Women and Heart Disease: Understanding Risk Factors for Coronary Artery Disease

Ahmad Alsarah[1*], Osama Alsara[1] and Heather S. Laird-Fick[2]

[1]Department of Internal Medicine, Michigan State University, East Lansing, MI, USA
[2]Associate Professor, Department of Internal Medicine, Michigan State University, East Lansing, MI, USA

ABSTRACT

Cardiovascular disease (CVD) is the leading cause of death in women in the US. Although the overall death rate due to CVD has decreased recently, it has actually increased in young women. Coronary Artery Disease (CAD), which may lead to myocardial infarction, congestive heart failure, and death, is an important focus for preventive efforts. The impact of traditional cardiovascular risk factors such as family history, diabetes mellitus, hypertension, hyperlipidemia, and smoking differs with gender. Women face unique risks related to pregnancy, menopause, and exogenous estrogen, and are more likely to develop other diseases (e.g autoimmune diseases, breast cancer) whose course or treatment may be complicated by CAD. This article will review CAD risk factors in women, tools to quantify that risk, and interventions to decrease it.

KEYWORDS: Women; Cardiovascular disease; Coronary Artery Disease; Risk factors.

ABBREVIATIONS: CAD: Coronary Artery Disease; CV: Cardiovascular; CVD: Cardiovascular disease; CAC: Coronary Artery Calcium; DM: Diabetes Mellitus; HDL: High Density Lipoproteins; hs-CRP: high sensitivity C-reactive protein; LDL: Low Density Lipoprotein; MI: Myocardial Infarction; OSA: Obstructive Sleep Apnea; PCOS: Polycystic ovarian syndrome.

INTRODUCTION

Cardiovascular disease (CVD), which includes structural and functional disorders of the heart and blood vessels, is the leading cause of death in both men and women in the United States. It causes 25% of overall mortality in women.[1] The number of CVD deaths in the last three decades was higher in women than in men,[2] and the mortality rate attributable to Coronary Artery Disease (CAD) in young women actually increased despite decreased mortality in the general population.[3] Reasons for these trends are complex. Typical symptoms of CAD are sometimes absent or subtle in women. Studies have shown that nearly two-thirds of women who die suddenly of CAD had no previous symptoms that might have triggered treatment.[4] Many CVD risk factors, such as Diabetes Mellitus (DM), High Density Lipoproteins (HDL) and triglyceride levels have greater impact on women than men.[5] Women face unique risks related to pregnancy, menopause, and use of exogenous estrogen for hormone replacement therapy or contraception.[6] Use and efficacy of primary prevention measures may vary in women.[7] Finally, women continue to receive less-aggressive therapy for established CVD despite evidence that they benefit from the same therapies as men.[8] This article will review the risk factors for CAD in women, and interventions to decrease that risk.

RISK OF CVD RELATED TO SOCIAL FACTORS AND FAMILY HISTORY

Family History

Clinicians routinely enquire about family history of premature CAD (younger than 50

years in male first degree relatives or 65 years in female degree relatives).[9] Yet in a multivariate analysis of traditional risk factors, family history was predictive only in women. Analysis of two large cohorts in the Physician's Health Study and Women's Health Study showed complex relationships. History of maternal Myocardial Infarction (MI) was associated with increased risk for men and women. Paternal MI at any age was associated with increased risk in men, but only premature paternal MI increased risk for women.[10,11]

Smoking

Smoking tobacco significantly increases Cardiovascular (CV) risk, even in those who smoke fewer than five cigarettes a day.[12] The effect of smoking may be greater in women due to the interactions between components of tobacco smoke and hormonal factors.[13] Since the risk in second hand smokers increases by 25-30%,[14] history of smoking should include these exposures as well. Some markers such as toenail nicotine levels can be used as an objective tool to estimate the average nicotine exposure. One study showed that toenail nicotine levels are predictive of CVD among women, independent of other risk factors.[15]

Alcohol Consumption

Although moderate consumption of alcohol (no more than one drink a day in women) may be beneficial for the heart health, heavy drinkers are at increased risk of DM, elevated triglycerides, weight gain, hypertension, stroke, heart failure and other cardiovascular diseases. Thus, the American Heart Association recommends against initiating or increasing alcohol consumption to lower CV risk.[16]

Physical Activity

Sedentary life is associated with increased risk of CVD in women. The Women's Health Initiative study showed that postmenopausal women who sit 10 hours or more a day have a greater incidence of CVD compared with women who sit 5 hours a day or less, regardless of leisure-time physical activity. This risk is significantly augmented in women with both low levels of physical activity and prolonged sitting.[17]

RISK OF CAD RELATED TO OTHER MEDICAL CONDITIONS

Hyperlipidemia

Hyperlipidemia is very important risk factor for CAD in both men and women. Higher levels of HDL are associated with lower risk of CAD, but the protective effect varies with gender. Women need higher levels of HDL to have the same level of protection; their threshold is 50 mg/dL, compared with 40 mg/dL in men.[18] While the role of triglycerides in CVD is more controversial, studies have shown that elevated triglycerides and low HDL levels were independent predictors of CVD mortality

in elderly women, and that risk quadrupled in women with both conditions.[19]

Hypertension

The prevalence of hypertension increases with age, particularly for women. In young adults, hypertension is more common in men, but the prevalence equalizes during middle age (45-65 years). After age 65 years, it is more common in women.[20,21] Elderly women also have the lowest rates of hypertension control.[22] Bearing in mind that women live longer than men on average, more attention should be paid to this risk factor to prevent MI, stroke, and heart failure.

