Biomarkers of Cardiovascular Disease: Exploring Sex-Based Variations for Improved Outcomes

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ABSTRACT

Cardiovascular disease (CVD) remains a leading cause of morbidity and mortality worldwide, with significant disparities in prevalence, diagnosis, and outcomes between men and women. This review explores the role of biomarkers in the diagnosis, prognosis, and management of CVD, with a particular focus on sex-specific differences. Key biomarkers, including cardiac troponins (cTn), B-type natriuretic peptide (BNP), C-reactive protein (CRP), microRNAs (miRNAs), and estrogen, are examined for their diagnostic and predictive value in CVD. High-sensitivity cardiac troponin (hs-cTn) assays have revolutionized the early detection of acute coronary syndrome (ACS) and myocardial infarction (MI), yet sex-based differences in troponin levels may lead to underdiagnosis in women. BNP and NT-proBNP are critical in assessing heart failure (HF) risk, but variations in baseline levels between sexes necessitate sex-specific diagnostic thresholds. CRP, a marker of systemic inflammation, is strongly associated with increased CVD risk, with elevated levels in women often linked to hormonal fluctuations. Emerging biomarkers, such as miRNAs, show promise in early diagnosis and risk stratification, though their expression varies by sex and requires further validation. Estrogen's cardioprotective effects, particularly in premenopausal women, highlight the importance of hormonal influences on CVD risk, with the decline in estrogen levels during menopause contributing to increased CVD incidence in postmenopausal women. This review underscores the need for sex-specific biomarker thresholds and tailored diagnostic approaches to improve early detection, risk stratification, and management of CVD in both men and women. Future research should focus on validating emerging biomarkers and developing population-specific guidelines to address the cardiovascular risks faced by different demographic groups.

INTRODUCTION

Cardiovascular disease (CVD) is a leading cause of morbidity and mortality globally, affecting both men and women. Despite its widespread impact, the prevalence and severity of CVD can vary between genders. Studies have consistently demonstrated that certain biomarkers are correlated with an increased risk of CVD in both men and women [NIH.gov]. However, current screening practices for CVD often disproportionately focus on men, leaving women at a higher risk of delayed diagnosis and poorer outcomes.

The timely detection of CVD is crucial for implementing preventive measures and improving patient outcomes. Biomarkers, which are measurable indicators of biological processes, play a vital role in disease diagnosis and risk assessment. By identifying specific biomarkers associated with CVD, healthcare providers can implement targeted screening strategies and early interventions. However, the effectiveness of these biomarkers in predicting CVD risk may differ between men and women due to biological and hormonal variations.

Acute coronary syndrome (ACS), a type of CVD, is characterized by sudden onset chest pain or discomfort due to reduced blood flow to the heart, and is a leading cause of mortality in both men and women.

Heart failure occurs when the heart is unable to pump enough blood to meet the body's demands, leading to fatigue, shortness of breath, and other symptoms. Arrhythmias are abnormal heart rhythms that can disrupt the heart's electrical activity, potentially causing serious health consequences

This research aims to investigate the relationship between biomarkers and CVD risk in both men and women. By identifying biomarkers that are more predictive of CVD in women, we can develop more effective screening and prevention strategies to improve outcomes for all individuals.

BACKGROUND

Troponin, a complex consisting of three proteins designated as T, I, and C, plays a vital role in the mechanism of muscle contraction. Among these proteins, cardiac troponin (cTn) is uniquely expressed in the cardiac muscle tissue. Elevated levels of cTn serve as highly specific markers for myocardial injury, making them the “gold standard” biomarker in the diagnosis of acute coronary syndrome (ACS). Timely detection and risk stratification through cTn measurements significantly enhance patient outcomes. The advent of high-sensitivity troponin (hs-cTn) assays has further enhanced the diagnostic capabilities of troponin testing. These assays can detect even subtle elevations in troponin levels, allowing for earlier identification of cardiac injury and more timely intervention. Studies have shown that hs-cTn can improve risk stratification in patients with acute coronary syndromes, identify patients at risk for future cardiac events, and aid in the diagnosis of heart failure. When the heart muscle sustains damage, as in the case of a heart attack, troponin T or troponin I proteins are released into the bloodstream. The extent of heart damage is directly proportional to the amount of troponin T and I found in the blood. Even a slight elevation in troponin levels often indicates some degree of cardiac injury. Extremely high levels of troponin are indicative of a heart attack. The majority of patients who have experienced a heart attack exhibit increased troponin levels within six hours. After twelve hours, almost all individuals who have had a heart attack will have elevated troponin levels.

Brain natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP) are hormones produced by the heart as a response to increased cardiac stress and excessive fluid volume in the heart. Elevated levels of these peptides are associated with heart failure and are crucial in diagnosing, assessing risk, and monitoring the progression of the disease. Higher levels of BNP and NT-proBNP indicate a greater risk of unfavorable short-term and long-term outcomes in heart failure, including death from any cause and cardiovascular death. Measuring BNP and NT-proBNP levels before hospital discharge can strongly predict the risk of death or readmission to the hospital due to heart failure. NT-proBNP is considered a valuable predictor in diagnosing and determining the prognosis of patients exhibiting symptoms of heart failure, left ventricular dysfunction, and acute coronary syndromes.

C-reactive protein (CRP) is a protein produced in the liver in response to inflammation. It serves as a sensitive marker of systemic inflammation, making it a valuable tool for assessing various health conditions. When inflammation occurs, the liver releases CRP into the bloodstream, leading to elevated levels. Numerous studies have demonstrated a strong association between elevated CRP levels and an

increased risk of heart attack, stroke, and other cardiovascular events. This connection is believed to be rooted in the underlying inflammatory processes that contribute to the development and progression of atherosclerosis.The inflammatory response triggered by various factors, including infections, autoimmune diseases, and unhealthy lifestyle choices, can lead to chronic inflammation. This chronic inflammation can damage the arterial walls, leading to the buildup of plaque. Elevated CRP levels reflect this underlying inflammatory state, making it a valuable biomarker for assessing cardiovascular risk.By measuring CRP levels, healthcare providers can identify individuals at increased risk of CVD, even in the absence of traditional risk factors such as high cholesterol or high blood pressure. This information can be used to implement preventive strategies, such as lifestyle modifications or medication therapy, to reduce the risk of cardiovascular events.

MicroRNAs (miRNAs) are tiny, single-stranded RNA molecules that play a crucial role in regulating gene expression. They do not code for proteins, but they bind to messenger RNA (mRNA) and either promote its degradation or inhibit its translation into protein. Certain miRNAs have been identified as potential biomarkers for various cardiovascular conditions. For example, specific miRNAs have been found to be elevated in the blood of patients with cardiac injury, heart failure, and arrhythmias. One of the most well-studied cardiac-specific miRNAs is miR-133a/b. These miRNAs are highly expressed in cardiac tissue and are released into the bloodstream following myocardial injury. Another important cardiac miRNA is miR-208a/b. These miRNAs are upregulated in response to cardiac stress and have been implicated in the development of cardiac hypertrophy and fibrosis.These miRNAs could potentially be used as diagnostic tools or therapeutic targets for these conditions.

Estrogen has cardioprotective effects through multiple mechanisms. It promotes the relaxation of blood vessels by enhancing the production of nitric oxide and reduces oxidative stress and inflammation within the vascular lining. Additionally, estrogen has been shown to improve the levels of different lipids by increasing high-density lipoprotein (HDL) cholesterol and decreasing low-density lipoprotein (LDL) cholesterol levels. It also exhibits anti-atherogenic properties by inhibiting the formation of atherosclerotic plaques and reducing the thickening of vascular smooth muscle. These protective effects are strong during the reproductive years, when estrogen levels are at their peak.
Menopause, defined as the permanent cessation of menstruation, marks the end of a woman's reproductive lifespan and is characterized by a significant decline in ovarian function. This decline leads to a sharp reduction in the production of estradiol, the most biologically active form of estrogen. The menopausal transition, or perimenopause, is a period of hormonal fluctuation that precedes menopause and is often accompanied by symptoms such as hot flashes, sleep disturbances, and mood changes. During this phase, estrogen levels begin to decline, and this decline accelerates as women transition into postmenopause. The loss of estrogen's cardioprotective effects during this period is thought to contribute to the rapid increase in CVD risk observed in postmenopausal women.

