

Gender-Based Issues in Interventional Cardiology: a Consensus Statement from the Women in Innovations (WIN) Initiative

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Cardiovascular disease is the leading cause of mortality in women, yet studies have suggested it is often under-recognized. Of particular concern is the apparent sub-optimal treatment of women in comparison to men, with less revascularization and use of evidence-based medications. The Women in Innovations group of cardiologists, aims to highlight these issues and change perceptions to optimize the treatment of female patients with cardiovascular disease, support future research, and encourage and guide the training of female interventional cardiologists.

Cuestiones relativas al sexo en cardiología intervencionista: declaración de consenso de la iniciativa *Women in Innovations (WIN)*

Aunque la enfermedad cardiovascular es la principal causa de mortalidad en las mujeres, los estudios existentes indican que con frecuencia es infradiagnosticada. Además, es motivo de especial preocupación el tratamiento aparentemente subóptimo que reciben las mujeres en comparación con los varones, con un menor uso de revascularizaciones y de medicaciones basadas en la evidencia. El grupo de especialistas en cardiología *Women in Innovations* tiene como objetivo poner de relieve estos problemas y modificar las percepciones existentes, con objeto de optimizar el tratamiento de las mujeres con enfermedad cardiovascular, respaldar la investigación futura y alentar y orientar la formación de mujeres como cardiólogas intervencionistas.

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INTRODUCTION

Worldwide, cardiovascular disease (CVD) is the single most common cause of death among women. Indeed, in Europe, CVD accounts for 55% deaths in females as compared with 43% deaths in men.¹ Over the past 40 years, age-adjusted mortality for CVD in Western countries has steadily fallen; however, the decline among women is smaller than that of men.¹ Furthermore, as life expectancy increases, particularly in women, the proportion of women with CVD has risen apace. The public health impact of CVD in women is related not only to the mortality rate, given that advances in medicine allow many women to survive longer with CVD, but also to the expanding female population at risk (almost 38.2 million women in the United States alone). As life expectancy continues to increase and economies become more industrialized, the burden of CVD in women and its impact on the global economy will continue to increase.

One of the concerns regarding the treatment of female patients with CVD is the apparent suboptimal use of both revascularization and appropriate medications. Despite the high burden of CVD, only an estimated 33% of percutaneous coronary interventions (PCI) are performed in women annually in USA and 20% in some European countries such as Spain.²

This is in spite of the established benefits of PCI in reducing fatal and nonfatal ischemic complications in patients with acute myocardial infarction (MI) and high-risk acute coronary syndromes (ACS).³ The National Registry of Myocardial Infarction is a large registry of all patients admitted with an MI to 2157 US hospitals.⁴ Analysis of data on more than 2.5 million patients between 1990 and 2006 concluded that female patients were significantly less likely to undergo revascularization or receive lipid-lowering therapy at discharge. Indeed, over the study period, the gap between male and female patients actually widened, despite evidence-based guidelines that both sexes should receive the same treatments.

BARRIERS TO APPROPRIATE CARDIOVASCULAR CARE IN WOMEN

There are numerous barriers to heart health in women; chief among them has been confusion due to mixed messages from the media as well as the tendency to underestimate the problem by women themselves. Policy makers, healthcare providers, and, above all, patients each have roles to play in maximizing adherence to optimal

primary and secondary prevention measures. It is also important to recognize that although the causes of CVD are common to all parts of the world, the approaches to its prevention at the societal or individual level will differ among countries for cultural, social, medical, and economic reasons.

Lack of awareness of the prevalence of CVD in women, on the part of both patients and healthcare providers, is in our opinion the main reason why it often goes under-diagnosed and under-treated. Importantly, studies have shown that one of the major barriers to being considered for revascularization is that female patients are less likely to undergo cardiac catheterization.^{5,6} In the Euro Heart Survey of 3779 patients with stable angina (42% female), women were significantly less likely to be referred for coronary angiography (odds ratio [OR], 0.59; 95% confidence interval [CI], 0.48–0.72).⁷ Furthermore, there is a common misconception amongst cardiologists that both PCI and coronary artery bypass graft surgery (CABG) in female patients is less successful and associated with a higher complication rate than when performed in men. Indeed, women with confirmed coronary artery disease (CAD) are less likely to undergo revascularization compared to men and are twice as likely to suffer a nonfatal MI or death during the subsequent year (HR, 2.09; 95% CI, 1.13–3.85). However, this worse outcome can be mostly explained by the higher risk profile seen in women and outcomes are similar once comorbidity factors are adjusted for.^{8,9}