Obstructive Sleep Apnea (OSA)

Obstructive Sleep Apnea (OSA) is defined as recurrent episodes of apnea (lack of breaths) or hypopnea (smaller breaths) during sleep because of soft tissue obstruction of the upper airway. Most frequently this is related to increased neck circumference, but tonsil enlargement and other maxillofacial factors may contribute as well. OSA has been linked to hypertension and arrhythmias, particularly with more frequent and prolonged episodes of apnea.[23] Research has linked OSA to endothelial dysfunction,[24] which can occur with even moderate OSA in women.[25] Severe OSA has been linked with higher mortality from CVD in women.[26]
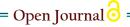
Autoimmune Disease

Rheumatoid arthritis and systemic lupus erythematosus, which are more common in women, are associated with increased risk of CVD. In turn, CVD is an important cause of morbidity (e.g. myocardial infarctions) and death in these patients, even controlling for other risk factors.[27] The reasons for these associations are not well understood.

Obesity

It is estimated that about 64% of American women are now either overweight or obese.[17] For many years, the relationship between obesity and CVD was thought to be due to higher rates of hypertension and DM. However, a 26 year follow-up of participants in the Framingham Heart Study indicated that obesity was a significant independent predictor of CVD, particularly among women.[28]

There are many measures to identify obesity. The most commonly used is the Body Mass Index (BMI), which is calculated using measurements of weight and height. However, other measures that reflect intra-abdominal obesity, such as waist/height ratio and waist/hip ratio, have been found to be better predictors of CVD among middle-aged and older women.[29] Current joint guidelines issued by the American College of Cardiology, American Heart Association, and The Obesity Society recommend that waist circumference and BMI should be obtained at

least annually. Women with BMI 25 or greater or waist circumference greater than 35 inches (88 cm) should be counseled regarding their elevated CVD risk.[30]

Diabetes Mellitus

DM affects about 11% of women in the US.[31] It is considered a "coronary equivalent" – that is, individuals with established diabetes have risk for CAD approaching that of people who have already had an MI. Among people with DM, the risk of CVD is greater for women than men.[32] Furthermore, diabetic women have higher mortality from MI compared to non-diabetic women and men with or without diabetes.[33]

Metabolic Syndrome

The metabolic syndrome is a clinical entity defined by the presence of at least three of the following: elevated systolic blood pressure (or treatment for hypertension), elevated blood glucose (or treatment for DM), low HDL cholesterol, high triglycerides, and increased waist circumference.[33] Metabolic syndrome is common, and prevalence increases in women after menopause.[34] A meta-analysis of 37 studies found that metabolic syndrome increases CV risk beyond that associated with its component risk factors, and that CV events and death were higher among women with metabolic syndrome than men.[35]

Polycystic ovarian syndrome (PCOS)

PCOS is a clinical syndrome defined by presence of two or more of the following: ovulatory dysfunction, hyperandrogenism, and polycystic ovaries. Between 6-20% of reproductive aged females are affected.[36] Women with PCOS may also meet diagnostic criteria for DM or metabolic syndrome. Controlling for BMI, PCOS has been linked to two-fold higher risk of CVD.[37]

Depression

There is a complex relationship between depression, stress, and heart disease that appears to be independent of self-care and adherence to medical therapy. A higher burden of stressors has been associated with worsening atherosclerosis, the underlying pathologic change in CAD.[38] Major depression is associated with changes in the hypothalamic-pituitary-adrenal axis, resulting in elevations of cortisol, a stress hormone that antagonizes insulin, influences fat distribution, and may affect fluid retention.[39] Studies have shown that major depression is a risk factor for congestive heart failure in older women, but not men.[40] Depression is also more common after MI in women than in men.[41]

Complications of Pregnancy

A history of certain complications during pregnancy confers long term CV risk. Women with pre-eclampsia and eclampsia may continue to have marked elevations in blood pressure even years after delivery.[42] They have a four-fold higher risk of hypertension and two-fold higher risk of CVD.[42] Similarly, roughly half of women with gestational diabetes develop DM in the future.[43] The placenta is a highly vascular structure; abruption and infarction of it predict future vascular disease like hypertension.[44]

