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In this issue we have selected eight recent interesting articles. Some of them are related with female conditions and others evaluate differences in the presentation and outcome of cardiovascular disease in both genders.

### Radiotherapy and risk of coronary events in breast cancer patients

Darby SC, Ewertz M, McGale P, Bennet AM, Blom-Goldman U, Brønnum D, et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. *N Engl J Med* 2013;368:987-98. <http://doi.org/m78>

Radiotherapy (RT) for early-stage breast cancer (BC) improves the outcome but can increase the risk of coronary events. A population-based case-control study conducted in Sweden and Denmark is very illustrative in that regard. Women with BC confirmed by histopathology and who received RT were included. In Sweden, women were considered for the study if they had received a diagnosis of BC between 1958 and 2001 and were younger than 70 years of age at the time of diagnosis. In Denmark, women were considered for the study if they had received the diagnosis of BC between 1977 and 2000 and were younger than 75 years at the time of diagnosis. Women with bilateral or metastatic disease or with a history of other cancer or previous thoracic radiotherapy to the thoracic area were excluded. Major coronary events (MCE) were defined as death from ischemic heart disease, diagnosis of acute myocardial infarction (AMI) or coronary revascularization. Women with a MCE that occurred after a diagnosis of BC were classified as case patients. Time period (TP) was defined as the time from BC diagnosis to the time of MCE. Patients with BC and RT selected at random and matched for age at the time of BC diagnosis and year of diagnosis, and who did not present a MCE during a period equivalent to the TP of the matched cases, were used as controls. The review of medical records and virtual simulation and planning based on computed tomography were used to define the total dose and the dose per RT field.

A total of 963 cases and 1205 controls were included in the study. Mean radiation dose was 4.9 Gy (range, 0.03 to 27.72). Among the case-defining MCEs, 44% occurred within 10 years after BC was diagnosed, 33% 10 to 19 years afterward, and 23% occurred 20 or more years later. The only characteristic associated with the incidence of MCE was BC location: the risk of MCE was 32% higher in women irradiated for cancer of the left breast compared to women irradiated for

cancer of the right breast. The history of coronary artery disease, diabetes, obesity or smoking habits was also associated with greater risk of MCE. The rate of MCE increased by 7.4% for each increase of 1 Gy in the mean radiation dose delivered, independently of the history or coronary risk factors and of tumor characteristics. Thus, for a mean radiation dose < 2 Gy, 2 to 4 Gy, 5 to 9 Gy, or 10 or more Gy, the percentage of increased risk, as compared with absence of RT, was 10%, 30%, 40%, and 116%, respectively. Risk started to increase within the first years after exposure and continued after 20 years without significant differences.

*This study confirms that RT increases MCE linearly and independently of preexisting coronary artery disease. This fact should be considered by the treating physicians when making decisions about the treatment of BC. It does not mean that RT has to be ruled out but perhaps more attention should be paid to dose and to the development of coronary artery disease in patients undergoing RT, even decades after its application.*

### Pregnancy in women with heart disease: data from the European registry

Roos-Hesselink JW, Ruys TP, Stein JI, Thilén U, Webb GD, Niwa K, et al. Outcome of pregnancy in patients with structural or ischaemic heart disease: results of a registry of the European Society of Cardiology. *Eur Heart J* 2013;34:657-65. <http://doi.org/m79>

In women with structural or ischemic heart disease, pregnancy constitutes a period of greater risk. There is little information about the outcome according to the type of heart disease and about maternal and fetal prognosis. In 2008, the European Registry on Pregnancy and Heart disease was initiated by the European Society of Cardiology to elucidate this issue. Since then, all women with structural or ischemic heart disease presenting with pregnancy are included prospectively. Pregnant patients from 2007 were included retrospectively at that time, as it was believed that the complete data of these patients would be easily available. Maternal baseline data were collected: age at conception, pregnancy duration, mode of delivery, maternal complications, obstetric complications and fetal complications. Estimation of maternal risk was done by classifying the patients according to the WHO in low, medium and high risk. Data for the normal population were obtained from publications and were used to make comparisons. Mean birth weight for the normal population was calculated based on statistical information from the countries that included more

cases in the registry.