For all of these reasons a consortium of interventional cardiologists from around the world with an interest in clinical and basic research in the field of cardiovascular interventions has decided to create a group called Women in Innovations (WIN). The general goals of WIN are:

- To change the perception of the treatment of women with CVD, who are too often under-diagnosed and under-treated, by addressing both physician and patient biases.
- To ensure that this effort is international by involving both individuals as well as principal cardiology and interventional cardiology associations from around the world.
- To develop a global position statement for distribution during relevant international meetings and publication in major journals.
- To include all interested interventional cardiologists in the organization (both male and female) in order to have a broad range of experts who will focus on various aspects of CVD in women and how to optimize patient and doctor awareness and treatment.

– To encourage female interventional cardiologists to become more meaningfully involved with their professional societies.

CORONARY REVASCULARIZATION IN WOMEN

Percutaneous Coronary Intervention

There is a lack of prospective studies specifically designed to evaluate the outcome of PCI or specific strategies for PCI in women. The data that have been published are often limited due to the relatively small number of female patients included and have generally been limited to comparisons between men and women. Several studies of patients undergoing coronary revascularization have reported a difference in outcome between men and women, with the conclusion in some, that procedures in female patients are associated with more adverse events. However, the reasons for the outcome differences seen in some publications are likely to be multifactorial. Largely because of the protective effects of estrogen until the menopause, women tend to be 10 years older than men at the time of presentation with CVD.³ In addition, they may present with more extensive disease as the diagnosis of coronary disease may be considerably delayed. Female patients are more likely to present with an atypical history and noninvasive investigations such as exercise testing or myocardial perfusion imaging may yield inconclusive or false-negative results.

Furthermore, a relatively low proportion of female patients is included in many studies. This may be attributable to the fact that they are excluded due to the complexity of their disease at the time of presentation. Female patients tend to have smaller, more tortuous coronary vessels and thus the frequency of stent implantation may be lower. However, the significant improvements in angioplasty techniques, and in particular, the introduction of drug-eluting stents (DES) and smaller size stents should help overcome these issues. DESs seem to be similarly efficacious in women and men, though it must be remembered that because women often make up a minority of the patients enrolled, studies are underpowered to effectively evaluate the results in this subgroup. In the recent Synergy between PCI with Taxus and Cardiac Surgery (SYNTAX) study of patients with multivessel and/or left main stem disease, randomized to either PCI with drug-eluting stents or CABG surgery, only 22% of those enrolled were female.¹⁰

Compared with bare metal stent (BMS) implantation, studies of both the sirolimus-eluting stent (Cypher, Cordis, Johnson & Johnson Company, Warren, NJ, USA) and paclitaxel-eluting stent (Taxus, Boston Scientific, Natick, MA, USA) demonstrated similar results in both men and women in reducing restenosis, target vessel revascularization (TVR), and major adverse cardiac events (MACE) at 1-year follow-up. This occurred despite the fact that women tended to be older and have more co-morbidities such as diabetes and hypertension.^{11,12} Long-term data from the TAXUS Woman analysis have been recently presented, evaluating the results of patients included in TAXUS I, II, IV, V and ATLAS.¹³ Compared to those treated with BMS, women treated with Taxus stents had a 46% relative reduction in TLR (12.0% vs 22.2%; $P < .001$), with comparable rates of death, MI, and stent thrombosis (ST) through 5 years between the 2 groups. TAXUS-treated women had comparable rates of death, MI, ST, and TLR to men, and multivariate analysis failed to demonstrate that gender was an independent predictor of any adverse outcome. Data has also been published to evaluate the influence of gender on outcome in patients with multivessel disease treated with sirolimus-eluting stents. At 3 years in the ARTS II study of 607 patients (23% female), there was no significant difference in the rate of MACCE (19.8% in men vs 17.6% in women; relative risk, 1.12; 95% CI, 0.75-1.68; $P = .63$).¹⁴

Importantly, there is now a prospective, open-label, single-arm, multicenter study specifically designed to evaluate the performance of the Everolimus-Eluting Coronary Stent System (Xience V, Abbott Vascular, Santa Clara, CA, USA) in the treatment of female patients with coronary artery lesions.¹⁵ This Xience V SPIRIT Women study is ongoing and will evaluate crucial aspects of women's health, such as menopausal status, use of hormonal contraceptives or their surrogates, and the referral path and symptoms at presentation. In addition, the trial design includes a prospective, single-blind, double-arm, randomized, multicenter substudy, in which patients will be randomized in a 2:1 ratio to the Xience V stent or Cypher. In total, approximately 2000 female patients will be enrolled at up to 130 sites outside of the United States.