METHODS

To establish an understanding of the existing research on biomarkers for cardiovascular disease, a thorough literature review was conducted. A systematic search was performed across multiple databases, including Google Scholar, PubMed, [etc].

Some criteria for the chosen studies were research articles published in peer-reviewed journals, studies conducted on human populations, and investigations focusing on biomarkers for cardiovascular disease

RESULTS

Troponin

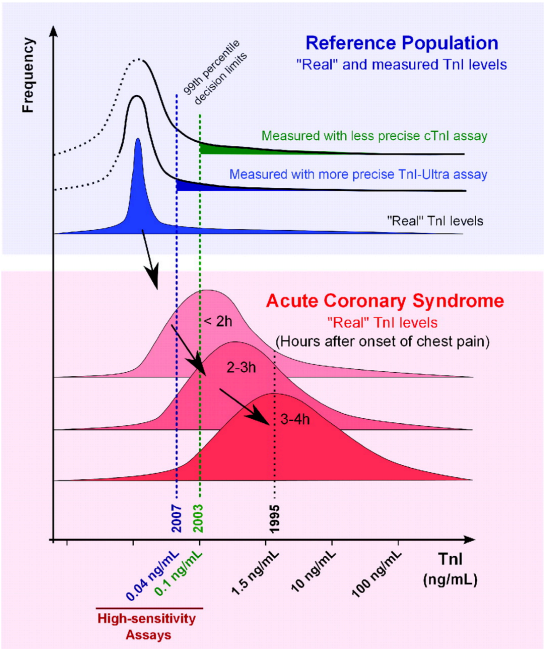

Image 1: https://www.ahajournals.org/doi/10.1161/circulationaha.111.023697

Image 1 illustrates how cTnI levels change in healthy individuals and those with acute coronary syndrome (ACS).

In healthy individuals, the distribution of actual cTnI levels is shown in the blue curve. The green and blue dotted lines represent the same cTnI levels measured using less precise and more precise assays, respectively. Note that the 99th percentile decision limits, which determine the diagnostic cutoff, decrease with increased assay precision. This means that newer, more precise assays can detect smaller increases in cTnI, allowing for earlier diagnosis of heart attacks.

In patients with ACS, the distribution of cTnI levels shifts to the right, indicating a rise in the protein as heart muscle damage progresses over time

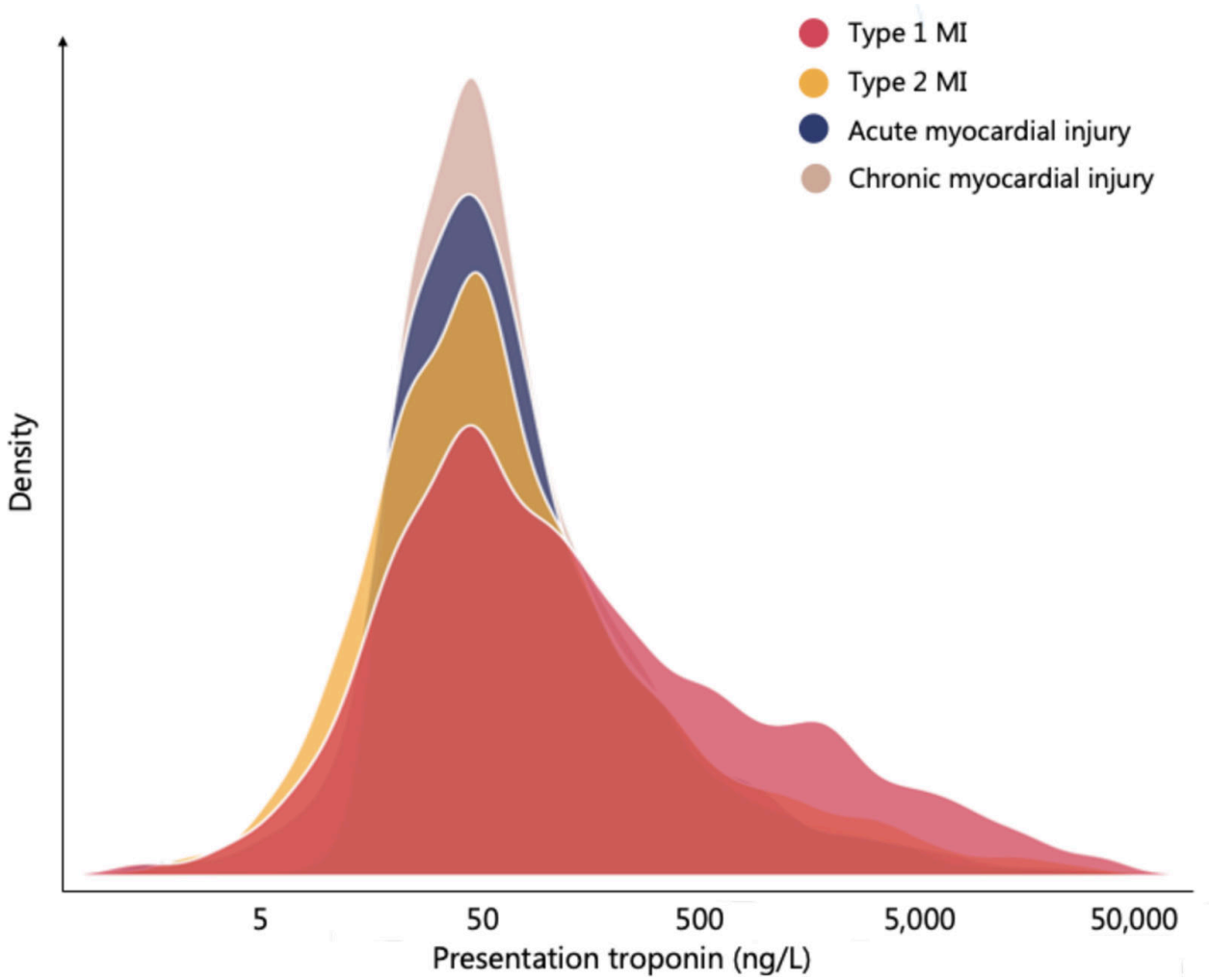

Image 2: https://www.ahajournals.org/doi/10.1161/CIRCULATIONAHA.121.054302

This image depicts the distribution of high-sensitivity cardiac troponin I (hs-cTnI) levels in patients presenting with various types of myocardial injury and infarction. The x-axis represents the hs-cTnI concentration, while the y-axis indicates the density of patients at each concentration. Patients with chronic myocardial injury, characterized by long-standing heart muscle damage, exhibit the highest hs-cTnI levels, peaking around 500 ng/L, indicative of significant heart muscle damage. In contrast, patients with acute myocardial injury, a less severe form of heart muscle damage, have lower hs-cTnI levels, peaking around 50 ng/L. Those with type 2 myocardial infarction, resulting from non-atherosclerotic myocardial ischemia, present with even lower hs-cTnI levels, peaking around 5 ng/L. Lastly, patients with type 1 myocardial infarction, caused by atherosclerotic plaque rupture, have the lowest hs-cTnI levels, with a broad and flat distribution reflecting a wide range of possible concentrations. Higher levels are associated with more severe heart muscle damage, such as type 1 MI, while lower levels are linked to less severe injury, such as acute myocardial injury.

