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SEX DIFFERENCES IN CORONARY ARTERY DISEASE SEVERITY AND MORTALITY: THE IMPACT OF CONVENTIONAL CARDIOVASCULAR RISK FACTORS

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Sex Differences in Coronary Artery Disease severity and Mortality: The Impact of Conventional Cardiovascular Risk Factors

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ABSTRACT

It is still unknown whether traditional risk factors may have a sex specific impact on the severity of coronary artery disease (CAD) and subsequent mortality in acute coronary syndromes (ACS). We identified 14 793 patients who underwent coronary angiography for acute coronary syndromes in the ISACS-TC (NCT01218776) registry from 2010 to 2019. The main outcome measure was the association between conventional risk factors and severity of CAD and its relationship with 30-day mortality. Risk ratios (RRs) and 95% CIs were calculated from the ratio of the absolute risks of women versus men using inverse probability of weighting. Severity of disease was categorized as obstructive (≥50% stenosis) versus nonobstructive CAD, specifically Ischemia with Non-obstructive coronary arteries (INOCA) and Myocardial Infarction with Non-obstructive Coronary Arteries (MINOCA). The RR ratio for obstructive CAD in women versus men among people without diabetes mellitus was 0.49 (95% CI, 0.41–0.60) and among those with diabetes mellitus was 0.89 (95% CI, 0.62–1.29), with an interaction by diabetes mellitus status of P =0.002. Exposure to smoking shifted the RR ratios from 0.50 (95% CI, 0.41–0.61) in nonsmokers to 0.75 (95% CI, 0.54–1.03) in current smokers, with an interaction by smoking status of P=0.018. There were no significant sex-related interactions with hypercholesterolemia and hypertension. Women with obstructive CAD had higher 30-day mortality rates than men (RR, 1.75; 95% CI, 1.48–2.07). No sex differences in mortality were observed in patients with INOCA/MINOCA. In conclusion, obstructive CAD in women signifies a higher risk for mortality compared with men. Current smoking and diabetes mellitus disproportionally increase the risk of obstructive CAD in women. Achieving the goal of improving cardiovascular health in women still requires intensive efforts toward further implementation of lifestyle and treatment interventions.

INTRODUCTION

Although cases of myocardial ischemia with no or little evidence of obstructive coronary artery lesions have been observed by physicians for at least fifty years[1-4] , a more in-depth knowledge of their clinical relevance was acquired only in the late 2000s[5], when it was first observed that the disease might be not as benign as previously thought, especially in the setting of acute coronary syndromes (unstable angina:UA and myocardial infarction: MI). Since then, increasing effort has been dedicated to achieve a better understanding of Ischemia with Non-obstructive coronary arteries (INOCA) and Myocardial Infarction with Non-obstructive Coronary Arteries (MINOCA) [5-33].

Overall, prevalence of MINOCA has been estimated to be around 6%, but an inter-study variability has been observed, with values ranging from 1 to 15%[34 35] . This rather wide span of reported pecentages partly depends on lack of consensus about the thershold used to define the presence of an obstructive stenosis, but it depends also upon the type of ACS observed in each study. To this regard, several authors reported lower rates of nonobstructive coronary artery disease (CAD) in STEMI patients [8 28 29] if compared with those affected by NSTEMI or NSTE-ACS[5-8 30-33 36] .

Regardeless the type of coronary ischemic disease diagnosed, patients with evidence of myocardial ischemia or myocardial infarction and nonobstructive coronary arteries are more likely to be women. Among 31,648 STEMI patients included in a study by Johnston et al, non-obstructive CAD showed a higher prevalence in women than in men (10.0% vs 5.9%)[36]. Smilowitz et al. observed lower rates of non-obstructive CAD in the overall STEMI population (2.2%). Still, prevalence of MINOCA was higher in female patients when compared with their male counterparts (3.6% vs 1.6%)[8]. Similar findings were seen in registries and clinical trials involving NSTE-ACS patients[5-8 30-33 36]. The TACTICS-TIMI

18 trial, which enrolled 1.646 patients with NSTEMI and unstable angina, documented INOCA/MINOCA in 17% of women versus 9% of men ($p<0.001$)[33].As well, the CRUSADE investigators found absence of significant CAD in 15.1% of women vs 6.8% of men[6] among 55,514 patients with NSTE-ACS.

The reasons behind discrepancy in terms of sex-related incidences of INOCA and MINOCA are most probably rooted into the different pathopisiologic mechanisms leading to myocardial ischemia in men and women. Although atherosclerosis is not the unique mechanism leading to CAD and, ultimately, to myocardial ischemia, it is widely known to be the most important factors contributing to the disease. In some patients, pathologically important atherosclerotic coronary disease may be present even in the absence of angiographically observed stenoses because atherosclerosis may occur in a diffuse manner and lead to remodeling of the arterial wall, where the wall thickens and expands outward without encroaching on the lume. A recent study on MINOCA, noted atherosclerotic plaque disruption by intravascular ultrasound in approximately one-third of patients affected by the disease. Of all the mechanisms that constitute the omni-comprehensive term "plaque disruption", plaque erosion (a thrombus contiguous to the luminal surface of a plaque without signs of rupture) is thought to play an important role in the developement of myocardial ischemia in absence of obstructive stenoses[34]. This is consistent with the different morphology of atherosclerotic plaque observed across sexes: in general, men are reported to present with increased atherosclerotic plaque burden and more high-risk plaque features compared with women. When observing coronary artery lesions through intravascular ultrasound, male patients showed an increased number of nonculprit lesions, higher frequency of plaque rupture and higher total necrotic core volume than their female counterparts[37]. Conversely, women are more likely to exhibit signs of plaque erosion, a feature that is also commonly associated with a decreased burden of standard modifiable cardiovascular risk factors[38].

A less favourable profile in terms of cardiovascular risk factors is another feature tipically observed in women when compared with men. For example, women are less likely to meet physical activity guidelines than men. The lack of physical activity can be in part explained by safety concerns with outdoor activities alone or at night. Smoking rates among women are rising and in high-income countries, rates of smoking are similar between young women and young men. Management of high blood pressure is of utmost priority for reducing the burden of cardiovascular disease in women as women appear to have a higher risk of acute myocardial infarction associated with prevalence of hypertension than men[39]. As well, elevated cholesterol is a major contributor to population attributable risk for myocardial infarction in women[39]. Studies suggest that diabetes tends to occur at a higher body-mass index, older age, and more advanced stage of disease progression in women than in men[40]. The prevalence of MINOCA or INOCA among women compared with men may provide a reason for the discrepancy in how the risk factor affects each sex. The WISE study found that under 20% of cases of non-obstructive CAD in women could be accounted for by the typical risk factors associated with CAD[41]. Thus, in line with these findings other non-traditional risk factors may play a major role in preducing ischemia in patients with nonobtructive disease. Prior studies have shown an association between higher levels of rheumatoid arthritis (RA) disease burden and markers of endothelial dysfunction, such as flow mediated dilatation[42]. Women were overrepresented in the RA arm of the study, which is consistent with RA predominance in women in the general population, identifying the chronic inflammatory state of RA as a risk factor that preferentially affects women

When taking into account all the elements mentioned above, it would seem logical to expect a better prognosis from ischemic heart disease in women than in men. In fact, a higher rate of non-obstructive CAD and overall lower prevalence of CAD-related diseases are all elements that theoretically predispose towards an improved likelihood of survival. So

far, however, prognostic investigations conducted on patients affected by ACS have provided seemingly paradoxycal observations that continue to spur much debate.

An analysis of 384,878 subjects enrolled in the National Registry of Myocardial Infarction (NRMI) from 1994 to 1998 highlighted that in-hospital mortality rates were 16.7% in women and 11.5% in men, a discrepancy that persisted after adjustement for clinical variables[43]. Some studies confirmed this trend after adjustment for age, comorbidities and evidence-based therapies, while others observed that the adjusted cardiovascular outcomes were not higher in women compared with men[15 43-51]. More recent investigations confirmed an excess of 30-day mortality in younger women after STEMI[51] .

This perceived gap in knowledge has led to considerable research on nontraditional risk factors as a cause of CHD in women. Prior work has suggested that abnormal values of ankle brachial index, high-sensitivity C-reactive protein level, coronary artery calcium score and coronary endothelial function are associated with cardiovascular morbidity and mortality in women,[52-56] but the evidence surrounding the clinical and pathophisiological impact of these emerging risk factors is still scarce[57] and some epidemiologic studies have suggested that conventional cardiovascular risk factors may still play a predominant role in producing CHD in women compared with men.[39 58-60]

Gaining a better insight into this issue is of fundamental importance to further improve both short and long term outcomes in men and women alike. Understanding why a predominance of MINOCA and INOCA in the female population does not necessarily translate into better outcomes, and investigating wether sex-related heterogeneity in the susceptibility to the most widely known cardiovascular risk factors could explain this phenomenon could have a marked effect on selecting sex-specific treatment and prevention strategies both for MINOCA/INOCA and for obstructive CAD patients. Consequently, we aimed to address these gaps in evidence by analyzing clinical outcomes by sex and severity

of CAD in a large cohort of patients presenting with ACS. We also aimed to estimate the relation between traditional risk factors and CAD status in women compared with men.

METHODS

Setting and design: The International Survey of Acute Coronary Syndromes (ISACS) Archives.

The ISACS Archives network (NCT04008173) is part of ISACS TC (NCT01218776) healthcare program. It is a collaborative network of research centers that support rapid development of new scientific information and analytic tools. The ISACS Archives uses an established informatics infrastructure, hosted and managed by the ISACS TC registry (NCT01218776) and the Department of Electrical and Computer Engineering, University of California, Los Angeles, which enables sharing of data. The ISACS Archives includes sites in which investigators are committed to collecting good-quality data without a strict proportionate sampling. Registries enrolled in the ISACS Archives use data definition for the measures/experiments that are harmonized to the standard variables of the ISACS –TC[61]. Participation in the research network does not eliminate the ability of any individual patient registry from analyzing only the data from the registry alone.

