2011

10Q Report:

Advancing Women's Heart Health through Improved Research, Diagnosis and Treatment

June 2011 • Washington, DC

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Coalition for Women
with Heart Disease

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WomenHeart: The National Coalition for Women with Heart Disease is the nation's only patient centered organization serving the 42 million American women living with or at risk for heart disease – the leading cause of death for women. WomenHeart is solely devoted to advancing women's heart health through advocacy, community education, and the nation's only patient support network for women living with heart disease. WomenHeart is both a coalition and a community of thousands of members nationwide, including women heart patients and their families, healthcare professionals, and health advocates, all committed to helping women live longer, healthier lives.

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The Society for Women's Health Research (SWHR), a national non-profit organization based in Washington DC, is widely recognized as the thought leader in research on sex differences and is dedicated to improving women's health through advocacy, education, and research.

Founded in 1990 by a group of physicians, medical researchers and health advocates, SWHR aims to bring attention to the myriad of diseases and conditions that affect women uniquely. Due to SWHR's efforts, women are now routinely included in most major medical research studies and scientists are beginning to consider biological sex as a variable in their research.

Today, SWHR advocates for greater public and private funding for women's health research and the study of sex differences that affects the prevention, diagnosis and treatment of disease; encourages the appropriate inclusion of women and minorities in medical research studies; promotes the analysis of research data for sex and ethnic differences; and informs women, health care providers, and policy makers about contemporary women's health issues through media outreach, Congressional briefings, public education campaigns, conferences and special events.

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June 2011

Dear Colleague,

Cardiovascular disease (CVD), a term used to describe diseases of the heart or blood vessels, is the leading cause of death for women in the United States, causing 8.6 million deaths among women annually [1, 2]. Experts estimate that one in two women will die of heart disease or stroke, compared with one in 25 women who will die of breast cancer. Despite the fact that more women than men die each year of heart disease [2], and that there are known sex differences in symptoms and treatment, medical treatment of women has not changed substantially nor has it resulted in appropriate research into the distinct sex differences that exist in CVD. Time is of the essence. CVD death rates are increasing for women under age 55, despite an overall decrease in death rates from CVD in recent years.

Conducting appropriate sex or race/ethnicity specific differences research and analysis of CVD trial results has been difficult due to insufficient recruitment of women and minorities into the trials. This has contributed to a lack of understanding of sex difference in CVD. Improved participation rates of women and minorities in CVD trials research would result in more appropriate prevention and early detection, accurate diagnosis and proper treatment of all women with heart disease.

In 2006, the Society for Women's Health Research (SWHR), a national organization whose mission is to improve the health of all women through research, education and advocacy and WomenHeart: The National Coalition for Women with Heart Disease, the nation's only patient centered organization serving the 8 million American women living with heart disease, joined forces to address issues in women's heart health. SWHR and WomenHeart consulted with cardiovascular experts to identify the top 10 unanswered research questions concerning the prevention, diagnosis and treatment of heart disease in women. The results were published as the *10Q Report: Advancing Women's Heart Health through Improved Research, Diagnosis and Treatment* (February 2006).

Despite this 2006 alert, these and other questions still lack answers; thus the SWHR and WomenHeart are issuing an updated 2011 10Q Report. In a time of limited budgets and a need to focus research funding appropriately, it is imperative that we obtain answers to the questions posed in this report. The 2011 10Q Report is a call to action to members of Congress, administration officials, researchers, health care providers and women about important unanswered questions in the prevention, diagnosis and treatment of women with heart disease.

Sincerely,

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Executive Summary

The 2011 10Q Report presents a consensus by leading experts on the top ten questions in cardio-vascular care for women. The report provides a road map for future research concerning women's cardiovascular health. Answers to the following ten questions should improve early detection, accurate diagnosis and treatment for women living with or at risk of heart disease.

1. What factors influence or explain disparities in cardiovascular disease epidemiology and disease outcomes between men and women?

2. What are the best strategies to assess, modify, and prevent a woman's risk of heart disease?

3. What are the most accurate and effective approaches to assess and recognize chest pain and other symptoms suggesting coronary heart disease in women?

4. What role does a woman's reproductive history and menopausal hormone therapy play in the development of heart disease?

