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Cardiovascular Disease in Women: The Differences in Genders

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Cardiovascular disease (CVD) is currently the leading cause of death in U.S. women. As of 2011, CVD events account for 52.8% of among this population (Heart Disease and Stroke, 2012). A greater portion of women die from cardiac death related to CVD prior to arrival to the hospital (52%) then men (42%) (Shaw, 2009). Cardiac related deaths in women still remain one of foremost public health concerns. These statistics in the female population have remained consistently high while those of male counterparts are shown to be decreasing (Shaw, 2009).

According to major U.S. healthcare organizations such as the American Heart Association (AHA), the Center for Disease Control (CDC), and the World Health Organization (WHO), CVD is considered to be the number one healthcare topic of healthcare related concern these days. CVD encompasses multiple symptoms and disease processes contributing to debilitating morbidities and fatal outcomes. Including of, but not limited to, coronary heart disease, hypertension, congestive heart failure, and stroke. Another concern emerging is the consequences of cardiovascular disease in the female population.

Commonly considered by most to be a disease process characterized by male prevalence with stereotypical symptoms, there are many varying factors concerning women and CVD. These factors are evolving trends and could guide decisions of healthcare providers in treating female patients as a separate entity. Thus promoting the most health merited benefits of therapy and treating existing disease effectively. Females exhibit difference in vasculature structure, endocrine changes, and responsiveness to medications that adversely affect structure and integrity of a finely balanced circulatory system, when compared to their male counterparts. Shared risk factors and these variances for men and women could potentate these risk factors and lead to higher threats of morbidity and morality among the female population. These combined

factors in conjunction with atypical symptom presentation often lead to misdiagnosis and under treatment, permitting CVD to remain the leading cause of death in women.

Cardiovascular Disease in Women: The Differences in Genders

Cardiovascular disease is an umbrella term used to encompass many diseases of the vascular system. Including, but not limited to, coronary artery disease, myocardial infarction, stroke, and hypertension. Top healthcare organizations such as WHO, CDC, and AHA consider these disease processes to be the number one health disparity and cause of mortality in today's society overall as well as specifically in women. These diseases are also a heavy financial pull on the healthcare system with the resulting treatment, rehabilitation and missed wages. Based on statistics from the AHA in 2009, CVD accounted for 236.1 per 100,000 deaths. That breaks down to a rate of 2150 deaths per day from CVD; or one death every 40 seconds (Statistical Fact Sheet Update, 2013). When evaluating heart disease specifically, it is still determined by the healthcare community, to be the number one killer in both men and women (Heart Disease Fact Sheet, 2012). CDC 2009 statistics, heart disease accounts for approximately 600,000 deaths annually, that is one death every minute from heart disease (Heart Disease Fact Sheet, 2012). The National Conference of State Legislatures attests that treatment for cardiovascular diseases accounts for nearly $1 of every $6 spent on health care in the United States. In 2010, an estimated $444 billion was spent on CVD, treatment, medication and lost productivity from disability.

In reviewing the impact CVD has on the female population, the mortality rates are much higher in females. Even though a higher percentage of males suffer from CVD insults, the mortality rates are higher in the female population from the effects (Shaw, 2009). One in three females has some form of cardiovascular disease (AHA, 2013). CVD has claimed the lives of

401,495 women in 2009. Compare this to 270,865 deaths caused by all combined cancers, making CVD accountable for 51% of deaths of this cohort (Statistical Fact Sheet, 2013).

The Women's Ischemia Syndrome Evaluation (WISE) study sponsored by the National Institute of Health (NIH) made significant discoveries in gender specific differences. These differences include; the pathophysiology of CVD processes, anatomy involved in this disease process and responses to therapies provided for the prevention and treatment of CVD and presenting symptoms (Finks, 2010). These differences can lead to significant consequences from failure to acknowledge the variances and treat accordingly.

The question addressed through this literature review is; if there is a measurable decrease in the number of deaths overall from CVD, leading to the belief that there are effective screening, identification and treatment of risk factors, why is there not a same measurable reduction in the number of women as an identifiable population suffering from CVD and heart disease (HD)?

Can men and women demonstrating risk factors or current disease processes of CVD be grouped together in the same assessment and treatment category, or are there definitive differences in the populations which would warrant distinguished assessment and treatment algorithms based on gender. In addition, are the commonly used treatment options beneficial to women who are at an increased risk of mortality and morbidity, and can this confirmed by current statistical research?

The purpose of this literature review is to: evaluate the current screening methods used to identify risks for CVD, and determine the effectiveness of therapy commonly prescribed in treatment of as women with this disease(s). Thus enabling providers to better manage these women at risk for CVD and prevent further progression into a higher risk category. Outcomes of

better therapy, including primary, secondary, and tertiary therapy, show effective measurable results of reducing incidence of CVD in women.

The framework used to guide this study was the Neuman's systems model. In preventing CVD in women, the three levels of prevention should be used to guide providers in optimal CVD therapy benefits. Primary prevention is determining a woman's potential for risk factors and promoting education on prevention of these risks. Secondary prevention would be effective screening and treatment of current risk factors and current disease processes in order to avoid progressing into a high level of risk. Tertiary prevention includes treatment of morbidities resulting from a CVD effect, and prevention of complications of further disease progression.

