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Coronary artery disease in women: From the yentl syndrome to contemporary treatment

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of coronary disease and female gender after the implementation of newer therapeutic interventional and pharmaceuticals' approaches of the modern era.

Key words: Yentl syndrome; Women coronary disease; Acute coronary syndromes; Female gender; Invasive treatment

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Core tip: Coronary disease although remains a leading cause of morbidity and mortality in women, is however underestimated mainly because of the protective role of estrogens that results in lower rates of the disease until the age of mid-fifty. In this review detailed information about the prevalence and the consequences of the disease in women are quoted as well as evidence concerning the results of invasive treatment and use of modern drug therapy.

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Abstract

In recent years attention has been raised to the fact of increased morbidity and mortality between women who suffer from coronary disease. The identification of the so called Yentl Syndrome has emerged the deeper investigation of the true incidence of coronary disease in women and its outcomes. In this review an effort has been undertaken to understand the interaction

INTRODUCTION

Coronary artery disease (CAD) constitutes a form of modern epidemic, as it still remains the leading cause of mortality and morbidity in the ageing western societies^[1]. The prevalence of CAD in the general population varies, depending on age and sex. In terms of age, there is a trend of more incidents in older ages. Concerning sex, until the age of 60 years old, the predicted probability of having an acute myocardial infarction (AMI) is by

Table 1 Remaining lifetime risks for cardiovascular disease and other diseases among men and women free of disease at 40 and 70 years of age remaining life^[57]

| Diseases | Remaining lifetime risk at the age of 40 yr | | Remaining lifetime risk at the age of 70 yr | |
|-----------------|---|----------------------|---|---------|
| | Men | Women | Men | Women |
| Any CVD | 2 in 3 ¹ | 1 in 2 ¹ | 2 in 3 ² | 1 in 2 |
| CHD | 1 in 2 | 1 in 3 | 1 in 3 | 1 in 4 |
| AF | 1 in 4 | 1 in 4 | 1 in 4 | 1 in 4 |
| CHF | 1 in 5 | 1 in 5 | 1 in 5 | 1 in 5 |
| Stroke | 1 in 6 ³ | 1 in 5 ³ | 1 in 6 | 1 in 5 |
| Dementia | ... | ... | 1 in 7 | 1 in 5 |
| Hip fracture | 1 in 20 | 1 in 6 | ... | ... |
| Breast cancer | ... | 1 in 8 | ... | 1 in 15 |
| Prostate cancer | 1 in 6 | ... | 1 in 9 | ... |
| Lung cancer | 1 in 13 | 1 in 16 | 1 in 15 | 1 in 20 |
| Colon cancer | 1 in 19 | 1 in 21 | 1 in 25 | 1 in 27 |
| DM | 1 in 3 | 1 in 3 | 1 in 9 | 1 in 7 |
| Hypertension | 9 in 10 ³ | 9 in 10 ³ | 9 in 10 | 9 in 10 |
| Obesity | 1 in 3 | 1 in 3 | ... | ... |

¹Age 45 yr; ²Age 65 yr; ³Age 55 yr. AF: Atrial fibrillation; CHD: Coronary heart disease; CHF: Congestive heart failure; CVD: Cardiovascular disease; DM: Diabetes mellitus; ...: Not estimated.

far higher in men than in women (60.6% *vs* 33.0%, respectively)^[1]. Therefore, CAD is widely believed to be a man's disease, although it accounts for more deaths in women at the age of 35 years than breast cancer (Table 1)^[2]. This has been mainly attributed to the protective role of estrogens in the cardiovascular system as they enhance vascular function, reduce the inflammatory response, increase metabolism and insulin sensitivity and finally promote cardiac myocyte and stem cell survival^[3]. As a consequence, female hormones may partially account for women's longevity observed in randomized control trials, where women with CAD are older than men and have more co-morbidities such as diabetes, hypertension and chronic kidney disease^[4,5]. At menopause, the lack of the protective effect of estrogens leads to a 10-fold increase in the prevalence of CAD in women compared to a 4.6 fold increase in men of the same age^[6]. Finally, by the 7th decade of life the increasing rate of CAD among women results in similar rates of the disease among the two genders, although lifestyle factors seem to have a different impact on clinical outcome between gender^[1,7,8].