As the aim of the current investigation was to analyze wether conventional risk factors may have a sex-specific impact on coronary artery disease(CAD) burden, a parameter which was estimated by qualitative assessment of epicardial coronary arteries stenoses, we identified pertinent data from a single large clinical registry providing such information from October 2010 to January 2019, namely the ISACS-TC registry (NCT01218776). In brief, the ISACS-TC registry collected data from 41 centers in 12 European countries: Bosnia and Herzegovina, Croatia, Italy, Kosovo, Lithuania, Macedonia, Hungary, Moldova, Montenegro, Romania, Russian Federation, and Serbia. Among these sites, there were 22 tertiary health care services providing percutaneous coronary intervention. The local research ethics committee from each hospital approved the study. Because patient

information was collected anonymously, institutional review boards waived the need for individual informed consent.

Patient Population

The initial study population consisted of 15,111 patients who underwent coronary angiography for ACS from January 1, 2010, to January 15, 2019 **(Figure 1).** Of these, a total of 318 patients with a history of percutaneous or surgical revascularization by coronary artery bypass grafting were excluded from the analysis, leaving a final cohort of 14,793 patients (29.4% women). Appropriateness of inclusion was adjudicated by a cardiology specialist, considering clinical history, physical examination findings, ECG, and cardiac biomarkers[62 63].

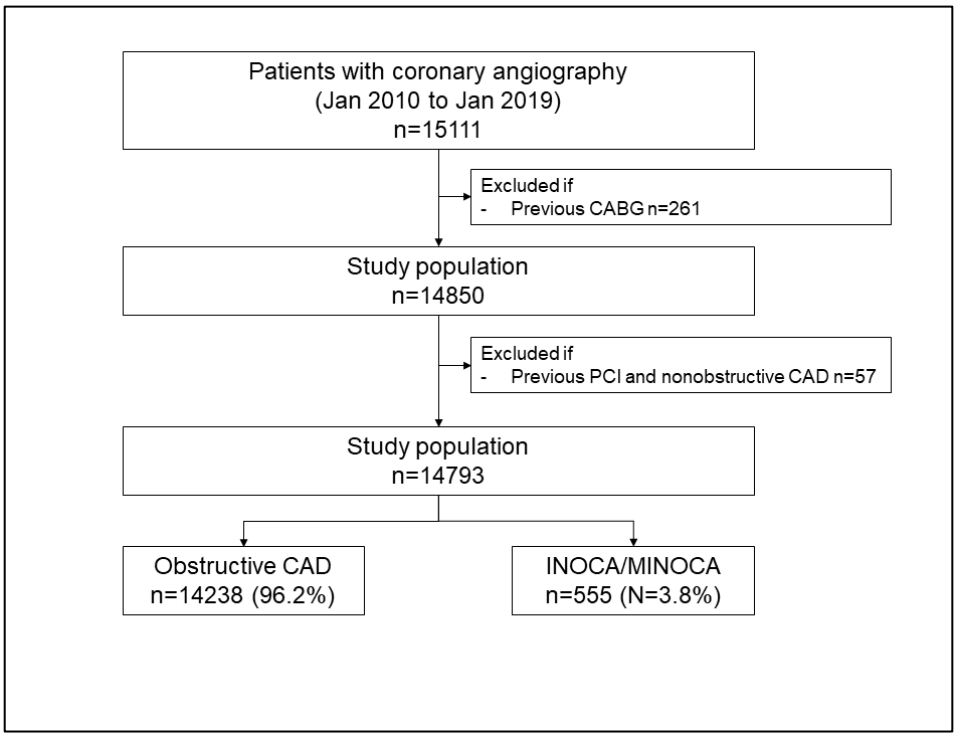

Figure 1: Study Flow Chart. Abbreviations: CABG= coronary artery bypass grafting; CAD= coronary artery disease; INOCA= ischemia with nonobstructive coronary arteries; MINOCA= myocardial infarction with nonobstructive coronary arterie; PCI= percutaneous coronary intervention

Outcome Measures and Definitions

INOCA/MINOCA and angiographic details

In 2016, the ESC Working Group on Cardiovascular Pharmacology published a Position Paper that served as a first attempt at providing a unified diagnostic approach for suspected MINOCA patients[35] .In the Position Paper it was underscored that a definitive diagnosis of MINOCA could be made only in presence of signs of myocardial infarction as per Third Universal definition of Myocardial Infarction and after a coronary angiography excluded presence of obstructive CAD[62]. The most recent ESC Guidelines on ACS without persistent ST segment elevation furhter implemented this definition by applying the criteria of myocardial injury reported in the Fourth Universal Definition of Myocardial infarction[63 64]. This update takes into consideration the fact that cardiac troponins are organ specific but not disease specific. It follows that some non-ischemic conditions (i.e. myocarditis, Takotsubo syndromes, pulmonary embolism) can lead to an increase in troponins without evidence of significant angiographic stenoses in epicardial coronary vessels. These alternative conditions (comprehensively termed as "myocardial injury" in the most recent Definition) should be evaluated and excluded before a diagnosis of MINOCA is made. As the study population included patients admitted to healthcare services between October 2010 and January 2019, mostly before the Fourth Universal Definition of Myocardial Infarction was issued, the Third Universal Definition of Myocardial Infarction was applied by cardiologist specialists to guide their diagnostic process in case of patients presenting with elevated cardiac biomarkers.

It should be noted that MINOCA does not include all patients presenting with ACS. To this regard, this term shows partial overlap with the more general definition of myocardial Ischemia with Non-Obstructive Coronary Arteries (INOCA)[65]. Although signs of ischemia are mandatory findings underlying both definitions, INOCA patients do not necessarily show elevated markers of cytonecrosis and could consequently be affected by stable or unstable angina. As this study focuses on predisposing and pathopysiological mechanisms leading to non-obstructive acute coronary syndromes (ACS) in men and women, thus including also some cases of unstable angina, the all-encompassing combination INOCA/MINOCA was deemed to be more appropriate for the population at hand.

An important element of the most recently updated MINOCA definitions pertains to the level of stenosis taken as a threshold to distinguish obstructive from nonobstructive coronary artery disease. As a matter of fact, in the past studies were carried out without unanimous agreement on the degree of lumen stenosis for the definition of non-obstructive CAD. Although most authors set the threshold at 50% epicardial lumen stenoses, some studies included solely smooth epicardial coronary arteries (0% lumen stenosis) or coronary arteries with minimal lumen irregularities (<20% lumen stenosis)[14 66-68] . Others defined MINOCA as the absence of any severe (>70%) epicardial lumen stenosis[69-71] . The choice of the 50% threshold, albeit somehow arbitrary, is in line with the recommendations provided by the American Heart Association/American College of Cardiology (AHA/ACC) Guidelines on coronary angiography, and was later endorsed by the AHA Scientific Statement on diagnosis and management of MINOCA[34 72]. Stricter angiographic criteria such as complete smooth coronary arteries at angiography were not endorsed by the ESC Position Paper, since this finding does not necessarily imply complete absence of atherosclerotic plaque. However, both the AHA Scientific Statement and the ESC Position Paper suggested that a further distinguo between patients with a minimal lumen occupation (<30% stenoses) and those with a mild to moderate plaque (30-50% stenoses) could be useful to implement prognostic estimation. Fractional flow reserve has also been taken into consideration to refine evaluation of plaque severity, but limited data is available pertaining its clinical usefuleness in MINOCA patients[34]. Following these considerations, in the present manuscript obstructive CAD was defined as at least one main branch of the epicardial coronary artery with a ≥50% stenosis. All vessels >1.5 mm in diameter were graded for stenosis severity.

Definitions of Cardiovascular Risk Factors

Smoking habits were self-reported. We defined current smokers as individuals who smoked 100 cigarettes in their lifetime and who smoked cigarettes, cigars, and cigarillos at the time of the index event. Everyday smokers or someday smokers were all included in this definition according to recommendations from the National Health Interview Survey[73]. Participants who have smoked at least 100 cigarettes in their lifetime but who were not active

smokers at the time of the index event were labelled as former smokers regardless of time since they quit. The remaining patients were classified as never smokers.

Hypertension, hypercholesterolemia and diabetes were assessed by designation of medical history prior to admission in the database.

Outcome Measures

The first outcome measure consisted of the assessment of sex-related differences in terms of CAD severity and their association with conventional risk factors. Secondary outcome implied the measurement of differences between men and women in regards to 30-day mortality rates both in INOCA/MINOCA and obstructive CAD patients.

Statystical Analysis

Multiple Imputation using Chained Equation (MICE) algorithm

Data regarding sex, age, CAD status, and 30-day mortality was complete in the selected population. Other variables presented with missing values that were managed using Multiple Imputation with Chained Equation (MICE)[74]. This is an efficient and popular method to fill in missing data by replacing missing values with a value obtained from related cases in the whole set of records. More specifically, MICE algorithm sequentially imputes the missing values of clinical features based on both observed values and previously imputed values. This sequential imputation is conducted via chained equations.

Multiple imputations using the MICE algorithm were attempted for the initial analyses to address the uncertainty in the imputation process and to check whether the conclusions were consistent across the different imputed datasets. After consistency across multiple imputed datasets was verified, a single imputed dataset by MICE algorithm was used as the final dataset to report the results of statistical analyses in the present paper.

Baseline characteristics

Variables included in the analyses are reported in **Table 1**. Baseline characteristics included demographic data (age), previous history of cardiovascular disease (history of angina or myocardial infarction, chronic heart failure, peripheral artery disease or history of cerebrovascular incidents) and cardiovascular risk factors (hypertension, hypercholesterolemia, diabetes, smoking status). Clinical characteristics on hospital admission were also collected (ECG details, systolic blood pressure, heart rate, serum creatinine, Killip Class), as were data on medications either administered in the acute phase (within 24 hours) and during hospitalization.

Baseline characteristics were reported as percentages for categorical variables and means with standard deviations for continuous variables. Comparisons between groups were made either by Pearson chi-square test for baseline categorical variables or 2-sample *t* test for continuous variables. A 2-sided *P* value <0.05 was considered statistically significant. Multivariable logistic regression analysis was applied to verify the association between female sex and the primary outcome. Results of the logistic regression analysis were presented as Odds Ratios (ORs) with their 95% Confidence Interval (CI). In this case too, as for in the Inverse Probability of Weighting (IPW) analyses, a 2-sided *P* value <0.05 was considered statistically significant.