Within the Neuman's model there are variables which must be incorporated into treatment and prevention in women. These include; the physiological structure and function of the body, the mental processes and relationships, the sociocultural and spiritual variables, and overall development. There are also known and measurable stressors as well as unknown and unforeseen stressors which can disrupt or change a balance in the variables, altering the effectiveness of outcomes of research or treatment therapy. All these play a role in deciding effective preventative measures, assessment techniques and treatment options.

In conducting this literature review, criteria in searching for articles included the phrases; women and cardiovascular disease, women and heart disease, heart disease and gender differences and cardiovascular disease. Articles were then chosen based on relevance to the topic of cardiovascular disease, inclusion of gender analysis and a patient population of more than 100 participants. No articles older than 2002 were included in this review in efforts to keep with the more up to date and accurate research within the previous 10 years. Statistical data

incorporated into this review was retrieved from credible healthcare organizations, including the CDC, WHO and AHA, from the year 2009 to present.

In shaping the underlying foundation in dissimilarity of the pathophysiology, presentation, risks for, and treatment of CVD in women, defining the potentials of these variations is vital. Once the root, or roots, for variation is discovered and established, it is necessary to evaluate treatment options commonly used. Then decide their benefit verses vulnerability in treating the female population at risk for or recovering from CVD. A secondary goal of this review is to raise awareness in providers to educate their women patients on their risk factors, both modifiable and non-modifiable, for CVD as well as the consequences of this disease and available optimal treatment methods.

Mosca, Manson, Sutherland, Langer, Manolio, et al, (2009), found that through education and raising awareness of the risk of CVD to women, there was a heightened awareness of individual risk and a sense of ownership of protecting one's health from those risk factors. The Heart Truth campaign initiated in 2001 is sponsored in the United States by the National Heart, Lung, and Blood Institute, more commonly known as the "Red Dress" campaign, which was designed to help raise public awareness of the risks of CVD knowledge and awareness of leading cause of death among women. This campaign hoped to lead an increase in public education and also evaluate the current public knowledge regarding CVD. Efforts of this campaign continue today, gaining popularity and raising awareness of the health disparities of CVD. Presently 55% of surveyed participants correctly identified heart disease as the leading cause of death compared to 30% in 1997 (Mosca et al., 2009). Before this public campaign effort there was a lack of discrepancy between the risk of men and that of women as CVD which was considered by the

public as a male population disease, and was studied and treated according to outcomes within this male population based research.

Oliver-McNeil and Artinian (2009) demonstrated that 93% of surveyed participants, although knew they had some risk for CVD, were not aware of their individual risk and what they could do to lower their risk of potentially suffering the effects of CVD. Worrall-Carter, Ski, Scruth, Cambell, & Page (2011) found that in the female population, most risk factors are modifiable and are simply overlooked or underestimated by providers and public alike. According to their study, women are often underrepresented in trials in identifying and treating risk factors. The highest risk factors associated with CVD in women were diabetes mellitus, smoking, and hypertriglyceridemia, (Worrall-Carter et al, 2011). These risks are all modifiable or preventable, meaning they are improvable and in turn, if treated appropriately, could lower the risk of a future CVD event (Worrall-Carter et al, 2011). However Mosca et al, (2009) found that more often than not, women were deemed by providers to be at low risk for CVD, therefor were under identified for these risk factors and not treated effectively to prevent further progression of CVD.

There was a lack of determining women with potential of developing CVD by healthcare providers, despite demonstrating the same risk factors listed as culprits by standardized national healthcare organizations. Physician awareness of three national CVD prevention guidelines (NCEP ATP III, JNC 7 and AHA) differed by specialty of practice; Family Practice, Obstetrics and Gynecology, and Cardiology. The rate of highest identification of potential CVD disease in the patient population was that of cardiologists (80%) although it was still not comparable to the rate of identification of CVD in the male population by cardiologists (95%). Rates of recognition lowest among OBGYN (58%), although their specialty is caring for the female

population, including women suffering with high risk cardiovascular processes such as eclampsia and pregnancy induced cardiomyopathy. Physician incorporation of therapy guidelines for women were again highest among cardiologists (59%) followed closely by PCPs (46%). The least likely to employ the guidelines for therapy were OBGYN physicians who specifically treated women (24%) (Mosca, Linfante, Benjamin, Berra, Hayes, et al., 2005).

In reviewing the pathophysiological differences of women in reference to CVD, Shaw (2009) determined women to have less anatomical and obstructive coronary disease (<50% of women with symptoms of cardiac disease), but found to have higher rates of ischemic disease, with a relatively preserved left ventricular function. This study also found this to contribute to women having an increased overall CVD mortality compared to similarly aged males. "The WISE study implicates abnormal coronary reactivity, microvascular dysfunction and plaque erosion with distal microembolization as female specific ischemic heart disease pathophysiology" (Shaw, 2009)

More than half of these women undergo repeated hospitalizations with signs and symptoms of heart ischemia without objective findings such as coronary artery disease. Thus leading Shaw (2009) to determine heart disease prevalence in women to be predominately ischemic heart disease (IHD) (Shaw, 2009). These findings limit conventional treatment measures, such as cardiac catherization or coronary bypass grafting from preventing the occurrence of mortality and morbidity from heart disease such as myocardial infarction, direct cardiac hypoxia, or atherosclerotic disease. A study of female sex as an independent predictor of survival and morbidity was conducted by Ahmed, Tully, Knight, and Baker (2011) who included a gender differential of their results from a study of 4,742 participants (23% of which were female) with a 7.9 year median follow up from receiving coronary artery bypass grafting

(CABG). The authors discovered that the women who suffered cardiac injury, despite receiving CABG, were associated with early morbidity and long-term cardiac mortality. They also note that more female participants were older in age, carried higher numbers of concomitant morbidities. Prior to undergoing coronary artery bypass grafting were already with greater proportion of cardiac risk factors once patients were identified to be in need for bypass grafting (Ahmed, et al., 2011).

