated for each patient using the equation: (heart rate x $[age/10]^2$/systolic blood pressure) [41]. Patients were categorized as belonging to one of the five incremental risk index ranges: <12.5, 12.5 to 17.5; 17.5 to 22.5; 22.5 to

30; and >30. Patients were subsequently, grouped in two simplified risk categories: low risk (range: <12.5) and medium-high risk (range: >12.5 to >30).

Percent diameter stenoses of 50% or less were defined as insignificant coronary disease.

2.1 STATISTICAL ANALYSIS

We compared the baseline characteristics, management, angiographic findings and clinical outcomes of younger patients, aged ≤ 45 years old, and older patients, aged > 45 years old. Baseline characteristics were reported as numbers and percentages for categorical variables and means (± standard deviation [SD]) for continuous variables. Comparisons between groups were made either by chi-square test for baseline categorical variables and a 2-sample t test for continuous variables. Estimates of the odd ratios (OR) and associated 95% confidence intervals (CI) were obtained with the use of multivariable logistic regression analysis to evaluate factors associated with ACS in the young population and with 30-day mortality.

Constant covariates included in the analyses were: sex; cardiovascular risk factors: (history of hypercholesterolemia, hypertension and diabetes, smoking status, family history of CAD, Body Mass Index [BMI]); clinical history of ischemic heart disease (prior angina pectoris, prior myocardial infarction, prior percutaneous coronary intervention [PCI], and prior coronary artery bypass graft [CABG] surgery), clinical history of cardiovascular disorders (prior peripheral artery disease, prior heart failure and prior stroke), severity of clinical presentation (STEMI at index event, systolic blood pressure, heart rate, TIMI risk index and chronic kidney disease) and time from symptoms onset to admission ≤ 12 hours.

Covariates introduced in the secondary analyses, as dummy variables, were: in-hospital acute medication, namely aspirin, clopidogrel, heparins, beta-blockers and ACE-Inhibitors and reperfusion therapy, including PCI and fibrinolysis.

Moreover, we performed secondary analyses to get insights on potential sex differences in the younger populations.

We had complete data on age, gender and 30-day mortality. Some patients had missing data on other variables. We imputed the missing values of the clinical variables whose missing rate was less than 10% using STATA software. For the clinical features, whose missing rate exceeded 10%, we carried out a Pearson Chi-square statistical test for independence between those features and mortality. Only the variable “hypercholesterolemia" had missing rates that exceeds 10%, and it was found to be statistically dependent on the endpoint mortality. We therefore did not dismiss this variable from the predictive model of mortality and we kept it as missing [42].

For all analysis, statistical significance was defined as a value of $p < 0.05$ and STATA 11 (StataCorp; College Station, Texas) was used.

CHAPTER 3

RESULTS

There were 14,931 patients with a diagnosis of ACS enrolled in the ISACS-TC registry between October 2010 and April 2016. The mean age of our cohort was 62.6 ± 11.9 years and 4,717 (31.6%) subjects were women. Of these patients, 1,182 (7.9%) were aged ≤ 45 years.

3.1 PATIENT CHARACTERISTICS

Clinical variables at baseline for the younger (aged ≤ 45 years old) and older groups (aged 46 years and older), are shown in **Table 1**. The proportion of women was significantly lower in the younger group. The analysis of the conventional cardiovascular risk factor profiles showed that current smoking was the most prevalent risk factor in young patients, with more than 60% of young patients being current smokers. This prevalence was significantly higher (P<0.001) than in the older

age group. Almost 40% of young patients had a family history of CAD, significantly more than in older patients. Young patients also had higher mean of BMI than the older one. On the other hand, diabetes, hypercholesterolemia and hypertension were less frequent in younger patients. As expected, younger patients had lower rates of history of ischemic heart disease and other comorbidities.

3.2 CLINICAL PRESENTATION AND MANAGEMENT

The distribution of STEMI and non ST-segment elevation ACS (NSTE-ACS) was significantly different between young and older patients: STEMI was the most common clinical manifestation of ACS in the younger cases (**Table 1**). Less than 12% of younger patients had a medium-high TIMI Risk Index, whereas this proportion significantly increased in older group. Moreover, a higher proportion of younger patients reached the hospital before 12 hours from symptoms onset.

The rate of administration of in-hospital medications, namely aspirin and clopidogrel, was higher in younger patients, but younger patients received less frequently angiotensin-converting-enzyme (ACE) inhibitors. A higher proportion of younger patients received percutaneus reperfusion therapy, both STEMI and NSTE-ACS (**Table 1**).