Inverse Probability of Weighting Analysis

IPW was used to balance the distribution of covariates between two patient groups (women versus men) and to assess the relative risk (RR) with their 95% CIs for the outcomes of interest. Logistic Regression analyses were used to estimate the propensity scores ((Z=1 | x)). More in detail, If *e* denotes the estimated propensity score (i.e. e=\hat(Z=1 | x), where the patient x is included in patient group 1; then, 1-e = \hat(Z=0 | x)), then the original sample is weighted by the following weights: Z/e+(1−Z)/ 1−e where Z represents the patient group.

For instance, women (Z=1) are assigned a weight equal to the reciprocal of the propensity score (1/e), while men (Z=0) are assigned a weight equal to the reciprocal of one minus the propensity score (1/1-e)[75].

For the primary outcome, a different model was developed for each risk factor. Findings were adjusted for demographics, cardiovascular risk factors, and history of ischemic heart disease or cardiovascular disorders. Patients were grouped according to the presence or absence of the risk factor under consideration. When examining the RRs for 30-day mortality according to sex and CAD severity, a new model was implemented by adding the following covariates: ST-segment shifts in anterior leads at ECG, systolic blood pressure at baseline, heart rate at baseline, serum creatinine at baseline (mg/dL), and Killip class ≥2. A further subgroup analysis was conducted on the secondary outcome to assess differences in 30-day mortality depending on sex, severity of CAD and ACS type (STEMI and NSTE-ACS)

Since IPW method can potentially result in unstable and biased estimates if some of the weights are very high, results were comparedwith other methods for handling confounding. Consequently, probability of treatment variables were included in a multivariable model. XGBoost, a decision-tree-based ensemble machine learning algorithm, was also used as an alternative multivariable model for estimating the probability of treatment. Conclusions from theses analyses were the same as presented results. Further, a threshold of 10 was applied for weights to avoid the impacts of the outliers.

Interaction test

The comparison of two estimated quantities, each with its standard error, is a general method that can be applied widely. We compared the risk ratios of 30-day mortality and obstructive CAD from two subgroups (women versus men) sorted by ACS type (STEMI vs NSTE-ACS) and presence or absence of conventional risk factors. These measures were always analyzed on the log scale because the distributions of the log ratios tend to be those

closer to normal than of the ratios themselves. If the estimates are $E1$ and $E2$ with standard errors SE($E1$) and SE($E2$), then the difference $d=E1 - E2$ has standard error SE(d)=Ö[SE($E1$)2 + SE($E2$)2] i.e., the square root of the sum of the squares of the separate standard errors. The ratio $z=d$/SE(d) gives a test of the null hypothesis that in the population the difference d is zero, by comparing the value of z to the standard normal distribution. The 95% confidence interval (CI) for the difference is d-1.96SE(d) to d+1.96SE(d) [76]

RESULTS

Overall, 14,793 patients were included in the study. Of these, 4,347 (29.4%) were women (**Table 1**). Obstructive CAD appeared to be prevalent in both sexes: stenoses<50% were observed in 5.2% of women and 3.1% of men, with a p-value<0.001. A mean older age was observed in female patients with obstructive CAD compared with those presenting with less severe angiographic features, but the same phenomenon was not observed in male patinents. In general, women were older than men both in the subgroup affected by obstructive CAD (65.4±11.2 vs 59.9±11.4, p<0.001) and in that presenting with INOCA/MINOCA (62.5±11.5 vs 59.8±12.3,p<0.001).

Baseline characteristics: standard modifiable risk factors across sexes and CAD severity.

Patients affected by nonobtructive CAD were affected by slightly lower rates of diabetes, although this difference was not statistically significant (P=0.18). They also showed lower rates of hypercholesterolemia (p<0.001), and were less frequently current smokers (p=0.0001). When analyzing sex differences within obstructive and non-obstructive CAD, it appeared that women with more severe angiographic features had a higher cardiovascular risk factors burden than men did, with the sole exception of smoking, which was more prevalent in male patients **(Table 1).** Converesely, in the subgroup of patients with MINOCA/INOCA the rate of conventional risk factors was equally distributed across sexes, with statistically significant discrepancies only seen in hypertension (82.0% in women and 74.3% in men, p=0.03) and current smoking (21.9% in women and 41.9% in men, p<0.001).

Table 1. Baseline characteristics of the overall population sorted by sex and CAD status in patients with acute coronary syndrome at index event

Characteristics	Obstructive CAD (stenosis ≥50%)			INOCA/MINOCA (stenosis <50%)		
	Women (n=4119)	Men (n=10119)	p value	Women (n=228)	Men (n=327)	p value
Age, years	65.4±11.2	59.9±11.4	<0.0001	62.5±11.5	59.8±12.3	0.0077
Cardiovascular risk factors						
Diabetes	1247 (30.3)	2196 (21.7)	<0.0001	46 (20.2)	74 (22.6)	0.4872
Hypertension	3228 (78.4)	6710 (66.3)	<0.0001	187 (82.0)	243 (74.3)	0.0288
Hypercholesterolemia	1929 (46.8)	4463 (44.1)	0.0031	96 (42.1)	121 (37.0)	0.2283
Current smokers	1344 (32.6)	4889 (48.3)	<0.0001	50 (21.9)	137 (41.9)	<0.0001
Former smokers	162 (3.9)	937 (9.3)	<0.0001	14 (6.1)	46 (14.1)	0.0016
Clinical history of ischemic heart disease						
Previous angina pectoris	705 (17.1)	1531 (15.1)	0.0038	52 (22.8)	52 (15.9)	0.0456
Previous myocardial infarction	504 (12.2)	1398 (13.8)	0.0103	30 (13.2)	34 (10.4)	0.3263
Previous heart failure	174 (4.2)	368 (3.6)	0.1070	10 (4.4)	16 (4.9)	0.7795
Clinical history of cardiovascular disorders (overall)						
Peripheral artery disease	61 (1.5)	189 (1.9)	0.0946	1 (0.4)	6 (1.8)	0.1063

Previous stroke	135 (3.3)	251 (2.5)	0.0121	6 (2.6)	9 (2.8)	0.9311
Clinical presentation at admission						
STEMI	2833 (68.8)	7027 (69.4)	0.4369	38 (16.7)	67 (20.5)	0.2521
ST-segment shifts in anterior leads (at ECG)	800 (19.4)	2189 (21.6)	0.0283	16 (7.0)	23 (7.0)	0.9942
Systolic BP at baseline, mmHg	140.1±27.8	139.4±26.7	0.1619	145.8±25.4	143±25.9	0.2047
Heart rate at baseline, bpm	80.3±18.2	80.2±17.9	0.6824	78.7±17.5	79.8±21.8	0.5134
Serum creatinine at baseline, mg/dl	1.0±0.5	1.1±0.7	<0.0001	0.9±0.3	1.1±0.7	0.0009
Killip Class ≥2	827 (20.1)	1547 (15.3)	<0.0001	28 (12.3)	55 (16.8)	0.1317

BP indicates blood pressure; CAD, coronary artery disease; ECG, electrocardiogram; INOCA, ischemia with nonosbtructive coronary arteries; MINOCA, myocardial infarction with nonobstructive coronary arteries; MI, myocardial infarction, PAD, peripheral artery disease, STEMI= ST-segment elevation myocardial infarction.

A similar trend could be observed also when considering the global burden of conventional cardiovascular risk factors in women and men across different degrees of CAD severity **(Figure 2).** In fact, in obstructive CAD absence of risk factors was found to be less frequent in women than men (7.7% vs 9.7%, respectively), and the same could be said for presence of a single risk factor (27.9% vs 29.7% respectively); opposedly, 2 or more risk factors were more common in women (64.4% vs 60.7%). Instead, female and male patients suffering from INOCA/MINOCA had comparable rates of cardiovascular risk factors burden burden, independently from the number of risk factors present.

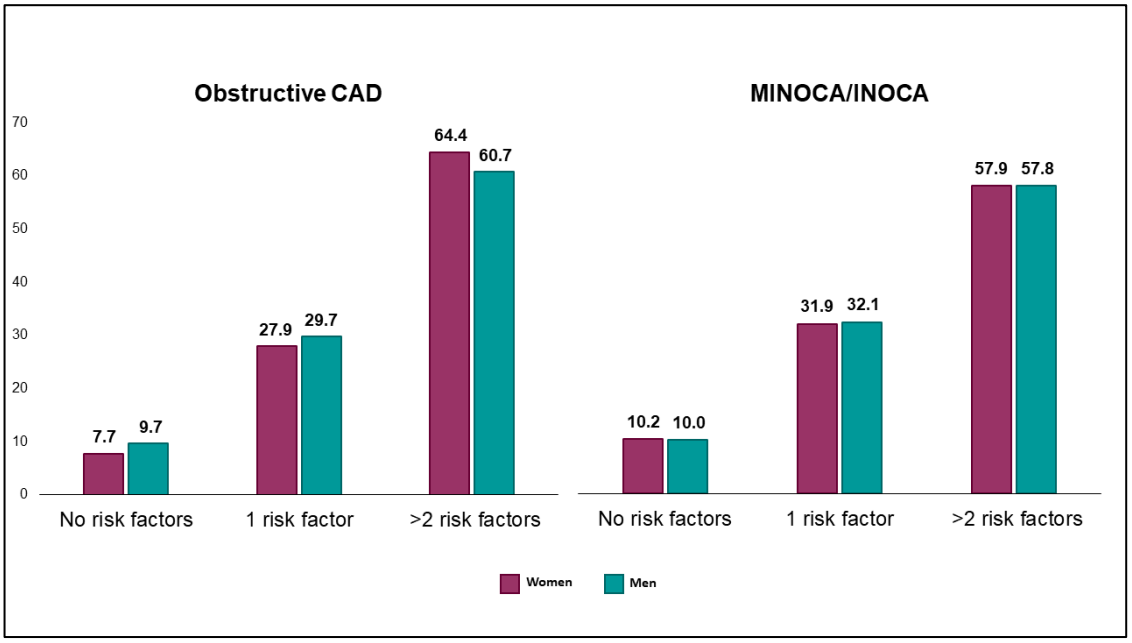

Figure 2 Dstribution of cardiovascular risk factors by sex and severity of CAD. Abbreviaton: CAD, coronary artery disease**.**

Clinical characteristics and treatment

In regards to clinical charateristics on hospital admission, MINOCA/INOCA patients showed lower rates of STEMI than those affected by increased atherosclerotic burden, with no significant sex differences in either subgroup (**Table 1**). No statistically or clinically significant discrepancy across sexes was also observed when analysing parameters like systolic blood pressure, heart rate or serum creatinine measured on admission. Although both

patients with and without obstructive CAD had comparable rates of acute heart failure on hospital admission (16.7% vs 15% respectively, p value 0.32), this complication was observed more frequently in women than in men only in presence of more severe coronary lesions (20.1% vs 15.3%, p value<0.001).

