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PRESIDENT'S PAGE

Differences in men and women in acute coronary syndromes

According to the World Health Organization, cardiovascular disease is the main cause of death and is expected to cause more than 23.6 million deaths till 2030.[1] The incidence of acute coronary syndromes (ACS) is lower in women than men in all ages.[2] While the overall cardiovascular mortality is higher in men than women, this difference appears to be eliminated in the last decade as men show a decrease with corresponding female increased mortality associated with coronary artery disease.[3,4] However, the effect of the acute myocardial infarction (AMI) in younger women[5] has increased and it may exhibit a higher risk of death compared to young men.[6] Generally women presented more often with AMI without ST elevation (NSTE-ACS) or unstable angina and less often with ST segment elevation (STEMI) compared to men.[7]

From pathophysiological aspect the use of newer invasive and noninvasive imaging techniques such as coronary artery grayscale-IVUS, VH-IVUS, OCT showed differences in acute coronary events between men and women.[8] In particular, women have smaller arteries[9] and therefore smaller plaque burden required for clot coronary disease events and further may have a higher restenosis risk.[10] In addition, women have a lower plaque burden, compared to males at all ages but culprit lesions are similar in OCT in both sexes. Autopsy studies have shown that the erosion compared to the plaque rupture is the principal mechanism of coagulation and erosion occurs more often in younger women.[11] In women <65 years old the not culprit lesions are fewer and with less focal atheromatosis and plaque ruptures in relation to men, while the difference is smoother after 65 years.[12] Regarding the non-atherosclerotic mechanisms of the ACS seems that women have often microvascular and endothelial dysfunction resulting in recurrent angina, hospitalizations and heart failure.[13]

Women with acute myocardial infarction (AMI) with elevation of the ST (STEMI) compared to men are older, more often have hypertension and diabetes and usually arrive later at hospital[2] where exhibit atypical symptoms such as vomiting, breathlessness, neck pain, palpitations.[2] Additionally women have more frequently angina or heart failure, and worse Killip class and compare to men develop often cardiogenic shock, pulmonary edema, sinus arrest, stroke, mechanical complications and major bleeding events even after statistical adjustment to age and comorbidities. Instead men often exhibit malignant ventricular arrhythmias and sudden cardiac death.[2] When women are diagnosed with STEMI receive less often proper therapy since the era of thrombolysis[14] including admission into intensive care unit,[15] aspirin and thrombolysis.[16] Primary angioplasty which is the best method of revascularisation for both men and women accompanied by higher rates of vascular complications in women.[16,17] Younger women with STEMI show higher rates of inhospital mortality than men, even after adjusting for the medical history, clinical severity and early treatment, while women <55 years old presented without chest pain show higher inhospital mortality compared to men.[18–20] Possible explanations of the higher short-term mortality of young women seem to be the highest pre-hospital mortality of men, most cardiovascular risk factors, most comorbidities in women with ACS, less typical symptoms and more doubtful diagnoses leading to suboptimal treatment, omission and failure to recognize in time of the basis of the guidelines symptoms and a lower percentage of treatments. As regards the long-term survival although less studied appears that women have better results after STEMI compared to men.[21]

Women with AMI without ST elevation (NSTE-ACS) compared with men seem to have suboptimal treatment at admission and after the hospital even though they have increased cardiovascular risk and lack of differences in guidelines.[2] The role of gender on prognosis of patients with NSTE-ACS is in doubt. Women have higher rates of non-obstructive epicardial coronary disease, compared to men, and this subpopulation shows better inhospital prognosis in both sexes compared to patients with significant

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atherosclerotic disease.[22] Rather worse prognosis show women with NSTE-ACS and significant epicardial coronary disease after PCI.[23] Overall, the data so far that determine the differences in the prognosis of both sexes after NSTE-ACS mainly based on statistical correlations, extent of coronary disease and maybe in a different response to antithrombotic therapeies.[24] Kragholm et al showed the reduced participation of women in clinical trials in patients with NSTE-ACS in the absence of improvement in recent years, while the treatments based on the instructions and the prognosis has improved between women.[25]

Pharmaceutical treatment of AMI shows no difference in efficacy between the two sexes. Beta blockers, statins, angiotensin-converting enzyme inhibitors and antithrombotic therapy in several studies is the appropriate evidence-based treatment of acute coronary syndromes. In particular recent studies demonstrate similar efficacy of anticoagulant therapy between two sexes.[26] However female sex has been associated with increased bleeding risk[27] among patients with ACS and features an important and independent predictor of in-hospital major bleeding factor in CRUSADE bleeding score.[28,29] Nevertheless other studies such as the ACUITY[30] study do not revealed significant interaction between gender antithrombotic treatment haemorrhagic risk after one year, whereas studies such as TRITON-TIMI 38,[26] PLATO[31] and CHAMPION PHOENIX[32] revealed similar results. This distinction between observational studies and subpopulations analyzes of clinical studies may be attributed to the reduced representation of women in clinical studies with ACS.[33] Another explanation might be the antithrombotic treatment dosage which is not adjusted on weight and renal function affecting mainly women.[26] Thus although women treated with the same pharmacological antithrombotic treatments with men, a closer monitoring by measuring body weight and creatinine clearance and dose adjustment is needed.[26]

