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LIPIDS (E MICHOS, SECTION EDITOR)

Lipids in Women: Management in Cardiovascular Disease Prevention and Special Subgroups

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Abstract

Purpose of Review As the adverse impact of cardiovascular disease continues to afflict women around the world, the identification and treatment of risk factors to reduce cardiovascular morbidity and mortality continue to rise in priority. Dyslipidemia is a significant risk factor for coronary heart disease and should serve as a strong focus point in both primary and secondary prevention. However, women remain undertreated compared with men and receive less evidence-based therapies including cholesterol management. Some of the unique risk factors in women that contribute to cardiovascular disease have been incorporated in the current cholesterol management guidelines.

Recent Findings The medical community and international organizations have helped reduce the annual cardiovascular mortality rates for women since 1984. However, more work remains to be completed as heart disease in women remains inadequately researched, underdiagnosed, and poorly managed. This review discusses contemporary management of dyslipidemia in women, with additional focus on special risk subgroups and integration of the new 2018 American Heart Association/American College of Cardiology Guidelines on the Management of Blood Cholesterol.

Summary Dyslipidemia management in women constitutes a substantial portion of the foundation of both primary and secondary prevention and is essential to reducing cardiovascular events in women. The current cholesterol guidelines focus on some of the risk factors for cardiovascular disease that are unique or more common in women. This is a review of how the current cholesterol management guidelines pertain to women specifically and address sex-specific cardiovascular risk factors in women.

Keywords Lipid · Cholesterol · Women · Sex differences · Primary prevention · Secondary prevention

Abbreviations

ACC	American College of Cardiology
AHA	American Heart Association
ASCVD	Atherosclerotic cardiovascular disease
CHD	Coronary heart disease
CV	Cardiovascular
CVD	Cardiovascular disease
FH	Familial hypercholesterolemia
HDL-C	High-density lipoprotein cholesterol
HIV	Human immunodeficiency virus
LDL-C	Low-density lipoprotein cholesterol
Lp(a)	Lipoprotein(a)
MetS	Metabolic syndrome
MI	Myocardial infarction
Non-HDL	Non-high-density lipoprotein
PAG	Physical activity guidelines
RA	Rheumatoid arthritis
SLE	Systemic lupus erythematosus
TG	Triglyceride

This article is part of the Topical Collection on *Lipids*

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Introduction

The high burden of cardiovascular disease (CVD) morbidity and mortality continues to plague women in the USA and globally despite more aggressive attempts to address traditional, non-traditional, and sex-specific contributors. Dyslipidemia management in women constitutes a substantial portion of the foundation of both CVD prevention

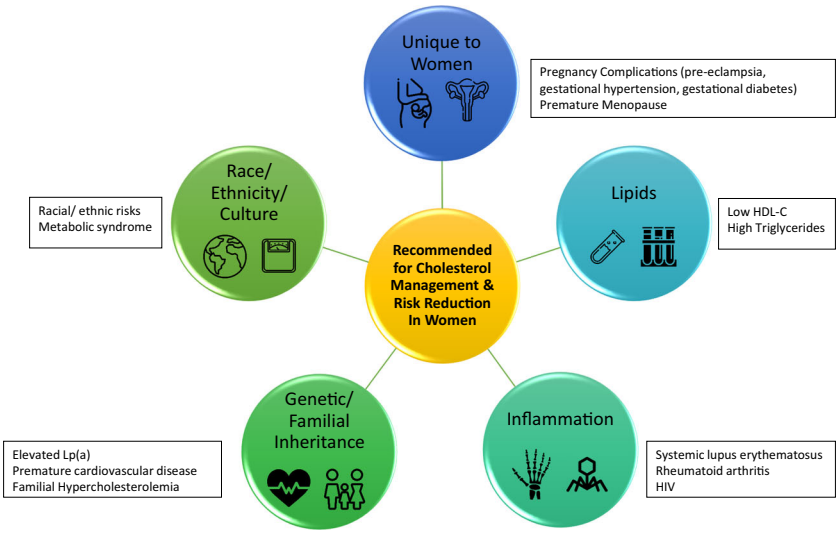

Fig. 1 Consideration for women in cardiovascular disease risk and cholesterol management. Lp(a), lipoprotein(a). HDL-C, high-density lipoprotein cholesterol. HIV, human immunodeficiency virus