Details on medications administered before index event and within 24 hours from hospital admission are represented in **Tables 2 and 3.** In the overall population, before hospitalization ACE inhibitors or ARBs and beta blockers use was more frequently observed in patients with less severe angiographic features (46.8% vs 41.1%, p=0.009, 40.9% vs 30%, p<0.001 for ACE/ARBs and beta blockers, respectively). When stratifying by sex, women received more evidence-based therapies before admission for ACS, namely aspirin, clopidogrel, β-blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers and statins, either in MINOCA/INOCA patients and in those with obstructive CAD, with the sole exception of statins and beta-blockers **(Table 2).**

Table 2. Therapy within 15 days before index event.

Characteristics	**Obstructive CAD (stenosis ≥50%)**			**MINOCA/INOCA (stenosis <50%)**		
	Women (n=4119)	**Men (n=10119)**	**p value**	**Women (n=228)**	**Men (n=327)**	**p value**
Aspirin	1212 (29.4)	2531 (25.0)	<0.0001	79 (34.6)	82 (25.1)	0.0162
Clopidogrel,	426 (10.3)	896 (8.9)	0.0071	36 (15.8)	32 (9.8)	0.0409
ACE-inhibitors /ARBs	2100 (51.0)	3766 (37.2)	<0.0001	122 (53.5)	138 (42.2)	0.0087
Beta-blockers,	1553 (37.7)	2721 (26.9)	<0.0001	104 (45.6)	123 (37.6)	0.0609
Statins,	949 (23.0)	1976 (19.5)	<0.0001	53 (23.2)	58 (17.7)	0.1175

Data are n (%). ACE=angiotensin-converting enzyme;
ACE indicates angiotensin-converting enzyme; ARBs, angiotensin II receptor blockers; CAD, coronary artery disease INOCA, ischemia with nonosbtructive coronary arteries; MINOCA, myocardial infarction with nonobstructive coronary arteries;

During the first 24 hours after hospitalization, MINOCA/INOCA patients still received more ACE-i/ARBs and beta blockers than did those affected by Obstructive CAD (82.2% vs 78.0%, p=0.02; 89.4% vs 76.6 %, p-value<0.001). On the opposite, they were administerd less frequently with anticoagulants and GP IIb/IIIa inhibitors (48.6% vs 57.7%,

p <0.001; 1.1% vs 12.9, p<0.001 for unfractionated heparin and gp IIb/IIIa inhibitors, respectively). Female patients with obstructive CAD received on average fewer revascularization procedures and fewer antiplatelet and anticoagulant agents compared with men. However, no such difference was observed in the MINOCA/INOCA population **(Table 3).**

Table 3. Use of revascularization therapies and medications within 24 hours from hospitalization sorted by sex (women versus men) and CAD status in the overall population of patients with acute coronary syndromes.

Characteristics	Obstructive CAD (stenosis ≥50%)			MINOCA/INOCA (stenosis <50%)		
	Women (n=4119)	Men (n=10119)	p value	Women (n =228)	Men (n =327)	p value
Aspirin	4071 (98.8)	10028(99.1)	0.1654	227 (99.6)	324 (99.1)	0.4857
Clopidogrel	3703 (89.9)	9000 (88.9)	0.0889	205 (89.9)	291 (89.0)	0.7278
Unfractionated heparin	2309 (56.1)	5905 (58.4)	0.0121	102 (44.7)	168 (51.4)	0.1239
LMWH	1960 (47.6)	4595 (45.0)	0.0184	131 (57.5)	174 (53.2)	0.3229
Heparins (overall)	3484 (84.6)	8735 (86.3)	0.0083	187 (82.0)	286 (87.5)	0.0837
GP IIb/IIIa inhibitor	511 (12.4)	1326 (13.1)	0.2552	4 (1.8)	2 (0.6)	0.2408
Beta-blockers	3132 (76.0)	7773 (76.8)	0.3225	204 (89.5)	292 (89.3)	0.9469
ARBs/ACE-inhibitors	3235 (78.5)	7873 (77.8)	0.3349	190 (83.3)	266 (81.3)	0.5450
Procedures						
PCI	3880 (94.2)	9626 (95.1)	0.0278	-	-	-

Data are n (%). ACE=angiotensin-converting enzyme; ARBs=angiotensin II receptor blockers; CAD=coronary artery disease; GP=glycoprotein; INOCA, ischemia with nonosbtructive coronary arteries; LMWH=low molecular weight heparins; MINOCA, myocardial infarction with nonobstructive coronary arteries; PCI, percutaneous coronary intervention.

Risk profile and severity of CAD across sexes

After multivariable logistic regression analysis adjusted for demographic characteristics, female sex appeared to be significantly associated with a higher likelihood of presenting with MINOCA/INOCA (OR: 1.78, 95%CI 1.49-2.13, p-value<0.001). Comparable results were obtained when further adjusting for cardiovascular risk factors and history of cardiovascular diseases **(Figure 3).**

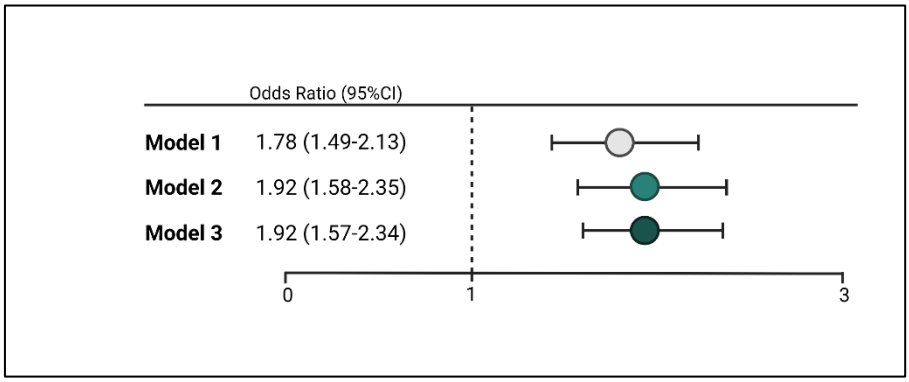

Figure 3: **Multivariable logistic regression analysis on association between female sex and incidence of INOCA/MINOCA**. Model 1= further adjusted for age; Model 2= Model 1 further adjusted for cardiovascular risk factors (hypercholesterolemia, hyertension, diabetes mellitus, current and former smoking status; Model 3= Model 2 adjusted for history of cardiovascular disease (history of angina, myocardial infarction, heart failure, stroke or peripheral artery disease)

In order to investigate the impact of conventional risk factors on severity of CAD across sexes, IPW analyses were conducted in subgroups stratified by presence or absence of diabetes mellitus, hypercholesterolemia, hypertension and current smoking status. The women-to-men RRs for obstructive CAD across risk factors are shown in **Figure 4**.

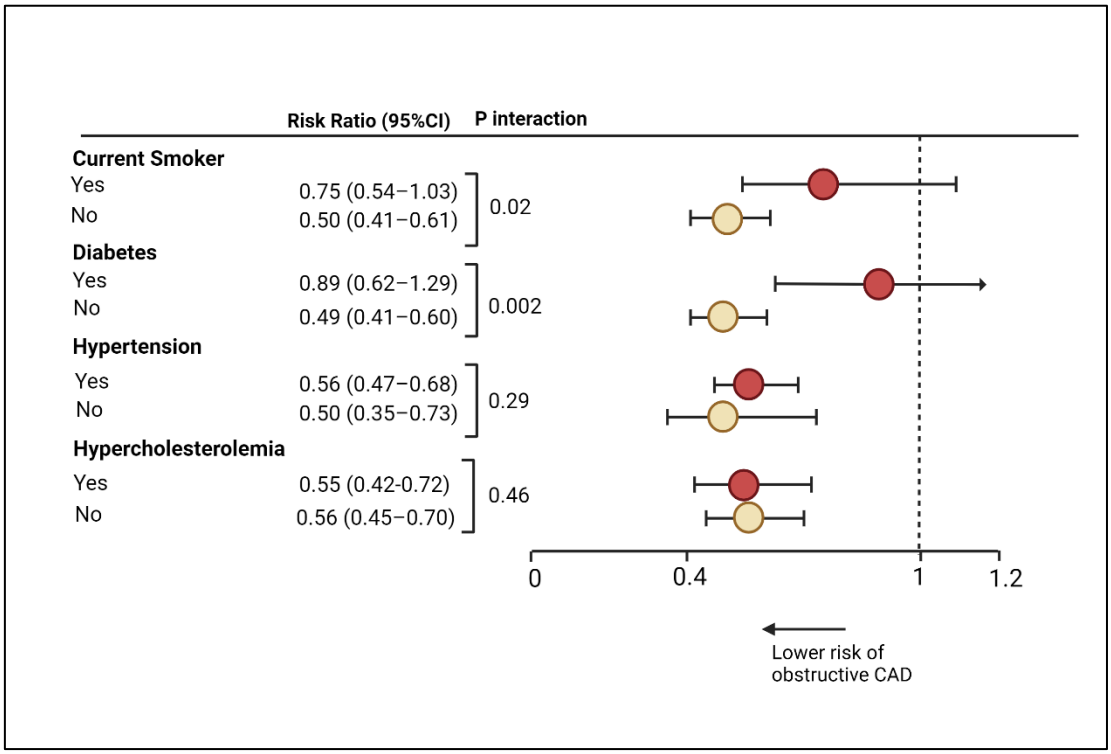

Figure 4: Female sex and obstructive coronary artery disease (CAD) sorted by the presence or absence of cardiovascular risk factors. Women-to-men risk ratios adjusted for variables presented in tables 4 to 7. CAD= coronary artery disease