The non-occlusive atherosclerotic disease, defined as $<$50% stenosis of the coronary vessel, is found in 5—20% of ACS.[34] In a recent study of patients with NSTE-ACS, the total mortality was higher in patients without obstructive coronary disease than obstructive, which was associated with higher non-cardiac mortality and reinfarction and unplanned revascularization was higher in patients with obstructive coronary artery disease.[35] An important cause of non-obstructive atherosclerosis acute coronary syndrome is the Takotsubo cardiomyopathy associated with 2—5% ACS and referred mainly in postmenopausal women after emotional or physical stress in$>$ 80%.[36]

The automatic dissection of coronary arteries (spontaneous coronary artery dissection, SCAD) is also a major cause of non-atherosclerotic coronary disease. It is a disease entity which is increasingly recognized as a common cause of AMI in young women often underdiagnosed as a cause of sudden cardiac death, ventricular tachyarrhythmia, STEMI and NSTE-ACS.[37,38] The incidence of SCAD is uncertain but according to retrospective studies based in angiographic data ranges from 0.07 to 1.1%.[39] The first description of the disease was in 1931 by Dr Pretty who described the sudden death of a 42years old female with multi pregnancies after angina while the autopsy revealed the dissection of the right coronary artery. More than 4% of ACS and over 40% of ACS in women $<$55 years of age may be due to automatic dissection of coronary artery.[37] Disease entities such as Marfan syndrome, systemic lupus erythematosus, the perinatal period in$>$ 25%, physical or emotional stress$>$ 55% and fibromuscular dysplasia of up to 70% associated with non-atherosclerotic automatic dissection of coronary arteries.[40,41] Moreover they have been reported familial cases according to the Mayo Clinic records and multiple arteries attact.[42] Various recurrence rates have been reported by 13% at 2 years, up to 20% after 10 years in different patients registries.[35,43] Younger imaging techniques such as IVUS and OCT improve the diagnostic imaging of the disease and may help to guide therapeutic decisions.[37] Angiographically includes three types 1) Multiple lumens (true, psefdolumen) 2) Mild diffuse stenosis 3) Imitates atherosclerosis.[44] The therapeutic approach varies leading some investigators to promote conservative treatment compared with angioplasty in fragile coronary arteries unless acute ischemia developed.[37] In particular based on the position that the vessels of SCAD can be treated concervatively[38,39] and in contrast with the treatment of atherosclerotic coronary artery disease by interventional cardiology becoming increasingly adopting the approach '' less is more ''. Therefore avoid coronary intervention in patients with stable SCAD with conserved flow and even with significant blockage or infraction.[41] However angioplasty or CABG remains the appropriate solution in patients clinically unstable or with complete obstruction, even in pregnant patients.[41] The rate and frequency of healing is not known. A significant percentage of patients under conservative treatment may experience disease progression and require revascularization requiring more thorough clinical monitoring of patients during acute phase.[41] Automatic dissections of other vessels are quite frequent and the risk of coronary angiography outweigh the possible benefits. Although the short-and long-term prognosis of these patients is good seems to remain the risk of major cardiovascular events[39] and would require continuous monitoring with corresponding cardiovascular imaging on clinical indications.

In conclusion, recognition and quality of care between sexes is not the same in ischemic heart disease, the presence of pathophysiological and psychosocial differences between sexes also appears to affect their prognosis after acute coronary syndrome and required greater representation of women in clinical trials acute coronary syndromes.

References

1. Smith Jr SC, Collins A, Ferrari R, et al. Our time: a call to save preventable death from cardiovascular disease (heart disease and stroke). *J Am Coll Cardiol*. 4 Dec 2012;60(22):2343—2348.
2. Andreotti F, Marchese N. Women and coronary disease. *Heart*. Jan 2008;94(1):108—116.
3. Rosamond W, Flegal K, Furie K, et al. Heart disease and stroke statistics — 2008 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation*. 29 Jan 2008;117(4):e25—146.
4. Wenger NK. Prevention of cardiovascular disease in women: highlights for the clinician of the 2011 American Heart Association Guidelines. *Adv Chronic Kidney Dis*. Sep 2013;20(5):419—422.
5. Towfighi A, Zheng L, Ovbiagele B. Sex-specific trends in midlife coronary heart disease risk and prevalence. *Arch Intern Med*. 26 Oct 2009;169(19):1762—1766.