Due to the above mentioned characteristics of the female gender, and the fact that the majority of trials more often enroll younger patients, the representation of women in clinical trials was until recently relatively low, approximately 30% (Table 2)^[9,10]. Even in one of the largest contemporary trials designed to compare outcomes between invasive and conservative pharmacological treatment in patients with stable CAD, the COURAGE trial (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation), men encountered for approximately 85% of the study group^[11]. As a result, women suffering from CAD are handled diagnostically and therapeutically based on conclusions drawn mainly from male populations. This observation underscores the need for a more gender focused approach both in every day clinical practice but also in large scale trials. The

purpose of the present review is to explore the available data depicting the best strategies to recognise and treat CAD in women.

WOMEN AND SYMPTOM PRESENTATION

It has been demonstrated that women tend to present for chest pain evaluation in the emergency room at a greater rate compared to men (4.0 million visits for women *vs* 2.4 million visits for men). However, women tend to present with less typical symptoms, such as fatigue (70.7%), sleep disturbance (47.8%) and shortness of breath (42.1%)^[12], back pain, indigestion, weakness, nausea/vomiting, dyspnoea and weakness^[13,14]. At an older age, with more co-morbidities including diabetes, peripheral vascular disease, chronic kidney disease and hypertension^[15]. A great amount of literature explored this phenomenon giving rise to large scale clinical trials which resulted in the identification of three paradoxes with regard to female sex and CAD manifestation^[13]. (1) Women have disproportionately lower burden of atherosclerosis and obstructive CAD compared with the extent of angina they complain for; (2) Compared to men, women have less severe CAD despite the fact that they are older with a greater risk factor burden; and (3) Even though CAD is less evident in women, as illustrated by invasive diagnostic imaging modalities, females still have a more adverse prognosis compared to men.

Another parameter of great importance is the increasing prevalence of the cardiac X syndrome or coronary microvascular dysfunction among women of post-menopausal age. It is evident that almost 40% of the operated coronary angiographies reveal non obstructive atherosclerosis although patients present with anginal symptoms and positive exercise training results^[16]. A large proportion out of 30% of these findings is attributed to coronary microvascular dysfunction as no other identifiable

Table 2 Women are considerably underrepresented in clinical trials^[9]

| Study | Sample MT,PCI | Enrollment <i>n</i> | Mean age (yr) | Male (%) | DM (%) | % Prior MI | 1/2/3-Vessel CAD | % No symptoms | % Mean EF | % Follow up, yr |
|--|------------------|---------------------|------------------|-------------|--------|------------|---------------------|------------------|-----------------|--------------------|
| RITA-2 | 514/504 | 1992-1996 | 58 (Median) | 82 | 9 | 47 | 60/33/7 | 20 | ND ¹ | 7 |
| ACME-1 | 115/112 | 1987-1990 | 60 | 100 | 18 | 31 | 100/0/0 | 9 | 68 | 2.4-5 ² |
| ACME-2 | 50/51 | 1987-1990 | 60 | 100 | 18 | 41 | 0/100/0 | 18 | 67 | 2.4-5 ² |
| AVERT | 164/177 | 1995-1996 | 59 | 84 | 16 | 42 | 56/44/0 | 16 | 61 | 1.5 |
| Dakik <i>et al</i> ^[58] | 22/19 | 1995-1996 | 53 | 59 | ND | 100 | 44/41/15 | 0 | 46 | 1 |
| MASS | 72/72 | 1988-1991 | 56 | 58 | 18 | 0 | 100/0/0 | 0 | 76 | 5 |
| MASS II | 203/205 | 1995-2000 | 60 | 68 | 30 | 41 | 0/42/58 | ND | 67 | 1 |
| ALKK | 151/149 | 1994-1997 | 58 | 87 | 16 | 100 | 100/0/0 | 0 | ND ³ | 4.7 |
| Sievers <i>et al</i> ^[59] | 44/44 | ND | 56 | ND | 0 | 55 | 100/0/0 | ND | ND | 2 |
| Hambrecht <i>et al</i> ^[60] | 51/50 | 1997-2001 | 61 | 100 | 23 | 46 | 58/27/15 | 0 | 63 | 1 |
| Bech <i>et al</i> ^[61] | 91/90 | ND | 61 | 64 | 12 | 25 | 66/28/6 | 0 | 65 | 2 |

¹Ninety-three percent of patients had very good or excellent wall motion score; ²Ninety-seven percent of patients were in New York Heart Association class 1;

³Follow-up was 2.4 years (mean) to follow-up interview, 3 years (mean) to follow-up exercise test, and 5 years (median) for ascertainment of deaths and MI events. MT: Medical treatment; DM: Diabetes mellitus; EF: Ejection fraction; ND: No data available.

cause can be found. The most interesting aspect of this group of patients is the fact that it is consisted in its great proportion (almost 70%) of post-menopausal women^[17]. In contrast to the findings of earlier studies that microvascular angina does not affect long term prognosis^[18], it is evident nowadays from a large retrospective analysis of 11223 patients referred for coronary angiography with stable angina, that patients with non-obstructive CAD consolidate a further increase in the risk of coronary events and of all-cause mortality (HR = 1.85; 95%CI: 1.51-2.28; and 1.52; 95%CI: 1.24-1.88, respectively)^[19].