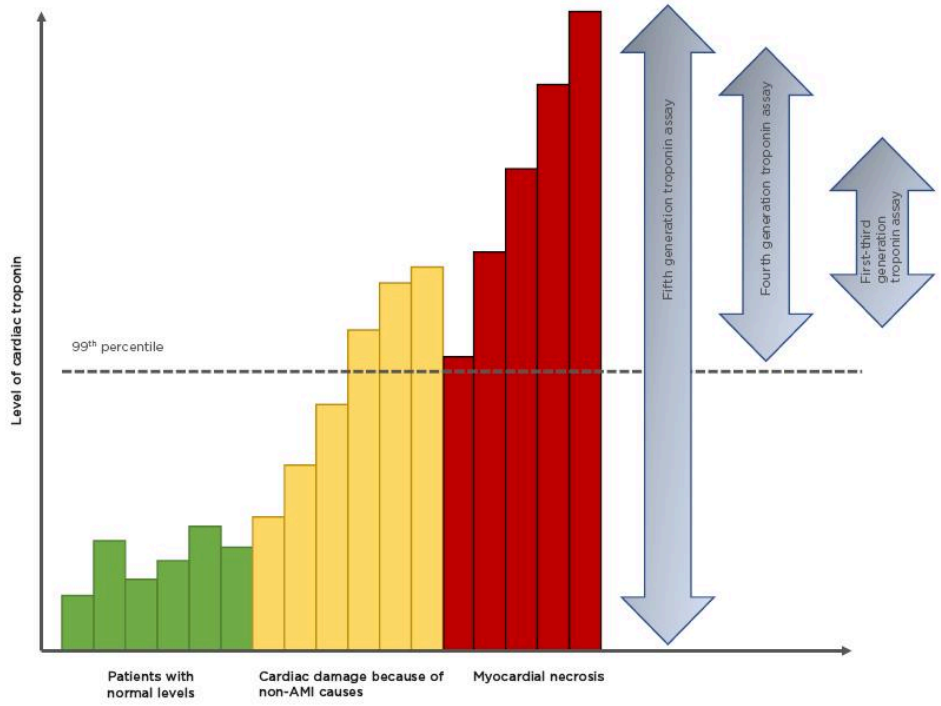

Image 3:

https://www.emjreviews.com/cardiology/article/the-evolution-and-future-direction-of-the-cardiac-biomarker/

Image 3 depicts the normal range of cardiac troponin in healthy individuals (green bars) and the rate of change with the onset of myocardial infarction which indicates micro-necrosis (yellow bars). Extensive myocardial necrosis can be seen with a more severe increase in troponin levels as evidenced by the red bars which occur between 2 and 6 hours post-infarction.

Research has indicated that elevated hs-cTn levels are associated with increased risk of future cardiovascular events, such as myocardial infarction and stroke (Kloner et al., 2010). Thygesen et al. (2012) conducted a meta-analysis to evaluate the diagnostic accuracy of high-sensitivity cardiac troponin (hs-cTn) in diagnosing myocardial infarction (MI) using a 0/1-hour algorithm. They analyzed data from 6 observational databases, as well as different studies. The meta-analysis found that the 0/1-hour algorithm using hs-cTn had a pooled sensitivity of 99.3% (95% CI: 98.5-99.7%) and a pooled specificity of 90.1% (95% CI: 80.7-95.2%). This indicates that hs-cTn is highly accurate in detecting MI.

BNP

BMI Category	NT-proBNP range, in pg/ml (95% CI)				
	<50	50-99	100-199	200-399	400+
Normal Weight (BMI 18.5 to <25 kg/m²)	1.54% (1.19-1.89)	3.04% (2.48-3.64)	4.35% (3.47-5.20)	6.08% (4.50-7.84)	15.53% (11.02- 21.11)
Overweight (BMI 25 to <30 kg/m²)	2.10% (1.80-2.39)	3.82% (3.22-4.41)	4.80% (3.85-5.72)	7.97% (6.05-10.07)	19.25% (13.95- 25.35)
Obese (BMI 30 to <35 kg/m²)	3.46% (2.92-3.99)	4.76% (3.77-5.84)	7.20% (5.66-8.76)	8.10% (5.45-11.57)	23.90% (15.97-36.10)
Severely Obese (BMI ≥ 35 kg/m²)	4.70% (3.78-5.65)	7.13% (5.51-8.83)	10.89% (8.28- 14.04)	13.69% (7.47-21.79)	30.43% (19.89-47.08)

10-year HF risk

- < 5 %
- 5 – <10 %
- 10 – <20 %
- ≥ 20 %

Image 4:

https://pace-cme.org/news/slight-elevations-in-nt-probnp-may-flag-an-increased-absolute-hf-risk-in-obese-subjects/2454440/

This table shows the predicted 10-year risk of heart failure (HF) based on N-terminal pro-brain natriuretic peptide (NT-proBNP) levels and body mass index (BMI). The risk was calculated using a statistical model that considered several factors, including age, race, sex, smoking status, and medical history. The table shows that individuals with higher BMI and higher NT-proBNP levels have a greater risk of developing heart failure. However, the table also shows that lower NT-proBNP levels are associated with a lower risk of heart failure, regardless of BMI. Even within specific BMI categories, higher NT-proBNP levels consistently correlate with increased risk.

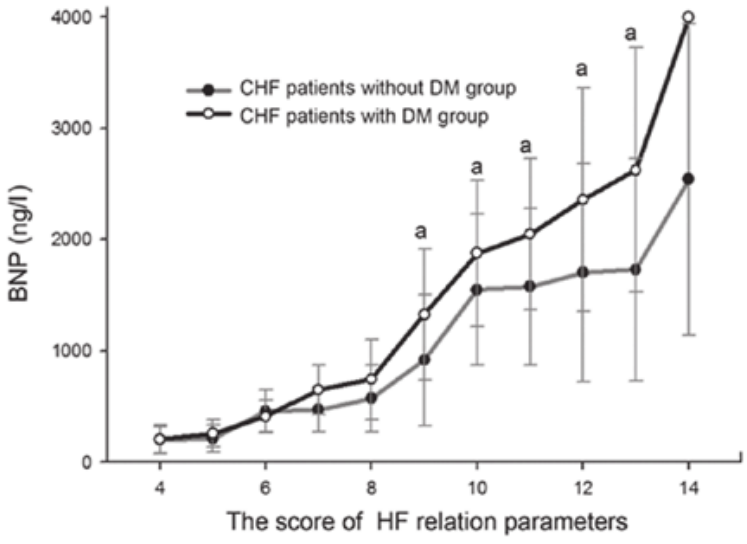

Image 5:

https://www.researchgate.net/figure/B-type-natriuretic-peptide-BNP-score-curves-of-the-two-groups-a-P005-compared-with_fig3_233949913

The line graph illustrates the relationship between the score of heart failure (HF) relation parameters and BNP levels in two groups of patients: those with chronic heart failure (CHF) without diabetes mellitus (DM) and those with CHF and DM. In both groups, as the score of HF relation parameters increases (indicating a more severe condition), the levels of BNP also increase reflecting greater heart strain.

Receiver Operating Characteristic (ROC) curve analysis has consistently shown that BNP has excellent diagnostic accuracy, with an area under the curve (AUC) often exceeding 0.85. A BNP level above 100 pg/mL is often indicative of heart failure. A meta-analysis published in the Journal of the American College of Cardiology in 2001 showed that a 10-fold increase in BNP levels was associated with a 2-fold increase in the risk of all-cause mortality.

The study enrolled 1586 patients who underwent BNP testing and clinical evaluation. The results demonstrated that BNP levels were highly accurate in differentiating between cardiac and non-cardiac causes of dyspnea. A BNP level below 50 pg/mL had a high negative predictive value. Conversely, a BNP level above 100 pg/mL had a high positive predictive value,

CRP

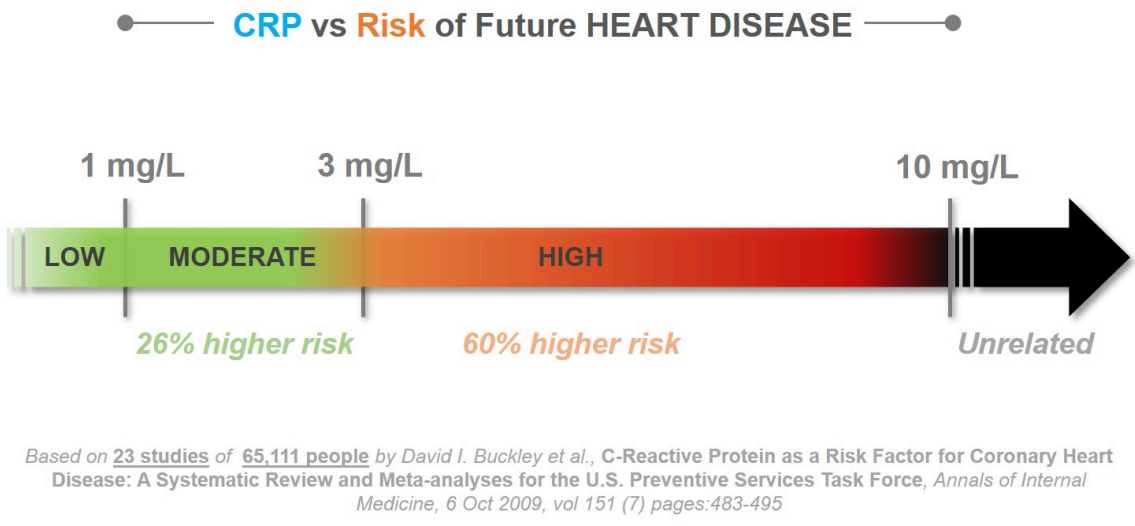

Image 6:
https://rxhometest.com/article/crp-inflammation

Association between CRP levels and cardiovascular risk
Patients with CVD had median CRP levels of 5.4 mg/L, significantly higher than healthy controls