5. What are the risk factors for cardiovascular disorders associated with pregnancy and how are they best treated?

6. What is the best method for studying sex differences in vascular injury so that cardiovascular repair therapies may be improved?

7. What are the most effective treatments for diastolic heart failure (heart failure with preserved pumping function of the heart) in women?

8. Why are young women more likely than men to die after a heart attack or after surgical revascularization procedure?

9. How do psychosocial factors affect cardiovascular disease in women?

10. What biological variables are most influential in the development and clinical outcomes of heart disease and what can be done to reduce mortality rates in women?

RECOMMENDATIONS

Despite the large number of women dying from CVD each year, women are underrepresented in cardiovascular clinical trials. Only one-third of cardiovascular clinical trials report sex-specific results, despite Food and Drug Administration regulations requiring sex stratification. This makes it difficult for researchers and clinicians to draw accurate conclusions about benefits or risks for women for a particular drug or device. Women are more likely than men to have delayed diagnosis and treatment due to heart attack symptoms that are overlooked or unrecognized. Women also are less likely than men to receive cardiovascular diagnostic tests and are less often prescribed life-saving therapy with aspirin, beta blockers, or statins.

More sex specific research and policies that increase access to affordable, high quality care for women will make a significant contribution to women's heart health. Changes must also be made to improve clinical training programs and continuing education so that clinicians recognize sex-specific symptoms of heart disease and use evidence-based cardiovascular guidelines in the treatment of women. The following recommendations are derived from the ten questions presented in this report.

Science

❤ The biological determinants of the sex-based disparity in the presentation, course and outcome of CVD have to be further studied.

❤ Sex-specific predictive tests and tools for the early detection of CVD have to be developed and/or refined.

❤ The link between reproductive history (e.g., pregnancy, pregnancy complications) and CVD has to be further explored.

❤ Sex-differences in the psychosocial risk factors for the onset and course of CVD have to be studied.

Policy

❤ The proportion of funding by the National Institutes of Health for heart disease and stroke research should be increased to more accurately reflect the impact of heart disease and stroke on morbidity and mortality rates in the United States.

❤ Funding for the National Heart, Lung and Blood Institute should be increased and research dollars should be specifically targeted to minimize the burden of cardiovascular disease in women.

❤ Congress should pass the HEART for Women Act, which requires GAO to conduct a study investigating compliance with the Food and Drug Administration requirements for presentation of clinical study safety and effectiveness data by sex, age, and racial subgroup, extends the WISEWOMAN program, and requires the DHHS to prepare and submit to the Congress a report on women with heart disease.

❤ Comparative effectiveness trials should be funded to determine the most effective diagnostic tests and treatments of CVD in women.

❤ Funding agencies need to include the study of female animals where appropriate as a requisite for scientific excellence.

Education

❤ Federal officials, industry experts, health care providers, and clinical researchers should increase efforts to ensure that all women are advised of their risk of heart disease and of clinical trials on cardiovascular disease, and that data are analyzed and reported by sex.

❤ Efforts should be made to design and disseminate appropriate educational tools for health care professionals and consumers, regarding the sex-specific differences in the signs and symptoms of heart disease.

1. What factors influence or explain disparities in cardiovascular disease epidemiology and disease outcomes between men and women?

Coronary heart disease (CHD), the most common form of cardiovascular disease (CVD), is caused by accumulation of plaque in the walls of the arteries, narrowing the vessels that supply blood and oxygen to the heart.