Table 1. Baseline characteristics of the study population

Variables	Younger patients ≤ 45 yrs. N=1,182	Older patients > 45 yrs. N=13,749	P value
Age - yrs	40.3 ± 4.5	64.6 ± 10.3	<0.001
Women	187 (15.8)	4,530 (32.9)	<0.001
Cardiovascular risk factors - *n (%)*			
Hypercholesterolemia - *n/total (%)*	409/1,060(38.6)	5,008/11,839(42.3)	0.019
Diabetes	117 (9.9)	3,624 (26.4)	<0.001
Hypertension	523 (44.2)	9,616 (69.9)	<0.001
Current smoker	723 (61.2)	4,636 (33.7)	<0.001
Body Mass Index – kg/m^2	27.4 ± 4.5	27.1 ± 2.9	0.0004
Family history of CAD	469 (39.7)	4,096 (29.8)	<0.001
Clinical history of ischemic heart disease - *n (%)*			
Prior angina pectoris	122 (10.3)	3,118 (22.7)	<0.001
Prior myocardial infarction	126 (10.7)	2,440 (17.7)	<0.001
Prior PCI	129 (10.9)	1,702 (12.4)	0.14
Prior CABG	9 (0.8)	373 (2.7)	<0.001
Comorbidities - no. (%)			
Prior heart failure	26 (2.2)	817 (5.9)	<0.001
Prior stroke	7 (0.6)	635 (4.6)	<0.001
Prior peripheral artery disease	12 (1.0)	339 (2.5)	0.002
Chronic kidney disease	20 (1.7)	921 (6.7)	<0.001
Clinical presentation - *n (%)*			
STEMI	804 (68.0)	8,193 (59.6)	<0.001

NSTEMI	305 (25.8)	4,167 (30.3)	<0.001
Unstable angina	73 (6.2)	1,389 (10.1)	<0.001
Systolic blood pressure at baseline - mmHg	139.6 ± 22.1	140.9 ± 24.1	0.09
Heart rate at baseline at baseline - beats per minute	81.0 ± 23.1	81.3 ± 21.6	0.65
TIMI Risk Index	9.8 ± 5.1	25.6 ± 13.5	<0.001
Medium-High TIMI Risk Index	143 (12.1)	12,896 (93.9)	<0.001
Time from symptoms onset to admission ≤ 12 hours	769 (79.4)	8,326 (71.9)	0.001
Hospital stay - days	6.0 ± 4.3	6.9 ± 6.2	<0.001
In - hospital acute medications - ***n (%)***			
Aspirin	1,157 (98.4)	13,199 (96.8)	0.003
Clopidogrel	1,092 (92.9)	12,071 (88.9)	<0.001
Heparins	840 (83.7)	9,112 (81.6)	0.087
β blockers	321 (27.4)	4,075 (30.0)	0.06
ACE inhibitors	301 (25.6)	4,294 (31.6)	<0.001
Reperfusion therapy - ***n (%)***			
STEMI patients			
Primary PCI	575 (71.5)	5,252 (64.1)	<0.001
Fibrinolysis	119 (14.8)	957 (11.7)	0.009
CABG	2 (0.2)	67 (0.8)	0.07
NSTE-ACS patients			
PCI	233 (62.5)	2,411 (43.9)	<0.001
CABG	12 (3.2)	292 (5.3)	0.07
Outcomes - ***n (%)***			
30-day all-cause mortality	16 (1.3)	950 (6.9)	<0.001

Data are n (%), mean (± Standard Deviation), unless stated otherwise.
CAD= coronary artery disease; PCI=percutaneous coronary intervention; CABG=coronary artery bypass graft; STEMI=ST-segment elevation myocardial infarction; NSTEMI= Non ST-segment elevation myocardial infarction; TIMI= Thrombolysis In Myocardial Infarction; ACE=angiotensin-converting-enzyme.

3.3 ANGIOGRAPHYC DATA

The extension and severity of angiographic-defined coronary artery disease are shown in **Figure 1**. Young patients showed less diffuse atherosclerotic lesions as compared to patients of the older age group. Younger patients had a higher incidence of insignificant coronary artery disease (7.6% versus 5.4%) and single vessel disease (66.9% versus 52.5%). Conversely, three-vessel disease was less common (7.7% versus 16.3%) in the younger patients.