Thus, women are frequently a clinical challenge for the cardiologist and their symptom misinterpretation may lead to the wrong diagnosis and treatment with potentially unfavourable consequences. Symptom evaluation and recognition in women is a matter of great importance, since it has been shown that when typical symptoms accompany an acute coronary syndrome (ACS) there is no difference in the disease diagnosis between women and men^[20]. Moreover, when prodromal symptoms are recognised in women before an ACS, women have better survival in comparison to men^[21].

WOMEN AND TREATMENT STRATEGIES

Not only diagnostic evaluation of women may be misleading, but also the appropriate treatment selection can be difficult. It was already recognized in 1991 that women suffering from CAD had less chances to be introduced either in coronary angiography or percutaneous coronary intervention (15.4% of women *vs* 27.3% of men, $P < 0.001$)^[22]. This approach was demonstrated even in cases were admission symptoms were more prominent in women than in men^[23]. Unlike men, women were submitted less frequently to any diagnostic or therapeutic intervention creating in this way dissimilarity on curing procedures. This alarming fact was described by Bernadine Healy, the first woman director of National Health Institute in United States, as the Yentl syndrome named after the Jewish heroine of Isaac Singer,

who was masqueraded as a boy in order to be educated in the Talmud philosophy. Healy concluded that when a woman has been shown to have extensive CAD, like men, only then she gets the appropriate treatment^[24]. Since, a plethora of studies examined gender differences in order to provide the best treatment options for women.

WOMEN AND PERCUTANEOUS CORONARY INTERVENTION

One of the first studies comparing the impact of percutaneous coronary interventions (PCI) with bare metal stent (BMS) implantation between females and males, revealed that women had 50% more chance of death in comparison to men after adjustment for age, comorbidities, and extend of coronary atherosclerosis^[25]. However, in the same analysis, after final adjustment for Body Surface Area, mortality rates were similar between the two genders, although a slighter increased rate of stroke, vascular complications and repeat in-hospital revascularization was observed in women^[25]. Similar results were reported in a retrospective analysis from Mayo Clinic investigating 18885 consecutive, patients who underwent PCI between 1979 and 1995 (early group) and between 1996 and 2004 (late group)^[26]. The results indicated no difference in terms of 30-d mortality, while after adjustment for baseline risk factors, again there was no difference observed in short or long term mortality between the two genders (Figures 1 and 2)^[26]. The study indicated that between the two groups a decrease in 30 d mortality was observed in both genders during the 25-year follow up period.

A retrospective study from Rotterdam investigated the outcomes of Sirolimus Eluting Stents, Paclitaxel Eluting Stents and BMS in women^[27]. In this study, even though women had worse baseline characteristics compared to men, no differences in 3-year outcomes were detected between males and females.

A recent meta-analysis, which included 43904 patients (26.3% women) in 26 trials, assessed the safety and

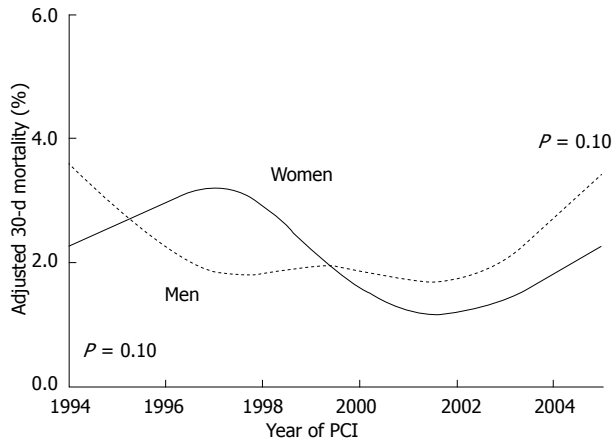


Figure 1 Mayo clinic percutaneous coronary interventions registry: 12798 pts adjusted 30-d mortality after percutaneous coronary interventions^[26].