Grines (2012) discussed the outcomes of women who presented for cardiac catheterzation, verse men in cardiac catheterizations with stent placement, and were older and with more comorbidities then men. Women were also at a higher risk for mortality after cardiac catheterization which was not consistently eliminated after adjustments for comorbidities. Women were also found to be at a higher risk for bleeding, incomplete revascularization and failure to deploy stent second to smaller coronary arteries (Grines, 2012).

So this raises the question; are there are specific female risk factors for CVD related to the circumstance of being of the XX gene as opposed to the XY gene or is it simply a matter of under education and treatment initiation by providers to a population at risk as the previous studies listed have demonstrated that leads to this health care crisis?

In reviewing some female specific issues concerning CVD, Miller & Best (2009) states that "the lack of attention to sex differences in etiology of cardiovascular disease has resulted in inadequate methodologies and strategies to prevent, diagnose, and treat cardiovascular disease in women compared to that in men." In reviewing sex disparities in associated risks of CVD, the authors review three categories of risks; conditions unique to one sex such as menopause and pregnancy induced hypertension in women, conditions which can occur in both sexes, and conditions that are occurring to both sexes but present differently per gender. Through their

research presentation, the authors emphasize the importance in the need for the developing a valid assessment tool for use, which will incorporate information regarding not only the risk factors found in both genders, but with given attention to reproductive history including hormone therapy, menopause, pregnancy exposure and complications or risks within the reproductive years which may contribute to a increased risk of developing CVD.

There has been a great deal of controversy over the role played by hormone therapy in relation to the progression of risk in CVD events and whether or not estrogen therapy is indeed beneficial in preventing these events. Or whether the risks associated with the therapy outweigh what benefit there may be. Miller (2010) found that sex steroids affect all components of the vascular wall, heart, as well as blood elements which come in contact with luminal surfaces of the vascular system. Once these hormonal levels are altered, the vasculature system becomes vulnerable to adverse effects of this change. This includes but not limited to poor vascular contractibility which can result in consistently constricted vessels, or thinning of luminal wall making the vessel exposed to damage. Estrogen was noted to carry a high role in the vascular dilation in premenopausal women by endothelium-dependent vascular relaxation through nitric oxide (NO), prostacyclin, and hyperpolarization pathways (Orshal & Kahlil, 2013). However, clinical trials such as the Heart and Estrogen/Progestin Replacement Study (HERS), HERS-II, and the Women's Health Initiative did not support the experimental findings and instead demonstrated adverse cardiovascular events of hormone therapy (HT) in aging women such as vascular embolization and heart failure. The lack of vascular benefits of HT may be related to the hormone used, the estrogen replacement, or the patient's particular cardiovascular condition or age (Qiao, McConall & Kahlil, 2008). These studies suggest not necessarily the need for HRT in order for vascular protection, but early identification and proper treatment in regards to

hypertension is the most beneficial form of CVD prevention and therapy for postmenopausal and premenopausal female patients.

Another area found to be at specific increased risk for the female patient was hypertriglyceridemia and diabetes mellitus. A Canadian led global INTERHEART standardized case-control study was conducted that measured the nine greatest risk factors for CVD. This study screened all patients admitted to the coronary care unit or equivalent cardiology ward for a first MI at 262 participating centers in 52 countries. Through this study it was determined that hypertriglyceridemia was an independent risk factor in determining a female risk for heart disease (O'Riordan, 2004). Diabetes mellitus (DM) was identified as having the greatest difference for developing CVD, placing women with DM at a 3-4 fold increase of developing CVD in comparison to women without DM (Worrall-Carter, et al., 2011). Matthews, Crawford, Chae, Everson-Rose, Sowers, et al. (2009) also concluded through their study that there was a measurable substantial increase in total cholesterol and low density lipoprotein (LDL) at the time of final menstrual period (FMP). Although the relationship between estrogen and lipid regulation is not completely understood, it stands to hypothesize that physiologic levels of estrogen are known to help maintain favorable lipoprotein profiles in women. Once a women enters menopause and the levels of estrogen rapidly declining, levels of high density lipoprotein (HDL)-cholesterol decrease while triglyceride levels and well as LDL- cholesterol levels begin to rise. A low HDL-cholesterol level is a strong forecaster of increased risk of CVD in women. The average HDL cholesterol level in moderately healthy adult women is 55 to 60 mg/dL. A decrease in HDL cholesterol level of 10 mg/dL increases overall coronary disease risk by an estimated 40 to 50 percent.

When evaluating treatment through pharmacological therapy for women, it was noted there was several treatment algorithms in which women either benefited or did not benefit in therapy at all in comparison to men or the average measured statistics. Walsh and Pigone, (2010) reviewed the most common medical management and the difference in effects on patients in regards to gender. In men there was a definite reduction of CVD events with preventative pharmacological therapy, regardless of the deemed level of risk. In women being treated with the same preventative pharmacological therapy, there was only a minimal reduction of risk within categories of women deemed to be a moderate to higher risk of CVD. An individual level of risk is determined by presence of current risk factors. This includes current presence of both modifiable and non-modifiable such as genetics, treatment and compliance with the treatment goals, as well as current presence of disease which exacerbates CVD such as hypertension, hyperlipidemia and diabetes. These factors are all used to assess and determine a person's risk for developing or experiencing a CVD occurrence when considering initiation of pharmacological therapy.