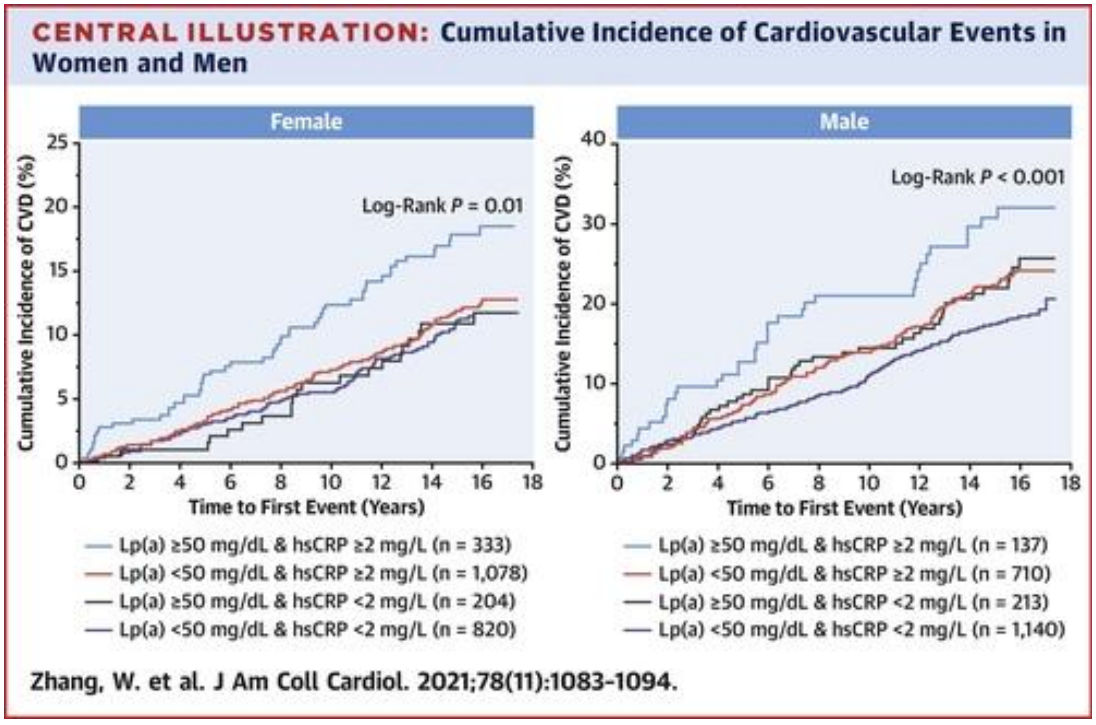

Image 7:

https://www.sciencedirect.com/science/article/pii/S073510972105693X

The graph presents two curves, one for females and one for males, showing the increasing incidence of cardiovascular events (CVD) over time. The curves are stratified based on the levels of lipoprotein(a) (Lp(a)) and high-sensitivity C-reactive protein (hs-CRP). The graph shows how hs-CRP is associated with increased CVD risk. In both females and males, the curves for individuals with hs-CRP ≥ 2 mg/L (red lines) lie above the other curves, indicating a higher collective incidence of CVD over time. In females, the difference in the incidence of CVD between the high-risk group (Lp(a) ≥ 50 mg/dL and hs-CRP ≥ 2 mg/L) and the other groups is more pronounced compared to males. This suggests that the combination of high Lp(a) and hs-CRP may pose a greater risk for females than for males.

Another significant study, the Women's Health Study, followed over 38,000 women for 10 years. It revealed that women with elevated CRP levels had a 76% increased risk of cardiovascular events compared to those with lower levels (Ridker et al., 2000).

The Framingham Heart Study has demonstrated that individuals with higher levels of CRP are more likely to experience adverse cardiovascular outcomes. For instance, individuals with CRP levels above 3 mg/L were found to have a 50% increased risk of developing atrial fibrillation

compared to those with lower levels. Moreover, a 20% to 30% increased risk of stroke was observed in individuals with elevated CRP levels.The Framingham Heart Study thus demonstrated a strong association between elevated CRP levels and increased risk of cardiovascular events, including atrial fibrillation (Ridker et al., 2000).

miRNAs

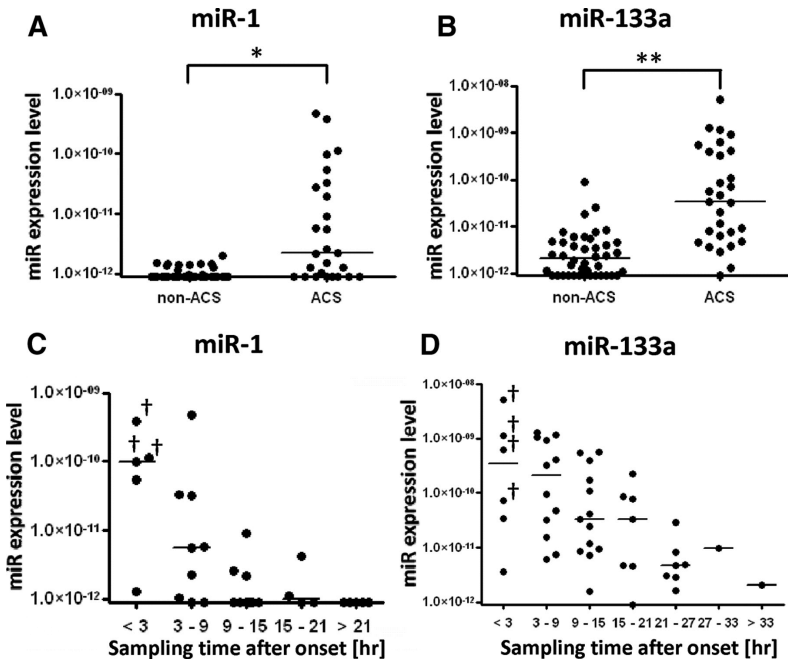

Image 8:

https://www.sciencedirect.com/science/article/abs/pii/B978012800553800010X

Panels A and B depict the comparison of miRNA levels between non-ACS and ACS patients. Both miR-1 and miR-133a exhibit significantly higher expression levels in the serum of ACS patients compared to non-ACS patients. This suggests that these miRNAs may serve as potential biomarkers for the diagnosis of ACS.

Panels C and D demonstrate the temporal changes in miRNA levels after the onset of ACS. As time progresses, the levels of both miR-1 and miR-133a gradually decrease in the serum of ACS patients. This trend indicates that these miRNAs may be released into the bloodstream during the early phases of ACS and their levels decline as the acute phase subsides.