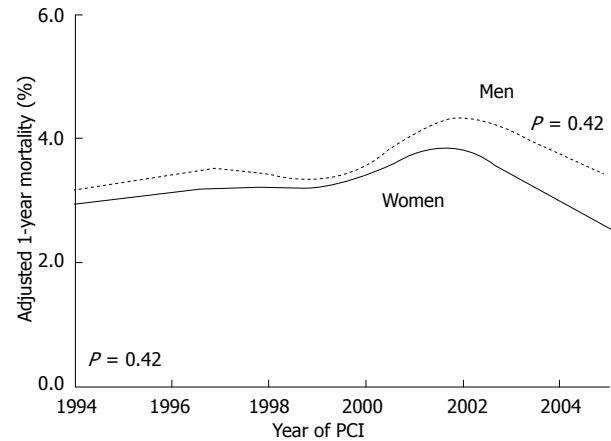


Figure 2 Mayo clinic percutaneous coronary interventions registry: 12798 pts Adjusted 1-year mortality after percutaneous coronary interventions^[26].

efficacy of DES in women^[28]. The study showed that DES implantation in women was more effective and safe than BMS implantation. Furthermore, it was observed that 2nd and 3rd generation DES, such as everolimus-eluting Xience and Promus stents, zotarolimus-eluting Endeavor and Resolute stents, biolimus-eluting Biomatrix and Nobori stents, and sirolimus-eluting Yukon stents, were associated with an improved safety profile compared with early-generation DES^[28]. These results suggest that women undergoing PCI may benefit more when DES and moreover newer generation DES are used.

An interesting meta-analysis was designed in order to evaluate whether female gender is an independent risk factor for repeated coronary revascularization after PCI. The results indicated that although female sex increases the short term rate of repeated revascularization after PCI the long term rate was the same between the two genders clarifying the fact that even for this parameter female gender is not an independent risk factor^[29].

Bleeding complications at the point of vascular puncture, hematomas and retroperitoneal bleedings are decreased in the current era. This is mainly due to introduction of less aggressive anticoagulant regimens, adjustment of heparin dose according to body mass index and smaller size catheters. However, women still continue to be at 1.5 to 4 times greater risk for bleeding in comparison to men (Table 3)^[30]. Reduced Body Surface Area, altered pharmacokinetics and diminished drug metabolism are the main aspects of female gender that attribute mostly in these higher bleeding rates.

Newer anticoagulant agents were recently introduced in clinical practice raising expectations for further bleeding risk reduction. In order to evaluate this hypothesis, novel studies were contacted to evaluate the action of direct thrombin inhibitor bivalirudin (ANGIOX[®]) in both genders who suffered from moderate and high-risk ACS^[31]. Out of 7789 patients submitted to PCI, 2561 received heparin and II b-IIIa glycoprotein inhibitor, 2609 received bivalirudin in combination to II b-IIIa glycoprotein inhibitor and 2619 received bivalirudin

solely. The group of patient to receive bivalirudin in comparison to the group of patient receiving heparin in combination to II b-IIIa glycoprotein inhibitor displayed the same degree of ischemic events but with a lesser degree of major bleeding (4% *vs* 7%, $P < 0.0001$)^[31]. Interestingly, bivalirudin alone decreased the variance of bleeding between the two genders, but it did not completely eliminate it.

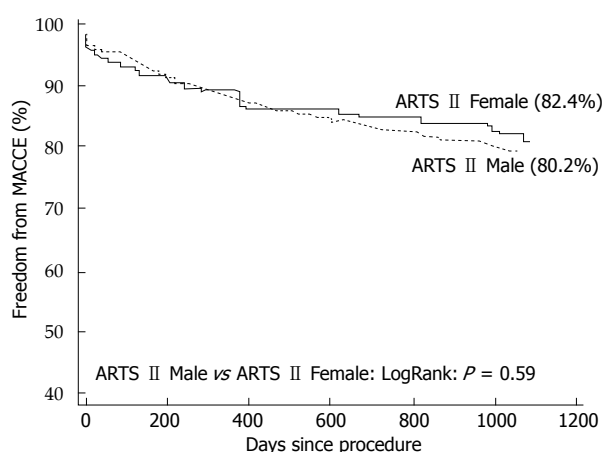
In order to achieve decreased bleeding rates in women, the idea of radial approach during intervention was implemented into clinical practice. However, due to women's smaller vessel size and lower pain threshold it was revealed that 14% of women were finally switched to femoral approach in contrast to 1.7% of men^[32]. In the same study however, during 299 radial interventions in women no major bleeding was observed, whereas in 601 femoral intervention, 25 major bleedings were recorded ($P = 0.0008$). In addition, radial approach was related with a lower rate of minor bleeding (6.4% *vs* 39.4% $P = 0.00001$). These favourable results indicate that radial approach during PCI in women is safer in terms of bleeding, even though there are more difficulties to initiate the procedure through the particular access site.