and reduction in CVD recurrence. Unique sex-specific biological influences, such as pregnancy-related complications and menopause, at least partly account for differences in lipid disorder pathophysiology and subsequently, for variations in cardiovascular (CV) outcomes between men and women with regard to disease epidemiology, presentation, and response to treatment. Family history, inflammatory disease states like rheumatoid arthritis and lupus, and societal and racial influences also play a role in influencing lipid profiles and CVD risk (Fig. 1). Despite the known benefits of CV risk assessment in all individuals, women are less likely to be evaluated for these risk factors and are less likely to be prescribed guideline-directed statin therapy compared with similarly aged men for both primary and secondary prevention. This review examines contemporary lipid management in primary and secondary CVD prevention in women, including an overview of special risk subgroups and incorporating the current American Heart Association (AHA)/American College of Cardiology (ACC) Guidelines on the Management of Blood Cholesterol.

Primary Prevention

Hyperlipidemia is one of several traditional, modifiable risk factors independently associated with the development of atherosclerotic cardiovascular disease (ASCVD) and carries the highest population attributable risk in women (47.1%) for acute myocardial infarction (MI) compared with other CVD risk factors, such as smoking, hypertension, diabetes, and obesity [1]. Obesity intensifies the risk of negative health consequences from dyslipidemia and is associated with CVD and all-cause mortality [2]. Despite these facts and the efforts put forth to reduce excess weight among individuals, the Centers for Disease Control and Prevention recently updated its obesity prevalence map to illustrate that as of 2017, all 50 of the USA had at least 20% of their adults with obesity [3].

Increased adherence to healthy dietary and exercise habits are associated with weight loss, improvement in abnormal lipid profiles, and fewer adverse events from CVD. Routine aerobic exercise is associated with a 3.0–6.0 mg/dL reduction in low-density lipoprotein cholesterol (LDL-C) levels and a 6 mg/dL decrease in non-high-density lipoprotein cholesterol (non-HDL-C) levels, and some data suggests resistance training results in a 6–9 mg/dL decrease in LDL-C, non-HDL-C, and triglyceride (TG) levels [4]. Based on this evidence, the 2013 AHA/ACC Guideline on Lifestyle Management for CVD risk reduction recommend 3–4 weekly moderate-to-vigorous intensity exercise sessions lasting an average of 40 min each, regardless of sex, for reduction in LDL-C and non-HDL-C (class of recommendation IIa, level of evidence A) [4]. Recently, the Physical Activity Guidelines (PAG) Advisory Committee reported that 80% of American adolescents and adults are not optimally active and suggested that approximately 10% of premature mortality in the USA is associated with physical inactivity [5]. The 2018 second edition of the PAG for Americans recommends three exercise regimens for general health promotion in adults: (a) 150–300 min weekly of moderate-intensity exercise; (b) 75–150 min weekly of vigorous-intensity aerobic exercise; or (c) equivalent combination of the aforementioned of moderate- and vigorous-intensity aerobic exercise. And in addition, at least 2 days a week of muscle-strengthening activities should be included.