Bleeding and Access Site Complications

Female patients undergoing PCI are significantly more likely than their male counterparts to suffer access site complications such as pseudoaneurysm and bleeding (1.5-4× higher).^{16,17} Nevertheless, the use of glycoprotein IIb/IIIa inhibitors during

PCI has not been reported as an independent, added risk for major vascular complications in women.¹⁷⁻¹⁹ The use of the direct thrombin inhibitor bivalirudin during elective PCI instead of unfractionated heparin appears to reduce the risk of bleeding in women in the same way as it does in men; however, women did have a higher rate of bleeding.²⁰ In a pooled analysis of the EPIC (Evaluation of 7E3 for the Prevention of Ischemic Complications), EPILOG (Evaluation in Percutaneous Transluminal Coronary Angioplasty to Improve Long-Term Outcome with Abciximab GP IIb/IIIa Blockade), and EPISTENT (Evaluation of Platelet IIb/IIIa Inhibitor for Stenting) trials, abciximab reduced the 30-day rate of MACE in women from 12.5% to 6.5% ($P<.0001$).¹⁸ Interestingly, major bleeding in women was similar with and without abciximab (3% vs 2.9%; $P=.96$), though there was a small but significant increased risk of minor bleeding with abciximab versus placebo (6.7% vs 4.7%; $P=.01$). In patients with unstable angina or NSTEMI, upstream use of eptifibatide or tirofiban before cardiac catheterization has been shown to benefit both men and women who are troponin positive.

Though associated with fewer access site complications, use of the radial approach is also problematic in women due to the relatively small size of the vessel; this increases the tendency to develop radial spasm and may limit the sheath size to 6F. A recent study has shown that even with the use of the radial route access, women remain more prone to bleeding complications compared to their male counterparts.²¹

CORONARY ARTERY BYPASS GRAFT SURGERY

In the majority of studies, women undergoing CABG surgery have greater operative mortality compared to men, with the relative risk for women ranging from 1.4 to 4.4.²²⁻²⁵ Indeed, the commonly used EuroScore to predict operative risk following CABG includes female gender as a variable that increases operative risk. In terms of intra- and peri-operative complications, several studies have demonstrated a higher incidence of stroke, postoperative hemorrhage, prolonged mechanical ventilation, and heart failure in women compared with men. Women undergoing CABG tend to be older, have more co-morbidities, smaller coronary arteries, a higher prevalence of urgent or emergent surgery, and in some studies they are less likely to receive an internal mammary graft. Lower body surface area in women has been found to be an independent predictor of increased operative

mortality.²⁵ However, similar to the results after PCI, following adjustment for these variables, the majority of studies of CABG surgery have demonstrated that gender per se is not an independent risk factor for operative mortality. In addition, there is no difference in long-term survival between men and women following CABG, although there are differences in quality of life results. Women remain more symptomatic compared to men, have a greater rate of graft occlusion, and at follow-up require more repeat revascularization.²⁶ Postoperatively, women also have a worse functional status and poorer mental health compared to men.²⁷

Although the use of off-pump CABG surgery remains controversial, in part because of issues of graft patency, the potential benefit of this form of surgery in women has been recently investigated. A study of 16 871 consecutive women comparing off-pump and on-pump CABG surgery demonstrated that those who underwent off-pump surgery had a better clinical outcome with reduced mortality, respiratory complications, and length of hospital stay.²⁸ Similarly, a more recent study investigated 7376 women undergoing CABG surgery.²⁹ Compared to a propensity-matched sample of females who underwent off-pump CABG surgery, women who underwent conventional CABG surgery had a 73% higher mortality rate, and a 47% higher complication rate due to bleeding.

GENDER DISPARITY IN THE TREATMENT OF PATIENTS WITH ACUTE CORONARY SYNDROMES

Multiple reports have shown increased mortality in women with MI compared with their male counterparts. In the GUSTO-IIb (Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes IIb) study³⁰ involving more than 12 000 patients, women were older at presentation with acute coronary syndrome (ACS) and had a higher prevalence of risk factors such as hypertension, diabetes, and hypercholesterolemia. However, a larger proportion of women with unstable angina or NSTEMI did not have significant large epicardial vessel CAD, suggesting a higher prevalence of microvascular endothelial dysfunction or non-stenotic atherosclerosis.