6. Otten AM, Maas AH, Ottervanger JP, et al. Is the difference in outcome between men and women treated by primary percutaneous coronary intervention age dependent? Gender difference in STEMI stratified on age. *Eur Heart J Acute Cardiovasc Care*. Dec 2013;2(4):334—341.
7. Rosengren A, Wallentin L, A KG, Behar S, Battler A, Hasdai D. Sex, age, and clinical presentation of acute coronary syndromes. *Eur Heart J*. Apr 2004;25(8):663—670.
8. Chandrasekhar J, Mehran R. Sex-based differences in acute coronary syndromes: insights from invasive and noninvasive coronary technologies. *JACC Cardiovasc Imaging*. Apr 2016; 9(4):451—464.
9. Kornowski R, Lansky AJ, Mintz GS, et al. Comparison of men versus women in cross-sectional area luminal narrowing, quantity of plaque, presence of calcium in plaque, and lumen location in coronary arteries by intravascular ultrasound in patients with stable angina pectoris. *Am J Cardiol*. 15 Jun 1997;79(12):1601—1605.
10. Kim SG, Apple S, Mintz GS, et al. The importance of gender on coronary artery size: in-vivo assessment by intravascular ultrasound. *Clin Cardiol*. May 2004;27(5):291—294.
11. Farb A, Burke AP, Tang AL, et al. Coronary plaque erosion without rupture into a lipid core. A frequent cause of coronary thrombosis in sudden coronary death. *Circulation*. 1 Apr 1996; 93(7):1354—1363.
12. Wykrzykowska JJ, Mintz GS, Garcia-Garcia HM, et al. Longitudinal distribution of plaque burden and necrotic core-rich plaques in nonculprit lesions of patients presenting with acute coronary syndromes. *JACC Cardiovasc Imaging*. Mar 2012;5(3 suppl l):S10—S18.
13. Reynolds HR, Srichai MB, Iqbal SN, et al. Mechanisms of myocardial infarction in women without angiographically obstructive coronary artery disease. *Circulation*. 27 Sep 2011; 124(13):1414—1425.
14. Vaccarino V, Rathore SS, Wenger NK, et al. Sex and racial differences in the management of acute myocardial infarction, 1994 through 2002. *N Engl J Med*. 18 Aug 2005;353(7):671—682.
15. Antman EM, Anbe DT, Armstrong PW, et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/ American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1999 Guidelines for the Management of Patients with Acute Myocardial Infarction). *Circulation*. 31 Aug 2004;110(9):e82—292.
16. Gan SC, Beaver SK, Houck PM, MacLehose RF, Lawson HW, Chan L. Treatment of acute myocardial infarction and 30-day mortality among women and men. *N Engl J Med*. 6 Jul 2000; 343(1):8—15.
17. Jacobs AK. Coronary intervention in 2009: are women no different than men? *Circ Cardiovasc Interv*. Feb 2009;2(1): 69—78.
18. Vaccarino V, Parsons L, Every NR, Barron HV, Krumholz HM. Sex-based differences in early mortality after myocardial infarction. National Registry of Myocardial Infarction 2 Participants. *N Engl J Med*. 22 Jul 1999;341(4):217—225.
19. Canto JG, Rogers WJ, Goldberg RJ, et al. Association of age and sex with myocardial infarction symptom presentation and in-hospital mortality. *JAMA*. 22 Feb 2012;307(8):813—822.
20. Zhang Z, Fang J, Gillespie C, Wang G, Hong Y, Yoon PW. Age-specific gender differences in in-hospital mortality by type of acute myocardial infarction. *Am J Cardiol*. 15 Apr 2012;109(8): 1097—1103.
21. Lawesson SS, Alfredsson J, Fredrikson M, Swahn E. A gender perspective on short- and long term mortality in ST-elevation myocardial infarction — a report from the SWEDEHEART register. *Int J Cardiol*. 30 Sep 2013;168(2):1041—1047.
22. Gehrie ER, Reynolds HR, Chen AY, et al. Characterization and outcomes of women and men with non-ST-segment elevation myocardial infarction and nonobstructive coronary artery disease: results from the Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the ACC/AHA Guidelines (CRUSADE) quality improvement initiative. *Am Heart J*. Oct 2009;158(4):688—694.
23. Glaser R, Selzer F, Jacobs AK, et al. Effect of gender on prognosis following percutaneous coronary intervention for stable angina pectoris and acute coronary syndromes. *Am J Cardiol*. 1 Dec 2006;98(11):1446—1450.
24. Crea F, Battipaglia I, Andreotti F. Sex differences in mechanisms, presentation and management of ischaemic heart disease. *Atherosclerosis*. Jul 2015;241(1):157—168.
25. Kragholm K, Halim SA, Yang Q, et al. Sex-Stratified trends in enrollment, patient characteristics, treatment, and outcomes among non-ST-segment elevation acute coronary syndrome patients: insights from clinical trials over 17 years. *Circulation Cardiovasc Qual Outcomes*. Jul 2015;8(4):357—367.
26. Wang WT, James SK, Wang TY. A review of sex-specific benefits and risks of antithrombotic therapy in acute coronary syndrome. *Eur Heart J*. 2 Feb 2016.
27. Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 15 Nov 2007;357(20):2001—2015.
28. Subherwal S, Bach RG, Chen AY, et al. Baseline risk of major bleeding in non-ST-segment-elevation myocardial infarction: the CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA Guidelines) Bleeding Score. *Circulation*. 14 Apr 2009;119(14):1873—1882.
29. Alexander KP, Chen AY, Newby LK, et al. Sex differences in major bleeding with glycoprotein IIb/IIIa inhibitors: results from the CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines) initiative. *Circulation*. 26 Sep 2006;114(13):1380—1387.
30. White HD, Ohman EM, Lincoff AM, et al. Safety and efficacy of bivalirudin with and without glycoprotein IIb/IIIa inhibitors in patients with acute coronary syndromes undergoing percutaneous coronary intervention 1-year results from the ACUITY (Acute Catheterization and Urgent Intervention Triage strategY) trial. *J Am Coll Cardiol*. 2 Sep 2008;52(10):807—814.
31. Husted S, James SK, Bach RG, et al. The efficacy of ticagrelor is maintained in women with acute coronary syndromes participating in the prospective, randomized, PLATelet inhibition and patient Outcomes (PLATO) trial. *Eur Heart J*. 14 Jun 2014; 35(23):1541—1550.
32. Berger JS, Frye CB, Harshaw Q, Edwards FH, Steinhubl SR, Becker RC. Impact of clopidogrel in patients with acute coronary syndromes requiring coronary artery bypass surgery: a multicenter analysis. *J Am Coll Cardiol*. 18 Nov 2008;52(21): 1693—1701.
33. Melloni C, Berger JS, Wang TY, et al. Representation of women in randomized clinical trials of cardiovascular disease prevention. *Circulation Cardiovasc Qual Outcomes*. Mar 2010;3(2): 135—142.
34. Niccoli G, Scalone G, Crea F. Acute myocardial infarction with no obstructive coronary atherosclerosis: mechanisms and management. *Eur Heart J*. 21 Feb 2015;36(8):475—481.
35. Planer D, Mehran R, Ohman EM, et al. Prognosis of patients with non-ST-segment-elevation myocardial infarction and nonobstructive coronary artery disease: propensity-matched analysis from the Acute Catheterization and Urgent Intervention Triage Strategy trial. *Circ Cardiovasc Interv*. Jun 2014; 7(3):285—293.