In addition to regular physical activity, diets rich in whole grains, fruits, vegetables, legumes, low-fat dairy, fish, and nuts, with limited intake of red meats and sweets, should be implemented to reduce ASCVD risk [6]. A meta-analysis and

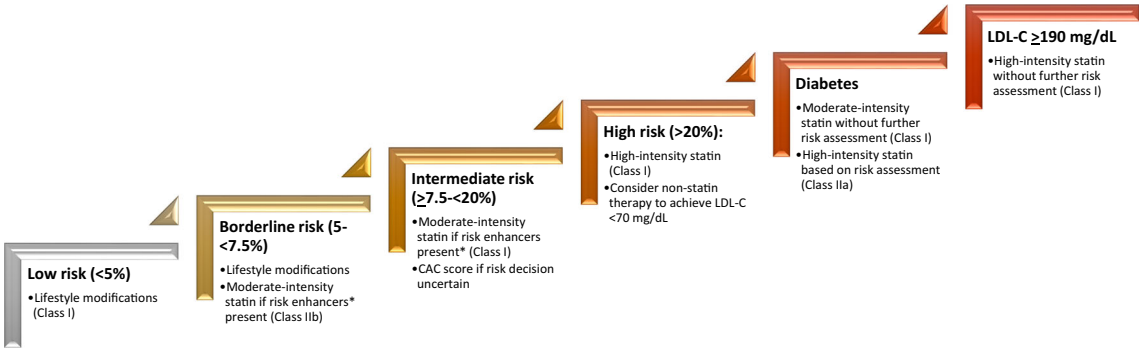

Fig. 2 2018 ACC/AHA cholesterol management recommendation for primary prevention in adults age 40–75 years. Risk assessment based on ASCVD Risk Calculator. From left to right, the first four risk groups apply to adults without diabetes and with LDL-C levels of ≥ 70 –< 190 mg/dL. Moderate-intensity statin signifies ≥ 30% LDL-C reduction. High-intensity statin signifies ≥ 50% LDL-C reduction. Data from Grundy et al. [6]

systematic review by demonstrated an approximate 17% reduction in LDL-C levels and 13% reduction in 10-year coronary heart disease (CHD) risk with a "portfolio diet," which consists primarily of four cholesterol-lowering food groups: nuts, plant protein (e.g., lentils, soy, and beans), viscous soluble fiber (e.g., berries, eggplant, oats, and barley), and plant sterols (e.g., plant sterol-enriched margarine) [7].

Pharmacologic therapy can supplement exercise and healthy eating for primary prevention of dyslipidemia if needed. Individuals aged 20 years or older who are not on lipid-lowering medications should have a screening lipid profile (fasting or non-fasting) checked to acquire baseline LDL-C levels and estimate cardiac risk (class of recommendation IB) [6]. If the non-fasting lipid profile results in a TG level of 400 mg/dL or greater, a fasting lipid profile should be conducted to establish fasting TG levels and baseline LDL-C levels before deciding on pharmacologic therapy [6].

The 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol introduced the concept of using estimated 10-year ASCVD risk profiles for patients, calculated via the pooled-cohort equations, to better stratify which adults may benefit from statin therapy compared with using pure cholesterol levels alone [8]. A clinician-patient risk discussion is warranted before statin initiation. Incorporating data from the subsequent 5 years, multiple professional medical societies collaborated to report the 2018 Cholesterol Guidelines, which restored ideal LDL-C "thresholds" for healthcare providers to obtain while still maintaining and even refining the concept of patient risk profile assessment for personalized care (Fig. 2) [6]. In patients with severe primary hyperlipidemia (LDL-C > 190 mg/dL), a high-intensity statin should be initiated without calculating 10-year ASCVD risk score, with possible addition of non-statin agents if LDL-C levels remain over 100 mg/dL [6].