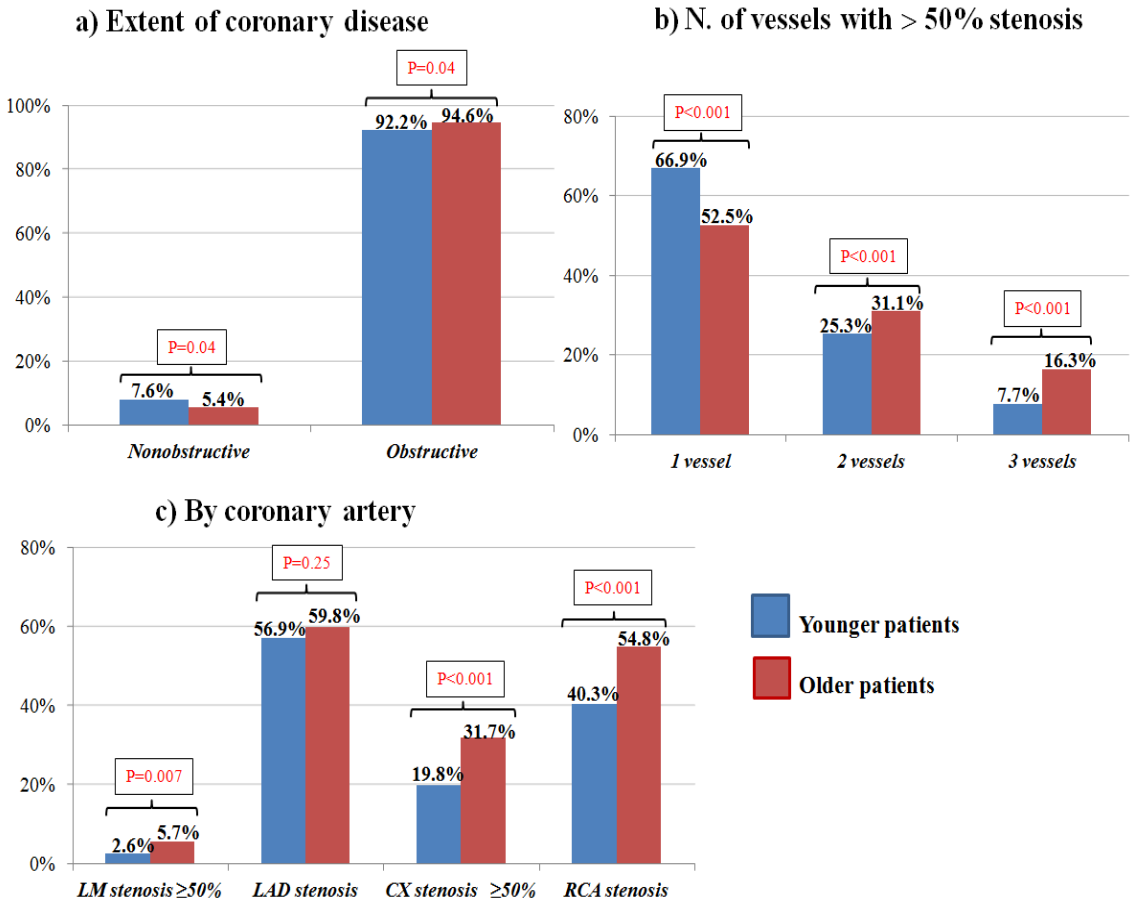

Figure 1.Extent, and severity of angiographic-defined coronary artery disease of population.

LM= left main; LAD= left anterior descending artery; CX= Circumflex artery; RCA, right coronary artery.

3.4 FACTORS ASSOCIATED WITH ACS IN YOUNG POPULATION

Predictors of ACS in the young population included male sex, smoking habit, family and higher BMI (**Table 2)**

Table 2. Multivariate analysis of factors associated with ACS in the young population

	OR	95%CI	P value
Male	2.21	1.86-2.62	<0.001
Diabetes	0.91	0.85-0.98	0.013
Hypercholesterolemia	1.08	0.94-1.24	0.26
Current smoker	1.10	1.06-1.16	<0.001
Hypertension	0.59	0.52-0.68	<0.001
Family history of CAD	0.99	0.96-1.02	0.36
Body Mass Index	1.04	1.01-1.06	<0.001
Prior angina pectoris	0.47	0.38-0.58	<0.001
Prior myocardial infarction	0.65	0.52-0.80	<0.001
Prior PCI/CABG	1.10	0.89-1.35	0.36
Prior heart failure	0.59	0.39-0.90	0.014
Prior stroke	0.13	0.05-0.32	<0.001
Prior peripheral artery disease	0.63	0.34-1.17	0.14
Chronic kidney disease	0.72	0.54-0.95	0.022

CAD= coronary artery disease; PCI=percutaneous coronary intervention; CABG=coronary artery bypass graft.