Women and men with CHD present with different symptoms, are often treated differently and have different outcomes. For instance, women are 1.5 times more likely than men to die within the year following a heart attack. Similarly, women with angina have twice the morbidity and mortality risk as men. Women, and particularly young women, have twice the morbidity and mortality of men following coronary artery bypass graft surgery, and twice the incidence of heart failure as men. These disparities are compounded by women of racial and ethnic minorities having poorer outcomes than Caucasian women[2].
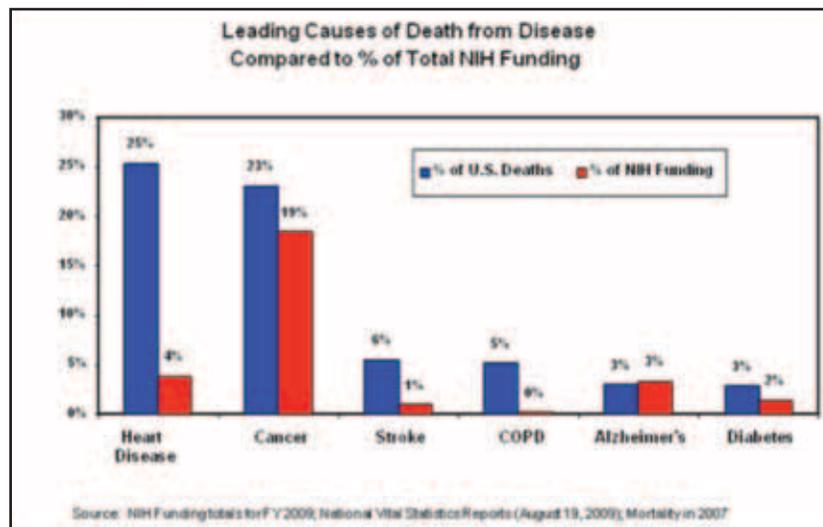
Women develop clinical manifestations of CHD about 10 years later than men, and at all ages the prevalence of coronary disease is lower among women than men[3]. But despite a lower prevalence of CHD and despite less obstruction in their coronary arteries, women have higher rates of morbidity and mortality from coronary heart disease than men[2.]

Although morbidity and mortality rates are decreasing for both women and men, the decrease in mortality has been less prominent for women, and mortality has increased in women younger than age 55[4]. Research suggests this may be due to women's hesitancy to seek care with known symptoms or not recognizing atypical symptoms. When women do seek care, they are also more likely than men to have substantial heart health risks, such as hypertension, hyperlipidemia, depression and diabetes[5].

Until research can explain these differences, and treatment can be specifically targeted to address these differences, disparities between women and men will remain. Therefore, CHD research should include consideration of sex differences such as the effects of premenopausal sex hormones[6]; the vasculature, including the distribution of atherosclerotic lesions; women's predisposition to bleeding complications[7]; and disparities in the delivery of care related either to sex bias or to lack of access to care[8].

Most importantly, heart disease and stroke continue to receive disproportionately low funding from the National Institutes of Health (NIH) compared with other diseases. Despite representing 25 percent of all deaths in the US, heart disease and stroke receive only four percent of NIH funding. (See figure below.)

HEART DISEASE & STROKE
Still Receive Disproportionately Low NIH Funding

Leading Causes of Death from Disease Compared to % of Total NIH Funding

Source: NIH Funding totals for FY 2009; National Vital Statistics Reports (August 19, 2009); Mortality in 2007

2. What are the best strategies to assess, modify, and prevent a woman's risk of heart disease?

Both women and men have heart attacks and stroke, but the standard methods for risk prediction of coronary heart disease (CHD) have not been as effective in women as in men. Approximately 64 percent of women who die suddenly of CHD had no previous symptoms[9], and traditional risk factors and scores underestimate CHD risk in women. Therefore, determining efficient and accurate ways to identify CHD risk in women is essential.

The Framingham Risk Score has been used for many years to estimate the risk of healthy individuals having a cardiac event and the need for prevention strategies[10]. The traditional risk factors identified by the Framingham Study include elevated total and low-density lipoprotein cholesterol, low high-density lipoprotein cholesterol, diabetes, hypertension, cigarette smoking, and age. A 10-year estimated risk of total cardiovascular events can be predicted for a given patient based on these major risk factors. Numerous research studies, however, have shown that the Framingham Risk Score fails to identify risk in a large number of women. Even up to age 80, more than three quarters of women are considered "low risk" by the Framingham Risk Score[11].

For women suspected of having CHD, diagnostic tests are less accurate than they are in men. Although the American College of Cardiology and the American Heart Association recommend an exercise ECG as the initial diagnostic test for CHD[12], it is less accurate in detecting CHD in women[13].

Many questions remain about how to prevent CHD in women. Aspirin, for example, has been a mainstay of the primary prevention of CHD for men since publication of the Physicians Health Study in 1988 (conducted on 22,000 predominately white male physicians)[14]. However, the use of aspirin as a preventive therapy for women was not studied until the Women's Health Study (WHS), published in 2005[15]. WHS results showed that aspirin had no effect on lowering the risk of a heart attack for women; however, it was associated with a decrease in risk for stroke in women.