A report of patients enrolled up June 2011 has been published recently. The registry included 1321 women in 28 countries. Median maternal age was 30 years (range 16–53), similar to the general population. Sixty-six percent had congenital heart disease, 25% had heart valve disease, 7% cardiomyopathy and 2% ischemic heart disease. Eighteen percent of patients had low risk, 39% medium risk, 38% high risk and 4% had formal contraindication for pregnancy. Patients with ischemic heart disease were older (median 37 years), had higher baseline risk (96% high risk, 4% with contraindication for pregnancy) and had greater requirements of cardiovascular medication. Patients with congenital heart disease had lower baseline risk (64% low or medium risk).

During pregnancy, 26% of women were hospitalized (more than 50% of cases for cardiac reasons) and maternal death occurred in 1%, compared with 2% and 0.007%, respectively, in the normal population ( $p < 0.001$  in both cases). Cesarean section was performed in 41% of cases vs. 23% in the general population. Of the total study population, 12% had at least one period of heart failure during or immediately after pregnancy. Preterm deliveries were also more common compared with the general population, as well as fetal mortality (1.7% vs. 0.35%). Maternal death was greater in patients with cardiomyopathies and heart valve disease: 2.4% and 2.1%, respectively. Cesarean section was more common in patients with cardiomyopathies and ischemic heart disease. The outcome of patients with congenital heart disease was relatively better. In developing countries, maternal mortality was higher than in developed countries (3.9 vs. 0.6%).

*This Registry contributes to define the outcome of pregnancy in the setting of diverse heart diseases and social and economical conditions, and to provide better counseling to our patients. The information reinforces the need of strict surveillance during pregnancy.*

### Do women with atrial fibrillation have a different outcome?

Andersson T, Magnuson A, Bryngelsson IL, Frøbert O, Henriksson KM, Edvardsson N, et al. All-cause mortality in 272,186 patients hospitalized with incident atrial fibrillation 1995-2008: a Swedish nationwide long-term case-control study. **Eur Heart J** 2013;34:1061-7. <http://doi.org/m8b>

Atrial fibrillation (AF) is associated with high morbidity and mortality. Although the CHA2DS2-Vasc score associates female gender with greater incidence of embolism, it is not clear whether the outcome of men with AF is different from that of women.

Since 1987, the Swedish National Patient Registry includes all hospitalizations. This registry allows the identification of the reasons of hospitalization, diagnoses and treatments by condition, and associated outcome. A recently published analysis refers

to the outcome of patients hospitalized with AF and the differences by gender. The study included 272186 patients up to 85 years of age, hospitalized with a diagnosis of incidental AF between 1995 and 2008 but without AF diagnosis between 1987 and 1994, thus making it more likely that the AF was truly incident. AF was the main cause of hospitalization in 44% of cases. For each AF patient, two controls with no hospital record of AF were selected and matched for age, gender, and calendar year of the AF diagnosis. Mean age was 72.3 years. The proportion of women was 44% and increased with age: 28% at an age younger than 65 years, 40% at age 65–74 years, and 52% at age 75–85 years. Women were older (mean age 74.8 vs. 70.4 years) and had greater prevalence of hypertension, cancer and history of stroke.

At the end of the 14-year follow-up period, the unadjusted mortality was greater in patients with AF vs. controls. In women with AF, annual mortality ranged from 2.5% in women < 65 years to 15.2% in those > 74 years, compared with 0.7% and 7.8%, respectively, in patients without AF. In men with AF, annual mortality ranged from 2.7% in patients < 65 years to 18.5% in those > 74 years compared to 1% and 10.8%, respectively, in patients without AF. Thus, mortality rate was lower in women than men. When adjusting for age and concomitant diseases, the relative risk of mortality in AF patients was higher in women at the 14-year follow-up period: 2.15 vs. 1.76 in patients < 65 years; 1.72 vs. 1.36 in those between 65 and 74 years, and 1.44 vs. 1.24 in those between 75 and 85 years.

*The information provided by this large cohort study confirms the adverse prognosis associated with AF, and although the outcome is better in women, the presence of arrhythmia implies a more adverse prognosis in women compared to men. This report did not consider concomitant treatment and different treatments by gender which might help to better explain the results.*

### Sex differences in the outcome of patients with hypertension

Daugherty SL, Masoudi FA, Zeng C, Ho PM, Margolis KL, O'Connor PJ, et al. Sex differences in cardiovascular outcomes in patients with incident hypertension. **J Hypertens** 2013;31:271-7. <http://doi.org/m77>

Hypertension (HT) is an established risk factor for coronary artery disease, heart failure, stroke and kidney failure. The extent to which women and men are at similar risk is not well known. A retrospective cohort study has been recently published providing novel information about this subject.