WOMEN AND CORONARY ARTERY BY-PASS GRAFTING

In the past, women submitted to CABG were shown to have higher perioperative morbidity and mortality compared to men^[33-35]. These first results raised the issue of CABG safety in women and initiated the conduction of several newer trials. Indeed, over 20 trials investigated the impact of CABG in women compared to men. A recent meta-analysis confirmed that women experience higher mortality rates in comparison to men in terms of short-, mid- and long-term follow-up with the higher mortality recorded in the short-term period^[36]. Several explanations for this observation have been proposed such as the delayed reference of women to CABG when

Table 3 Women have higher rate of vascular complications after percutaneous coronary interventions^[30]

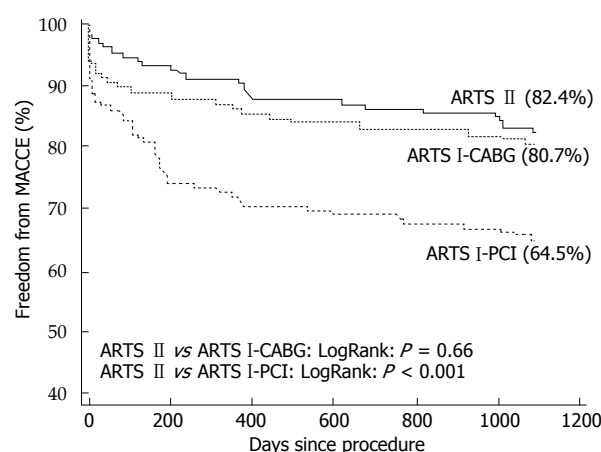
| Study | n | Vascular complications | | |
|------------|--------|------------------------|-------------------|---------|
| | | Women | Men | P-value |
| Alfonso | 981 | 11/157 (7.0%) | 16/824 (2.0%) | < 0.01 |
| Antoniucci | 1019 | 14/234 (6.0) | 24/785 (3.0%) | 0.01 |
| BOAT | 989 | 6/237 (2.5%) | 6/752 (0.8%) | 0.05 |
| CAVEAT | 512 | 14/128 (10.8%) | 22/384 (5.8%) | 0.003 |
| NACI | 2855 | 39/971 (4.0%) | 28/1884 (1.5%) | < 0.05 |
| NCN | 109708 | 1955/36204 (5.4%) | 1985/73504 (2.7%) | < 0.001 |
| NHLBI | 2136 | 24/555 (4.4%) | 36/1581 (2.3%) | < 0.05 |
| NHLBI | 2524 | 44/883 (5.0%) | 43/1641 (2.6%) | < 0.01 |
| STARS | 1965 | 44/570 (7.8%) | 39/1395 (2.8%) | < 0.01 |
| Trabatoni | 1100 | 15/165 (9.3%) | 33/935 (3.5%) | 0.004 |
| Welty | 5989 | 34/2096 (1.6%) | 23/3893 (0.6%) | < 0.001 |
| WHC | 7372 | 78/2064 (3.8%) | 125/5308 (2.4%) | < 0.001 |
| Combined | 137150 | 2278/44264 (5.1%) | 2380/92886 (2.6%) | |

**Figure 3** Freedom from major adverse cardiac and cerebrovascular events after percutaneous coronary intervention in Arterial Revascularization Therapies Study-Part II^[41].

CAD extends to a greater degree, the smaller size of women coronary vessels that creates technical issues to the surgeon or finally the limited use of left internal mammary artery in women^[37-39].

Arterial Revascularization Therapies Study Part I (ARTS I) was one of the first studies to compare CABG and PCI in women. The study demonstrated that for a total of 1205 patients there was no significant difference in terms of death, stroke, or myocardial infarction between the two genders. However, stenting was associated to a greater need for repeated revascularization^[40,41].