Analysis of the Get With the Guidelines–Coronary Artery Disease database has shown sex differences in care processes and in-hospital death among 78 254 patients (39% women) with MI in 420 US hospitals (2001-2006).³¹ In this

large database, women were older, had more co-morbidities, and less often presented with STEMI. Though the unadjusted in-hospital death rate was higher in women than men (8.2% vs 5.7%; $P<.0001$), after multivariable adjustment, this difference was no longer observed in the overall MI cohort (adjusted OR, 1.04; 95% CI, 0.99-1.10) but persisted among STEMI patients (10.2% vs 5.5%; $P<.0001$; adjusted OR, 1.12; 95% CI, 1.02-1.23) with an excess of very early deaths. Similarly, a study of >74 000 patients hospitalized with MI in France demonstrated a significantly higher rate of hospital mortality in women (14.8% vs 6.1% in men; $P<.0001$).³² Women tended to be older, although the increase in mortality remained evident even after adjustment for age. These results may be partly explained by the fact that compared with men, women were less likely to receive early medical treatments (aspirin and beta blockers), acute reperfusion therapies, timely pharmacological, and mechanical reperfusion, and invasive procedures.^{32,33}

In a recent report from the American College of Cardiology (ACC)-National Cardiovascular Data Registry (NCDR), a large registry of 199 690 patients (34% women) with ACS treated in 2004 to 2006, a higher proportion of women than men presented with unstable angina or NSTEMI (82% vs 77%; $P<.001$).³⁴ In-hospital, women were less likely to receive aspirin, glycoprotein IIb/IIIa inhibitors, or statins, and at discharge they were also less frequently prescribed aspirin or statins. Adjusted in-hospital mortality rates were similar for the sexes although numerically higher in women (1.4% in men vs 2.2% in women; adjusted OR, 0.97; 95% CI, 0.88-1.07; $P=.52$). Conversely, even with adjustment for potential confounding factors, women were significantly more likely to have cardiogenic shock, congestive heart failure, bleeding, and vascular complications.

INFLUENCE OF SEX HORMONES

Differences in sex hormones may help partially explain some of the discrepancy between men and women in the way in which CVD manifests. Sex hormones are known to affect vascular tone, and estrogen, progesterone, and testosterone receptors have been identified in vascular cells. The sex hormone-induced stimulation of endothelium-dependent mechanisms of vascular relaxation and inhibition of mechanisms of vascular smooth muscle contraction may contribute to the gender differences in vascular tone.³⁵ However,

few published clinical studies of contemporary therapy of women with CVD have assessed female patients in sufficient detail to determine whether they are pre- or post-menopausal. Further studies are needed to evaluate the biological and pathophysiological differences in CVD in women and men through clinical trials focused on biological and genetic markers. In the future, this may help to more specifically target treatment to female patients.

THE MISSIONS OF WOMEN IN INNOVATIONS (WIN)

WIN will address specific topics in the areas of research, education, mentorship, and innovation.

1. Research

- There is a need to explore the biological and pathophysiological differences in CVD in women through clinical trials focused on biological and genetic markers that may be specific to disease processes and outcomes in women.

- The group will petition interventional cardiology organizations, the NIH and other sponsoring bodies to strengthen the commitment to ensure that clinical trials in cardiovascular disease have pre-specified endpoints for women. Enrollment should include a predefined number of women (eg, 40% female inclusion in all trials) so that future studies are adequately powered to address the applicability of the results to the female population. Studies should also include female-specific questions such as menopausal status, children, use of oral contraceptives, etc).

- The group will support a yearly research grant to address pertinent issues in interventional cardiology related to women.

2. Education

- Through collaboration with national and international medical societies (such as SCAI, SOLACI, ESC, AHA, SEC, and ACC), the group aims to educate the medical community, including primary care providers and non-interventional cardiologists regarding CVD frequency, diagnosis, and treatment in women. This will involve the organization, promotion, and participation in educational forums/courses on interventional therapies for CVD in women.

- Interested interventional leaders from around the world (both female and male) will be invited to join the program and encouraged to participate in achieving the WIN goals.

- The group aims to create forums in which patients and professional communities can be educated regarding the prevalence, investigation, and treatment of CVD in women to include both primary and secondary prevention measures.

3. Mentorship and Support/Guidance for Female Interventional Cardiologists

The field of interventional vascular medicine has undergone tremendous growth over the years. Even as more women pursue careers in cardiology, women remain underrepresented in the subspecialty of interventional cardiology. There are many reasons for this, including lack of mentorship and the challenge of balancing career and family. One of the missions of WIN will be to establish a mentorship program in which grants will enable female interventional cardiologists in training to have open access to exchange programs and training at an international level.