3.5 FACTORS ASSOCIATED WITH 30-DAY ALL-CAUSE MORTALITY: THE ROLE OF AGE

When all of the baseline variables (constant covariates) were assessed simultaneously in multivariable analysis (**Table 3**), there were 8 factors associated with 30-day all-cause mortality: women, history of diabetes, medium-high TIMI Risk Index , STEMI as index event, chronic kidney disease, clinical presentation with higher heart rate or lower systolic blood pressure, and clinical history of cardiovascular disorders. Age of 45 years or less had a significant protective effect on mortality (OR: 0.48; 95% CI 0.25-0.92). Linear regression analysis was repeated separately in men and women (**Table 3**). Interestingly, young age remained a factor associated with survival in men (OR 0.25, 95% CI 0.10-0.64), but not in women (OR 1.51, 95% CI 0.55-4.18). Moreover, current smoker and STEMI as index event were factors associated with 30-day mortality in women, but not in men. A shorter delay from symptoms onset to hospital admission had a protective effect only for women and not for men. Whereas a higher BMI had a positive effect for the prognosis of men, but not of women. The adjusted OR for mortality associated with younger age did not change when controlling for medications used at admission (**Table 4**) and reperfusion therapy.

Table 3. Multivariate analysis of factors associated with 30-day all-cause mortality in overall population and according to sex

Variables	Overall population		Women		Men	
	OR (95%CI)	P value	OR (95%CI)	P value	OR (95%CI)	P value
Female	1.57 (1.32-1.84)	<0.001	-	-	-	-
Age ≤ 45 yrs.	0.48 (0.25-0.92)	0.028	1.51 (0.55-4.18)	0.42	0.25 (0.10-0.64)	0.004
Diabetes	1.05 (1.002-1.12)	0.042	1.06 (0.97-1.17)	0.20	1.06 (0.99-1.13)	0.11
Hypercholesterolemia	0.40 (0.33-0.49)	<0.001	0.39 (0.29-0.52)	<0.001	0.41 (0.32-0.53)	<0.001
Current smoker	1.03 (0.97-1.08)	0.32	1.08 (1.01-1.16)	0.032	0.97 (0.89-1.06)	0.55
Hypertension	1.08 (0.99-1.17)	0.064	1.05 (0.92-1.19)	0.48	1.09 (0.98-1.21)	0.087
Family history of CAD	1.01 (0.98-1.04)	0.58	1.001 (0.95-1.05)	0.94	1.01 (0.97-1.05)	0.56
Body Mass Index	0.96 (0.94-0.99)	0.011	0.99 (0.96-1.03)	0.72	0.93 (0.90-0.98)	0.002
Medium-High TIMI Risk Index	2.07 (1.51-4.83)	0.001	4.14 (1.41-12.17)	0.010	2.21 (1.10-4.41)	0.025
STEMI	1.39 (1.15-1.68)	0.001	1.63 (1.21-2.20)	0.001	1.21 (0.97-1.59)	0.086
Systolic blood pressure at baseline	0.98 (0.97-0.98)	<0.001	0.97 (0.97-0.98)	<0.001	0.97 (0.97-0.98)	<0.001
Heart rate at baseline at baseline	1.01(1.002-1.007)	<0.001	1.004 (1.001-1.01)	0.014	1.005 (1.001-1.01)	0.006
Time from symptoms onset to admission ≤ 12 hours	0.75 (0.63-0.88)	0.001	0.64 (0.49-0.85)	0.001	0.83 (0.66-1.05)	0.14

Chronic kidney disease	1.32 (1.23-1.42)	<0.001	1.25 (1.11-1.41)	<0.001	1.36 (1.24-1.50)	<0.001
Clinical history of ischemic heart disease	1.11 (0.94-1.32)	0.22	0.96 (0.73-1.25)	0.75	1.22 (0.97-1.53)	0.085
Clinical history of cardiovascular disorders	2.02 (1.65-2.48)	<0.001	1.66 (1.19-2.31)	0.003	2.26 (1.74-2.94)	<0.001

CAD= coronary artery disease; TIMI= Thrombolysis In Myocardial Infarction; STEMI=ST-segment elevation myocardial infarction; PCI=percutaneous coronary intervention; CABG=coronary artery bypass graft.