Lipid lowing pharmacological therapy initiated in women patients with hyperlipidemia, defined as an increased level of serum cholesterol and triglycerides, was found to reduce incidence of CHD by 50% (Mosca, et al., 2009). Use of these agents in women without a demonstrated case of CVD, although a reduction in CHD events was determined, there was not a proven reduction in overall CVD mortality. In women with known CVD, use of anti-hyperlipidemia medications found a decrease in more CHD events and associated mortality (Walsh & Pigone, 2004).

In evaluating antithrombotic therapy, women were found to be at a disadvantage with the pharmacological treatment. Aspirin therapy affects women differently than men as deduced

through a study by Xhyheri & Buliardini (2010), finding that aspirin is more effective in preventing a MI in men (32%), but decreased stroke risk in women (17%). Plavix was found to be less effective in reducing the risk of a CVD event in women (7%) then men (16%) while therapy was associated with an increased risk of bleeding in women (43%) then men (22%).

Hypertensive therapy is also complicated in women as earlier discussed by the loss of sex steroids in post-menopausal women, reducing the vasodilation response of the vascular system. Traditional treatment options studied by Xhyheri & Bulgiardini (2010), which were used for post therapy after a cardiovascular event, was determined to have a different effect on women. ACE inhibitors used in post recovery from MI or CHF events was shown to have less effectiveness in women (22%) then men (37%). Beta blockers were found to be more effective in women (31%) then in men (5%).

Through the research conducted for this review, it was noted that multiple articles either cited or demonstrated the lack of female participants within the current research regarding the study of risks of developing CVD, as well as the treatment, and consequences of CVD. Many reasons for this lack of inclusion were listed including, risk of injuring a fetus by including women of child bearing age, altering fertility abilities, variability in data results by incorporating women undergoing hormone therapy, or lack of participants by failing to recognize pertinent risk factors or symptoms for research inclusion. Worrall-Carter cited that not only women were underrepresented in CVD prevention and treatment trials (30%) nut were not represented properly as most women included were statistically older with more comorbidities then the male counterparts. There was also a under representation of gender differences in research studies. Only one-third of studies evaluated cited these gender specific findings. This leads most

outcome based treatment theories being predominately geared towards a male population (Worrall-Carter, et al., 2011).

The Framingham study is considered a landmark research study, as it incorporates the female population individually as well as gives particular details to the risk assessment, treatment and trending details about cardiovascular disease in women. According the Framingham website, they state:

> "Since our beginning in 1948, the Framingham Heart Study, under the direction of the National Heart, Lung and Blood Institute (NHLBI), formerly known as the National Heart Institute, has been committed to identifying the common factors or characteristics that contribute to cardiovascular disease (CVD). We have followed CVD development over a long period of time in three generations of participants."
>
> (Framinghamheartstudy.org).

This study is currently ongoing, presently in the fourth generation of study, and focuses on using the data collected to the development, progression, and effects of treatment of cardiovascular disease. Over the years, careful monitoring of the Framingham Study population has led to the identification of major CVD risk factors. This study contributes valuable information on the effects of these risk factors, such as blood pressure, blood triglyceride and cholesterol levels, age, gender, and psychosocial issues in the development of CVD in women. This landmark research raised awareness to there being a prevalent gender difference in regards to CVD. Risk factors for other physiological conditions in women, such as dementia, have been and continue to be investigated. In addition, the relationships between physical traits and genetic patterns predisposing women the CVD processes are continued to be studied (Framinghamheartstudy.org).

In exploring the literature in this study, there is a definite difference in the process of identifying CVD in women and ideal treatment therapy. The research determined not only is there a lack of identification by providers of women presenting with risk factors, there is suboptimal therapy initiated if any therapy prescribed at all. This deficiency of healthcare to a population at risk is contributing to a failure in declining the statistics of morbidity and mortality of women, as well as using a great deal of healthcare dollars on highly preventable disease. In treatment of the disease process encompassed in CVD, there is a need for a sex based screening and gender based treatment algorithm for providers.

Increasing public awareness of this issue would raise knowledge of risk factors to those demonstrating these threats which in turn would possible, prompt further cessation of risk. Promoting behavior through a sense of health conscious ownership as well as encouraging women to discuss concerns with their healthcare providers.

The limitations of this study are the lack of substantial gender based data. There is a consistent acknowledgement of a lack of women participants or gender distinction in studies or reviews conducted. Even with the inclusions of the available data for gender discernment in these trials, there was a definite greater participation of men which leads to question the validity of the results from these trials. The Framingham study which was created in effort to include women and gender differences over a period of generations acknowledges the lack of female participants. There needs to be more focused research on the adequate treatment of CVD as it pertains to female population well as reducing the risk of developing high risk probability of an event and providing pertinent education to the patients in reducing their risk. Development of a gender based assessment and treatment algorithm. If available to providers, it would be beneficial in identifying a women's tendency to developing CVD as well as prime treatment

therapy to decrease her risk of suffering the effects of this disease process. This in turn could aid in decreasing the devastating statistics currently plaguing the women of America today.