Exogenous Estrogen and Progesterone

Use of exogenous estrogen has been linked to elevations in diastolic and systolic blood pressure, particularly at higher doses, and can be prothrombotic.[45,46] Estrogen-containing oral contraceptives should generally be avoided in women with known hypertension, and should not be used in women aged 35 years and older who smoke, as they increase the risk of MI in this population.[47] On the other hand, post-menopausal hormone replacement with estrogen, at doses lower than in oral contraceptives, was once thought to lower the risk for CAD.[48] The Women's Health Initiative, however, found a small increase in the absolute risk for CVD with combined therapy.[49] Due to the side effects associated with using hormonal replacement therapy, the harm of combined therapy, and the small overall net benefit of estrogen alone, the American Heart Association (AHA) has recommended against using hormonal replacement therapy for CVD prevention.[18]

Left Chest Wall Irradiation

Breast cancer is the most common cancer in women and localized disease is routinely treated with excision and chest wall irradiation. Other neoplastic conditions, such as esophageal cancer, lung cancer, and lymphoma, can also be treated with thoracic irradiation. Unfortunately, radiation to the left chest wall has been associated with increased risk of cardiac complications because of resulting fibrotic changes within the coronary arteries and other structures. Risk is related to cumulative radiation doses, and is further modified by the presence of other cardiovascular risk factors.[50]

PREDICTIVE VALUE OF SCREENING TESTS

Exercise Stress Testing

Exercise stress testing can provide significant prognostic information in men and women.[51] Two specific abnormalities – reduced exercise capacity and poor heart rate recovery – have been shown to be independent predictors of death in asymptomatic women.[52,53] At this time, however, there is insufficient evidence to support routine screening for asymptomatic or low-risk patients.[54]

Coronary Computed Tomography Angiography (CTA)

Coronary CTA is a newer non-invasive test that detects calcium deposition within coronary arteries. The Coronary

Artery Calcium (CAC) score predicts adverse cardiovascular events,[55] improving assessment of women otherwise classified as low or intermediate risk using traditional risk calculators. It can be used to target statin therapy to those individuals most likely to benefit for primary prevention of CAD, which may have economic benefits.[56] There is also an association between high sensitivity C-reactive protein (hs-CRP) and CAC score in women, but not men.[57]

hs-CRP

hs-CRP is a marker of inflammation. Elevated hs-CRP levels are associated with increased cardiac risk in older men and women, and higher CV mortality in men but not women.[58] The American Heart Association (AHA) does not endorse its routine use, however, since reducing hs-CRP has not been shown to improve clinical outcomes.[18]

Uric Acid Level

Uric acid is another biomarker may be useful in identifying women at high risk of CV events. Elevated uric acid levels may negatively affect endothelial function and oxidative metabolism.[59] In a cross-sectional retrospective study of 607 premenopausal women who had undergone coronary angiography, serum uric acid levels were associated with the presence of CAD.[60] This finding was confirmed in patients with transient ischemic attacks or stroke; an elevated uric acid level independently predicted long-term CAD in women but not men.[61] It is as yet unclear whether lowering uric acid levels reduces CVD risk.[62]

RISK CALCULATORS

It is difficult for busy clinicians to quantify the cumulative risk of multiple predisposing factors in individual patients. Therefore, algorithms have been developed to do so. Overall risk has then guided the use of preventive measures like statin and aspirin therapy in individuals.

The Framingham and American Heart Association (AHA) Risk Scores are the best known and most widely used in the United States. The Framingham score incorporates age, hypertension, hyperlipidemia, diabetes, smoking, and aspects of lifestyle like unhealthy diet and sedentary lifestyle. It does not account for menopausal status or pregnancy.[63] Old American Heart Association guidelines classified women into three risk categories based on the presence of comorbidities (e.g chronic kidney disease, diabetes, hypertension, hyperlipidemia, metabolic syndrome, subclinical atherosclerosis, and systemic autoimmune disease), central adiposity, lifestyle factors (e.g diet, physical inactivity, and exercise tolerance), family history of premature CAD, and history of pregnancy complications (Table 1).[18]

High risk (>=1 high-risk states)
• Clinically manifest CVD
• Clinically manifest cerebrovascular disease
• Clinically manifest peripheral arterial disease
• Abdominal aortic aneurysm
• End-stage or chronic kidney disease
• Diabetes mellitus
• 10-y Predicted CVD risk 10%
At risk (>=1 major risk factor[s])
• Cigarette smoking
SBP>120 mm Hg, DBP>80 mm Hg, or treated hypertension
• Total cholesterol >200 mg/dL, HDL-C<50 mg/dL, or treated for dyslipidemia
• Obesity, particularly central adiposity
• Poor diet
• Physical inactivity
• Family history of premature CVD occurring in first-degree relatives in men <55 y of age or in women<65 y of age
• Metabolic syndrome
• Evidence of advanced subclinical atherosclerosis (e.g coronary calcification, carotid plaque, or thickened IMT)
• Poor exercise capacity on treadmill test and/or abnormal heart rate recovery after stopping exercise
• Systemic autoimmune collagen-vascular disease (e.g lupus or rheumatoid arthritis)
• History of preeclampsia, gestational diabetes, or pregnancy-induced hypertension
Ideal cardiovascular health (all of these)
• Total cholesterol <200 mg/dL (untreated)
• BP <120/80 mm Hg (untreated)
• Fasting blood glucose <100 mg/dL (untreated)
• Body mass index <25 kg/m2
• Abstinence from smoking
• Physical activity at goal for adults >20 y of age: 150 min/wk moderate intensity,75 min/wk vigorous intensity, or combination
• Healthy (DASH-like) diet

Table 1: AHA Classification of CVD Risk in Women.