36. Schneider B, Athanasiadis A, Stollberger C, et al. Gender differences in the manifestation of tako-tsubo cardiomyopathy. *Int J Cardiol*. 1 Jul 2013;166(3):584—588.
37. Hayes SN. Spontaneous coronary artery dissection (SCAD): new insights into this not-so-rare condition. *Tex Heart Inst J*. Jun 2014;41(3):295—298.
38. Alfonso F, Bastante T, Rivero F, et al. Spontaneous coronary artery dissection. *Circulation J*. 2014;78(9):2099—2110.
39. Tweet MS, Hayes SN, Pitta SR, et al. Clinical features, management, and prognosis of spontaneous coronary artery dissection. *Circulation*. 31 Jul 2012;126(5):579—588.
40. Saw J, Aymong E, Sedlak T, et al. Spontaneous coronary artery dissection: association with predisposing arteriopathies and precipitating stressors and cardiovascular outcomes. *Circ Cardiovasc Interv*. Oct 2014;7(5):645—655.
41. Tweet MS, Eleid MF, Best PJ, et al. Spontaneous coronary artery dissection: revascularization versus conservative therapy. *Circ Cardiovasc Interv*. Dec 2014;7(6):777—786.
42. Goel K, Tweet M, Olson TM, Maleszewski JJ, Gulati R, Hayes SN. Familial spontaneous coronary artery dissection: evidence for genetic susceptibility. *JAMA Intern Med*. May 2015;175(5):821—826.
43. Lansky AJ, Pietras C, Costa RA, et al. Gender differences in outcomes after primary angioplasty versus primary stenting with and without abciximab for acute myocardial infarction: results of the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) trial. *Circulation*. 5 Apr 2005;111(13):1611—1618.
44. Saw J. Coronary angiogram classification of spontaneous coronary artery dissection. *Catheter Cardiovasc Interv*. 1 Dec 2014;84(7):1115—1122.

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