Survival and quality of life for women with CHD or at risk of CHD could be greatly improved with advances in the development of sex-specific diagnostic and preventive strategies and risk assessment methods.

Approximately 64 percent of women who die suddenly of CHD had no previous symptoms, and traditional risk factors and scores underestimate CHD risk in women.

3. What are the most accurate and effective approaches to assess and recognize chest pain and other symptoms suggesting coronary heart disease in women?

The accurate evaluation of women with symptoms of myocardial ischemia (inadequate blood supply to heart muscle) associated with CHD represents a significant clinical challenge. Angina, defined as chest pain, pressure, or discomfort of cardiac origin, is the most common symptom of myocardial ischemia. While more women than men have angina[16], women also experience other less typical symptoms of myocardial ischemia including shortness of breath, malaise, fatigue, and non-chest pain symptoms. This can present a confusing picture and delay making an accurate diagnosis. For many women this results in numerous and repeated tests prior to a definitive diagnosis and increased anxiety and depression[17].

Although more evidence for the use of cardiac diagnostic testing in women has become available within the last decade[18], there remains little comparative effectiveness research as to the optimal strategy to effectively diagnose suspected cardiac symptoms in women. The current diagnostic strategy to detect CHD focuses on detecting obstructions (plaque) in the coronary arteries. But women are less likely to have obstructive lesions and may instead have symptoms provoked by vascular dysfunction or atherosclerotic changes that do not obstruct blood flow[1].

Therefore, the optimal diagnostic test is one that can identify myocardial ischemia and the etiology of symptoms even for women with non-obstructive coronary artery disease. Stress myocardial perfusion (SPECT), stress positron emission tomography (PET), stress echocardiography, stress cardiovascular magnetic resonance (CMR) imaging and coronary computed tomographic angiography (CCTA) are imaging techniques that have shown evidence or promise to help provide an accurate diagnosis, assess the extent and severity of the burden of atherosclerotic plaque and myocardial ischemia, or provide definitive information for the prognosis for women suspected of having CHD[17]. Each of these modalities has known strengths and limitations, such as ionizing radiation exposure in SPECT and CCTA, but the lack of sex-specific data means that we do not know which of these or other tests are the most appropriate, safe and effective for women[19].

Comparative effectiveness research is needed to determine the most efficient and accurate modalities for the detection of CHD and etiology of symptoms in women. With this knowledge, targeted diagnostic plans could diagnose ischemia and minimize radiation.

4. What role does a woman's reproductive history and menopausal hormone therapy play in the development of heart disease?

Hormones present prior to menopause may protect against coronary heart disease and may explain the approximately 10-year later onset of CHD in women[4].

Increases in cardiovascular risk have been reported in women with an above-average number of children, and women who have disturbances in ovarian function; however, the mechanisms that link the premenopausal hormonal environment to cardiovascular risk are not well understood [20, 21]. The cardiovascular impact of oral contraceptives is mixed. Oral contraceptives increase a woman's risk of blood clot formation, but long-term use may protect against plaque formation[22]. Oral contraceptives vary by type and dose of estrogen and progestin; few long term data are available for the newer formulations.

Disorders such as gestational diabetes, hypertension, preeclampsia, or eclampsia that commonly occur during pregnancy significantly increase the risk of a cardiovascular event later in life. Research into these complications of pregnancy is needed to improve pregnancy outcomes and guide efforts to improve risk factors and lower cardiovascular risk after pregnancy.

Cardiovascular risk factors in women increase in the menopausal years. It remains controversial whether these changes in risk factors are related to chronologic aging, changes in the hormonal environment, or both [23]. Menopausal hormone therapy had been widely used in an attempt to restore the hormonal environment to the pre-menopausal state not only to treat menopausal symptoms, but also to "turn back the clock" regarding cardiovascular risk[24]. Clinical trials to date have not shown that hormone therapy offers protection from cardiovascular events, and in fact, they have shown potential harm in older women [25].