The new American Heart Association CV risk calculator was introduced in 2014, and includes only age, gender, smoking status, systolic blood pressure, total cholesterol, HDL cholesterol, and DM.[64] Its use has been validated only for whites and blacks, not other ethnic and racial groups.

The Reynolds Risk Score (RRS), unlike the others, was developed using data specifically for women. It adds hs-CRP and parental history of MI before age 60 years to the variables used in the Framingham risk score in an attempt to better risk stratify women.[65]

Unfortunately, none of these tools is perfect. A recent analysis found that Framingham and American Heart Association scores overestimate CV risk in women, while the Reynolds score underestimates it.[66] These scores may help clinicians initiate discussions about CV risk, but their limitations should be acknowledged as part of shared decision making.

PREVENTION OF CVD IN WOMEN

Some risk factors are clearly modifiable. Smoking cessation and avoidance of environmental tobacco smoke are well-accepted approaches for preventing MI.[18] Developing healthy lifestyles among young women and maintaining these behaviours through mid life may substantially lower the incidence of CVD.[67] Management of hypertension also lowers CVD risk, although the newest guidelines for blood pressure targets are controversial (Table 2).[68]

High-risk women

• Aspirin therapy (75–325 mg/d) should be used in women with CVD unless contraindicated (Class I; Level of Evidence A).

• Aspirin therapy (75–325 mg/d) is reasonable in women with diabetes mellitus unless contraindicated (Class IIa; Level of Evidence B).

• If a high-risk woman has an indication but is intolerant of aspirin therapy, clopidogrel should be substituted (Class I; Level of Evidence B).

Other at-risk or healthy women

• Aspirin therapy can be useful in women >65 y of age (81 mg daily or 100 mg every other day) if blood pressure is controlled and benefit for ischemic stroke and MI prevention is likely to outweigh risk of gastrointestinal bleeding and hemorrhagic stroke

(Class IIa; Level of Evidence B)

• Routine use of aspirin in healthy women<65 years of age is not recommended to prevent MI. (Class III, Level of Evidence B)

Table 2: Use of Aspirin in prevention of CVD in women.

Aspirin has been the cornerstone of prevention for atherosclerotic diseases like MI and stroke for many years, but comes at a price. While aspirin at doses of 81 mg daily or 325 mg every other day[69] lowers risk of MI in men, in women it only lowers risk of thrombotic stroke.[70] Benefits of therapy are partially offset by an increased risk for bleeding.[71]

LDL cholesterol has been a target for CV prevention for several decades. Statin therapy lowers the incidence of CV events, even in people with normal LDL cholesterol levels.[72] Research suggests that this class of medications has beneficial actions that extend beyond its lipid-lowering effects.[73]

Interventions for other metabolic risk factors are variably effective. Tight glycemic control in patients with DM has not been associated with CVD risk reduction.[74] On the other hand, early lifestyle interventions aimed at treating obesity and hyperlipidemia in women with PCOS impact the development and progression of atherosclerosis.[75] For patients with autoimmune disorders, disease modifying agents are preferred over corticosteroids, which have been linked to development of metabolic syndrome and premature atherosclerosis.[76] Biologics such as tumor necrosis factor antagonists and anti-CD40 agents are associated with lower rates of CVD.[77]

CONCLUSION

The prevention and diagnosis of CVD in women are clinically challenging. Women have unique risk factors that are often underappreciated, including polycystic ovarian syndrome and connective tissue diseases. Other traditional risk factors, such as family history and comorbid conditions, have different predictive values in women. Existing risk calculators can under or overestimate the risk of individual women. Of these, the Reynolds Risk Score (RRS) appears to be the most accurate, but requires an additional laboratory test (hs-CRP). Additional research to refine our risk calculators is needed.

Women at risk for CVD derive benefit from some standard pre ventive therapies, like statins. Current evidence does not support use of aspirin for primary prevention of myocardial infarction in women, and the benefits for ischemic stroke are counter balanced by an increased risk in hemorrhagic stroke.

Women with CAD events may have subtle or atypical symptoms; the majority present with sudden cardiac death as their first event. This finding highlights the need for better primary prevention efforts and for public health outreach and education directed specifically at women.