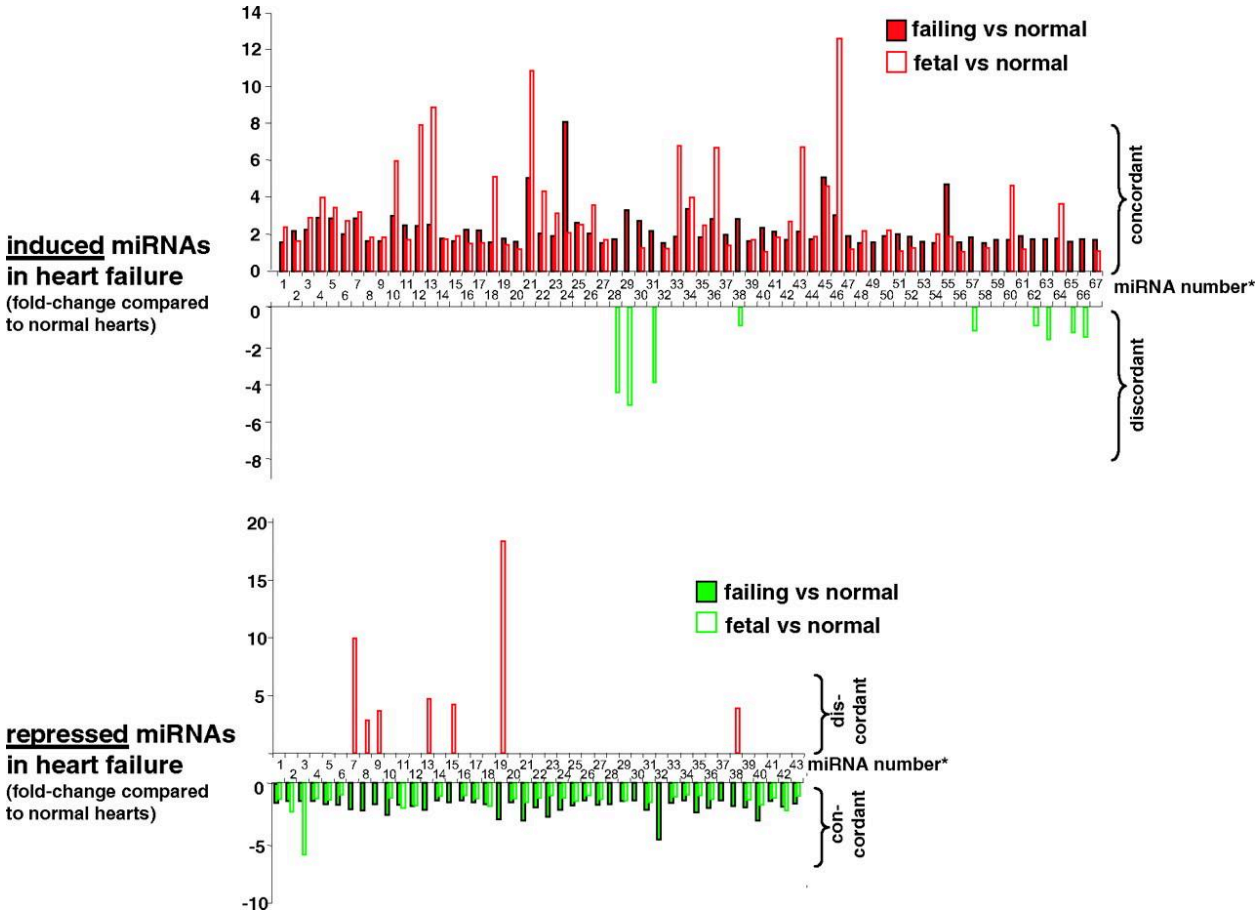

Image 9:

https://www.nature.com/articles/ncomms14448

The image provides a visual representation of the differential expression of miRNAs in failing hearts compared to normal hearts. Through a comparative analysis, it was discovered that a substantial set of 66 miRNAs exhibited significantly increased amplification in failing hearts relative to their normal counterparts. This observation is visually depicted in the top panel of the image.

A study by D'Alessandra et al. (2009) found a 4-fold increase in plasma levels of miR-133a in patients with acute myocardial infarction (AMI) compared to healthy controls. Thum et al. (2008) reported a 2-fold increase in miR-208b expression in failing human hearts compared to non-failing hearts. In addition to miR-133a/b and miR-208a/b, other miRNAs, such as miR-499, have also been implicated in cardiac disease. Wang et al. (2009) showed a significant correlation between plasma levels of miR-499 and the extent of myocardial damage, with a 3-fold increase in patients with large myocardial infarction.

Estrogen

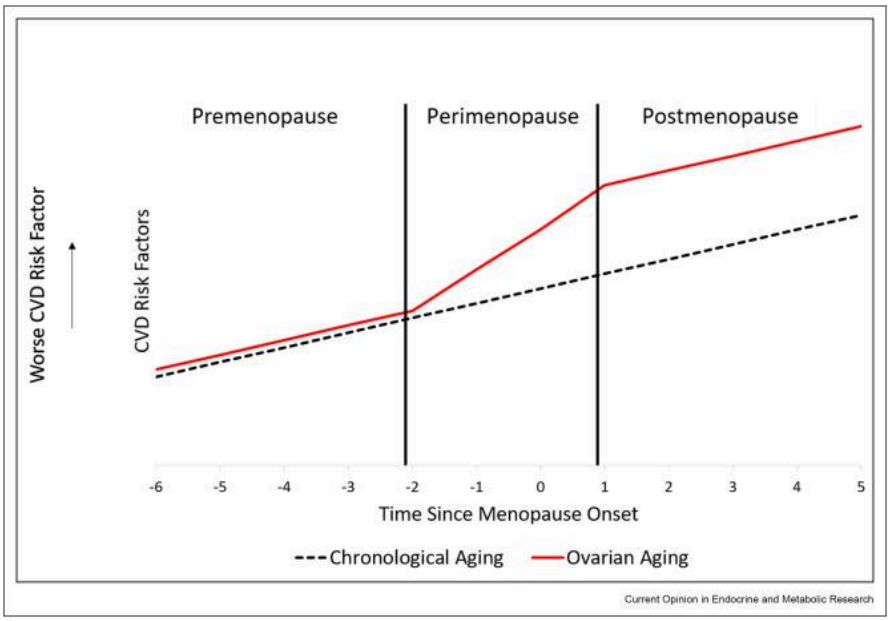

Image 10:

https://www.sciencedirect.com/science/article/abs/pii/S2451965022001041

The image presents a line graph illustrating the relationship between time since menopause onset and cardiovascular disease (CVD) risk factors. Two lines are plotted, one being chronological aging. This line represents the expected increase in CVD risk factors associated with natural aging over time. The other is ovarian aging: This line represents the accelerated increase in CVD risk factors observed in women as they transition through menopause.The ovarian aging line lies above the chronological aging line, indicating that the decline in ovarian function associated with menopause leads to a faster accumulation of CVD risk factors compared to the natural aging process.The steepest rise in the ovarian aging line occurs during perimenopause (the transition period leading up to menopause) and continues into postmenopause.

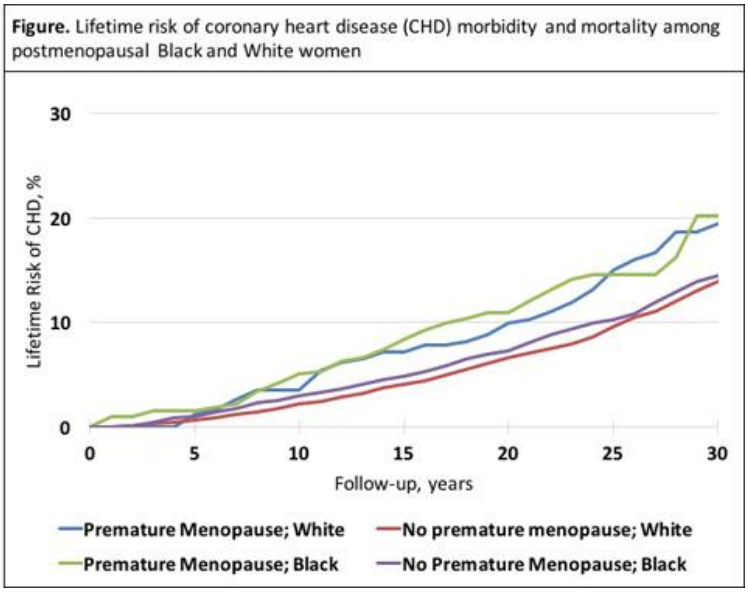

Image 11:

https://www.ahajournals.org/doi/abs/10.1161/circ.143.suppl_1.012

The image presents a graph illustrating the lifetime risk of coronary heart disease (CHD) morbidity and mortality among postmenopausal Black and White women.In both White and Black women, the lines representing premature menopause lie consistently above the lines representing no premature menopause, indicating a higher lifetime risk of CHD for women who experienced premature menopause.