After matching, nonsmoking women showed a lower risk for more severe angiographic features than their male counterparts (RRs 0.50; 95% CI, 0.41–0.61). Exposure to smoking **(Table 4)** shifted the RRs to 0.75 (95% CI, 0.54–1.03; interaction P=0.018)**.** Diabetes equalized the risk of obstructive CAD by sex. In fact, while The RRs among patients without diabetes mellitus was 0.49 (95% CI, 0.41–0.60), the RRs resulted in being not statistically significant when considering the subgroup of patients affected by diabetes (RR 0.89; 95% CI, 0.62–1.29, interaction p =0.002) (**Table 5**).. The RRs for the absence or presence of hypercholesterolemia were 0.56 (95% CI, 0.45–0.70) and 0.55 (95% CI, 0.42–0.72), respectively **(Table 6**). The RRs for the absence or presence of hypertension were 0.50 (95% CI, 0.35–0.73) and 0.56 (95% CI, 0.47– 0.68), respectively **(Table 7**). There were no significant sex-related interactions for hypercholesterolemia and hypertension. All results of ineraction testing pertaining to subgroup analysis by risk factors are shown in **Table 8.**

Table 4. Inverse probability of weighting: incidence of obstructive CAD sorted by sex (women versus men) and smoking status.

Characteristics	Current smokers			Non-smokers		
	Women (n=1394)	Men (n=5026)	p value	Women (n=2953)	Men (n=5420)	p value
Age, years	56.7±10.1	56.8±10.2	0.8585	64.8±11.7	65.0±11.3	0.5535
Cardiovascular risk factors						
Diabetes	18.7	18.7	1.0000	28.1	28.2	0.9226
Hypertension	64.0	64.5	0.7302	73.9	74.3	0.6896
Hypercholesterolemia	48.5	49.2	0.6437	40.3	41.0	0.5334
Clinical history of ischemic heart disease						
Previous angina pectoris	12.9	13.3	0.6967	17.4	17.6	0.8182
Previous myocardial infarction	11.8	11.5	0.7567	14.5	14.6	0.9014
Previous heart failure	3.1	2.8	0.5530	4.6	4.6	1.0000
Clinical history of cardiovascular disease						
Peripheral artery disease	1.6	1.6	1.0000	1.8	1.8	1.0000
Previous stroke	1.8	1.8	1.0000	3.4	3.4	1.0000
Outcome						
Obstructive CAD	96.3	97.2	0.0778	93.2	96.5	<0.0001
Risk Ratio (95% CI)	0.75 (0.54 – 1.03)		0.0788	0.50 (0.41 – 0.61)		<0.0001

Data are %, mean (SD) or relative risk ratios (95% CI). CAD=coronary artery disease.

Table 5. Inverse probability of weighting: incidence of obstructive CAD sorted by sex (women versus men) and history of diabetes.

Characteristics	Diabetes			No Diabetes		
	Women (n=1293)	Men (n=2270)	p value	Women (n=3054)	Men (n=8176)	p value
Age, years	64.1±10.6	64.5±10.4	0.3282	60.3±11.9	60.4±11.8	0.4990
Cardiovascular risk factors						
Hypertension	83.5	83.3	0.8775	65.3	65.8	0.6196
Hypercholesterolemia	51.6	51.4	0.9086	41.7	42.4	0.5040
Current smokers	33.7	33.8	0.9516	46.3	46.5	0.8500
Former smokers	10.4	9.7	0.5026	7.7	7.3	0.4712
Clinical history of ischemic heart disease						
Previous angina pectoris	20.3	19.6	0.6145	14.3	14.6	0.6882
Previous myocardial infarction	17.1	16.9	0.8785	12.3	12.1	0.7730
Previous heart failure	5.5	5.4	0.8994	3.5	3.3	0.6004
Clinical history of cardiovascular disease						
Peripheral artery disease	2.8	2.8	1.0000	1.3	1.4	0.6876
Previous stroke	3.8	3.9	0.8822	2.5	2.4	0.7576
Outcome						
Obstructive CAD	96.3	96.7	0.5434	93.9	96.9	<0.0001
Risk Ratio (95% CI)	0.89 (0.62 – 1.29)		0.5435	0.49 (0.41 – 0.60)		<0.0001

Data are %, mean (SD) or relative risk ratios (95% CI). CAD=coronary artery disease.

Table 6 Inverse probability of weighting: incidence of significant CAD sorted by sex (women versus men) and history of hypercholesterolemia.

Characteristics	Hypercholesterolemia			No Hypercholesterolemia		
	Women (n=2025)	Men (n=4584)	p value	Women (n=2322)	Men (n=5862)	p value
Age, years	61.1±11.2	61.2±11.3	0.6409	61.3±12.1	61.6±11.8	0.3712
Cardiovascular risk factors						
Diabetes	27.6	27.7	0.9332	20.6	21.1	0.6162
Hypertension	79.2	79.6	0.7106	61.9	62.3	0.7366
Current smokers	47.9	48.0	0.9402	39.8	39.8	1.0000
Former smokers	10.3	9.7	0.4511	7.1	6.4	0.2502
Clinical history of ischemic heart disease						
Previous angina pectoris	21.8	21.7	0.9276	11.0	11.1	0.8967
Previous myocardial infarction	16.0	16.2	0.8385	11.0	10.9	0.8961
Previous heart failure	5.0	5.0	1.0000	3.1	2.9	0.6281
Clinical history of cardiovascular disease						
Peripheral artery disease	2.2	2.3	0.8018	1.2	1.3	0.7144
Previous stroke	2.7	2.8	0.8204	2.8	2.7	0.8014
Outcome						
Obstructive CAD	95.3	97.3	<0.0001	93.9	96.5	<0.0001
Risk Ratio (95% CI)	0.55 (0.42 – 0.72)		<0.0001	0.56 (0.45 – 0.70)		<0.0001

Data are n %, mean (SD) or relative risk ratios (95% CI). CAD=coronary artery disease.

Table 7. Inverse probability of weighting: incidence of significant CAD sorted by sex (women versus men) and history of hypertension.

Characteristics	Hypertension			No Hypertension		
	Women (n=3415)	**Men (n=6953)**	**p value**	**Women (n=932)**	**Men (n=3493)**	**p value**
Age, years	62.9±11.1	63.2±11.1	0.4263	57.2±11.9	57.3±11.6	0.7736
Cardiovascular risk factors						
Diabetes	28.5	28.6	0.9156	13.1	13.4	0.8107
Hypercholesterolemia	50.3	50.7	0.7018	30.1	30.4	0.8595
Current smokers	39.7	40.0	0.7694	51.5	51.5	1.0000
Former smokers	9.8	9.1	0.2497	5.2	5.0	0.8034
Clinical history of ischemic heart disease						
Previous angina pectoris	18.6%	18.6%	1.0000	9.7%	9.5%	0.8535
Previous myocardial infarction	14.7	14.6	0.8923	9.9	10.1	0.8569
Previous heart failure	4.6	4.5	0.8177	2.6	2.2	0.4696
Clinical history of cardiovascular disease						
Peripheral artery disease	2.0	2.1	0.7363	0.8	0.9	0.7767
Previous stroke	3.5	3.4	0.7924	1.2	1.3	0.8079
Outcome						
Obstructive CAD	94.0	96.5	<0.0001	95.4	97.6	0.0003
Risk Ratio (95% CI)	0.56 (0.47 – 0.68)		<0.0001	0.50 (0.35 – 0.73)		0.0004

Data are %, mean (SD) or relative risk ratios (95% CI). CAD=coronary artery disease.

Table 8. Interaction test calculations for comparing two estimated risk ratios (relative risks of women versus men) by inverse probability of weighting: diabetes, current smoking, hypercholesterolemia, hypertension for obstructive CAD.

	Presence of risk factor	Absence of risk factor	Interaction P
Current smoker	0.75 (0.54 – 1.03)	0.50 (0.41 – 0.61)	0.02
Diabetes	0.89 (0.62 – 1.29)	0.49 (0.41 – 0.60)	0.002
Hypertension	0.55 (0.42 – 0.72)	0.56 (0.45 – 0.70)	0.46
Hypercholesterolemia	0.56 (0.47 – 0.68)	0.50 (0.35 – 0.73)	0.29

CAD=coronary artery disease.

Sex and outcomes in INOCA/MINOCA and obstructive CAD

After clinical baseline characteristics were well matched between women and men using inverse probability of weighting, female sex was associated with a higher risk of STEMI in patients presenting with obstructive CAD (RR ratio, 1.12; 95% CI, 1.03–1.21). No sex difference in STEMI rates were observed in patients with nonobstructive CAD (RR ratio, 0.92; 95% CI, 0.60–1.43) **(Table 9).** However, the RRs from the 2 subgroups did not significantly differ from each other (interaction test, P=0.1913) **(Table 10).** Among patients with obstructive CAD, women had higher 30-day mortality than men (5.8% versus 3.4%, respectively) (RR ratio, 1.75; 95% CI, 1.48–2.07). No sex difference in mortality was observed with patients with nonobstructive CAD (1.5% versus 1.9%, respectively) (RR ratio, 0.79; 95% CI, 0.31–1.74). The interaction test between the outcomes of obstructive versus nonobstructive CAD was highly significant (P=0.038) **(Table 11).** The absence of sex-related difference regarding 30-day mortality in INOCA/MINOCA patients persisted after stratifying for ACS type (RR 0.57, 95%CI0.18 – 2.09 for STEMI; RR 1.40, 95%CI 0.23 – 4.63 for NSTE-ACS, respectively) **(Tables. 12 to 15**). However, it should be noted that, while in women affected by STEMI and obstructive CAD still presented a higher risk of 30-day mortality than threir male counterparts, the same was not observed in NSTE-ACS.