In summary, CVD is an increasingly important cause of morbidity and mortality in women. Clinical and public health approaches to women at risk for and with CAD should be informed by the known differences of risk, clinical presentation, and response to preventive therapies of women compared to men. Additional research is needed that includes women of child bearing age and the elderly, if we are going to effectively improve health care and outcomes.

REFERENCES

1. Kochanek KD, Xu JQ, Murphy SL, Miniño AM, Kung HC. Deaths: final data for 2009. *National vital statistics reports*. 2011; 60(3).

2. AHA. Statistical Fact Sheet 2013, 2013. Available at: https://my.americanheart.org/idc/groups/heart-public/@wcm/@sop/@smd/documents/downloadable/ucm_319576.pdf Accessed March 29, 2015.

3. American Heart Association. 1997 Heart and Stroke Facts: Statistical Update. Dallas, Tex: American Heart Association; 1996.

4. Roger VL, Go AS, Lloyd-Jones DM, et al. American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics-2012 update: a report from the American Heart Association. *Circulation*. 2012; 125(1): e2-e220. doi: 10.1161/CIR.0b013e31823ac046

5. Huxley R, Barzi F, Woodward M. Excess risk of fatal coro-

nary heart disease associated with diabetes in men and women: meta-analysis of 37 prospective cohort studies. *BMJ*. 2006; 332: 73-78. doi: 10.1136/bmj.38678.389583.7C

6. Kuhl H1. Hormonal contraception and substitution therapy: the importance of progestogen for cardiovascular diseases. *Obstetrics Women*. 1992; 52(11): 653-662. doi: 10.1055/s-2007-1026140

7. Basili S1, Raparelli V, Proietti M, Tanzilli G, Franconi FJ. Impact of sex and gender on the efficacy of antiplatelet therapy: the female perspective. *Atheroscler Thromb*. 2015; 22(2): 109-125. doi: 10.5551/jat.24935

8. Ashley KE1, Geraci SA. Ischemic heart disease in women. *South Med J*. 2013; 106(7): 427-433.

9. Wood D, De Backer G, Faergeman O, et al. Together with members of the Task Force. Prevention of coronary heart disease in clinical practice. Recommendations of the second Joint Task Force of European and other Societies on coronary prevention. *Eur Heart J*. 1998; 19: 1434-1503.

10. Sesso HD, Lee IM, Gaziano JM, et al. Maternal and paternal history of myocardial infarction and risk of cardiovascular disease in men and women. *Circulation*. 2001; 104: 393-398. doi: 10.1161/hc2901.093115

11. Friedlander Y, Arbogast P, Schwartz SM, et al. Family history as a risk factor for early onset myocardial infarction in young women. *Atherosclerosis*. 2001; 156(1): 201-207. doi: 10.1016/S0021-9150(00)00635-3

12. Bjartveit K, Tverdal A. Health consequences of smoking 1-4 cigarettes per day. *Tob Control*. 2005; 14(5): 315-320. doi: 10.1136/tc.2005.011932

13. Prescott E, Hippe M, Schnohr P, Hein HO, Vestbo J. Smoking and risk of myocardial infarction in women and men: longitudinal population study. *BMJ*. 1998; 316(7137): 1043-1047. doi: 10.1136/bmj.316.7137.1043

14. US. Department of Health and Human Services. Let's Make the Next Generation Tobacco-Free: Your Guide to the 50th Anniversary Surgeon General's Report on Smoking and Health. Atlanta: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2014 Available at: http://www.surgeongeneral.gov/library/reports/50-years-of-progress/consumer-guide.pdf Accessed March 5, 2014

15. Al-Delaimy WK, Stampfer MJ, Manson JE, Willett WC. Toenail nicotine levels as predictors of coronary heart disease among women. *Am J Epidemiol*. 2008; 167(11): 1342-1348. doi: 10.1093/aje/kwn061

16. Alcohol and Heart Health. AHA. website: http://www.heart.org/HEARTORG/GettingHealthy/NutritionCenter/HealthyEating/Alcohol-and-Heart-Health_UCM_305173_Article.jsp Accessed at: January 12,2015.

17. Chomistek AK, Manson JE, Stefanick ML, et al. Relationship of sedentary behaviour and physical activity to incident cardiovascular disease: results from the Women's Health Initiative. *J Am Coll Cardiol*. 2013; 61(23): 2346-2354. doi: 10.1016/j.jacc.2013.03.031

18. Mosca L, Benjamin EJ, Berra K, et al. Effectiveness-based guidelines for the prevention of cardiovascular disease in women--2011 update: a guideline from the American heart association. *Circulation*. 2011; 123(11): 1243-1262. doi: 10.1161/CIR.0b013e31820faaf8

19. Mazza A, Tikhonoff V, Schiavon L, Casiglia E. Triglycerides + high-density-lipoprotein-cholesterol dyslipidaemia, a coronary risk factor in elderly women: the cardiovascular study in the elderly. *Intern Med J*. 2005; 35(10): 604-610. doi: 10.1111/j.1445-5994.2005.00940.x

20. Mozzafarian D, Benjamin EJ, Go AS, et al. Heart Disease and Stroke Statistics-2015 Update: a report from the American Heart Association. *Circulation*. 2015; e29-e322. doi: 10.1161/CIR.0000000000000152

21. Wenger NK. Hypertension and other cardiovascular risk factors in women. *Am J Hypertens*. 1995; 8(12 Pt 2): 94s-99s. doi: 10.1016/0895-7061(95)99306-1

22. Wilkins K, Gee M, Campbell N. The difference in hypertension control between older men and women. *Health Rep*. 2012; 23(4): 33-40.