The 2018 Cholesterol Guidelines also present additional "ASCVD risk enhancers" to include in patients' risk profiles when deciding statin pharmacotherapy, including some specific to women, such as history of pregnancy-related conditions and/or premature menopause (Table 1). If further risk delineation is desired after calculating one's 10-year

Table 1 ASCVD risk factors unique to or commonly observed in women

ASCVD risk factors	Unique in women	Common in women	Similar in women and men	Important for consideration of cholesterol management
Pregnancy complication (preeclampsia, gest HTN, gest DM)	*			*
Premature menopause	*			*
Low HDL-C		*		*
High triglycerides		*		*
Metabolic syndrome		*		*
SLE/RA		*		*
HIV			*	*
Lp(a)			*	*
Premature CVD			*	*
Racial/ethnic risk			*	*

ASCVD, atherosclerotic cardiovascular disease; *gest HTN*, gestational hypertension; *gest DM*, gestational diabetes; *HDL-C*, high-density lipoprotein cholesterol; *SLE*, systemic lupus erythematosus; *RA*, rheumatoid arthritis; *Lp(a)*, lipoprotein(a); *CVD*, cardiovascular disease

Table 2 Prevalence of coronary heart disease and myocardial infarction in US women

	Total (%)	Non-Hispanic Whites (%)	Non-Hispanic Blacks (%)	Hispanics (%)
Coronary heart disease	5.0	4.6	7.0	5.9
Myocardial infarction	1.8	1.8	2.2	1.7

Data from Mozafarrian et al. [9]

ASCVD risk and considering these risk-enhancing factors, the new guidelines are now recommending coronary artery calcium scoring for intermediate risk patients to guide treatment decisions.

Secondary Prevention

Attention to dyslipidemia is important in the care of women who have experienced or are at high risk of experiencing cardiac events to minimize further morbidity. Approximately 15.5 million Americans of or over the age of 20 years have CHD, and its prevalence is estimated to increase by 18% by 2030 (Table 2). The CHD incidence in women lags 10 years behind that of men, with the average age of first MI for a woman being 71.8 years [10]. Patients with premature ASCVD remain an important group for targeting lipid therapy. Females under the age of 65 with a CV event who are found to have ASCVD are considered to have "premature ASCVD." Increased total cholesterol and LDL-C are predictors of cardiac mortality in middle- and older-aged women, while reduced HDL-C and elevated TG levels are strong CHD risk factors [11]. Multiple studies have illustrated that women benefit with statin therapy for secondary prevention as much as men [9, 12]. However, women, especially Hispanic and Black women, are less likely to (a) have their lipid profiles tested, (b) receive guideline-directed medical therapy, including statins, on presentation to the hospital or on hospital discharge, (c) be referred for coronary angiography, and (d) achieve secondary prevention targets for dyslipidemia [11, 13, 14].

Several reasons explain these discrepancies, including atypical acute coronary syndrome (ACS) presentations in women that result in MI misdiagnosis or delayed diagnosis, compounded further by underrepresentation of women in randomized controlled trials that limits appropriate understanding of CVD management in this population [15, 16]. Additionally, while obstructive CHD is the primary cause of acute MI in both women and men, the underlying cause of ACS events in women extends beyond "culprit lesion" only mechanisms and include a conglomerate of etiologies, including nonobstructive coronary plaque, coronary microvascular disease, spontaneous coronary artery dissection, and coronary spasms, in addition to a higher incidence of coronary plaque erosion rather than coronary plaque rupture as seen in men with ACS [11, 17–19]. Moreover, while increased estrogen levels in women play a protective role against CVD risk factors though improvement of lipid levels and reduced diabetes risk, its reduction at menopause promotes vascular lipid accumulation and consequently hastens the development of atherosclerosis [20–22].

The 2018 AHA/ACC Guidelines on the Management of Blood Cholesterol advocate for the reduction of clinical ASCVD through lipid control utilizing more intensive approaches and additional risk assessment tools. These guidelines are the same for both women and men. In addition to adherence to healthy dietary and exercise habits, they recommend using high-intensity or maximally tolerated statin therapy as the primary pharmacological avenue by which to reduce LDL-C by at least 50% in patients with clinical ASCVD (CHD, ACS, stroke or transient ischemic attack, and peripheral vascular disease) [6]. In those patients with very high-risk ASCVD, an LDL-C threshold of < 70 mg/dL is recommended, and non-statin medications can be used if this threshold is not attained by statins alone, including ezetimibe and PCSK9 inhibitors.