Many unanswered questions regarding potential benefits and risks of menopausal hormonal treatment specifically relating to CVD remain. The type, timing, dosage, route of administration, and duration of therapy are important considerations, as are the potential differences among subgroups of women. All women would benefit from a better understanding of the associations between reproductive hormones, cardiovascular health, and hormone therapy risks and guidance regarding appropriate actions to take to protect their heart health.

Disorders such as gestational diabetes, hypertension, preeclampsia, or eclampsia that commonly occur during pregnancy significantly increase the risk of a cardiovascular event later in life.

5. What are the risk factors for cardiovascular disorders associated with pregnancy and how are they best treated?

Cardiovascular disorders associated with pregnancy are common. One in five women in the United States has gestational diabetes, hypertension, preeclampsia, or eclampsia during at least one pregnancy. With the increases in maternal age, obesity and diabetes, the number of women at risk for these disorders during pregnancy will continue to rise. Most women and many healthcare providers are unaware that these disorders during pregnancy significantly increase the risk of a cardiovascular event later in life[26, 27].

Pregnancy is a time of dramatic change in a woman and in many respects mimics an early cardio metabolic "stress test"[28]. Accommodations for the growing fetus increase the size and number of blood vessels; create changes in blood volume, heart size and pumping capacity; and increase the vulnerability of blood vessels to injury[29]. Preexisting or previously undiagnosed congenital cardiovascular conditions, such as arrhythmias, valve and muscle abnormalities may first become apparent during the cardiovascular demands of pregnancy[28,30]. Pregnancy is an especially vulnerable time for women with conditions such as auto-immune and clotting disorders that may also affect the heart.

Several cardiovascular disorders are unique to or predominantly affect women during pregnancy or during the peripartum period. These include spontaneous dissection of the aorta or coronary arteries; and peripartum cardiomyopathy[31], a poorly understood condition where the heart's ability to pump blood is compromised in the late stages of pregnancy or shortly after delivery. These conditions often occur suddenly and catastrophically, threatening the lives of both mother and child.

Health care providers face a critical knowledge gap regarding optimal care of both mother and child when cardiovascular disease complicates pregnancy. This is because reproductive potential and pregnancy are often considered absolute exclusion criteria for participation in cardiovascular clinical trials. Even the best practice for resuscitation of a woman presenting with sudden cardiac arrest in late pregnancy is unknown[32]. Health practitioners often perform diagnostic and therapeutic interventions on these two vulnerable patients, with little or no scientific evidence to support their decisions[33].

Increased funding to address cardiovascular complications in pregnancy would:

♥ Promote the development of better methods (e.g., genetic test, bio-markers) to predict at-risk women and prevent complications earlier and more effectively;

♥ Expand the knowledge of how to lower a woman's cardiovascular risk during pregnancy without placing the fetus at risk, and throughout her life;

♥ Include pregnancy complications in risk scoring for women;

♥ Encourage the use of multi-center and multi-ethnic registries to better understand how treating the mother impacts the child's future health;

♥ Optimally treat the rare, but often fatal complications of pregnancy such as heart attack, stroke, arterial dissection and cardiac arrest;

♥ Provide valuable insights into the physiology of blood vessel growth during pregnancy and its potential for restoring blood flow to affected organs after heart attack or stroke.

6. What is the best method for studying sex differences in vascular injury so that cardiovascular repair therapies may be improved?

There are fundamental biological differences in the blood vessels of females and males that contribute to differences in how cardiovascular diseases develop, progress and respond to treatment. Recommendations put forward in 2001 by the Institute of Medicine stated that results from studies in the basic sciences could not be translated to improving human health without attention to the sex, hormonal status, and age of the laboratory animals – including their cells or tissues - used in the experiments[34].

There remains a lack of information regarding basic physiological processes affecting the function of blood vessels in female animals. The three areas of research with the highest potential to impact women's health are studies in physiology, pharmacology, and endocrinology. A survey of scientific articles published in 2009 found that 60 percent of studies in these three areas used only male animals[35]. Sex differences must be considered in all phases of research, and the priorities of funding agencies have to include the study of female animals as a requisite for scientific excellence[36].

Researchers' efforts must be directed toward understanding the basic biology of sex differences in the functions of blood vessels and the heart to reduce disparities in CVD outcomes. When these basic sex differences in the function and response of blood vessels and heart tissue are better understood, effective, personalized, sex specific therapies can be targeted to reduce disparities in CVD outcomes between women and men.