Radiation Exposure

A specific concern relates to the perception of the risk of radiation exposure for women in this field. Worldwide, there is very little if any guidance as to what female interventional cardiologists should do once they become pregnant, with little consensus between different countries as to whether they should continue to perform interventions at all. High levels of radiation exposure have been shown to cause congenital anomalies and mental retardation of the foetus in a dose dependent manner, particularly if exposure occurs during the first 15 weeks.^{36,37} After this time, the dosage needed to cause significant harm to the foetus would need to be extremely high—certainly more than would be expected from performing angioplasty and enough to be associated with radiation sickness in the mother. There are additional concerns that radiation exposure during pregnancy may increase the baby's lifetime risk of cancer. However, studies suggest that the dosage needed to increase this risk by less than 2% above the normal lifetime risk is relatively high (comparable to a single exposure equivalent to 500 chest x-rays at one time).

However, all of these data are based on results from animal studies together with the experience of high dose exposure seen in atomic bomb survivors. The risk from chronic low level radiation exposure, as seen in contemporary interventional cardiology practice, seems to be less clear. In some countries, pregnant employees are forced to stop working in the catheterization laboratory completely;

elsewhere, guidelines vary and recommend that the total dose received during pregnancy should not exceed 2-5 mGy during the entire pregnancy.^{38,39} One of the first goals of WIN is to develop a (preferably evidence-based) position paper on this topic, with universally acceptable guidelines for female interventionists who become pregnant. An additional concern relates to the need to educate all trainees on the importance of radiation safety with appropriate use of shielding screens and properly-fitting lead aprons.

4. Innovation

- The group aims to support and encourage innovative ideas, devices, and therapies specifically tailored to female patients. This will involve the development of “think tanks” and “tracks” to enable innovators to accomplish their visions (by directing them to patent lawyers and potential collaborators and by providing advice and assistance, etc).

CONCLUSIONS

Cardiovascular disease is the leading cause of death amongst females yet this is not, at present, a common perception in the general population, emphasizing the need for improved education of both the general public and health care workers. Of concern, female patients with CVD are treated with suboptimal use of appropriate medications, cardiac catheterization, and revascularization, which needs to be highlighted amongst health care providers. Some previous studies have suggested that female gender is an independent predictor of adverse events following revascularization; however, the proportion of females included in such studies is often low. At present, it is unclear why female patients are not included in studies more frequently, and it is important that future research has a predefined number of women enrolled to enable studies to be adequately powered to address the applicability of the results to the female population. The WIN initiative is a collaboration that is open to all interested cardiologists and aims to address these issues, thereby striving to improve the management and outcomes of women with cardiovascular disease; in addition, the intention is to help support the training of female interventional cardiologists and assist the development of innovations tailored to female patients.

Conflict of interest

Drs Chieffo, Ammerer, Mauri, and Presbitero have nothing to report. Dr Hoye is on the advisory

board of Abbott, BSC, and Medicines Co. Dr Mikhail attended an advisory board meeting for Boston Scientific. Dr Grines has received grant/research support from Cardium Therapeutics, CRF, and Portola Pharmaceuticals; she is a consultant for Abbott, Boston Scientific, Medtronic Pharmaceuticals, Possis Medical, InfaRedx, Therox, and Nile Therapeutics; she is on the advisory board of Abbott, Boston Scientific, Pfizer, InfaRedx, Svelte Medical Systems, and Bristol Myers Squibb. Dr Grines has received speaker's fees from Abbott, Pfizer, and Bristol Myers Squibb and is the editor of the Journal of Interventional Cardiology. Dr Grinfeld is on the advisory boards of Abbott, and Amgen, and is a consultant for Cordis. Dr Madan has received speaker's

fees and research support from Pfizer and Merck, has consulted for Astra Zeneca, and is on the advisory board of Eli Lilly. Dr Skelding has received speaker's fees from Medtronic. Dr Weiner has received grant/research support from Boston Scientific Corporation, Medtronic, TherOx, and Abbott Vascular. She is a consultant for C.R., Labcoat, Davol, AtheroMed, and Boston Biomedical. Dr Weiner is a major stock holder in Imaging Core Lab Services, and has received other financial or material support from SCAI (Honoraria-Board Memberships). Dr Mehran is a consultant for Abbott Vascular, Cordis, BSC, TMC, Bracco, and Medtronic, and has received speaker's fees from Abiomed, Guerbert, Regado, Eli Lilly, Daiichi, and Sanofi/Aventis.

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