Special attention should be paid to those women diagnosed with MI with nonobstructive CHD to ensure that they, too, are prescribed statins as secondary MI prevention to avoid further morbidity and mortality. The 2018 Fourth Universal Definition of MI acknowledges this phenomenon with the introduction of the term MINOCA (myocardial infarction with nonobstructive coronary arteries), confirming the existence of ischemic myocyte injury without obstructive CHD and opening an uncharted area of further exploration for this specific mechanism of ACS more commonly observed in women [23].

High-risk patients with residual risk from hypertriglyceridemia despite statin therapy may warrant additional therapy with high dose EPA. The Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial (REDUCE-IT) compared daily administration of 4 g of a highly purified omega-3 fatty acid, icosapent ethyl, versus placebo in approximately 8000 patients with hypertriglyceridemia and established ASCVD or diabetes with additional CV risk factors who were already well treated on statins [24]. After a median of approximately 5 years, the researchers found reductions in TG levels, major adverse CV events, and CV deaths, citing a statistically significant 26.5% relative risk reduction (3.6% absolute risk

reduction) in the composite of CV death, non-fatal MI, and non-fatal stroke. Statistical significance was lost with subgroup analysis of females, but the trend still suggested CV risk benefit in the icosapent ethyl group (hazard ratio 0.82, CI 0.66–1.01) [24]. This recent trial showed a significant reduction in CVD outcomes through diet modification alone and interestingly, via a non-LDL-C pathway.

Challenges in Lipid Treatment for Women Patients

For sexually active women of childbearing age who are already on statins, counseling on using reliable forms of contraception should be provided due to the teratogenic effects of statin therapy. Women of childbearing age on statin therapy should stop the medication 1 to 2 months prior to attempting pregnancy, and statins should be stopped immediately if a woman discovers she is pregnant while on the medication. Since TG and cholesterol levels increase during pregnancy, pregnant women with genetic lipid disorders may want to consult with a lipidologist [6].

Translation of dietary, physical activity, and pharmacotherapy guidelines into clinical practice remains a challenge. Women are less likely than men to undergo proper CVD risk assessment by their providers, and younger to middle-aged women specifically are less likely than their male counterparts to be prescribed statin therapy [25]. Moreover, women are less likely to meet guideline-based recommendations on routine physical activity compared with men (46.1% vs. 54.2%, respectively), with inactivity rates only rising with age [10]. These data call for healthcare providers to allocate adequate time for evaluation of traditional and non-traditional cardiac risk factors in their female patients, education on the short- and long-term impacts of healthy lifestyle practices, and initiation of pharmacotherapy for reduction of abnormal lipid levels where appropriate.

Lipids and Menopause

Prior to menopause, women tend to have higher levels of HDL-C and lower levels of LDL-C and TGs compared with women after menopause [25]. As women get closer to menopause, the HDL-C levels begin to drop, the LDL-C levels rise, and the TG levels also rise. These cholesterol levels change within months of menopause and continue thereafter. This is known as the Lipid Triad [26]. Menopause also triggers an increase in insulin resistance, decreased insulin secretion, increased visceral fat, and increasing blood pressure [27]. As aforementioned, estrogen levels decrease at menopause, resulting in negatively altered lipid profiles. All these sex-specific biologic changes are contributory to women having similar risks for CVD to men after menopause and generally 10 years later than seen in men.

Special Groups and Risk-Enhancing Factors

A family history of premature ASCVD increases a woman's risk of CVD twofold [28]. While family history is a significant risk factor, over 80% of CV risk can be reduced even in patients with a strong family history of premature CVD [29]. Women with healthy diet and exercise have seen 84% less CVD events than women who do not maintain a healthy lifestyle but unfortunately, very few women meet those criteria [10, 30]. When a family has a strong history of premature CVD, all modifiable risk factors should be aggressively treated including lipids.