Researchers' efforts must be directed toward understanding the basic biology of sex differences in the functions of blood vessels and the heart to reduce disparities in CVD outcomes.

7. What are the most effective treatments for diastolic heart failure (heart failure with preserved pumping function of the heart) in women?

Diastolic heart failure is the accumulation of fluid in the body caused by stiffening of the heart. When the heart does not relax fully, the cavity inside the heart remains small and is unable to fill with the amount of blood needed to circulate around the body. Patients feel short of breath and may complain of chest pain, leg swelling, and the need for extra pillows to breathe at night. Their symptoms and signs are similar to patients with systolic heart failure caused by a weakened heart[37] (often referred to as heart failure with impaired systolic function) and their prognosis is poor.[37, 38] In fact the morbidity and mortality caused by diastolic heart failure (often referred to as heart failure with preserved systolic function) is very similar to systolic heart failure and together the estimated health care cost is over 39 billion dollars in the United States for 2010[4].

Identifying the most effective treatment for diastolic heart failure remains an important question given the predominance of women with diastolic heart failure[39], lack of specific therapies [40-42], and high morbidity and mortality associated with this problem[37, 38].

Treatment for diastolic heart failure remains limited and few drugs have been shown to be beneficial based on randomized clinical studies[42]. Contrast this with systolic heart failure which affects more men than women and has numerous effective therapies that improve morbidity and mortality[43]. This likely explains why survival has improved and hospitalizations have declined for systolic heart failure patients over the last fifteen years and the prognosis of patients with diastolic heart failure has not changed. The paucity of research has been attributed to a lack of consensus on who to enroll in diastolic heart failure studies, since no one diagnostic study defines the disease. This was a barrier previously, whereas there is now growing consensus regarding diagnostic criteria[44] and recommendations have been published on how to proceed with clinical trials[45].

If funds were available to pursue the most effective treatments for diastolic heart failure, a disease which mostly affects women, research in this field potentially could impact survival, quality of life and reduce hospitalizations for all patients with this deadly disease.

Identifying the most effective treatment for diastolic heart failure remains an important question given the predominance of women with diastolic heart failure[39], lack of specific therapies [40-42], and high morbidity and mortality associated with this problem[37, 38].

8. Why are young women more likely than men to die after a heart attack and surgical revascularization?

Coronary heart disease (CHD), a disorder linked to narrowed coronary arteries, may lead to myocardial infarction, commonly known as a "heart attack" Because CHD occurs earlier in men than women, much of the early research exclusively, or disproportionately, enrolled male patients. This fostered a perception that coronary heart disease is a "man's disease" and likely contributed to inequalities in access to care or suboptimal care for at-risk women.

Although knowledge of sex-specific differences has improved, women under the age of 50 are still three times more likely than men to die after a heart attack or coronary artery bypass graft (CABG) surgery[5, 46]. Women's higher mortality rate may be due to increased risk factors such as older age, hypertension, diabetes, heart failure, anemia, autoimmune disorders, and high cholesterol, as well as increased susceptibility to complications during and after surgical revascularization procedures.

Another potential explanation for women's poorer outcomes is the differences in vascular structure and function. The very tiniest of blood vessels – the microvasculature – may play a greater role in supplying blood to the heart and are more likely to be dysfunctional in women than men[5, 47, 48]. Other factors include atypical symptoms in women, which often go unrecognized by the patient and the physician[5, 47, 48]. Hormonal changes cause "positive remodeling" of the blood vessel walls so that plaque may accumulate for a period of time without symptoms, leading to a late diagnosis[47, 48], and differences in intensity of appropriate medical care.

Women are significantly less likely to receive pharmaceutical and procedural therapies such as fibrinolytic therapy (clot busters) or stents compared to men when presenting with myocardial infarction[47, 48].

Important next steps to improving the detection, assessment and treatment of CHD in women, and particularly in younger women, include a better understanding of sex differences in all aspects of CVD including the microvasculature symptoms, risk factors, the role of sex hormones and the contributors to delayed diagnosis and treatment of coronary heart disease in women[47, 48].

Findings from these studies will provide a better understanding of why younger women are more likely to die from myocardial infarction and CABG procedures, and should lead to better outcomes for women.