Table 4. Multivariate models to assess the impact of various in-hospital acute medications and procedure on the odds of mortality for young patients: the role of young age

	Overall population		Women		Men	
	OR (95%CI)	**P value**	**OR (95%CI)**	**P value**	**OR (95%CI)**	**P value**
Model 1: Demographic and clinical factors						
30-day mortality	0.48 (0.25-0.92)	0.028	1.51 (0.55-4.18)	0.42	0.25 (0.10-0.64)	0.004
Model 2: Model 1 including aspirin						
30-day mortality	0.48 (0.25-0.92)	0.027	1.63 (0.58-4.57)	0.35	0.24 (0.09-0.62)	0.003
Model 3: Model 1 including aspirin and/or clopidogrel						
30-day mortality	0.48 (0.25-0.92)	0.027	1.53 (0.54-4.32)	0.42	0.25 (0.10-0.64)	0.004
Model 4: Model 1 including heparins						
30-day mortality	0.48 (0.24-0.98)	0.046	1.68 (0.57-4.96)	0.34	0.21 (0.07-0.64)	0.006
Model 5: Model 1 including β blockers						
30-day mortality	0.50 (0.26-0.98)	0.043	2.03 (0.68-6.06)	0.20	0.24 (0.09-0.62)	0.003
Model 6: Model 1 including ACE inhibitors						
30-day mortality	0.46 (0.24-0.89)	0.021	1.53 (0.53-4.38)	0.43	0.23 (0.09-0.59)	0.002

Model 7: Model 1 including reperfusion therapy

30-day mortality	0.51 (0.26-0.98)	0.043	1.61 (0.57-4.55)	0.37	0.26 (0.10-0.67)	0.005

ACE=angiotension converting enzyme; STEMI=ST-segment elevation myocardial infarction; NSTE-ACS= Non ST-segment acute coronary syndrome; PCI=percutaneous coronary intervention

3.6 MORTALITY IN THE YOUNG POPULATION

Of the 14,931 patients, 966 (6.5%) died at 30-day follow-up. Outcomes were better in young than in older patients. Thirty-day unadjusted survival rates were 98.7% versus 93.1% for young and older patients, respectively. Length of hospital stay was significantly shorter in the young population (6.0 ± 4.6 versus 6.9 ± 6.2 days) (**Table 1**).

Linear regression analysis in the younger (**Table 5**) revealed that the only variable associated with 30-day mortality was female sex: younger women had worse outcomes than men of a similar age (OR 6.84, 95% CI 2.23-20.97), even after adjusting for use of guideline-recommended acute medications and reperfusion therapy (**Figure 2**).

Table 5. Multivariate analysis of factors associated with 30-day all-cause mortality in the young population

	OR	95%CI	P value
Female	6.84	2.23-20.97	0.001
Diabetes	0.66	0.11-3.88	0.65
Hypercholesterolemia	1.58	0.48-5.14	0.45
Current smoker	0.96	0.49-1.89	0.91
Hypertension	0.92	0.35-2.34	0.85
Family history of CAD	1.01	0.77-1.30	0.94
Body Mass Index	0.90	0.75-1.09	0.30
Medium-High TIMI Risk Index	1.54	0.26-9.14	0.63
STEMI	1.70	0.33-8.64	0.52
Systolic blood pressure at baseline	0.99	0.96-1.02	0.73
Heart rate at baseline at baseline	1.0002	0.95-1.04	0.99
Time from symptoms onset ≤ 12 hours	0.64	0.17-2.39	0.51
Chronic kidney disease	1	-	-
Clinical history of ischemic heart disease	0.83	0.19-3.55	0.81
Clinical history of cardiovascular disorders	1.21	0.12-11.34	0.86

CAD= coronary artery disease; TIMI= Thrombolysis In Myocardial Infarction; STEMI=ST-segment elevation myocardial infarction; PCI=percutaneous coronary intervention; CABG=coronary artery bypass graft.