Table 9. Inverse probability of weighting: outcomes sorted by sex (women versus men) and CAD status in patients with acute coronary syndrome at index event

Characteristics	Obstructive CAD (stenosis ≥50%)			MINOCA/INOCA (stenosis < 50%)		
	Women (n=4119)	Men (n=10119)	p value	Women (n=228)	Men (n=327)	p value
Age, years	61.4±11.9	61.4±11.5	0.8232	60.9±11.7	60.8±12.2	0.9484
Cardiovascular risk factors						
Diabetes	24.4	24.1	0.7045	20.2	22.1	0.5914
Hypertension	69.7	69.6	0.9063	78.6	77.5	0.7589
Hypercholesterolemia	44.5	44.7	0.8277	39.3	38.4	0.8308
Current smokers	43.3	43.9	0.5129	35.1	34.3	0.8458
Former smokers	7.4	7.8	0.4157	9.9	10.8	0.7337
Clinical history of ischemic heart disease						
Previous angina pectoris	15.3	15.6	0.6541	17.8	18.3	0.8806
Previous myocardial infarction	13.0	13.3	0.6320	12.4	12.1	0.9156
Previous heart failure	3.6	3.8	0.5680	3.8	4.4	0.7279
Clinical history of cardiovascular disorders						
Peripheral artery disease	1.6	1.8	0.4067	1.2	1.3	0.9180
Previous stroke	2.7	2.7	1.0000	3.4	2.9	0.7385
Clinical presentation at admission						
ST-segment deviation in anterior leads (at ECG)	20.6	21.0	0.5945	7.2	7.0	0.9280

Systolic BP at baseline, mm Hg	139.6±28.0	139.6±26.6	0.9856	143.2±25.5	143.7±26.1	0.8476
Heart rate at baseline, bpm	80.1±17.9	80.2±17.9	0.7351	79.1±18.3	79.0±20.7	0.9650
Serum creatinine at baseline, mg/dl	0.99±0.50	1.05±0.60	0.0001	96.9±0.30	1.03±0.50	0.1501
Killip Class ≥2	16.5	16.5	1.0000	12.6	14.9	0.4425
Outcomes						
30-day mortality	5.8	3.4	<0.0001	1.5	1.9	0.7236
Risk Ratio (95% CI)	1.75 (1.48 – 2.07)		<0.0001	0.79 (0.31 – 1.74)		0.7237
STEMI	70.7	68.4	0.0064	17.8	18.9	0.7243
Risk Ratio (95% CI)	1.12 (1.03 – 1.21)		0.0064	0.92 (0.60 – 1.43)		0.7238

Data are %, mean (SD) or relative risk ratios (95% CI). CAD= coronary artery disease; BP, blood pressure; MINOCA, myocardial infarction with nonobstructive coronary arteries; STEMI= ST-segment elevation myocardial infarction.

Table 10. Interaction test: calculations for comparing two estimated RR ratios (women versus men) by inverse probability of weighting: STEMI in obstructive versus nonobstructive CAD in patients with acute coronary syndrome at index event**.**

		Group 1 [Obstructive CAD] (n =14238)	**Group 2 [MINOCA/INOCA] (n= 555)**
1	**RR**	1.12	0.92
2	**log RR**	0.1133	-0.0834
3	**95% CI for RR**	1.03 – 1.21	0.60 – 1.43
4	**95% CI for log RR**	0.0296 – 0.1906	-0.5108 – 0.3577
5	**Width of CI**	0.1611	0.8685
6	**SE (=width / (2*1.96))**	0.0411	0.2216
Difference between log risk ratios			
7	**d (=$E1-E2$)**	**0.1967**	
8	**SE (d)**	**0.2253**	
9	**CI (d)**	**-0.2449 – 0.6384**	
10	**Test of Interaction**	**0.8730 (p-value: 0.1913)**	
Ratio of risk ratios			
11	**RRR ratio(=exp(d))**	1.2174	
12	**CI (RRR ratio)**	0.7827 – 1.8934	

Table 11. Interaction test: calculations for comparing two estimated RR ratios (women versus men) by inverse probability of weighting: 30-day mortality in obstructive versus nonobstructive CAD in patients with acute coronary syndrome at index event.

		Group 1 [Obstructive CAD] (n =14238)	**Group 2 [MINOCA/INOCA] (n= 555)**
1	**RR**	1.75	0.79
2	**log RR**	0.5596	-0.2357
3	**95% CI for RR**	1.48 – 2.07	0.31 – 1.74
4	**95% CI for log RR**	0.3920 – 0.7275	-1.1712 – 0.5539
5	**Width of CI**	0.3355	1.7251
6	**SE (=width / (2*1.96))**	0.0856	0.4401
Difference between log risk ratios			
7	**d (=$E1-E2$)**	**0.7953**	
8	**SE (d)**	**0.4483**	
9	**CI (d)**	**-0.0834 – 1.6740**	
10	**Test of Interaction**	**1.7740 (p-value: 0.0380)**	
Ratio of risk ratios			
11	**RRR (=exp(d))**	2.2151	
12	**CI (RRR)**	0.9200 – 5.3335	

Table 12. Inverse probability of weighting: outcomes sorted by sex (women versus men) and CAD status in patients with STEMI at index event

Characteristics	Obstructive CAD (stenosis ≥50%)			MINOCA/INOCA (stenosis <50%)		
	Women (n=2833)	Men (n=7027)	p value	Women (n=38)	Men (n=67)	p value
Age, years	61.0±12.1	60.9±11.6	0.6309	65.5±12.3	62.1±13.2	0.1967
Cardiovascular risk factors						
Diabetes	22.9	22.4	0.5911	20.6	21.5%	0.9149
Hypertension	66.3	66.4	0.9242	86.6	77.0%	0.2364
Hypercholesterolemia	43.1	43.5	0.9169	38.4	30.4%	0.4082
Current smokers	46.2	47.0	0.4713	33.7	36.9%	0.7457
Former smokers	7.0	7.3	0.6027	12.3	10.6%	0.7935
Clinical history of ischemic heart disease						
Previous angina pectoris	11.1	11.4	0.6703	10.4	8.2%	0.7092
Previous myocardial infarction	10.3	10.3	1.0000	7.7	9.6%	0.7462
Previous heart failure	2.7	2.7	1.0000	5.8	5.3%	0.9149
Clinical history of cardiovascular disease						
Peripheral artery disease	1.6	1.7	0.7245	1.2	0.0%	0.3718
Previous stroke	2.8	2.7	0.7841	3.3	3.6%	0.9368
Clinical presentation at admission						
ST-segment shifts in anterior leads (at ECG)	28.7	29.3	0.5530	26.6	23.8%	0.7528

Systolic BP at baseline, mm Hg	137.3±28.4	137.3±27.1	0.9831	136.7±30.4	137.6±27.6	0.8767
Heart rate at baseline, bpm	80.1±18.1	80.3±18.10	0.6535	82.8±19.1	81.2±25.9	0.7528
Serum creatinine at baseline, mg/dl	0.99±0.50	1.05±0.60	0.0001	0.97±0.50	1.06±0.90	0.5230
Killip Class ≥2	17.6	17.5	0.9059	14.4	18.2%	0.6216
Outcome						
30-day mortality	7.2	4.0	<0.0001	3.7	6.2%	0.5810
Risk Ratio (95 %CI)	1.89 (1.57 – 2.27)		<0.0001	0.57 (0.18 – 2.09)		0.5804

Data are %, mean (SD) or relative risk ratios (95% CI). BP=blood pressure; CAD=coronary artery disease; MINOCA, myocardial infarction with nonobstructive coronary arteries; STEMI=ST-segment elevation myocardial infarction.

Table 13. Inverse probability of weighting: outcomes sorted by sex (women versus men) and CAD status in patients with NSTE-ACS at index event.

Characteristics	Obstructive CAD (stenosis ≥50%)			MINOCA/INOCA (stenosis <50%)		
	Women (n=1286)	Men (n=3092)	p value	Women (n=190)	Men (n=260)	p value
Age, years	62.2±11.4	62.5±11.1	0.4882	59.9±10.7	60.5±12.0	0.5957
Cardiovascular risk factors						
Diabetes	27.3	27.7	0.7874	20.8	22.1	0.7411
Hypertension	77.0	76.7	0.8305	78.4	78.0	0.9194
Hypercholesterolemia	47.0	47.3	0.8563	40.2	39.3	0.8475
Current smokers	37.0	37.1	0.9503	33.8	33.3	0.9118
Former smokers	8.0	8.7	0.4503	9.4	10.8	0.6289
Clinical history of ischemic heart disease						
Previous angina pectoris	24.3	25.2	0.5307	19.1	20.5	0.7139
Previous myocardial infarction	18.9	20.1	0.3639	13.0	12.5	0.8754
Previous heart failure	5.6	6.1	0.5246	3.4	4.0	0.7408
Clinical history of cardiovascular disease						
Peripheral artery disease	1.4	2.0	0.1803	0.0	1.3	0.1208
Previous stroke	2.7	2.8	0.8535	2.9	2.5	0.7951
Clinical presentation at admission						
ST-segment shifts in anterior leads (at ECG)	2.4	2.3	0.8420	2.9	2.6	0.8479

Systolic BP at baseline, mm Hg	144.8±25.7	144.7±25.0	0.9532	145.3±24.1	145.3±25.1	0.9983
Heart rate at baseline, beats per minute	80.0±17.1	80.8±17.5	0.9242	78.2±18.5	77.9±18.8	0.8628
Serum creatinine at baseline, mg/dl	0.98±0.40	1.06±0.60	0.0001	0.94±0.30	1.01±0.40	0.0539
Killip Class ≥2	13.9	14.4	0.6667	11.1	13.5	0.4484
Outcome						
30-day mortality	2.6	2.2	0.4202	1.2	0.9	0.7183
Risk Ratio (95% CI)	1.19 (0.78 – 1.82)		0.4207	1.40 (0.23 – 4.63)		0.7188