9. How do psychosocial factors affect cardiovascular disease in women?

Psychosocial factors such as depression, anxiety, inadequate social and economic resources, caregiver stress, marital stress, and adversities early in life are highly prevalent in women, and have been linked to adverse cardiovascular outcomes[49-52]. Research demonstrates that psychosocial factors affect women differently than men. For example, while marriage largely reduces cardiovascular risk in men, the stress of marriage increases cardiovascular risk in women[50, 53].

Although major coronary disease events in women tend to occur later in life than in men, women who have clinical events at a younger age have a worse prognosis than men[54]. Psychosocial factors may play a role in this context since they are more common in women, particularly in younger women, than in men[55]. Further research is necessary to show whether differences in the effects of psychosocial factors contribute to sex-related disparities in cardiovascular morbidity and mortality.

Psychosocial risk factors have also been linked to behaviors that have a negative impact on cardiovascular health, such as non-adherence to treatment recommendations, lower levels of physical activity, unhealthy dietary habits, and tobacco use[56, 57]. Unfortunately, effective intervention methods to counteract women's psychological stress have not been demonstrated, and recent randomized behavioral interventional trials have failed to yield cardiovascular benefits in women[58]. Limited literature suggests that women with coronary heart disease respond less well to standard psychological treatments such as cognitive-behavioral therapy, and that management of psychosocial risk factors should be tailored to the individual woman[59].

Studies are needed to better understand the role of psychosocial risk factors in women, how to manage these risk factors, and how psychosocial risk factors impact the onset and outcome of heart disease. Further research is needed to assess how psychosocial risk factors impact women with cardiovascular disease versus men. More research on effective interventions for women could lead to a delayed onset of heart disease, improved survival rates and enhanced quality of life.

Although major coronary disease events in women tend to occur later in life than in men, women who have clinical events at a younger age have a worse prognosis than men.

10. What biological variables are most influential in the development of heart disease and can they be used to reduce mortality rates?

Given that approximately 64 percent of women who died suddenly of CHD had no previous symptoms4 and that traditional risk factors and scores underestimate CHD risk in women, there is a need to identify unique markers for women at risk for CHD[60].

Early detection and correction of such variables as elevated cholesterol, hypertension, diabetes and cigarette smoking, can reduce atherosclerosis (the main cause of CHD) and improve outcomes. These are modifiable to some extent with changes in lifestyle, improved diet, exercise and smoking cessation. Psychosocial risk factors, such as low socioeconomic status, anxiety, and depression have also been linked to CHD and should be evaluated.

There are also biomarkers, biomediators, neurohormones, and surrogate markers which can signal CHD. Some of these can be modified, including

♥ neurohormones which are part of the renin-angiotensin-aldosterone system that directly impact angiotensin II and arginine vasopressin[1, 61, 62]

♥ markers of the inflammatory processes such as C-reactive protein which may be a useful predictor of CVD and correlates significantly with future risk of developing hypertension[63, 64]

♥ markers of heart failure such as B-type natriuretic peptide

Surrogate markers of atherosclerosis and CHD risk include left ventricular hypertrophy, intima-media arterial wall thickness, proteinuria and microalbuminuria, endothelial dysfunction, coronary calcification and anemia[1, 62]. Research shows that a variety of treatments – from lifestyle/behavioral changes, medications, and interventional treatments – can interrupt the progression of CHD. Further research is needed to demonstrate whether lifestyle and behavioral changes in women with known or suspected CHD can improve prognosis. Innovative approaches to care management that encourage changes in lifestyle should be considered. These include customized care management and the use of multidisciplinary teams of health practitioners who coordinate care for women at risk. Further research is needed to determine whether reducing or minimizing the novel biomarkers associated with CHD will result in lower mortality rates.

In the future, a genetic assessment of a woman's individual's risk for the development of CHD may be possible and may guide lifestyle modification prescription and the choice and dosage of select pharmaceuticals. Further research into the biological variables that influence the development and outcomes of CHD will benefit the clinical course of all patients.

Glossary

Angina - a type of chest pain or discomfort caused by reduced blood flow to the heart muscle.

Atherogenesis - the process of forming atherosclerotic plaque.