23. Chahal CA, Somers VK. Secondary hypertension: Obstructive sleep apnea. *J Am Soc Hypertens*. 2015; 9(3): 244-247. doi: 10.1016/j.jash.2015.02.001

24. Budhiraja R, Parthasarathy S, Quan SF. Endothelial dysfunction in obstructive sleep apnea. *J Clin Sleep Med*. 2007; 3(4): 409-415.

25. Kohler M1, Craig S, Nicoll D, Leeson P, Davies RJ, Stradling JR. Endothelial function and arterial stiffness in minimally symptomatic obstructive sleep apnea. *Am J Respir Crit Care Med*. 2008; 178(9): 984-988. doi: 10.1164/rccm.200805-717-OC

26. Won C, Guilleminault C. Gender differences in sleep disordered breathing: implications for therapy. *Expert Rev Respir Med*. 2015; 9(2): 221-231. doi: 10.1586/17476348.2015.1019478

27. Zhang J, Chen L, Delzell E, et al. The association between

inflammatory markers, serum lipids and the risk of cardiovascular events in patients with rheumatoid arthritis. *Ann Rheum Dis*. 2014; 73; 1301-1308. doi: 10.1136/annrheumdis-2013-204715

28. Hubert HB, Feinleib M, McNamara PM, Castelli WP. Obesity as an independent risk factor for cardiovascular disease: a 26-year follow-up of participants in the Framingham Heart Study. *Circulation*. 1983; 67(5): 968-977. doi: 10.1161/01.CIR.67.5.968

29. Page JH, Rexrode KM, Hu F, Albert CM, Chae CU, Manson JE. Waist-height ratio as a predictor of coronary heart disease among women. *Epidemiology*. 2009; 20(3): 361-366. doi: 10.1097/EDE.0b013e31819f38fl

30. Jensen MD, Ryan DH, Apovian CM, et al. American College of Cardiology/American Heart Association Task Force on Practice Guidelines; Obesity Society. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. *Circulation*. 2014; 129(25 Suppl 2): S102-S138. doi: 10.1161/01.cir.0000437739.71477.ee

31. National diabetes statics report 2014, 2014. Available at: http://www.cdc.gov/diabetes/pubs/statsreport14/national-diabetes-report-web.pdf Accessed November 12, 2013.

32. Roeters van Lennep JE, Westerveld HT, Erkelens DW, van der Wall EE. Risk factors for coronary heart disease: implications of gender. *Cardiovasc Res*. 2002; 53(3): 538-549. doi: 10.1016/S0008-6363(01)00388-1

33. Grundy SM, Brewer HB Jr, Cleeman JI, Smith SC Jr, Lenfant C. American Heart Association; National Heart, Lung, and Blood Institute. Definition of metabolic syndrome: Report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. *Circulation*. 2004; 109(3): 433-438. doi: 10.1161/01.CIR.0000111245.75752.C6

34. Carr MC. The emergence of the metabolic syndrome with menopause. *J Clin Endocrinol Metab*. 2003; 88(6): 2404-2411. doi: 10.1210/jc.2003-030242

35. Gami AS, Witt BJ, Howard DE, et al. Metabolic syndrome and risk of incident cardiovascular events and death: a systematic review and meta-analysis of longitudinal studies. *J Am Coll Cardiol*. 2007; 49(4): 403-414. doi: 10.1016/j.jacc.2006.09.032

36. Sirmans SM, Pate KA. Epidemiology, diagnosis, and management of polycystic ovary syndrome. *Clin Epidemiol*. 2013; 6: 1-13. doi: 10.2147/CLEP.S37559

37. de Groot PC1, Dekkers OM, Romijn JA, Dieben SW, Helmerhorst FM. PCOS, coronary heart disease, stroke and the influence of obesity: a systematic review and meta-analysis. *Hum Reprod Update*. 2011; 17(4): 495-500. doi: 10.1093/humupd/dmr001

38. Low CA, Matthews KA, Kuller LH, Edmundowicz D. Psychosocial predictors of coronary artery calcification progression in postmenopausal women. *Psychosom Med*. 2011; 73(9): 789-794. doi: 10.1097/PSY.0b013e318236b68a

39. Bose M, Oliván B, Laferrère B. Stress and obesity: the role of the hypothalamic-pituitary-adrenal axis in metabolic disease. *Curr Opin Endocrinol Diabetes Obes*. 2009; 16(5): 340-346. doi: 10.1097/MED.0b013e32832fa137

40. Williams SA, KasI SV, Heiat A, Abramson JL, Krumholz HM, Vaccarino V. Depression and risk of heart failure among the elderly: a prospective community- based study. *Psychosomat Med*. 2002; 64: 6-12.