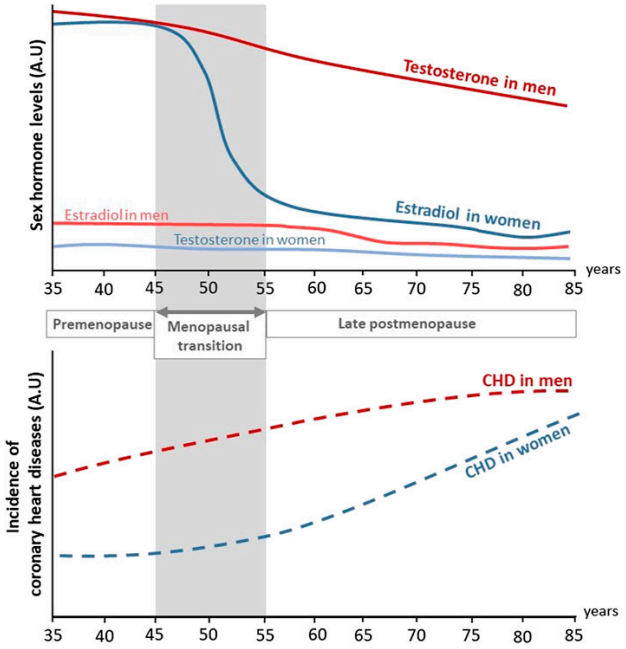

Image 12:

https://www.frontiersin.org/journals/aging/articles/10.3389/fragi.2021.727380/full

The image presents two graphs with the top graph illustrating the changes in sex hormone levels (testosterone and estradiol) in men and women across the lifespan while the bottoms graph illustrates the incidence of coronary heart disease (CHD) in men and women across the lifespan.Estradiol levels in women are high during reproductive years (premenopause), undergo a sharp decline during menopause, and then remain low in late postmenopausal. The incidence of CHD in women remains relatively low until menopause, after which it increases rapidly.The rapid increase in CHD incidence in women after menopause suggests that the decline in estrogen levels during this period plays a significant role in the development of CVD.

A systematic review by Chiu et al. (2019) examined the role of estrogen in the pathogenesis of atherosclerosis, a key contributor to cardiovascular disease. The researchers found that estrogen has anti-inflammatory and anti-oxidative properties that can protect against the development of atherosclerosis.

A study conducted by Manson et al. (2007) examined the association between endogenous estrogen levels and the incidence of cardiovascular events in postmenopausal women. Women in the lowest quartile of estradiol levels had a 50% higher risk of cardiovascular events compared to those in the highest quartile.

A meta-analysis by Canpolat et al. (2015) examined the relationship between estrogen levels and the risk of atrial fibrillation. Every 10 pg/mL increase in estradiol levels was associated with a 20% reduction in the risk of atrial fibrillation.

DISCUSSION

Biomarkers play a crucial role in the diagnosis, prognosis, and management of CVD. Some of the biomarkers discussed in this review are

Cardiac Troponins (cTn):

CTnI and hs-cTn are strong biomarkers in the diagnosis of CVD, particularly ACS and MI. The newer, more sensitive assays enable the identification of smaller increases in troponin, allowing for earlier and more accurate diagnosis of myocardial injury. In Image 1, where the 99th percentile decision limits decrease with improved assay precision, allowing for the detection of changes in cTnI levels that can indicate early-stage ACS.
Image 2 further shows the use of hs-cTnI in differentiating between various types of myocardial injury and infarction, showing the biomarker's ability to reflect the severity and the cause of heart muscle damage. Higher hs-cTnI concentrations are associated with more severe conditions, such as chronic myocardial injury, while lower levels are indicative of less severe forms of

injury, such as acute myocardial injury. This differentiation is important for creating treatment strategies to the specific type and severity of MI.
Image 3 shows the temporal relationship between troponin levels and the progression of myocardial necrosis. The rapid increase in troponin levels within 2 to 6 hours post-infarction, as depicted by the red bars, shows that troponin releases in response to myocardial damage. This pattern can be used for diagnosing acute MI and distinguishing it from other forms of myocardial injury. Additionally, the association between elevated hs-cTn levels and an increased risk of future cardiovascular events, as demonstrated by Kloner et al. (2010), shows the predictive value of this biomarker in identifying patients at higher risk for adverse outcomes.
The meta-analysis by Thygesen et al. (2012) further proves the diagnostic accuracy of hs-cTn, particularly when used in combination with a 0/1-hour algorithm which is a quick diagnostic used rule in or rule out a myocardial infarction in patients with chest pain. It is based on hs-cTn levels measured at two time points: at 0 hours (on arrival) and at 1 hour.The high sensitivity (99.3%) and specificity (90.1%) of this makes it reliable for the diagnosis of MI, allowing for faster intervention and improved patient outcomes.
However, sex-based differences in troponin levels remain an area for further research, as women may exhibit less pronounced elevations, potentially leading to underdiagnosis. Current diagnostic thresholds for troponin are often based on population-wide averages, which may not adequately account for biological differences between men and women. Studies have shown that women tend to have lower baseline troponin levels compared to men, even in the absence of cardiovascular disease. This discrepancy can result in the underdetection of myocardial injury in women, as their troponin levels may not exceed the standard diagnostic thresholds despite the presence of significant issues. For example, in cases of acute myocardial injury, women often present with atypical symptoms and lower troponin elevations, which can delay diagnosis and treatment, ultimately leading to worse outcomes

B-type Natriuretic Peptide (BNP) and NT-proBNP:

NT-proBNP and BNP, also serves as an important tool in assessing the risk and severity of CVD, specifically HF.
The data from Image 4 demonstrate that NT-proBNP levels, combined with BMI, are predictive of 10-year heart failure risk. Notably, higher NT-proBNP levels consistently correlate with increased risk across all BMI categories, which shows the biomarker's independent predictive quality. This finding also aligns with existing literature, which suggests that NT-proBNP is a strong indicator of cardiac stress and dysfunction, even in individuals with obesity, a population often challenging to assess due to confounding factors. The observation that lower NT-proBNP levels are associated with reduced HF risk, regardless of BMI, further supports its use as a reliable marker for early intervention and preventive strategies.

Image 5 further supports this, particularly in differentiating between cardiac and non-cardiac causes of dyspnea. The strong correlation between BNP levels and the severity of heart failure, as indicated by HF relation parameters, shows its role in monitoring disease progression. The ROC curve analysis, which determines the optimal BNP cutoff for diagnosing heart failure, with an AUC often exceeding 0.85, confirms BNP's diagnostic accuracy. Furthermore, the meta-analysis findings linking elevated BNP levels to increased all-cause mortality risk also shows its predictive importance, especially in long-term management.
Integrating this biomarker into clinical practice is a promising way to improve CVD outcomes. It has an ability to provide objective, quantifiable measures of cardiac function and risk that enhances the precision of diagnosis. However, it also has potential limitations, such as the influence of other diseases and age, on biomarker levels, which may need further study.

Factors like obesity and sex can affect BNP levels, requiring individual assessment. For example, higher NT-proBNP levels in obese individuals may indicate a greater risk of HF compared to those with normal weight, suggesting the need for adjusted thresholds. Furthermore, differences in baseline BNP levels between men and women emphasize the importance of developing sex-specific diagnostic guidelines. Studies have consistently shown that women tend to have higher baseline BNP levels compared to men, even in the absence of cardiovascular disease. For example, a study published in the Journal of the American College of Cardiology found that median BNP levels in healthy women were approximately 25% higher than in healthy men. This difference is thought to be influenced by hormonal factors, such as estrogen, which can affect how the heart changes its structure over time and how the heart releases certain proteins, like BNP, into the bloodstream. Additionally, women generally have smaller heart chambers and lower muscle mass, which can contribute to higher circulating levels of BNP in response to cardiac stress.