Data are %, mean (SD) or risk ratios (95% CI). BP=blood pressure; CAD=coronary artery disease; MINOCA, myocardial infarction with nonobstructive coronary arteries; NSTE-ACS = non- ST-segment elevation acute coronary syndrome

Table 14. Interaction test: calculations for comparing two estimated risk ratios (women versus men) by inverse probability of weighting: 30-day mortality in obstructive versus nonobstructive CAD in patients with STEMI at index event**.**

		Group 1 [Obstructive CAD] (n=9860)	**Group 2 [MINOCA/INOCA] (n=105)**
1	**RR**	1.89	0.57
2	**log RR**	0.6366	-0.5621
3	**95% CI for RR**	1.57 – 2.27	0.18 – 2.09
4	**95% CI for log RR**	0.4511 – 0.8198	-1.7148 – 0.7372
5	**Width of CI**	0.3687	2.4520
6	**SE (=width / (2*1.96))**	0.0941	0.6255
	Difference between log risk ratios		
7	**d (=$E_1 - E_2$)**	**1.1987**	
8	**SE (d)**	**0.6325**	
9	**CI (d)**	**-0.0410 – 2.4384**	
10	**Test of Interaction**	**1.8952 (p-value: 0.0290)**	
	Ratio of risk ratios		
11	**RRR (=exp(d))**	3.3158	
12	**CI (RRR)**	0.9598 – 11.4547	

Table 15. Interaction test: calculations for comparing two estimated risk ratios (women versus men) by inverse probability of weighting: 30-day mortality in obstructive versus nonobstructive CAD in patients with NSTE-ACS at index event.

		Group 1 [Obstructive CAD] (n=4378)	**Group 2 [MINOCA/INOCA] (n=450)**
1	**RR**	1.19	1.40
2	**log RR**	0.1740	0.3365
3	**95% CI for RR**	0.78 – 1.82	0.23 – 4.63
4	**95% CI for log RR**	-0.2485 – 0.5988	-1.4697 – 1.5326
5	**Width of CI**	0.8473	3.0023
6	**SE (=width / (2*1.96))**	0.2161	0.7659
	Difference between log risk ratios		
7	**d (=$E_1 - E_2$)**	**-0.1626**	
8	**SE (d)**	**0.7958**	
9	**CI (d)**	**-1.7223 – 1.3973**	
10	**Test of Interaction**	**-0.2042 (p-value: 0.4191)**	
	Ratio of risk ratios		
11	**RRR (=exp(d))**	0.8500	
12	**CI (RRR)**	0.1787 – 4.0443	

DISCUSSION

This study explored the relationships between risk factors, sex, and CAD severity on 30-day mortality after an ACS. Our results demonstrate that the excess risk of death in women compared with men is limited to patients with obstructive CAD, with no significant differences across sexes being observed in INOCA/MINOCA patients. Obstructive CAD is, therefore, the most life-threatening event in women, and as so, warrants intensified efforts to prevent its occurrence.

Our results also shed light on the relationship between traditional risk factors and CAD severity in women. While presence of a history of hypertension or hypercholesterolemia did not alter women's higher likelihood of presenting with MINOCA/INOCA, current smoking status and diabetes mellitus increased the risk of more severe angiographic findings to a greater extent in female than in male patients. These data raise potential challenges, which warrant further considerations.

Impact of conventional risk factors across sexes: the elusive connection between coronary artery disease and coronary heart disease

Cigarette smoking, hypertension, diabetes mellitus, and hypercholesteremia are factors of recognized importance in the development of CHD in the general population. However, the term CHD holds multiple mechanisms that may contribute to ischemic events, and not all of them are necessarily related to the severity and extension of atherosclerosis. For instance, hypercholesterolemia, diabetes and hypertension have been proved to play an important role in the development of coronary microvascular dysfunction (CMD), which has emerged as one of the main mechanisms leading to both INOCA and MINOCA[77]. The mechanisms underlying CMD in non-obstructive CAD are still somehow elusive, and imply both functional and structural changes. These alterations comprise reduced nitric oxide (NO) bioavailability with consequent attenuation of endothelium-dependent vasodilation[78] and increased vasoconstrictor responses to endothelin-1 (ET-1), prostaglandin H2, and thromboxane A2,[79] , all mechanisms that were primarily observed in animal models affected by metabolic dysregulation. The presence of metabolic syndrome is also associated

with an increased sympathetic activity that produces exaggerated alpha-adrenergic coronary vasoconstriction[80]. Likewise, in patients with pre-hypertension and metabolic syndrome, activation of the renin– angiotensin–aldosterone system increases angiotensin II-mediated vasoconstriction in the coronary circulation[81]. These alternative pathways of interplay between conventional risk factors and CHD in absence of obstructive CAD may also offer a partial explaination as to why women, who have been shown to present higher rates of MINOCA and INOCA than men, are burdened with paradoxycally worse outcomes after acute myocardial ischemia. Indeed, women could be particularly susceptible to the vasocostricting and mircovascular effects of conventional risk factors. Still, there is a substantial void in current understanding as to whether there are sex differences in the 4 traditional cardiovascular risk factors and how these differences may impact the severity of CAD and its relation with outcomes.

We approached this issue by reviewing the presence of traditional risk factors in 14 793 patients who were referred to coronary angiography for an ACS. Our data indicate that conventional risk factors are present at a much higher prevalence than previously thought[82] with only 8% to 10% of patients lacking any of the conventional risk factors for the disease. This overall pattern was largely independent of sex and severity of CAD. Therefore, in contrast to prior suggestions[83] we found that only a small minority of patients with nonobstructive CAD lacks conventional risk factors.

It is difficult to establish the precise sex-specific impact of each of the 4 major risk factors on development of significant CAD. Potential confounding is worth considering. Sex is an important confounder for cardiovascular disease. Each of the traditional risk factors increases the rates of cardiovascular mortality and may represent residual confounding. Smokers have more adverse cardiovascular risk factors, such as dyslipidemia and hypertension, than neversmokers. Therefore, nonsmokers may have more protection against development of significant CAD compared with smokers, independently of smoking status. This reasoning applies equally well to all risk factors[84]. To try to circumvent this issue we matched patients sorted by sex and each individual risk factor using

inverse probability of weighting. The weights created a population where the weighted risk factors and control groups were representative of the patient characteristics in the overall population of women and men. Balanced covariates, including age, could not be confounders anymore, a property that would be expected under randomization.

Smoking and CAD severity in women and men

Although cigarette smoking is harmful for any sex, there are some discrepancies between studies in demonstrating a different effect of smoking as a risk factor for CHD in women. Some authors have suggested that smoking has a similar effect on increasing the risk of CHD in both men and women[39] . Others have shown that smoking has a much larger relative detrimental impact on CHD in women[60]. Conflicting results between studies may be related to many factors including definition of smokers and synergisticaction of smoking with other conventional risk factors. Of note, cigarette smoking interacts with other conventional risk factors to greatly increase the risk for cardiovascular disease. The US Surgeon General report suggests that the presence of another major risk factor with smoking is estimated to quadruple the risk of CV disease[85]. Thus, a lower relative risk of smoking may simply be a result of studying a population that has few other risk factors for the disease.

In a recent investigation conducted on patients included in the ISACS Archives network, [86] it was possible to confirm the presence of sex difference in susceptibility to tobacco smoking with regards to incidence of STEMI. The largest risk difference between male and female current smokers was found in young-middle aged people defined as those below 60 years of age. In young middle-aged women, the estimated effect of smoking was a 90% increase in risk of STEMI, which was statistically significant, compared with a 68% increase in young middle-aged men. The relative risks from these subgroups significantly differed from each other using a formal test of interaction[76]. The RR for smoking was remarkably higher among women than men at any level of smoking intensity: the RR for STEMI among young middle-aged women who smoked 1 to 10 cigarettes per day was

1.51 representing a 34% excess RR compared with young middle-aged men smoking the same number of cigarettes per day (RR 1.17). Although heavy smokers (over 20 cigarettes per day) had more adverse cardiovascular events than light smokers, the relative risk for STEMI was still 40% higher among women (RR 2.29) than men (RR 1.89).

A possible mechanism for the increased risk of STEMI among women may involve endothelial function. Smoking causes endothelial dysfunction that persists for years[87], and women have more endothelial dysfunction that men [88]. Early autopsy studies demonstrate that smoking contributes to development of plaque erosion [89], and women show more plaque erosion than men [90]. Recent work also showed that smoking may increase the risk of CHD by promoting coronary atherosclerosis progression and that the greatest impact of smoking can be observed in women[91]. If this is true, the primary benefit from quitting smoking in women would be to prevent further accumulation of exposure, thus progression of atherosclerosis.

In the current study we addressed these pathophysiological interrogatives by investigating whether current smoking status could play a different role in atheroslerosis progression in women versus men. It emerged that while in nonsmokers the strong association between female sex and INOCA/MINOCA presentation persisted, this phenomenon diseappeared in women who were current smokers. In fact, this patient subgroup had a much greater risk of obstructive CAD with statistical evidence of interaction. This finding serves as a further confirmation that the harm of smoking differs by sex. Moreover, our study adds to the understanding of the relationship between smoking and CHD events by suggesting an important mechanistic basis: its association with severe atherosclerotic plaques in the coronary arteries. Excess risk of obstructive CAD in female compared with male smokers might have some potential explanations. Chemical constituents of smoke have high oxidant and inflammatory power that can potentiate inflammatory response[92], and women might extract a greater quantity of toxic agents from the same number of cigarettes than men[93]. Plasma levels of estrogen are lower in smoking than in nonsmoking women, which may lead to accelerated progression of CAD[94]. However, in light of the available evidence, no definite answer can be given.

Unfortunately, there is an alarming trend toward increased smoking in women and, therefore, better methods leading to prevention and cessation of smoking are needed.