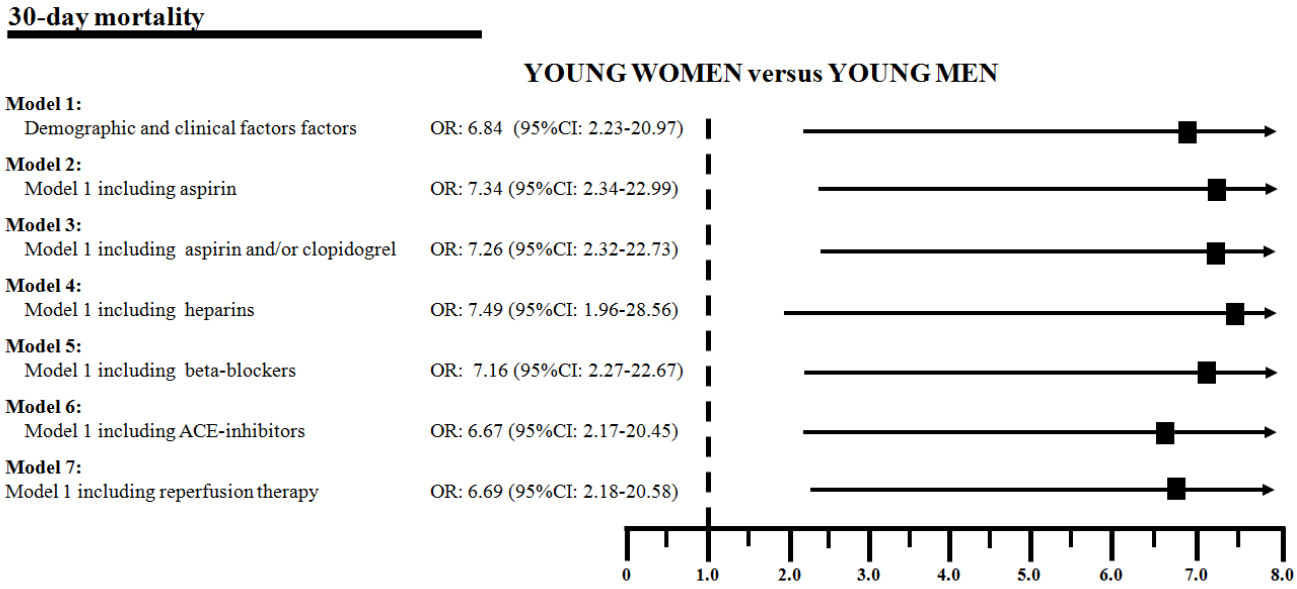

Figure 2. Multivariate models to assess the association of young women and outcomes: impact of various medications and procedures on the odds of mortality for young women.

ACE=angiotension converting enzyme

CHAPTER 4

DISCUSSION

The current study represents a contemporary analysis of young patients with ACS, from a large and multinational cohort study of ACS patient enrolled in 41 centres in 12 countries in Europe.

Our study indicated that approximately 8% of ACS patients referred to ISACS-TC Registry were younger than 45 years old and women represented a minority of this younger population. The main risk factor in young patients was smoking, together with higher BMI and positive family history of CAD. ACS at a young age was characterized by less severe coronary artery disease and worse clinical presentation. Younger patients had a better outcome than older patients, but younger age had a significant protective effect on mortality only in men and not in women. Indeed, younger women had worse outcome than men of a similar age.

4.1 IS ACS IN YOUNG PATIENT A REAL ISSUE?

Between the 70s and the 80s, there was an incidence of myocardial infarction in young patients of approximately 2% to 6% [19,43]. In the 90s, this incidence was shown to grow up ranging around 4% to 10% of myocardial infarctions [19-21,44]. Other studies underlined that the incidence of ACS in young patients may vary depending on the cut-off age used in the study and may be as low as 0.4% or as high as 19% of the population under scrutiny [14-18, 25]. The present study showed that nearly 8% of all patients hospitalized with ACS were aged ≤45 years old. This finding is consistent with recent work. [9,17, 45-51]. Indeed in the Global Registry of Acute Coronary Events (GRACE) study, the prevalence of young ACS patients was 6.3% [48]; in the Thai ACS Registry it was 5.8% [49]; and in the ACS Spain registry it was 7% [17].

The mean age of our young ACS cohort was 40.3 ±6 years, which is consistent with earlier studies [14, 48, 52]. Sex distribution also followed a pattern already observed in previous studies, with a lower percentage of women in the young-age group [48, 53, 54]. Women have been described to represent a minority of the young patients with MI ranging from 5% to 25 % of the overall population under investigation [19-21] [9,14,22,23]. In our cohort 16% of the young patients with ACS were women, a percentage, which consistent with prior findings.