Appendix	Design and Purpose	Population (*N*)	Intervention/Interpretation	Findings
Oliver-McNeil, S., Artinian, N. & Beaumont, W. (2002). Women's Perceptions of Personal Cardiovascular Risk and Their Risk-Reducing Behaviors. *American Journal of Critical Care, 11,* 221-227.	Descriptive study conducted at a 925-bed teaching hospital to describe perceptions of cardiovascular risk factors and risk-reducing behaviors among women patients newly diagnosed with cardiovascular disease.	33 women > 18 years or older with CAD diagnosed with angiographic findings or confirmation of a MI within the preceding 7 days Mentally competent as evidences by living independently in the community, no prior history o Cad and able to read and write english	SPSS descriptive statistics were used to analyze all study variables and the research questions.	This study concluded that women included had limited awareness of their personal risk limiting their ability to participate in CHD prevention Documented risk factor in medical records did not correlate with patients perceived risks, however did correlate with the AHA cardiovascular risk factors excluding body mass index and life stress Despite 93% of participants knew they had some risk for CAD, they were unaware they had multiple risk factors or the impact these risks held for their overall health There was no identified relationship between risk identification and risk-reducing behaviors.
Mosca, L., Mochari, H., Christian, A., Berra, K., Taubert, K., Mills, T., et al. (2006). National Study of Women's Awareness, Preventive Action, and Barriers to Cardiovascular Health. *Circulation, 113,* 525-534.	A meta-analysis study conducted through surveys to determine the current knowledge of cardiovascular disease in public women.	1485 women >25 years of age completed the survey. A total of 18905 calls were made to include the number of volunteer participants.	.Statistical analysis of the data was completed using SPSS. Logistic regression models were used to determine knowledge of variables. X2 analysis was used to determine the association of perceived risk and defined risk.	55% correctly identified CVD as the leading cause of death compared with 30% in 1997 ($P<0.05$) 63.1% of cited CVD as the leading cause of death in men. Awareness among women who considered themselves at an increased risk (moderate or high) was higher then women who perceived themselves to be at a lower risk (59.4% vs 60.9% vs 49.0%) 81% of women said they had heard or read about the prevalence of heart disease in the past 12 months. These women were more likely to be aware of CVD as the leading cause of death in women (68.9% vs 51.2%; $P<0.0001$) 88% confirmed they had yearly checkups with their healthcare provider. 54% said their healthcare provider discussed their risk factors for CVD. Overall statistics showed the women who were more aware of the risks for CVD

				deemed themselves at a moderate to high risk level. These women were more proactive in decreasing their risk factors then those women who considered themselves at low risk.
Weiss, A. (2009). Cardiovascular Disease in Women. *Primary Care Clinic Office, 36*, 73-102.	This descriptive study was conducted to discern the gender specific differences in the physiology, presentation of symptoms' and treatment of cardiovascular disease			CVD affects women disproportionately then it does men as it is diagnosed less frequently, treated less effectively, and carries a higher mortality rate in women. Today CVD affects 42.1 million women (36.6% of the female population) and accounts for 41.3% of all deaths of American women. The cost of healthcare for CVD in 2005 was projected at $394 billion: $242 billion in direct healthcare costs and $152 billion in lost production and wages. The lifetime risk for CVD in 2 in 3 for men and 1 in 2 for women. Annual rates of first major CVD event for women track those of men but are delayed by 10 years. In persons younger the 75 years of age, more CVD events occur in men because of CHD than women, whereas more CHF events occur in women than men. There are less "common" presentation symptoms of CVD/CAD in women than in men which often lead to a misdiagnosis. The lifetime risk of dying from a stroke is twice that of men (16% vs 8%) Two thirds of sudden deaths in women occurred in women without and history of symptoms whereas only 50% of men were similarly affected. Women have a higher incidence of death in the first year after a heart attack then men (38% compared to 25%), twice as likely as men to die after bypass surgery, a higher rates of disability due to heart failure within 6 years after a MI (46% to 22%)
Vaid, I., Wigington, C., Borbely, D., Ferry, P. &	This open cohort study design assesses and	WISEWOMAN began in 1993 to	The current (4th) phase of WISEWOMAN	Women with low income endure a disproportionate