Patients with incident HT in three integrated health systems in the USA were identified between 2001 and 2006. Elevated blood pressure (BP) was defined as >140/90 mm Hg or 130/80 mm Hg for those with diabetes mellitus or chronic kidney failure. Incident HT was defined as two consecutive elevated office BP measurements with subsequent prescription

of antihypertensive treatment; or three consecutive elevated BP measurements regardless of subsequent treatment in patients with no prior diagnosis or treatment for HT in the previous year. Renal function was evaluated using the MDRD formula which considers age, gender, creatinine levels and race.

Among 177521 patients with incident HT included in the study, 55% were women. Compared with men, women were older (median age 56 vs. 53 years), and had more prevalence of concomitant diseases: cancer, depression, thyroid disease, chronic pulmonary disease or kidney disease. Diabetes and coronary artery disease were less common in women. Median follow-up was 3.2 years. During follow-up, the annual incidences of adverse outcomes were: AMI 3.25%, hospitalizations due to heart failure 1.53%, hospitalizations due to stroke 2.82%, and kidney function impairment (glomerular filtration rate < 60 ml/min/1.73 m<sup>2</sup>) 25.86%. Annual mortality rate was 13.24%. In the multivariate analysis, after adjustment for baseline characteristics (as BP) and concomitant diseases, women were less likely to die of any cause (HR 0.85, 95% CI 0.80–0.90) and had lower incidence of AMI (HR 0.44, 95% CI 0.39–0.50) or stroke (HR 0.68, 95% CI 0.60–0.76). There was no significant difference in the incidence of heart failure. The incidence of kidney dysfunction was higher in women (HR 1.17, 95% CI 1.12–1.22)

*Of interest, these findings are similar to those of some previous registries but differ from others. These differences may be explained by the baseline characteristics of the population, the definition used for renal dysfunction, the high proportion of women and the short follow-up period (partially balanced by the high number of observations). The practical consequence of this information is the need of performing frequent surveillance of renal function in women with hypertension to adopt adequate decisions about treatment targets and avoid nephrotoxic drugs.*

### Women, diabetes and coronary artery disease

Tamis-Holland JE, Lu J, Korytkowski M, Magee M, Rogers WJ, Lopes N, et al. Sex differences in presentation and outcome among patients with type 2 diabetes and coronary artery disease treated with contemporary medical therapy with or without prompt revascularization: a report from the BARI 2D Trial (Bypass Angioplasty Revascularization Investigation 2 Diabetes). *J Am Coll Cardiol* 2013;61:1767-76. <http://doi.org/m76>

Previous studies have demonstrated that women with coronary artery disease (CAD) have less anatomic disease. At the same time, women with CAD are treated less aggressively than men. These differences in clinical presentation and management may act as confounders when analyzing whether CAD in women has a different outcome. After adjusting for severity of CAD and treatment, some studies have demonstrated

that men and women have a similar outcome.

The BARI 2D study, published in 2009, randomly assigned patients with CAD to undergo either aggressive medical treatment or revascularization (percutaneous coronary intervention or surgery, left at the discretion of the treating physician) and to receive different modalities of diabetes therapy. Unstable patients requiring revascularization, those with severe left main coronary artery disease, patients who had undergone revascularization within the previous year, or with creatinine levels > 2 mg/dL were excluded from the study. Thus, the study represents an opportunity to evaluate the differences in presentation and treatment of CAD between men and women, as patients were randomly assigned to treatments with no gender-related influence in decision making. A sub-study of the BARI 2D trial has been recently published and analyzes this issue.

Among the 2368 patients included in the study, 29.6% were women. The prevalence of hypertension and obesity was higher in women, and time since diabetes diagnosis was longer. On the contrary, smoking habits and history of AMI were less common among women, as well as adequate control of LDL or glycated hemoglobin levels. Women reported more angina than men (67% vs. 58%, with greater prevalence of FC III-IV or unstable angina) and angina equivalent symptoms (73% vs. 60%). As in previous studies women had less anatomical disease, with lower prevalence of total occlusions and better ventricular function. After adjustment for these differences, there were no significant differences in the indication of percutaneous coronary intervention or surgery between men and women. The type of PCI procedure and the initial results were similar in both genders. However, even after adjusting for baseline characteristics, the number of bypass grafts was slightly lower in women (mean 2.55 vs. 2.88). There were no significant differences in drug therapy during the study, except for diuretics, which were more common in women.