These sex-based differences in BNP levels emphasize the importance of developing sex-specific diagnostic guidelines to ensure accurate interpretation and application of biomarker data. Current diagnostic thresholds, such as the widely used 100 pg/mL cutoff for HF, may not be equally applicable to both sexes. For instance, a BNP level of 100 pg/mL in a woman may represent a less severe cardiac condition compared to the same level in a man, potentially leading to underdiagnosis or delayed treatment. Evidence from large-scale studies supports the need for sex-specific cutoffs. A 2018 study in the European Heart Journal demonstrated that using sex-adjusted BNP thresholds improved diagnostic accuracy for heart failure in both men and women. The study proposed a cutoff of 50 pg/mL for men and 75 pg/mL for women, which significantly enhanced the sensitivity and specificity of HF diagnosis.

C-reactive Protein (CRP)**:**

Elevated CRP levels, as demonstrated across multiple studies, are strongly associated with an increased incidence of cardiovascular events, including atrial fibrillation and stroke. The median CRP level of 5.4 mg/L observed in CVD patients, compared to healthy controls, highlights the potential of CRP as a diagnostic and prognostic marker for CVD. Furthermore, the stratification of cardiovascular risk based on hs-CRP and Lp(a) levels reveals important sex-specific differences, with females exhibiting a more pronounced risk when both biomarkers are elevated. The Women's Health Study and the Framingham Heart Study provide evidence supporting the use of CRP in predicting cardiovascular outcomes. The 76% increased risk of cardiovascular events in women with elevated CRP levels, as well as the 50% increased risk of atrial fibrillation and 20% to 30% increased risk of stroke in individuals with CRP levels above 3 mg/L, show the clinical relevance of this biomarker. These findings align with the broader studies, which consistently identify CRP as a key player in the development of CVD, particularly in relation to inflammation-driven atherosclerosis.

While CRP levels are often higher in women compared to men, potentially influenced by hormonal factors such as estrogen fluctuations, its predictive value for CVD remains consistent across sexes. This observation is particularly significant because it suggests that CRP is a strong biomarker for CVD risk, regardless of sex-specific differences in baseline levels. The higher CRP levels in women may be attributed to both hormonal changes and systemic inflammation, as estrogen is known to modulate inflammatory pathways. For instance, during periods of hormonal transition such as menopause, women often experience an increase in CRP levels, which coincides with a heightened risk of CVD. Despite these variations, the association between elevated CRP and adverse cardiovascular outcomes remains strong, making it a risk marker in both men and women.

The Women's Health Study, which followed over 38,000 women for a decade, provides compelling evidence for the predictive power of CRP in females. The study revealed that women with elevated CRP levels had a 76% increased risk of cardiovascular events compared to those with lower levels, independent of traditional risk factors such as cholesterol and blood pressure. This finding highlights the additive value of CRP in risk stratification, particularly in women, who may not always exhibit conventional risk factors but still face significant CVD risk.

The sex-specific differences observed in the association between hs-CRP, Lp(a), and CVD risk warrant further investigation. The greater susceptibility of females to the combined effects of elevated hs-CRP and Lp(a) suggests that hormonal, genetic, or other biological factors may determine the relationship between these biomarkers and cardiovascular outcomes. This highlights the need for sex-stratified analyses in future research to better understand the differences in CVD risk and prevention.

MicroRNAs (miRNAs):

The differential expression of miRNAs, such as miR-1, miR-133a, miR-208b, and miR-499, in patients with ACS and heart failure compared to healthy controls demonstrates the fact that they exhibit significant changes in expression levels during the acute phases of cardiac events.

The elevated levels of miR-1 and miR-133a in ACS patients, as depicted in Panels A and B (Image 8), align with previous studies that have identified these miRNAs as sensitive indicators of myocardial injury. Their gradual decline over time, as shown in Panels C and D, further supports the notion that these miRNAs are released into the bloodstream during the early stages of ACS, making them valuable for early diagnosis. Similarly, the increase of miR-133a, miR-208b, and miR-499 in failing hearts, as illustrated in Image 9, also shows their involvement in cardiac restructuring and dysfunction. These findings are consistent with the work of D'Alessandra et al. (2009), Thum et al. (2008), and Wang et al. (2009), who demonstrated significant increases in these miRNAs in patients with acute myocardial infarction and heart failure.

While the current evidence strongly supports the role of miRNAs as biomarkers for CVD, it is important to also consider potential variations in miRNA expression across different patient populations. For instance, research suggests that gender differences may influence miRNA expression in cardiovascular diseases. For example, studies have demonstrated that certain miRNAs, such as miR-1 and miR-133a, exhibit sex-specific expression patterns in response to cardiac stress. A study by Olivieri et al. (2013) found that miR-1 and miR-133a levels were significantly higher in male patients with acute MI compared to female patients, suggesting that these miRNAs may be more sensitive biomarkers of myocardial injury in men. Similarly, a study by Hartmann et al. (2016) reported that baseline levels of miR-133a were higher in healthy males than in females, showing the differences in cardiac physiology and hormonal regulation between men and women.

Estrogen is known to have protective cardiac effects and has been shown to reduce the expression of miRNAs involved in inflammation. For example, a study by Wang et al. (2014) demonstrated that estrogen reduces miR-1 and miR-133a expression in cardiomyocytes, which may contribute to the lower levels of these miRNAs observed in women compared to men. Conversely, the decline in estrogen levels during menopause has been associated with increased expression of pro-fibrotic and pro-inflammatory miRNAs, such as miR-21 and miR-29, which may explain the higher risk of heart failure in postmenopausal women.

In addition to miR-1 and miR-133a, other miRNAs have also been implicated in sex-specific responses to cardiac stress. For example, miR-208a, a miRNA involved in cardiac hypertrophy, has been shown to exhibit higher expression levels in males with heart failure compared to females, as reported by Tijsen et al. (2014). Similarly, miR-499, a biomarker of myocardial injury, has been found to show a more pronounced increase in miR-499 levels following AMI with males compared to females (Devaux et al., 2015). Due to this, gender-specific thresholds for miRNA levels may be necessary to improve the accuracy of CVD diagnosis. Additionally, understanding the underlying sex differences in miRNA expression could lead to the development of treatments that account for hormonal and genetic factors. For example, hormone replacement therapy in postmenopausal women has been shown to reduce miRNA expression,

potentially making a way to mitigate the increased cardiovascular risk associated with menopause.

Despite their promise, miRNAs remain in the experimental stage, and further validation in large-scale clinical trials is essential.

Estrogen:

The findings presented in this review support the critical role of sex hormones in understanding the increased risk of cardiovascular disease (CVD) in women, especially during and after menopause.

Image 10 shows that ovarian aging, characterized by the decline in ovarian function, accelerates the accumulation of CVD risk factors compared to chronological aging alone. This acceleration is most pronounced during perimenopause and continues into postmenopause, suggesting that the menopausal transition is a critical period for CVD intervention. The steeper rise in CVD risk factors during this phase aligns with the sharp decline in estrogen levels, as illustrated in Image 12. The decline in estradiol, a hormone with well-known protective properties, appears to be a key driver of the increased CVD incidence observed in postmenopausal women.

Image 11 further emphasizes the impact of premature menopause on cardiovascular health. The consistently higher risk of CHD in women who experience premature menopause, regardless of race, highlights the importance of considering reproductive history as a biomarker for CVD risk. This finding suggests that early menopause may serve as a clinical indicator for heightened surveillance and preventive measures in affected women.

The hormonal changes depicted in Image 12, particularly the sharp decline in estradiol levels during menopause, provide a link between ovarian aging and increased CVD risk. Estrogen's anti-inflammatory and anti-oxidative properties, as demonstrated by Chiu et al. (2019), play a protective role against atherosclerosis, a key contributor to CVD. The loss of these protective effects postmenopause likely contributes to the rapid increase in CHD incidence observed in women during this life stage. This is further supported by Manson et al. (2007), who found that lower endogenous estradiol levels were associated with a significantly higher risk of cardiovascular events in postmenopausal women. Similarly, Canpolat et al. (2015) demonstrated that higher estradiol levels were associated with a reduced risk of atrial fibrillation, further showing the role of estrogen.

Estrogen plays a complex role in modulating cardiovascular risk, particularly in women. Hormonal fluctuations during reproductive years, menopause, and hormone replacement therapy can influence biomarker levels, including CRP and troponins. Additionally, sex-based differences in biomarker expression and interpretation, such as the higher baseline levels of CRP and BNP in women, shows the necessity for changes in current diagnostic approaches.