Manheim, D. (2011). WISEWOMAN: Addressing the Needs of Women at High Risk for Cardiovascular Disease. *Journal of Women's Health, 20*(7); 977-982.	discusses the finding of the WISEWOMAN study program.	extend preventative health services offered to women who participated in the National Breast and Cervical Cancer Early Detection Program (NBCCEDP).	supports grantees in developing partnerships that will bring about policy, environment, and system changes in efforts to support heart healthy behaviors.	impact of the burden of CVD resulting from limited access to healthcare resulting from being uninsured or limited financial means.
Wenger, N. (2012). Women and Coronary Heart Disease: A Century After Harrick:Understudied, Underdiagnosed and Undertreated. *Circulation, 126*, 604-611.	A primary study of descriptive design to discuss the current status of studies of CHD in women from 1992-2012 including the challenges met with these studies and the proposed treatment outcomes hypothesized.			Lack of public awareness of CHD in women in risk determination, symptom presentation, screening techniques, diagnostic procedures, and sex disparities in application of evidence based therapies contribute to poor CHD outcomes. Despite CVD burden, women remain unrepresented in clinical and are at a disadvantage by absence of sex –specific analysis.
Mosca, L., Linfante, A., Benjamin, E., Berra, K., Hayes, S., Walsh, B., et al. (2005). National Study of Physician Awareness and Adherence to Cardiovascular Disease Prevention Guidelines. *Circulation, 111*, 499-510.	Online cross-sectional survey including case studies to assess knowledge of screening, preventative and interceptive therapies and tools	500 randomly selected physicians (300 primary care, 100 OB/GYN, 100 cardiologists) drawn from the J. Reckner Associated database	Descriptive statistics of physician practices and preventative recommendations were presented as proportions	Physician awareness of 3 national CVD prevention guidelines (NCEP ATP III, JNC 7 and AHA) differed by specialty of practice Physician recommendations about lifestyle interventions, supplements, and aspirin therapy were sub optimal among low-risk patients across the specialties Supplements were more highly recommended among the mid to high risk populations Results for correctly identifying risks for patient populations considering gender difference were similar across the specialties. Women risks were identified less often than that of males. Women were also more likely to be assigned to a low risk category despite being a similar calculated risk as men
Mochari-Greenberger, H., Mills, T., Simpson, S. & Mosca, L. (2010). Knowledge, Preventive Action, Barriers to Cardiovascular Disease Prevention by Race and Ethnicity in Women; An American Heart Association National Survey. *Journal of Women's Health, 19(*7): 1243-1249.	Survey using standardized questionnaire about knowledge of healthy risk factor levels, preventative actions and barriers to preventative actions. The purpose of this study was to assess differences in CVD knowledge, preventative actions, and barriers to prevention by racial/ethical group in a nationally representative	1008 women >25 years of age with at least one person living in their household or one person not living in their household for whom they made healthcare decisions for	Descriptive statistics of respondents' characteristics, knowledge level, preventative actions and barriers to these actions were evaluated between the ethnic groups.	Knowledge that CHD is the leading cause of death varied by racial/ethnic groups which were independent of age, marital status, education, employment, income level or having children Hispanic populations was more likely to be unaware of the correlation between blood pressure and CVD

	sample of women.			Blacks and Hispanics were less likely than Caucasian/other groups to be aware that lipid levels were in correlation with the risk of CVD Race/ethnicity was not associated with the risk of increased fasting blood glucose levels in relation to CVD, although those respondents with <4 years of college education were 25% less likely to know optimal fasting blood glucose level
Heidenreich, P., Trogdon, J., Khavjou, O., Butler, J., Dracup, K., Ezekowitz, M., et al. (2011). Forecasting the Future of Cardiovascular Disease in the United States: A Policy Statement From the American Heart Association. *Circulation*, 123, 933-944.	A case study using primary, secondary studies randomized and controlled studies to forecast the future costs and national effects needs for treating cardiovascular disease from the year 2010 – 2030.			CVD is responsible for 17% of national health care expenditures and expected to increase as the population ages. By 2030 – 40.5% of the US population is predicted to have some form of CVD. People >65 years of age is determined to have a higher prevalence of CVD, and this population segment is expected to grow significantly over the next two decades. Between the years of 2010-2030, projected healthcare costs for treating CVD is forecasted to triple from $273 billion/year to $818 billion/year. Indirect costs such as lost wages due to CVD disease is projected to increase by 61% (from $172 billion in 2010 to $276 billion in 2030.
Shaw, L., Bugiardini, R. & Merz, N. (2009). Women and Ischemic Heart Disease. *Journal of the American College of Cardiology*, *54*(17): 1561-1575.	This study was a cross-sectional design conducted to evaluate the authors given hypothesis that women experience more adverse outcomes compared with men in the treatment of CAD because obstructive CAD remains the current focus of therapeutic strategies.			Cardiac death remains the leading cause of death in women of all ages. Women have less anatomical obstructive CAD yet greater rates of myocardial ischemia and mortality compared with similarly aged males. Contributing factors to higher female ischemic cardiac rates include abnormal coronary reactivity, microvascularization dysfunction, and plaque erosion, and distal microembolization . A greater proportion of women die from sudden cardiac death prior to arrival at the hospital (52%

				compared with 42% of men). More than 80% of midlife women have 1 or more traditional cardiac risk factors. Over half of symptomatic women without obstructive CAD continue to have symptoms and undergo multiple hospitalizations and testing which result in diagnostic and therapeutic uncertainty.
Gleeson, D. & Crabbe, D. (2009). Emerging Concepts in Cardiovascular Disease Risk Assessment: Where do Women Fit In? *American Academy of Nurse Practitioners, 21,* 480-487.	The purpose of this review of literature was to determine and highlight the limitations in the assessment of women and discuss the current information in the process of assessment of risk factors in the female patient population, the pitfalls of these processes and the role these risk factors play in CVD.			Use of oral contraceptives in conjunction with smoking is associated with a significant risk of developing thrombosis and CVD complications. The mortality among males with diabetes is twofold higher, and fourfold higher than the general population for CV illness. Women have a one in six chance of developing heart failure from hypertension etiology while men have a one in nine chance. Women have been observed to have more tendencies towards diastolic heart failure as opposed to systolic heart failure.
Douglas, P. & Poppas, A. (2012). Determinants and Management of Cardiovascular Risk in Women. *UpToDate*. Retrieved January 12, 2013 from www.uptodate.com	Literature review to identify the clinical presentation of heart disease and diagnostic testing considering gender differences.			Women with CHD are generally about 10 years older than men at the time of presentation which carries a greater burden of risk factors. Women are less likely than men to have typical angina (28% verses 55%) Silent myocardial infarctions were illustrated to be significantly higher in younger women than men (42% verses 30.7%). Incidence was noted to be higher in younger women then older women (41% verses 24%) A higher fraction of sudden deaths in women verses men occurred in the absence of prior CHD (63% verses 44%) Many of the diagnostic testing statistics were considered by the authors to be less than accurate due to