Diabetes and CAD severity in women and men

There is strong evidence from many studies that women with diabetes mellitus face an increased cardiovascular risk relative to men[95] Large-scale meta-analyses summarizing all the evidence available to date have provided compelling evidence that diabetes confers a 44% greater excess risk of coronary heart disease and a 27% greater excess risk of stroke in women than in men, independent of sex differences in other major risk factors[96].[97]Still, the level to which presence of other conventional risk factors may influence this sex related discrepancy is unclear . Several potential interacting factors may contribute to the acceleration of CHD risk in women with diabetes mellitus. Diabetes mellitus is more likely to be associated with elevations in systolic and diastolic blood pressure in both sexes, and with current somking in female patients[98] [99]. We tried to circumvent such issues by matching patients with inverse probability of weighting. We found that in patients without diabetes significant CAD rates were lower in women compared with men (RR: 0.49; 95%CI, 0.41 – 0.60). The presence of diabetes equalized rates of significant CAD by sex (RR: 0.89; 95% CI,0.62 – 1.29), as confirmed by the interaction test between the two RRs (p=0.002). The higher relative risk of significant CAD conferred by diabetes in women has several possible explanations. Inflammatory factors may have a greater role in perturbing insulin action in women.[100] Genes may influence the effect of diabetes differentially by sex.[101] Women have worse glycemic control, which may have a consistent effect on risk of progression of CAD.[102] In addition, a consistent effect on CAD risk may be the duration of diabetes.[103] These hypotheses, however, are still assumptions. We do not have data from our cohort to clarify why diabetes is a stronger risk factor for developing significant CAD in women compared with men.

The higher RR of mortality after ACS conferred by obstructive CAD in women compared with men may find explaination in this higher susceptibility of female patients to diabetes[104] [105].

Screening for prediabetes mellitus combined with more stringent follow-up of women with a history of gestational diabetes mellitus has the potential to dramatically reduce the burden of CAD and sex differences in outcomes.

Hypercholesterolemia, hypertension and CAD severity in women and men

Hypercholesterolemia and hypertension are both well-documented primary risk factors for CHD, independently from sex. The MONICA (Monitoring of Trends and Determinants in Cardiovascular Disease) study reported that the increase in CHD events with increasing total cholesterol holds over the entire range of patient characteristics[106]. The INTERHEART study[39] demonstrated that hypertension was significantly associated with acute MI, with directionally similar odds ratios in women and men. This comparable impact of hypercholesterolemia and hypertension on CHD across sexes was reflected in the current study by the finding that their presence did not alter women's higher incidence of INOCA/MINOCA. The observation of a nonsignificant impact of these two factors on severity of CAD in women compared with men highltights the nonlinear fashion with which risk factors, atherosclerosis and clinical manifestations of myocardial ischemia interact. As mentioned above, both hypertension and dyslipidemia have been proved to play an important role in the development of microvascular dysfunction, which is in turn one important determinant of INOCA and MINOCA, and is most prominent in women. It should be noted that early studies on use of lipid lowering treatment in patients with angina and normal or near normal coronary arteries were of the utmost importance in the process of gaining insight into the pathogenesis of the disease. In 2000, Houghton et al. assessed statin effects on coronary resistance in patients with a history of chest pain and normal angiograms[107]. Coronary endothelium-independent and dependent vasodilatation were examined using intracoronary administration of adenosine and acetylcholine, respectively, and coronary blood flow was measured with an intracoronary flow Doppler wire. After 6 months of 20 mg pravastatin daily, the authors found no significant differences in adenosine-mediated increase in coronary blood flow compared to baseline (i.e. there were no changes in endothelium-independent

vasodilation) but a significant difference in acetylcholine infusion peak (endothelium-dependent vasodilation), which rose from 97 ± 13% to 160 ± 16% (p=0.01). There was also a strong correlation (r=-0.87, p=0.02) between improvement in coronary flow reserve (CFR) and reduction in LDL cholesterol, suggesting that endothelial function may depend upon circulating lipid profiles, among other factors[107]. Further insights into the role of statins in coronary circulation were elucidated by Caliskan et al., who explored the effect of 20 mg atorvastatin per day in patients with normal epicardial angiograms but slow coronary flow (i.e. late coronary opacification during angiography, defined as corrected thrombolysis in MI frame count >2 standard deviations from the normal published range)[108]. Previous acute MI was an exclusion criterion in this study. CFR, using transthoracic Doppler echocardiography, was evaluated at baseline and after 8 weeks of statin treatment. At follow-up, the authors observed significant increases in CFR (from 1.95 ± 0.38 to 2.54 ± 0.56, p<0.001) and hyperaemic diastolic peak flow velocity (from 45.4 ± 12.7 cm/s to 53.0 ± 15.8 cm/s, p=0.01) and a significant decrease in diastolic peak flow velocity (from 23.3 ± 5.6 cm/s to 20.7 ± 3.5 cm/s, p=0.02) in atorvastatin-treated patients, demonstrating that statin therapy significantly improves the microvascular function of patients with normal angiograms and slow coronary flow[108]. In light of these considerations, hypertension and hypercholesterolemia, remain targets for potential strategies of primary prevention remains pivotal even in female sex, as their treatment may improve prognosis and quality of life even in absence of obstructive CAD.

Sex Differences in Severity of CAD and Mortality From ACS

The results of current study challenge and provide further insight into the seemingly paradoxical phenomenon typically observed in female patients affected by ACS, which is usually described as follows : women with myocardial ischemia, whether it be ACS or otherwise, have more adverse outcomes than their male counterparts, even though they are more likely to have insignificant CAD.[66] [109] Although sex differences in mortality after acute myocardial infarction have been

confirmed in several studies, extending these observations to the overall INOCA/MINOCA female population is an assumption that is not confirmed by the current analyisis.

In our cohort, approximately 4% of women and men undergoing angiography had INOCA/MINOCA, a finding that is concordant with prior work exploring obstructive CAD status in myocardial infarction. Although female sex was indeed associated with a higher risk of INOCA/MINOCA after multivariable logistic regression analysis, a sex-related excess in 30-day mortality risk was observed only in patients with obstructive CAD (RR 1.75, 95% CI 1.48 – 2.07), while no difference was found in patients presenting with milder angiographic features (RR 0.79, 95% CI 0.31 – 1.74).

There is a paucity of studies on outcomes of patients categorized as obstructive versus nonobstructive CAD among women and men[109-111]. The sole study that investigated these associations in ACS derived data from the The National Cardiovascular Data Registry ACTION Registry-GWTG (Acute Coronary Treatment and Intervention Outcomes Network Registry–Get With the Guidelines)[8]. In this investigation, the authors evaluated 18,918 MI patients with nonobstructive CAD defined as <50% stenosis of all major epicardial vessel. Analyses revealed that a similar proportion of women and men with nonobstructive CAD died during hospital stay. On the opposite, women with obstructive CAD experienced less favorable short-term mortality than men.

One limitation of the ACTION Registry-GWTG study is that interaction between sex and type of MI at index admission was not evaluated. STEMI and NSTEMI are clinical entities that differ considerably in the pathophysiology and management options.[8 112]. Previous studies found a sex-ACS subtype interaction in a large sample of participants in clinical trials, whereby women with STEMI fared worse, and women with non- STEMI (NSTEMI) fared better than men with similar clinical presentation, but this data was not unanimously confirmed by other investigations[113] . In this era of quality-improvement initiatives, researchers might consider several approaches including matching to identify sex difference in outcomes sorted by selected characteristics. In 2018, an investigation

from the ISACS-TC registry provided evidence that female sex was associated with an increased risk of 30-day mortality rates after STEMI[51]. In line with these findings, and in order to circumvent potential issues derived from investigating outcomes after ACSs at population level and not at individual level, in the present studies we further stratified the analysis on 30-day mortality based on ACS type, namely STEMI and NSTE-ACS. The results showed that, while in STEMI the association between sex and outcomes was similar to the general cohort, with female sex deterimining an excess in 30-day mortality risk only in presence of more severe angiographic features, a different picture was delineated in NSTE-ACS patients, who did not show sex-related differences in outcomes at any level of CAD severity.

In sum, although the results of our study do not deny the concept that INOCA/MINOCA is associated with a significant and quantifiable risk for cardiovascular morbidity and mortality, they also underscore that CAD severity should be considered a better proxy for prognosis and that women with obstructive CAD fare worse than men, especially if presenting with STEMI.

Limitations

Our study has several potential limitations. First, an observational study is potentially open to confounding. We minimized this factor by using a study design based on matching on the propensity score and inverse probability of weighting to balance the sex-specific covariate distributions. On the other hand, randomized controlled trials are not a viable option as it is unethical to administer an exposure to one or more risk factors. Second, patients who have had coronary angiography do not necessarily represent the general ACS population since those who died before hospital admission are missing. Yet, most of the RRs associated with 30-day mortality among women and men are similar to those reported in recent large cohort studies dealing with the incidence of obstructive CAD in ACS, and support the external validity of the study. Third, some of the risk factors were ascertained by the general practitioner, which might have led to error in some individuals. Although we acknowledge some potential misclassifications, it is unlikely that these misclassifications differentially affect

women over men and, thus, are unlikely to modify the sex differences that we found. Fourth, our study used the predominant method of CAD diagnosis in current clinical practice, coronary angiography. Angiographic evaluations were carried out at local level and hence, the reliability of the observations, especially as it relates to minimal CAD (stenosis < 50%) are difficult to assess. However, this individual characterization of CAD reflects the real-world CAD categorization. Finally, residual confounding from concomitance of non-traditional risk factors such as stress, family history and adherence to healthy lifestyle behaviors cannot be excluded.

CONCLUSIONS

The current study found greater 30-day mortality related to obstructive CAD in women compared with men. Cigarette smoking and diabetes mellitus disproportionally increase the risk of obstructive CAD in women, and as so they are key factors in explaining sex differences in outcomes from ACS. Intense efforts to reduce tobacco use and increase screening for prediabetes mellitus have potential to decrease the sex lag in cardiovascular disease mortality in women compared with men.

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