Newer studies in the Drug Eluting Stent (DES) era sought to further investigate the effect of gender on PCI and CABG outcomes. The multicenter randomized study Arterial Revascularization Therapies Study-Part II (ARTS II) was designed to evaluate the outcomes of Sirolimus Eluting Stent implantation in comparison to BMS implantation and Coronary Artery Bypass Grafting (CABG) in patients with multivessel CAD^[41]. In ARTS II, although women tended to have more risk factors compared to men, they experienced the same rate of adverse events with men at 30 d, one year and three years

**Figure 4** Freedom from major adverse cardiac and cerebrovascular events after coronary artery by-pass grafting and percutaneous coronary intervention with bare metal stent and sirolimus eluting stent implantation in women^[41].

after Sirolimus Eluting Stent implantation (Figure 3)^[37]. Additionally, it was observed that both genders had a more favorable clinical outcome with Sirolimus Eluting Stents compared with BMS but similar to CABG (Figure 4)^[41].

These results could potentially institute PCI as the first choice treatment in women with multivessel disease.

WOMEN AND ACUTE CORONARY SYNDROMES

The vast majority of women, about 60%, experience an acute coronary syndrome (ACS) or sudden cardiac death as the first manifestation of the disease^[42]. The initial results comparing gender differences in patients with ACS were presented in the pre-thrombolytic era, where a 28% mortality rate was demonstrated in women compared to a 16% mortality among men^[43]. Women also experienced a 3 fold higher rate of reinfarction. In the following years, the introduction of thrombolysis decreased the total mortality rates in the general population. However,

a discrepancy was still evident between the two genders (30 d unadjusted mortality rate was 13.1% in women and 4.8% in men)^[44]. Newer, large scale studies were undertaken in order to re-evaluate these results in the modern era of invasive approach to ACS. One of the largest trials investigating these aspects enrolled 78254 patients (39% women) with AMI in 420 United States hospitals from 2001 to 2006^[45]. The results reconfirmed the data observed in previous trials. The study showed that women with ACS are older, with more comorbidities such as hypertension, diabetes, and metabolic syndrome and tend to present less often with ST-elevation AMI^[46-48]. Adjusted analysis revealed no differences in terms of mortality between the two genders for ACS, but in the subgroup of ST Elevation Myocardial Infarction (STEMI) there was a statistically significant and almost double proportion of mortality in women (10.2% women *vs* 5.5% men, $P < 0.0001$). An important conclusion from this trial was the fact that women received less often aspirin and b-blockers and were less often treated in an invasive manner with percutaneous transluminal coronary angioplasty.

This approach was also noticed in an earlier contacted study in Minnesota (46% less chances of invasive approach) as well as in a Swiss national registry where the rate of women introduced in PCI was significantly lower than men (OR = 0.70; 95%CI: 0.64 to 0.76)^[15,48].

These observations raised the question of whether physicians prefer more conservative strategies because women have higher mortality rates with invasive procedures or whether women are less willing to undergo such a procedure. PRimary Angioplasty in patients transferred from General community hospitals to specialized PTCA Units with or without Emergency thrombolysis 1 and 2 studies evaluated 520 patients with STEMI treated with thrombolytics and 530 patients treated with primary PCI. Women treated with thrombolytics had almost two fold higher mortality than women treated with primary PCI ($P = 0.043$)^[49]. Therefore, although patient demographic data were not adjusted to body mass index, which could have an effect on the unadjusted doses of streptokinase used, it can be concluded that primary PCI to treat women with AMI is superior to a more conservative approach. Similar results were demonstrated in the Global Utilization of Streptokinase and TPA for Occluded Coronary Arteries II-B and in a sub-analysis of the Primary Angioplasty in Myocardial Infarction trial comparing newer thrombolytic agents *vs* PCI^[50,51]. More recent studies showed that mortality and major adverse cardiac events, though higher among women with primary PCI in unadjusted analyses, are comparable in both genders after adjusting for age, hypertension, smoking, diabetes mellitus, stent diameter, and time between symptoms onset and ambulance arrival^[52-55]. A meta-analysis that included 8 trials and almost 10115 patients, demonstrated that low-risk women with ACS may benefit from a more conservative approach. However, males and high-risk females with ACS treated with an invasive strategy have similar clinical outcome in

terms of death, MI, or rehospitalisation for ACS^[56].

CONCLUSION

It has been consistently shown that women who are suffering from CAD usually present with less typical symptoms, at an older age and with more co-morbidities compared with men. Therefore, they constitute a high risk group that potentially poses a diagnostic and therapeutic challenge. However, it seems that in the modern era, where sophisticated interventional and surgical techniques have emerged, women significantly benefit from an early invasive approach provided an intense medical monitoring is implemented.

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