41. Drory Y, Kravetz S, Hirschberger G, Israel Study Group on First Acute Myocardial Infarction. Long-term mental health of women after a first acute myocardial infarction. *Arch Phys Med Rehabil*. 2003; 84: 1492-1498. doi: 10.1016/S0003-9993-(03)00316-2

42. Bellamy L, Casas JP, Hingorani AD, Williams DJ. Pre-eclampsia and risk of cardiovascular disease and cancer in later life: systematic review and meta-analysis. *BMJ*. 2007; 335(7627): 974. doi: 10.1136/bmj.39335.385301.BE

43. Grant PT, Oats JN, Beischer NA. The long-term follow-up of women with gestational diabetes. *Aust N Z J Obstet Gynaecol*. 1986; 26(1): 17-22. doi: 10.1111/j.1479-828X.1986.tb01521.x

44. Siddiqui N, Hladunewich M. Understanding the link between the placenta and future cardiovascular disease. *Trends Cardiovasc Med*. 2011; 21(7): 188-193. doi: 10.1016/j.tcm.2012.05.008

45. August P. Hypertension in women. *Adv Chronic Kidney Dis*. 2013; 20(5): 396-401. doi: 10.1053/j.ackd.2013.07.002

46. Eisenberger A, Westhoff C. Hormone replacement therapy and venous thromboembolism. *J Steroid Biochem Mol Biol*. 2014; 142: 76-82. doi: 10.1016/j.jsbmb.2013.08.016

47. Shifren JL, Gass ML. NAMS Recommendations for Clinical Care of Midlife Women Working Group. The North American Menopause Society recommendations for clinical care of midlife women. *Menopause*. 2014; 21(10): 1038-1062. doi: 10.1097/GME.0000000000000319

48. The Women's Health Initiative Steering Committee. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *JAMA*. 2004; 291: 1701-1712. doi: 10.1001/jama.291.14.1701

49. Manson JE, Hsia J, Johnson KC, et al. Estrogen plus progestin and the risk of coronary heart disease. *N Engl J Med*. 2003; 349(6): 523-534. doi: 10.1056/NEJMoa030808

50. Darby SC, Ewertz M, McGale P, et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. *N Engl J Med*. 2013; 368(11): 987-998. doi: 10.1056/NEJMoa1209825

51. Laddu AA, Alderson L, Chaitman BR. Exercise Testing, Coronary Artery Disease. *Cardiovascular Medicine*. 2015; 181-203.

52. Gulati M, Pandey DK, Arnsdorf MF, et al. Exercise capacity and the risk of death in women: the St James Women Take Heart Project. *Circulation*. 2003; 108(13): 1554-1559. doi: 10.1161/01.CIR.0000091080.57509.E9

53. Nishime EO, Cole CR, Blackstone EH, Pashkow FJ, Lauer MS. Heart rate recovery and treadmill exercise score as predictors of mortality in patients referred for exercise ECG. *JAMA*. 2000; 284(11): 1392-1398. doi: 10.1001/jama.284.11.1392

54. Chou R. High Value Care Task Force of the American College of Physicians. Cardiac screening with electrocardiography, stress echocardiography, or myocardial perfusion imaging: advice for high-value care from the American college of physicians. *Ann Intern Med*. 2015; 162(6): 438-447. doi: 10.7326/M14-1225

55. Budoff MJ, Young R, Lopez, et al. Progression of coronary calcium and incident coronary heart disease events: MESA (Multi-Ethnic Study of Atherosclerosis). *J. Am. Coll. Cardiol*. 2013; 61: 1231-1239. doi: 10.1016/j.jacc.2012.12.035

56. Roberts ET, Horne A, Martin SS, et al. Cost-Effectiveness of Coronary Artery Calcium Testing for Coronary Heart and Cardiovascular Disease Risk Prediction to Guide Statin Allocation: The Multi-Ethnic Study of Atherosclerosis (MESA). *PLoS One*. 2015; 10(3): e0116377. doi: 10.1371/journal.pone.0116377

57. Zeb I, Budoff M. Coronary Artery Calcium Screening: Does it Perform Better than Other Cardiovascular Risk Stratification Tools?. *Int. J. Mol. Sci*. 2015; 16: 6606-6620. doi: 10.3390/ijms16036606

58. Cushman M, Arnold AM, Psaty BM, et al. C-reactive protein and the 10-year incidence of coronary heart disease in older men and women: the cardiovascular health study. *Circulation*. 2005; 112(1): 25-31. doi: 10.1161/CIRCULATIONAHA.104.504159