4.2 RISK FACTORS PROFILE OF YOUNG ACS PATIENTS

Risk factors play a role in the younger patients who had ACS. In the current study, smoking and higher BMI **(Table 2)** were independent predictors of ACS in the young population. Obesity is related to cardiovascular risk factors and is an independent risk factor for developing coronary artery disease (CAD) [55]. Obesity may, also, confers

excess risk of acute coronary events [56] by producing an inflammatory state, which may trigger thrombosis and sympathetic nervous and renin-angiotensin system activation [57]. Nonetheless, increased BMI did not correlate with increased mortality in the young population. These results are concordant with previous findings where obesity independently predicted in-hospital death in the older, but not in the younger, patients [58]. The reasons for these findings are still unknown. Obese patients may have better tolerance to afterload-reducing medications [59]. However, such hypothesis does not seem to be a plausible explanation for our findings, as a greater proportion of patients were given renin-angiotensin system inhibitors in the older patients. Smokers currently have only a vague understanding of the increased risk of an acute coronary event that smoking confers. Our cohort consisted of 61.2% current smokers in the young versus 33.7% in the old population. Compared with older patients, smokers who were younger than age 45 had a significant increase of the risk of ACS (OR 1.10; 95% CI 1.06-1.16). These data are consistent with previous work that has shown that among patients presenting with myocardial infarction, from 76% to 90% of young patients are smokers compared with 40% of older patients [5, 60], and that smokers who were younger than age 50 had the worst discrepancy in risk of more than eight times that of former and never smokers (RR 8.47; 95% CI 6.80-10.54) [61]. The reason why smoking imparts such a high risk of acute STEMI among those who are youngest remains unclear, since studies of young smokers have confirmed that they have fewer traditional cardiovascular risk factors than older people. Independently from the pathways mediating its effect, we may emphasize that smoking is the most powerful of all risk factors, exerting its effect much sooner than any other.

4.3 CONFOUNDERS AND TRADITIONAL RISK FACTORS

We have not information on the rates of substance abuser (particularly marijuana and sympathomimetic amines) [51]. Cocaine use is associated with various cardiac complications including ACS. Cocaine effects can present up to 76 hours after its use. Most of the patients who use cocaine are also smokers and this makes them more vulnerable to develop an ACS. Cocaine use results in ACS by various mechanisms including coronary vasospasm and heightened sympathetic activity [62]. Alcohol abuse has also been reported to be associated with developing ACS in young people, although the mechanism is not entirely clear [63].

The presence of hyperlipidemia, hypertension and diabetes were more common in older age group, which is consistent with previous studies [5,64-65]. Although genetic studies were not performed, we found that a family history of CAD was not a prominent risk factor for ACS in younger patients, a finding that instead is supported by the work of others[1,4-9, 66-68]. Chromosomal abnormities were suggested to contribute to the onset of ACS by genomic studies [69].

4.4 CLINICAL PRESENTATION, MANAGEMENT AND CORONARY ANGIOGRAPHIC FEATURES

The clinical presentation of ACS in young adults differs from their older counterparts for many reasons. Firstly, because STEMI is the most common clinical manifestation of ACS in the younger cases. In our study population, almost seven of ten younger cases were admitted with STEMI as index event. This prevalence is slightly less than that reported in the PRIAMHO II study [17], in which almost the 80% of younger patients suffered from STEMI. Younger patients had lower TIMI risk index and they

reached the hospital earlier than their older counterpart. Moreover they received a more aggressive management [4, 48-50], both medical therapy and coronary revascularization, except for ACE-inhibitors, possibly because of the lower occurrence of previous cardiovascular disease and the lower TIMI risk index at admission.

Angiographic characterization of our younger cohort confirmed evidences from previous studies: ACS at a young age is characterized by a higher incidence of normal coronary arteries and single vessel coronary artery disease than do older patients [5, 65, 60, 70, 71]. In our study ACS at a young age was characterized by less severe coronary disease: 7% of younger patients had an insignificant coronary disease and one third of them had single vessel disease. Our data are in keeping with the CASS trial [5], one of the largest reports of angiographic findings in young patients with CHD. Zimmerman et al. have shown that normal coronary arteries and single vessel coronary disease were more common in the young patients (respectively 18% versus 3% and 38% versus 24%) and that three-vessel disease was less common (14% versus 39%) in the younger patients. Difference in proportion might be due to different inclusion criteria. In young ACS patients, the predilection for involvement of the left anterior descending artery followed by the right coronary and left circumflex arteries has been confirmed in the present study [65,71]. Other studies instead did not report such finding [5,17].