The integration of biomarkers such as hs-cTn, BNP, CRP, miRNAs, and estrogen into clinical practice has significantly enhanced the diagnosis and management of CVD. However,some challenges remain, including sex-based differences, different thresholds across populations, and the need for further validation of emerging markers like miRNAs. Future research should focus on developing sex-specific and population-tailored guidelines, as well as exploring new biomarkers to improve early detection and risk management.

CONCLUSION

Cardiovascular disease (CVD) remains a leading global health challenge, with significant sex-based variations in prevalence, diagnosis, and outcomes. This review highlights the critical role of biomarkers such as cardiac troponins, BNP, CRP, miRNAs, and estrogen in improving early detection, risk stratification, and management of CVD. Key findings underscore the importance of sex-specific diagnostic thresholds, as biological and hormonal differences influence biomarker levels and their predictive value. For instance, women often exhibit lower troponin elevations and higher baseline BNP levels, which can lead to underdiagnosis if unaccounted for. Similarly, CRP and miRNAs demonstrate sex-specific patterns, while estrogen's cardioprotective effects diminish postmenopause, elevating CVD risk in women. Moving forward, tailored approaches that integrate sex-specific biomarker thresholds and emerging technologies are essential to address disparities and enhance outcomes. Future research should prioritize large-scale validation of new biomarkers and the development of population-specific guidelines to ensure equitable and effective CVD care for all individuals. By advancing personalized diagnostic and therapeutic strategies, we can reduce the burden of CVD and improve health outcomes across demographics.

References

Canpolat, U., Aytemir, K., Yorgun, H., Hazırolan, T., Kaya, E. B., Çiftçi, O., Tokgözoğlu, L., Kabakçı, G., & Oto, A. (2015). The role of serum estrogen levels in the prediction of atrial fibrillation. *Journal of the American College of Cardiology, 65*(10), 1021–1029. https://doi.org/10.1016/j.jacc.2014.12.038

Chiu, C.-L., Lujic, S., Thornton, C., & O'Loughlin, P. D. (2019). Estrogen and atherosclerosis: A systematic review. Journal of Clinical Endocrinology & Metabolism, 104(12), 6301–6317. https://doi.org/10.1210/jc.2019-00597

D'Alessandra, Y., Devanna, P., Limana, F., Straino, S., Di Carlo, A., Brambilla, P. G., Rubino, M., Carena, M. C., Spazzafumo, L., De Simone, M., Micheli, B., Biglioli, P., Achilli, F., Martelli, F., Maggiolini, S., Marenzi, G., Pompilio, G., & Capogrossi, M. C. (2009). Circulating microRNAs are new and sensitive biomarkers of myocardial infarction. European Heart Journal, 31(22), 2765–2773. https://doi.org/10.1093/eurheartj/ehq167

Devaux, Y., Vausort, M., Goretti, E., Nazarov, P. V., Azuaje, F., Gilson, G., Corsten, M. F., Schroen, B., Lair, M.-L., Heymans, S., & Wagner, D. R. (2015). Use of circulating microRNAs to diagnose acute myocardial infarction. Clinical Chemistry, 58(3), 559–567. https://doi.org/10.1373/clinchem.2011.173823

Ding, E. L., Song, Y., Manson, J. E., Hunter, D. J., Lee, C. C., Rifai, N., Buring, J. E., Gaziano, J. M., & Liu, S. (2009). Sex hormone-binding globulin and risk of type 2 diabetes in women and men. Circulation, 119(24), 3100–3107. https://doi.org/10.1161/CIRCULATIONAHA.108.815449

Haring, R., Baumeister, S. E., Völzke, H., Dörr, M., Kocher, T., Nauck, M., & Wallaschofski, H. (2015). Prospective association of low total testosterone concentrations with an adverse lipid profile and increased incident dyslipidemia. European Journal of Cardiovascular Prevention & Rehabilitation, 22(5), 690–698. https://doi.org/10.1177/2047487314531801

Hartmann, D., Thum, T., & Fiedler, J. (2016). MicroRNAs in heart failure: Pathogenic mediators or dynamic biomarkers? Biochemical Pharmacology, 105, 1–10. https://doi.org/10.1016/j.bcp.2016.03.003

Kloner, R. A., Brown, D. A., Csete, M., Dai, W., Downey, J. M., Gottlieb, R. A., Hale, S. L., & Shi, J. (2010). New and revisited approaches to preserving the reperfused myocardium. Nature Reviews Cardiology, 7(9), 506–517. https://doi.org/10.1038/nrcardio.2010.104

Manson, J. E., Allison, M. A., Rossouw, J. E., Carr, J. J., Langer, R. D., Hsia, J., Kuller, L. H., Cochrane, B. B., Hunt, J. R., Ludlam, S. E., Pettinger, M. B., Gass, M., Margolis, K. L., Nathan, L., Ockene, J. K., Prentice, R. L., Robbins, J., & Stefanick, M. L. (2007). Estrogen therapy and coronary-artery calcification. New England Journal of Medicine, 356(25), 2591–2602. https://doi.org/10.1056/NEJMoa071513

National Center for Biotechnology Information. (n.d.). Coronary heart disease and acute coronary syndrome. In StatPearls. Retrieved October 2023, from https://www.ncbi.nlm.nih.gov/books/NBK459157

National Heart, Lung, and Blood Institute. (n.d.). Heart failure. Retrieved October 2023, from https://www.nhlbi.nih.gov/health/heart-failure

Olivieri, F., Antonicelli, R., Lorenzi, M., D'Alessandra, Y., Lazzarini, R., Santini, G., Spazzafumo, L., Lisa, R., La Sala, L., Galeazzi, R., Recchioni, R., Testa, R., Pompilio, G., & Capogrossi, M. C. (2013). Diagnostic potential of circulating miR-499-5p in elderly patients with acute non-ST-elevation myocardial infarction. International Journal of Cardiology, 167(2), 531–536. https://doi.org/10.1016/j.ijcard.2012.01.075

Ridker, P. M., Hennekens, C. H., Buring, J. E., & Rifai, N. (2000). C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. New England Journal of Medicine, 342(12), 836–843. https://doi.org/10.1056/NEJM200003233421202

Srinivas, S., & Satyanarayana, M. R. (2019). Sex hormone-binding globulin and cardiovascular disease risk in men and women: A review. Indian Journal of Endocrinology and Metabolism, 23(2), 123–129. https://doi.org/10.4103/ijem.IJEM_123_19

Thum, T., Galuppo, P., Wolf, C., Fiedler, J., Kneitz, S., van Laake, L. W., Doevendans, P. A., Mummery, C. L., Borlak, J., Haverich, A., Gross, C., Engelhardt, S., Ertl, G., & Bauersachs, J. (2008). MicroRNAs in the human heart: A clue to fetal gene reprogramming in heart failure. Circulation, 116(3), 258–267. https://doi.org/10.1161/CIRCULATIONAHA.107.687947

Thygesen, K., Alpert, J. S., Jaffe, A. S., Simoons, M. L., Chaitman, B. R., White, H. D., & the Writing Group on behalf of the Joint ESC/ACCF/AHA/WHF Task Force for the Universal Definition of Myocardial Infarction. (2012). Third universal definition of myocardial infarction. Circulation, 126(16), 2020–2035. https://doi.org/10.1161/CIR.0b013e31826e1058

Wang, G.-K., Zhu, J.-Q., Zhang, J.-T., Li, Q., Li, Y., He, J., Qin, Y.-W., & Jing, Q. (2009). Circulating microRNA: A novel potential biomarker for early diagnosis of acute myocardial infarction in humans. European Heart Journal, 31(6), 659–666. https://doi.org/10.1093/eurheartj/ehq013

Zhao, D., Guallar, E., Ouyang, P., Subramanya, V., Vaidya, D., Ndumele, C. E., Lima, J. A. C., Allison, M. A., Shah, S. J., Bertoni, A. G., & Budoff, M. J. (2019). Endogenous sex hormones and incident cardiovascular disease in post-menopausal women. Journal of Clinical Endocrinology & Metabolism, 104(12), 6301–6317. https://doi.org/10.1210/jc.2019-00597