				the underrepresentation by women as well as the older age of then women who were included.
Tamis-Holland, J., Lu, J., Bittner, V., Magee, M, Lopes, N., Adler, D., et al. (2011). Sex, Clinical Symptoms, and Angiographic Findings in Patients With Diabetes Mellitus and Coronary Artery Disease (from the Bypass Angioplasty Revascularization Investigation [BARI] 2Diabetes Trial). *American Journal of Cardiology, 107,* 980-985.	This study was of observational design of the results concerning the BARI (2D) study. The purpose of this study was to determine the relationship between symptoms and extent of CAD in patients with type 2 diabetes mellitus and known CAD enrolled in the Bypass Angioplasty Revascularization Investigation 2 Diabetes trial.	2,368 patients from 49 clinical sites were enrolled over a period of 50 months. Inclusion criteria was type 2 DM, documented CAD involving >1 coronary vessel treatable and no previous cardiovascular treatment interventions or documented or known kidney disease.	Baseline angiographies were assessed locally at clinical sites and sent to centralized core laboratory where it is analyzed for use in this study. Interpretation for inclusions in the study excluded 546 patients who were determined to not meet criteria.	Of the remaining 1,775 patients examined, 533 were women (representing 30% of total population inclusion). Women had less severe and significant CAD and less likely to have severe disease on coronary arteriogram as defined by multiple diseased LV regions (women vs men 0.59, p <0.0001) Women vs men with significant occluded lesions on angiography 29% vs 42%, p<0.001, Atypical symptomatic presentation: atypical angina 71% vs 58% p<0.001, Nausea 24% vs 11% p<0.001
Worrall-Carter, L., Ski, C., Scruth, E., Campbell, M. & Page, K. (2011). Systematic Review of Cardiovascular Disease in Women: Assessing the Risk. *Nursing Health and Sciences, 13*, 529.535.	Systemic review using primary, secondary randomized and controlled studies The purpose of the review was to examine the cardiovascular disease risk in women to increase awareness of sex specific symptoms presentation, and risk factors to improve clinical outcomes.	Women >18 years of age with at least one newly diagnosed or existing cardiovascular risk factor		INTERHEART study identified highest risk factors for myocardial infarction in women as diabetes mellitus and hypertension. It also identified hypertriglyceridemia as a known independent risk factor in women. Smoking was associated with a greater risk of AMI among women <45 years of age. The INTERHEART study concluded that 29% of AMI were a byproduct of smoking. DM was identified as having the greatest sex difference for developing CVD. Women with diabetes had a 3-4 fold increased risk of developing CVD. Most CVD risks in women are modifiable. A study by the Nurses Health Study concluded that women were able to decrease their risk of developing CVD by eliminating their modifiable risk factors and maintaining a moderate healthy lifestyle. Women we underrepresented in CVD prevention and treatment trails or sex differences were not accounted for. The mean percentage of women enrolled in these trials was 30% while only one-third of

				trials reported results by gender. This leads to treatment recommendations tailored towards results from a predominantly male population.
Matthew, K., Crawford, S., Chae, C., Everson-Rose, S., Sowers, M., Sternfield, B., et al. (2009) Are Changes in Cardiovascular Disease Risk Factors in Midlife Women Due to Chronological Aging or Menopausal Transition? *Journal of the American College of Cardiology, 54*(25), 2366-2373.	Longitudinal study over a timeframe of 10 years to examine whether changes in traditional and oval coronary heart disease risk factors are greater within a year of the final menstrual period, relative changes that occur before or after that interval, in a multiethnic cohort.	1054 women who had their FMP by the end of 9 years of follow up in SWAN (a longitudinal multisite, community based study)	The SWAN participants were questioned annually about health, lifestyle, and psychological factors. Anthropometric measurements and fasting blood draws were obtained at early follicular phase of the menstrual cycle at specific time intervals to allow a standardized hormonal milieu. The groups were divided into three time periods relative to FMP and the analytic sample was compared using chi-square and *t* tests.	Increases in total cholesterol and LDL were substantial around time of FMP No difference was noted within ethnicity and these changes only in baseline weight measurements The analysis shows no influence of FMP on blood pressure, insulin, glucose or inflammatory factors
Miller,V. & Best, P. (2009). Sex Differences in Cardiovascular Disease. *Cardiovascular Disease, 9*(3): 21-28.	Exploratory design intent on building groundwork of understanding the gender specific pathophysiology of cardiovascular disease in order to construct a risk assessment and treatment course tailored for women.		Effects of sex steroids on the factors contributing to cardiovascular disease were reviewed. Determine the participation rate in women in ongoing studies of CVD and how the representation of women are adequately or inadequate in current ongoing research.	The proposed hypothesis shows validated assessment tool specific for women which incorporates information and history about pregnancy, reproductive history, and hormone exposure, might improve cardiovascular risk stratification for targeting early intervention in women as they age. CVD falls into 3 general categories with regard to sex disparity: 1) conditions unique to one sex, 2) conditions which occur in both sexes but have unique presentations in each sex, 3) those which have disparate prevalence rates yet occur in both genders. Sex steroids affect all components of the vascular wall, heart, as well as blood elements which come in contact with luminal surfaces.
Finks, S. (2010). Cardiovascular Disease in Women. *Cardiology, 7*, 179-199.	The design of this study is of action research design. The purpose of this research was using both literature review, applying evidence based treatment guidelines and designing an optimal treatment options.			An estimated 66,000 more women than men die after acute myocardial infarction and intervention. Women also experience a higher mortality rate and poorer outcomes then men. Inflammatory markers indicating risk for CVD such as C-reactive protein