Over the 5-year follow-up there were no significant differences in the incidence of death or major events. Women still reported more angina than men (OR 1.51, 95% CI 1.21-1.77;  $p < 0.0001$ ). Also, women had lower self-reported functional capacity and perception of wellness than men. Both women and men achieved target blood pressure and glycated hemoglobin levels, but LDL goal < 100 mg/dl was less commonly achieved by women (OR 0.62, 95% CI 0.50-0.77;  $p < 0.01$ ).

*This publication confirms the presence of differences in CAD between men and women in a defined population (diabetics with stable CAD), and suggests that the vital outcome is similar with identical treatment and after adjustment for baseline characteristics. Other factors that have not been considered might explain the lower functional capacity and the greater prevalence of angina despite less anatomical disease: microvascular disease, concomitant diseases, family support or psychosocial barriers. Although these*

conclusions are highly suggestive, they should not be automatically extrapolated to other clinical conditions in the wide scope of CAD.

### Are the outcomes of coronary artery bypass grafting worse in women?

Alam M, Bandeali SJ, Kayani WT, Ahmad W, Shahzad SA, Jneid H, Birnbaum Y, et al. Comparison by meta-analysis of mortality after isolated coronary artery bypass grafting in women versus men. *Am J Cardiol* 2013 (in press) <http://doi.org/m73>

Several retrospective and prospective studies have reported differences in the outcome of coronary artery bypass grafting (CABG) between men and women, with conflicting results. This issue has been investigated by a meta-analysis available online which will be soon published in printed version.

This meta-analysis includes 20 studies (13 retrospective studies and 7 prospective studies) published until May 2012, comparing men and women who underwent isolated CABG and reporting the outcome of men and women separately. From a total of 966492 patients included in the study, 29% were women. Compared with men, women were more likely to be older (mean age 66.7 vs. 63 years), had significantly greater prevalence of hypertension, diabetes, dyslipidemia, peripheral vascular disease, stroke and kidney failure, and had lower prevalence of smoking habits and history of AMI. Women had less anatomical disease (three-vessel disease in 58% of women vs. 68% in men;  $p < 0.01$ ), but were more likely to undergo urgent CABG (51% vs. 44% in men).

Perioperative mortality (within 30 days) was significantly higher in women (4.28% vs. 2.53%, OR 1.77, 95% CI 1.67 to 1.88). Mortality remained high in women compared with men after one and five years, but was progressively lower (OR 1.31 and 1.14, respectively). Women remained at increased risk when only propensity score-matched studies were considered and in four propensity score-matched studies conducted to analyze the baseline differences between men and women. These four studies included 11522 patients and the meta-analysis of these studies showed similar results, with increased risk for 30-day mortality in women (OR 1.36, 95% CI 1.04-1.78).

*The differences observed may be due to the fact that women were older at the moment of CABG, had more prevalence of risk factors and concomitant diseases. Propensity score-matched studies may in part correct this phenomenon although some differences may not have been considered when the score was developed. Nevertheless, other explanations should be explored as the trend across these studies is similar to the global trend. The results may be explained by the higher prevalence of urgent CABG (due to delayed indication, lack of alarm in previous situations, absence of appropriate initial diagnosis or severe clinical presentations despite less anatomical disease) and anatomical*

*characteristics (vessels with smaller diameter in women).*

### ST-segment elevation acute myocardial infarction and gender

Juliard JM, Golmard JL, Himbert D, et al. Comparison of hospital mortality during ST-segment elevation myocardial infarction in the era of reperfusion therapy in women versus men and in older versus younger patients. *Am J Cardiol* 2013;111:1708-13. <http://doi.org/m75>

According to several publications, women with ST-elevation myocardial infarction (STEMI) seem to have higher mortality than men. The reasons explaining this difference are that women are older, have atypical presentation, delayed first consultation and undergo less aggressive therapeutic approach. The aim of the study was to explore the interaction between age and gender influencing the outcome of STEMI.

Between 1988 and 2011 2600 patients with STEMI within 6 hours after symptom onset were admitted to the Bichat Hospital (University of Paris). The treatment algorithm in this center is independent of gender and includes primary percutaneous coronary intervention (PCI) or pre-hospital fibrinolysis followed by coronary angiography within 60-90 minutes plus rescue PCI if necessary, or conservative medical approach for patients with limited life expectancy due to concomitant diseases or contraindication for reperfusion therapy.