Atherosclerotic (Atherosclerosis) – refers to the build up of plaque, the accumulation of dead cells, cell debris, cholesterol, fatty acids, and calcium in a blood vessel wall which can progress to obstruct blood flow, or break off and cause obstructions in smaller vessels.

Cardiovascular Disease (CVD) - an umbrella term referring to diseases of the heart or blood vessels, including: hypertension, coronary heart disease, stroke, and heart failure.

Coronary Artery Bypass Graft (CABG) Surgery - a surgical procedure in which blood is redirected around a blockage in a coronary artery via an artery or vein grafted from another part of the body. This improves the blood flow to the heart and can relieve symptoms.

Coronary Calcification - refers to the bone-like mineralization of atherosclerotic plaque in the walls of the coronary arteries. Its presence indicates increased risk of heart attack.

Coronary Heart Disease (CHD) - also referred to as coronary artery or ischemic heart disease, is the most common form of cardiovascular disease, a narrowing of the arteries supplying blood to the heart as a result of the accumulation of atherosclerotic plaque in arterial walls.

Diastolic Heart Failure – a condition in which the heart does not pump enough blood to meet the body's needs due to its inability to properly relax or fill with blood between contractions. Generally, systolic function (contraction) is maintained.

Dyslipidemia – abnormal blood lipid levels.

Endothelial Dysfunction - a dysfunction of the lining of the blood vessels. The endothelium maintains arterial health and controls blood flow.

Heart Failure - a condition in which the heart can no longer adequately pump blood to the rest of the body, associated with fluid accumulation in the feet, legs, lungs, and other areas of the body.

Hypertension - sustained, chronic high blood pressure, defined by the American Heart Association as > 140 mmHg/90 mmHg.

Intima-Media Wall Thickness - a measurement of the thickness of the arterial wall that is used to determine the extent of atherosclerotic plaque accumulation.

Ischemic Heart Disease (myocardial ischemia) - a condition in which there is reduced blood supply to the heart muscle, most commonly associated with chest pain, pressure, or discomfort, and commonly presents as angina or myocardial infarction.

Left Ventricular Hypertrophy - a thickening of the muscular walls of the left ventricle, the heart's main pumping chamber.

Menopause - occurs when estrogen and progesterone levels decrease, causing the cessation of the menstrual cycle. A woman is considered to have reached menopause when she has not menstruated for 12 months or when the ovaries have been surgically removed.

Microvasculature - the smallest blood vessels in the body, including the capillaries, arterioles, and venules.

Morbidity - disability or complications resulting from a disease.

Mortality – death resulting from a disease.

Myocardial Infarction (MI) - commonly referred to as heart attack, myocardial infarction is permanent damage to heart muscle due to absent or severely reduced blood supply to the heart, usually resulting from atherosclerotic plaque accumulation and clot formation in the coronary arteries.

Oral Contraceptives - more commonly referred to as birth control pills, oral contraceptives are hormonal medications taken by mouth for the prevention of pregnancy.

Positive Remodeling - an expansion of the external elastic membrane, one of the many layers of the walls of arteries, at the site of atherosclerotic plaque accumulation. This expansion allows the diameter of the blood vessel lumen to remain the same as plaque accumulates in the wall of the artery.

Proteinuria - a high level of protein in the urine, indicative of kidney disease.

Psychosocial Factors - Components of health related to psychological or social well-being such as: depression, anxiety, educational attainment, social and economic resources.

Renin-Angiotensin-Aldosterone System - a hormonal cascade that regulates blood pressure by controlling water and electrolyte balance.

Revascularization Procedures – procedures designed to improve blood flow to the heart. The most common are percutaneous coronary artery balloon angioplasty with or without stenting and coronary artery bypass surgery.

Surrogate Markers – indirect evidence of a disease or condition. Surrogate markers are measured instead of the actual disease when the disease or condition itself may be difficult to detect or measure.

Systolic Heart Failure - a condition in which the heart does not pump enough blood to meet the body's needs due to its inability to contract vigorously enough.

Vascular Injury - damage to vessel walls caused by factors such as hypertension, diabetes, and oxidative stress. This damage can lead to the formation of atherosclerotic plaque or abnormal blood vessel constriction.

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Acknowledgements