				(hsCRP) are higher at baseline in women than men. Women with diabetes are 3-7 times more at risk for developing or dying of CVD then women without diabetes. Premenopausal women have lower LDL and higher HDL levels then men whereas postmenopausal women experience elevated levels of LDL cholesterol and HDL levels continue to decline. A meta-analysis revealed a 37% increased risk of CVD events in women with higher concentrations of triglycerides then that in men which showed a 14% increased risk. Hypertension in women is associated with a 2.5 higher risk of cardiovascular death, MI, stroke and heart failure in women compared to a 1.6 increased risk in men with the same hypertension parameters.
Mosca, L., Manson, J., Sutherland, S., Langer, R., Manolio, T., & Barrett-Conner, E. (2009). Cardiovascular Disease in Women : A Statement for Healthcare Professionals From the American Heart Association. *Circulation.* Retrieved March 17, 2013 from www.circ.ahajournals.org/content/96/7/2468.full	Cross-sectional design study conducted to determine the public awareness and knowledge of CVD as well as risk factor awareness as well as primary, secondary and tertiary prevention strategies.		Descriptive statistics of respondents characteristics, awareness, and preventative barriers were conducted to present the findings in relations to population proportions	In evaluation of knowledge and awareness of leading cause of death among women, 55% correctly identified heart disease as the leading cause of death compared to 30% in 1997. 81% answered they had read, seen, or heard information regarding heart disease in the past 12 months. Tobacco use is attributed to 50% of myocardial infarctions among middle aged women. Approximately half of all deaths in persons with non-insulin dependent diabetes mellitus are due to heart disease. Hormone replacement therapy may indicate false ST depression. A meta analysis demonstrated a reduction of a second vascular event of 25 % by using aspirin therapy. Lipid lowering therapy provides beneficial therapy

				in women by decreasing hyperlipidemia and reducing mortality of women with CHD by >50%. Women were found to be less likely to enroll in rehabilitation then men (6.9% vs 13.3%) Women were less likely to undergo bypass surgery (20.4% vs 24.6%) then men. Incidence of stroke is higher in men (19%) then women, although women are more likely to die from a vascular occurrence (16% vs 8%).
Walsh, J. & Pignone, M. (2004). Drug Treatment of Hyperlipidemia in Women. *American Medical Association, 291,*(18); 2243-2252.	Literature review including 13 studies Studies that including gender differences, treatment duration of at least a year,	6 trials included 11435 women without CVD and using lipid lowering medications 8 trials included 8272 women with CVD and assessed the effects of lipid lowering medications	MEDLINE database was used Inclusions were 1) randomized clinical trials of outpatients with or without CVD, 2) treatment duration of at least a year, 3) classified the study as either primary (without prior CVD) or secondary (known CVD), 4) Provided data on women and the effect of lipid-lowing drug therapy	Use of lipid-lowering medications in women without CVD, there was a possible reduction in CHD events (RR, 0.80; 95% CI, 0.71 – 0.91) but not mortality. (RR, 0.95; 95%CI, 0.62 – 1.46) In women with known CVD or at high risk, use of antihyperlipidemia medications showed a reduction in CHD events and CHD associated mortality. (RR 0.74;95% CI, 0.62-1.68)
Xhyheri, B. & Bugiardini, R. (2010). Diagnosis and Treatment of Heart Disease; Are Women Different From Men? *Progress in Cardiovascular Disease, 53*, 227-236.	Literature review design which reviews current diagnostic and treatment options in reference to gender differences.			Aspirin therapy for CVD affects women differently than men. While it is more effective in preventing an MI in men (32%), it is more beneficial in preventing a stroke in women (17%). There is a lower level of preventative treatment of therapy in use of statins in women than men. Although the available literature concerning the use of ACE inhibitors in women in minimal, the research that is available shows a lower rate of effectiveness in women (22%) then men (37%) concerning recovery from a MI and treatment for CHF. The benefit of the use concerning clopidogrel in treatment following a CVD event was lower in women (7%) then in men (16%) while the risk of bleeding from the use of clopidogrel was greater in women (43%) then in men (22%)

				The benefits of B-blockers were shown in some trials to be more effective in women (31%) then in men (5%)
Ahmed, W., Tully, P., Knight, J. & Baker, R. (2011). Female Sex as an Independent Predictor of Morbidity and Survival After Isolated Coronary Artery Bypass Grafting. The Annuls of Thoracic Surgery, 92(1); 59-67.	Case study design that sought to determine whether female sex was an independent risk factor for combined in-hospital morbidity, mortality, and long term survival after coronary artery bypass grafting (CABG).	Data was collected for 1,114 women and 3,628 men who underwent coronary bypass grafting between January 1 1996 and December 31 2004 with a median follow up of 7.9 years.	Surgical coronary artery bypass grafting and in hospital rehabilitation	The female sex was associated with being an increased risk factor in undergoing a CABG (adjusted odds ratio 1.29; 95% CI, 1.04 to 1.59, p = 0.02). Adjusted survival mode showed female sex was associated with cardiac mortality (hazard ratio 1.28; 95% CI, 0.96 to 1.73; p = 0.10) Females were older with lower body surface area and more significant comorbid conditions then did males ($p<0.05$)

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