4.5 30-DAY MORTALITY: THE ROLE OF AGE AND SEX

We found a strikingly low hospital mortality: only 16 young patients died during the 30-day follow-up and they also had a shorter length of hospital stay than the older

group [9,23,72]. Although STEMI is the most common clinical manifestation of ACS in younger, they had a low TIMI risk index, a less severe coronary disease and they more frequently received timely and more aggressively in-hospital medical and reperfusion therapy [9, 17, 23, 46- 50, 68, 73, 74]. The different twist of our study is that the protective effect on mortally associated with lower age, applies only to young men, but not to young women. In the present study, indeed, female sex represented the only independent factor associated with mortality. Vaccarino *et al*. showed that young or middle-age women aged <55 years presenting with myocardial infarction had a worse long term prognosis than men of the same age [75]. Additionally, the mortality of women decreased with increasing age [76]. However, no studies have been addressed to investigate whether sex differences in mortality persist in the "true young age" i.e. in those patients aged 45 years old or less. In the present study, there were 16 patients aged 45 years or less (7 men and 9 women) who had evidence of ACS and died. Among these patients, we found at least 50% narrowing of a major coronary arterial branch in 11 (7 men and 4 women). Under these circumstances, some other contributing cause for a disparity between myocardial oxygen supply and demand in women is present. Severe aortic stenosis, systemic arterial hypotension due to a variety of causes, stress-induced heart disease and coronary dissection have been recognized as selected conditions that may cause ischemia in the absence of demonstrable significant coronary artery [77,78]. None of our patients had any of these conditions. Nonobstructive CAD is highly prevalent in women and implies different sex specific mechanisms that may lead to ACS. Activation of the coagulation system and myocardial and vascular function and growth occurs in a sex specific manner [79]. Oral contraceptives have been implicated in thromboembolic disease [80]. Likewise, functional disorders of the coronary arteries, such as spasms of

epicardial arteries or disease of small coronary arteries may arise as a consequence of a disturbed interaction between estrogen and vasoprotective nitric oxide system, which is probably more pronounced in women than in men [81]. The presence of coronary endothelial coronary dysfunction predicts adverse outcome [82]. However, we have not available data on endothelial dysfunction in our cohort, and specific mechanisms responsible for increased mortality after ACS in women remain understood.

4.6 CLINICAL IMPLICATIONS

ACS at a young age exits and it is characterized by several different aspects than those we already know about ACS in middle-aged and elderly patients. First, because younger patients have a different risk factors profile. Importantly, rates of ACS were compared for age and current smokers were more likely to have an ACS in the young group, confirming suggestions from other studies that giving up smoking reduces the incidence of acute coronary events in such population. Second, because the most common manifestation of ACS in the young is STEMI as index even, which implies several years of potential life lost, and long-term disability [1,6,10-12].

4.6 LIMITATIONS

There are some limitations that must be noted. The current analysis is an observational study, therefore we cannot excluded possible confounding variables not controlled. ACS diagnosis in young patients could be a problem because myocarditis can mimic an acute MI, therefore the prevalence of ACS at a young age might be influenced by an over or mis-diagnosis. We have no data about the use of substance in our patients, particularly marijuana and sympathomimetic amines, which have been

found correlated to ACS at a younger age [51]. Further, the lack of universal definition of "young" patients, made hard the comparison among the few studies about this topic. Finally, we have not analyzed long-term follow-up.

CHAPTER 5

CONCLUSIONS

Our cohort consisted of nearly 1,200 patients younger than 45 years enrolled in the ISACS-TC Registry. ACS at a young age is characterized by different risk factors profile, less severe coronary disease, worse clinical presentation and higher mortality in women. In the present era of preventive cardiology, there are still a number of concerns regarding factors underlying ACS in young patients and their mortality rates that warrant further investigation, despite the fact that ACS in young patients are associated with low incidence and mortality risk. Future analysis will find different disease process underlying atherosclerosis manifesting in young patients. However, nowadays, both patients and physicians should collaborate to improve and to follow public health programmes and anti-smoking campaigns in order to have better prognosis and decrease overall morbidity and mortality from CHD.

ACS at a young age remains a challenge for clinicians, particular attention should be deserved to this age-subgroup, especially if they have a positive family history of CAD, if they are smokers or have high BMI, and, mainly, if they are young women.

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