Women with familial hypercholesterolemia (FH) are at significantly increased risk for future CVD events. According to AHA Guidelines, FH is defined as an LDL-C > 190 mg/dL in an adult with a first-degree relative who either also has an LDL-C > 190 mg/dL or has premature coronary heart disease [8]. Early diagnosis in childhood or early teen years is extremely important for all children with FH, but especially for females, so therapy can be implemented prior to the childbearing years [31]. Most women with FH will withhold statin, ezetimibe, and PCSK9 inhibitor therapy once they start trying to conceive children and will definitely withhold therapy during pregnancy and during breast-feeding. Implementing statin, ezetimibe, and PCSK9 inhibitor therapy before and after the childbearing years is recommended to significantly reduce CV events in these high-risk women [31].

Premature menopause is defined as menopause before the age of 40 and occurs in about 1% of the female population. Menopause causes multiple CV and biological changes in vasoreactivity, coagulation, insulin resistance, endothelial function, lipids, blood pressure, and visceral fat [32]. History of premature menopause is a risk-enhancing factor for ASCVD and should be considered in the determination of statin therapy in women at risk for CVD. A history of pregnancy-associated conditions that increase a woman's risk for CVD, such as preeclampsia and gestational hypertension, should also be considered when evaluating CVD risk in women and cholesterol management [6, 33]. Gestational diabetes increases a woman's risk for CVD with a 59% increased risk for MI and fourfold increased risk for diabetes [34]. All women with a history of pregnancy complications and premature menopause should be assessed for CVD risk factors and evaluated for lipid reducing therapy. Increased awareness among all physicians of the risk of CVD in women with complications of pregnancy is essential to proper screening and risk assessment in young women.

Metabolic syndrome (MetS) is associated with increased risk for CVD and diabetes in women [35]. The 2018 AHA/ACC Guidelines for the Management of Blood Cholesterol defines metabolic syndrome as three or more of the following: mildly elevated blood pressure (≥ 130/85 mmHg), waist measurement over 88 cm, fasting blood glucose over 100 mg/dL, HDL-C under 50 mg/dL, and TG levels over 175 mg/dL [6]. The risk for CV events including death increases as the number of MetS components increases, with hazard ratios from over 3 with one or two components to nearly 6 for greater than three components [36]. Women meeting three criteria for MetS should be recommended for lifestyle changes and considered for statin therapy.

Women with elevated levels of lipoprotein(a) [Lp(a)] are also at increased risk of CVD events. The 2018 AHA/ACC Guidelines on the Management of Blood Cholesterol includes patients with elevated Lp(a) as having increased risk for CVD and should be given consideration for lipid reducing therapy even if overall LDL-C levels are not over 160 mg/dL or even if ASCVD risk is not over 7.5% for 10-year risk [6]. These guidelines recommend consideration of treatment if Lp(a) > 50 mg/dL or > 125 nmol/L. While statins may not reduce Lp(a), lowering LDL-C is advised until newer therapies that target Lp(a) are approved. Modest reductions of Lp(a) levels have been seen with PCSK9 therapy and new drugs are in the pipeline. Historically, these levels have been considered elevated at > 30 mg/dL and > 75 nmol/L [37]. Women with elevated Lp(a) have increased risks of ASCVD and significant calcification of the aortic valve [38].

Chronic inflammation is a significant contributor to atherosclerosis. The Justification for the Use of Stains in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) Trial, which had almost 40% female participation, showed that women without dyslipidemia and with increased inflammatory state, as evidenced by elevated high-sensitivity C-reactive protein levels, experienced a large decrease in major cardiac events, illustrating both the link between inflammation and CVD and also a method to reduce the latter by minimizing the former [39]. Rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) are two inflammatory conditions more common in women and are also related to increased CVD in women [33]. Women with SLE have a threefold higher risk and women with RA have a fourfold risk of CV events [40]. Women with human immunodeficiency virus (HIV) infection have an increased risk of CVD events even if the viral load is well controlled with antiretroviral therapy [41]. Lipid levels are increased with protease inhibitors which add to the risk for CVD in women with HIV [42]. The 2018 AHA/ACC Guidelines for the Management of Blood Cholesterol recommend that men and women with RA, SLE, and HIV be considered for statin therapy as these chronic inflammatory states are risk-enhancing factors for ASCVD [6].