59. Butler R, Morris AD, Belch JJ, Hill A, Struthers AD. Allopurinol normalizes endothelial dysfunction in type 2 diabetics with mild hypertension. *Hypertension*. 2000; 35: 746-751. doi: 10.1161/01.HYP.35.3.746

60. Zhang JW, He LJ, Cao SJ, Yang Q, Yang SW, Zhou YJ. Association of serum uric acid and coronary artery disease in premenopausal women. *PLoS One*. 2014; 9(9): e106130. doi: 10.1371/journal.pone.0106130

61. Koton S, Howard SC, Warlow CP, Murphy MF, Rothwell PM. Serum urate predicts long-term risk of acute coronary events in women after a transient ischemic attack and stroke. *Cerebrovasc Dis*. 2008; 26(5): 517-524. doi: 10.1159/000155990

62. Alderman M1, Aiyer KJ. Uric acid: role in cardiovascular disease and effects of losartan. *Curr Med Res Opin*. 2004; 20(3): 369-379. doi: 10.1185/030079904125002982

63. Grundy SM, Pasternak R, Greenland P, Smith S Jr, Fuster V. Assessment of cardiovascular risk by use of multiple-risk-factor assessment equations: a statement for healthcare professionals from the American Heart Association and the American College of Cardiology. Circulation. 1999; 100(13): 1481-1492. doi: 10.1161/01.CIR.100.13.1481

64. Goff DC Jr, Lloyd-Jones DM, Bennett G, et al. American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014; 129(25 Suppl 2): S49-S73. doi: 10.1161/01.cir.0000437741.48606.98

65. Cook NR, Paynter NP, Eaton CB, et al. Comparison of the Framingham and Reynolds Risk scores for global cardiovascular risk prediction in the multiethnic Women's Health Initiative. *Circulation*. 2012; 125(14): 1748-1756, S1-11. doi: 10.1161/CIRCULATIONAHA.111.075929

66. DeFilippis AP, Young R, Carrubba CJ, et al. An analysis of calibration and discrimination among multiple cardiovascular risk scores in a modern multiethnic cohort. *Ann Intern Med*. 2015; 162(4): 266-275. doi: 10.7326/M14-1281

67. Chomistek AK, Chiuve SE, Eliassen AH, Mukamal KJ, Willett WC, Rimm EB. Healthy lifestyle in the primordial prevention of cardiovascular disease among young women. *J Am Coll Cardiol*. 2015; 65(1): 43-51. doi: 10.1016/j.jacc.2014.10.024

68. James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA*. 2014; 311(5): 507-520. doi: 10.1001/jama.2013.284427

69. Heart and Circulation. Using Aspirin for the Primary Prevention of Cardiovascular Disease - Provider Fact Sheet, 2009. Available at: http://www.ahrq.gov/professionals/clinicians-providers/resources/aspprovider.pdf Accessed April, 2009.

70. Internet Citation: Recommendation Summary. U.S. Pre-

ventive Services Task Force, 2009. Available at: http://www.uspreventiveservicestaskforce.org/Page/Topic/recommendation-summary/aspirin-for-the-prevention-of-cardiovascular-disease-preventive-medication Accessed March, 2009.

71. Wolff T1, Miller T, Ko S. Aspirin for the primary prevention of cardiovascular events: an update of the evidence for the U.S. Preventive Services Task Force. *Ann Intern Med*. 2009; 150(6): 405-410.

72. Ridker PM, Danielson E, Fonseca FA, et al. JUPITER Study Group. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med*. 2008; 359(21): 2195-2207. doi: 10.1056/NEJMoa0807646

73. Howard-Alpe G1, Foëx P, Biccard B. Cardiovascular protection by anti-inflammatory statin therapy. *Best Pract Res Clin Anaesthesiol*. 2008; 22(1): 111-133. doi: 10.1016/j.bpa.2007.08.001

74. Gerstein HC, Miller ME, Byington RP, et al. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med*. 2008; 358(24): 2545-2559. doi: 10.1056/NEJMoa0802743

75. Christian RC, Dumesic DA, Behrenbeck T, Oberg AL, Sheedy PF 2nd, Fitzpatrick LA. Prevalence and predictors of coronary artery calcification in women with polycystic ovary syndrome. *J Clin Endocrinol Metab*. 2003; 88(6): 2562-2568. doi: 10.1210/jc.2003-030334

76. Zeller CB, Appenzeller S. Cardiovascular disease in systemic lupus erythematosus: the role of traditional and lupus related risk factors. *Curr Cardiol Rev*. 2008; 4: 116-122. doi: 10.2174/157340308784245775

77. Manzi S, Wasko MC, Manzi S. Inflammation-mediated rheumatic diseases and atherosclerosis. *Ann Rheum Dis*. 2000; 59(5): 321-325. doi:10.1136/ard.59.5.321