Of the 2600 patients, 1765 were < 65 years and 11.3% were women. Women and men in this age group did not differ in age, prevalence of diabetes, hypertension, dyslipidemia or site of AMI. The time interval from symptoms to admission was 12 minutes longer in women. History of AMI and two-vessel disease or more was less frequent in women (2.5% vs. 9.5% and 27% vs. 40%, respectively). Sixty-two percent of women and 65 % of men underwent primary PCI, without significant difference. The primary success rate of PCI was similar in men and women. Time to thrombolysis and to TIMI flow grade 3 was also similar.

The remaining 835 patients were > 65 years and 32% were women. In this age group, women were 4 years older than men, with greater prevalence of hypertension. Anterior AMI was less common in women. History of AMI was less frequent in these women (7% vs. 14%) but there were no differences in the presence of two-vessel disease or more (61% vs. 58%). Sixty-seven percent of women and 68% of men underwent primary PCI, without significant difference. The primary success rate of PCI was similar in men and women. Time to thrombolysis or PCI was longer in younger patients and significantly longer in women (33 minutes longer to thrombolysis and 26 minutes longer to TIMI flow grade 3).

Primary success rate of PCI was similar in men and women in both age groups. Multivariate

analysis showed that age, but not gender, was an independent predictor of mortality. Yet, a thorough analysis revealed an interaction between age and gender. Up to the age of 74 years, the risk for death increased linearly with age with no significant differences between men and women, reaching approximately 10% at the age of 74. In patients  $\geq 75$  years, women were at greater risk than men, with hospital mortality of 22% vs. 14% in men ( $p = 0.03$ ).

*Despite this study was retrospective and extended for over two decades, it shows that older women with STEMI represent a high-risk group. Although their baseline characteristics cannot be modified, early diagnosis, shorter time to admission and to reperfusion may save lives.*

### **Differences in mode of death between men and women with heart failure. Do implantable cardioverter-defibrillators have any influence?**

Rho RW, Patton KK, Poole JE, Cleland JG, Shadman R, Anand I, et al. Important differences in mode of death between men and women with heart failure who would qualify for a primary prevention implantable cardioverter-defibrillator. **Circulation** 2012;126:2402-7. <http://doi.org/m74>

Practice guidelines recommend implantable cardioverter-defibrillator therapy for primary prevention in patients with heart failure, ejection fraction  $\leq 35\%$  and FC II-III. Recently, several meta-analyses have suggested that women might benefit less than men from implantable cardioverter-defibrillator (ICD) therapy. One of the reasons of this phenomenon is reported by an interesting study.

A database of collected data from patients who were enrolled in three randomized trials (COMET, VAL-HeFT and PRAISE) and two heart failure registries (one from Italy and the other from the USA) was used to select patients who were candidates for

primary prevention ICD by current standards of care. Patients with an ICD already implanted and those who underwent cardiac transplantation were excluded. The Seattle score was used to define the risk of annual mortality according to baseline characteristics but excluding patient gender. Low, intermediate and high risk corresponded to annual mortality rates of 5%, 10-15% and 25%, respectively.

Among the 8337 patients included in the study, 20% were women. Compared to men, women were two years older, and were less likely to have ischemic heart disease and to be treated with neurohormonal antagonists and statins. Mortality rate was 26.3% after a mean follow-up of 2.4 years. Overall, 48% of patients died suddenly, 30% of progressive heart failure, and 22% of other causes. Age adjusted all-cause mortality was 24% lower for women than for men (95% CI 15-32). Age adjusted mortality from sudden death was 32% lower for women compared with men (95% CI 20-42). There were no significant differences in mortality rate for progression of heart failure. Additional adjustments for other baseline characteristics and treatment did not modify the risk relation between men and women. This difference persisted for total mortality and sudden death in each risk category.

*The mode of death of heart failure patients is sometimes difficult to determine due to the different definitions used and to the presence of competitive risks. The results of this study may be partially explained by the lower prevalence of ischemic etiology in women. Some publications have reported sex differences in cardiac electrophysiology, as calcium and potassium channel kinetics and autonomic modulation which might contribute to understand these findings. Practice guidelines do not consider gender for indicating ICD therapy, and this approach should not be modified for the time being: although sudden death is less common, it also occurs in women with heart failure. Further research in this field and others may contribute to indicate ICD therapy according to baseline risk.*