Racial and ethnic risks are also important in the 2018 Guidelines for Management of Cholesterol [6]. Asian Americans, Hispanic/Latino Americans, and Blacks have greater prevalence of ASCVD risks such as MetS, hypertension, and diabetes, and Hispanic/Latino women have a higher prevalence of low HDL-C compared with Hispanic/Latino men [6]. Additionally, Black women have an increased risk of ASCVD compared with White women, and Black males and females have higher HDL-C levels and lower TG levels compared with non-Hispanic Whites or Mexican Americans [6]. Low HDL-C is most common in Hispanic and White females at over 10% of the population and least common in Asian females at less than 7% of the population [36]. The prevalence of CVD is greatest in Black females at over 47% of the population and lowest in East Asian females at 27%, with Hispanics and Whites at 33% and 35%, respectively [36]. Finally, because South Asians have a baseline increased risk of ASCVD, South Asian ethnicity is listed as an ASCVD risk-enhancing factor by the 2018 AHA Guidelines. Racial and ethnic risks should also be considered in evaluating women for CVD risk and initiation of lipid therapy. There should also be awareness of the influence of race and ethnicity on ASCVD risk estimations, i.e., the pooled cohorts equation may overestimate ASCVD risk in East Asians but underestimate in South Asians [6].

Conclusions

Since 2000, women have experienced a steeper decline than men in CVD mortality, and 2013 marks the first year since 1984 in which fewer women died from CVD than men [10]. These changes are likely multifactorial in etiology, stemming from increased awareness of the biological differences in heart disease manifestation between the sexes to stronger emphasis on CHD prevention in general. Recent publications, such as the 2018 AHA/ACC Guidelines on the Management of Blood Cholesterol and the 2018 Fourth Definition of Myocardial Infarction consensus statement, call to attention the sex- and gender-specific differences in pathophysiology, risk stratification, and management of heart disease, marking a paradigm shift in the practice of CV medicine beyond a “one size fits all” treatment algorithm.

The treatment of dyslipidemia and especially elevated LDL-C levels in women is one established mechanism by which CV mortality can be reduced. Hormonal and biological changes in women, in addition to pregnancy complications and chronic inflammatory conditions, present unique yet challenging scenarios for understanding the multifactorial issues that contribute to ASCVD in women. Combining sex-specific CVD risk markers with evidence-based guidelines for CVD risk reduction makes for effective clinical care of women and future research.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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management in primary healthcare. Heart. 2017;103(7):492–8 **Given the current environment of high sensitivity troponin, the fourth update of the universal definition of myocardial infarction clarifies the difference between myocardial infarction and myocardial injury, and it discusses circumstances in which troponin levels may be increased from non-myocardial infarction phenomena. The established myocardial infarction classification system (types 1 through 5) is still used but updated.**

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28.•• Aggarwal NR, Patel HN, Mehta LS, Sanghani RM, Lundberg GP, Lewis SJ, et al. Sex differences in ischemic heart disease: advances, obstacles, and next steps. Circ Cardiovasc Qual Outcomes. 2018;11(2):e004437 **Dr. Agarwal et al. present a comprehensive review of sex differences in the pathophysiology, presentation, and management of heart disease in women compared to men. The paper discussed social/gender-related and and sex-specific etiologies for the variability in heart disease presentations and outcomes between men and women. In addition, the authors offer solutions to several public health challenges, such as the red dress campaign to raise community awareness, implementation of dedicated women's heart centers, and call for sex- and gender-specific guidelines.**
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