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INVITED REVIEW ARTICLE

Challenges in Optimizing Lipid Management in Women

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Abstract

While there are physiologic differences in lipid metabolism in men and women, pharmacologic therapy is very effective in both with similar management strategies recommended in the current guidelines for the management of dyslipidemia. Despite similar guidelines for treatment, studies have shown that women have worse control of dyslipidemia than their male counterparts. This may stem from multiple contributing factors including underestimation of cardiovascular disease risk in women, decreased prescription and utilization of lipid-lowering therapies, decreased medication adherence, and higher risk of statin intolerance, all of which may contribute to lower attainment of lipid targets. Furthermore, heart disease is the leading cause of mortality in women, with heart disease noted an average of 7–10 years later than in men. This has historically led to the misperception that women are protected from heart disease and can be treated less aggressively. In fact, traditional risk factors for atherosclerotic cardiovascular disease often impact risk in women to a greater extent than they do in men. Unique risk factors such as pregnancy-related disorders also contribute to the level of risk and therefore warrant consideration in risk stratification. This review summarizes the efficacy of contemporary lipid-lowering therapies in women versus men and discusses the challenges that arise with lipid management in women along with potential ways to tackle these obstacles.

Keywords Dyslipidemia · Atherosclerotic cardiovascular disease

Physiologic Sex Differences in Lipid Metabolism

Sex-specific factors and hormonal effects account for sex-based variations in lipid metabolism [1–4] with a more favorable lipoprotein profile noted in women, especially in the reproductive age [1–4]. Women have higher high-density lipoprotein cholesterol (HDL-C), lower triglycerides (TG) and apolipoprotein B, and larger low-density lipoprotein cholesterol (LDL-C) and HDL-C particle size than men [1–4]. However, this beneficial difference is diminished in the postmenopausal state, when higher total cholesterol, TG, very-low density lipoprotein cholesterol (VLDL-C), and LDL-C are noted, as well as lower HDL-C and smaller HDL-C particle size compared to premenopausal status [1, 2, 4]. Furthermore, sex-specific differences exist at the level of hepatic metabolism, with higher expression of the LDL-receptor gene, apolipoprotein A-V gene, and *ABCA1* (transporter involved in removing cholesterol from macrophages) in females [5].

Obesity, defined as a BMI ≥30 kg/m^2, is not only an important cardiovascular (CV) risk factor, but plays an important role in lipid metabolism and is more prevalent in women (40.4%) compared to men (36%) [6]. Obesity leads to increased free fatty acid release in the blood, which are delivered to the liver where they are assembled into TG and packaged into TG-rich VLDL particles [7]. Previous studies have revealed that women secrete TG-rich VLDL particles as compared to men, thereby preventing liver fat accumulation [8]. There is also accelerated clearance of VLDL-TG in women leading to lower plasma VLDL-TG levels with obesity [9]. These differences in VLDL and TG may be due to liver estrogen signaling, as deficiency of estrogen after menopause has shown to increase risk of non-alcoholic fatty

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liver disease [10]. Mechanistic studies in mice models have indicated that estrogen signaling can suppress liver lipogenesis through a variety of signaling pathways [11, 12].

Hepatic regulation of LDL-receptors is important in LDL-C degradation. Proprotein convertase subtilisin/kexin type 9 (PCSK9) binds to the LDL-receptor and promotes its lysosomal degradation. Interestingly, small-scale animal and human studies have shown evidence for increasing levels of PCSK9 with the loss of endogenous estrogen during menopause which may contribute to the increase in LDL-C in women during this time period [13]. Furthermore, it is suggested that estrogen signaling may promote reverse cholesterol transport [14]; however, there is inconsistent evidence that this specific mechanism is mediated by estrogen as a small study did not show differences among groups of premenopausal women, postmenopausal women, or men in the efflux-promoting ability of HDL-C [15].

In addition to influencing lipid metabolism, estrogen also leads to a difference in fat distribution pattern in females. Women possess more subcutaneous fat, while men on average have more visceral fat, which is considered more atherogenic. However, loss of estrogen after menopause leads to redistribution of fat storage with subsequently more visceral fat distribution in females [7]. Abdominal obesity, which may indicate increased visceral fat accumulation, is a stronger predictor of atherosclerosis and coronary heart disease [16, 17].

Efficacy of Lipid-Lowering Therapies

Underrepresentation of Women in Trials

While statins are the standard of care for dyslipidemia and for prevention of atherosclerotic cardiovascular disease (ASCVD) in both men and women, more controversy exists for their use in women due to limited clinical trial data. The paucity of data stems from multiple factors that influence clinical trial enrollment [18]. As women typically develop heart disease later in life than men, less women may be recruited in trials that exclude older individuals. Inclusion/exclusion criteria that consider sex differences in pathophysiology such as age, glomerular filtration rate, body size, and other biomarkers and diagnostic criteria may also lead to preferential recruitment of males, as well as exclusion of pregnant patients or women of childbearing age. Furthermore, lack of willingness to participate could be due to the possibility of perceiving increased risk of harm or being less aware of CV risk. In addition, implicit bias and disparities due to social gender-related factors and cultural practices for women (caretaking roles, lower socioeconomic status, etc.) may also be important contributing barriers to enrollment [18, 19]. A systematic review of 60 lipid-lowering drug trials between 1990 and 2018 revealed only a modest increase in enrollment of women from 19.5 to 33.6%; however, only a total of 53% [95% confidence interval (CI) 41.8–65.3%] of randomized trials reported outcomes according to sex, which did not increase over time [20]. Other studies demonstrated no significant increase in representation of women in CV trials [21, 22]. A study that analyzed 10-year trends in enrollment of women in pivotal cardio-metabolic drug trials, including hypercholesterolemia therapeutics, revealed that there was some increase in the enrollment of women from 29.6% in 2008 to 48.6% in 2017; however, the overall trend was not statistically significant ($p = 0.29$) [21].

Statins

Primary Prevention

Efficacy of statins for primary prevention in women has been long disputed due to limited sex-specific data. Earlier primary prevention clinical trials either did not include enough women to allow sex-specific analyses or did not report separate results in women, hence most sex-specific data are derived from meta-analyses (Table 1). A meta-analysis from 2004 of six primary prevention trials ($N = 36{,}425$; 31% women) demonstrated that lipid-lowering therapies, primarily statins, did not reduce total mortality [relative risk (RR) 0.95; 95% CI, 0.62–1.46], cardiovascular heart disease (CHD) mortality (RR 1.07; 95% CI, 0.47–2.40), nonfatal myocardial infarction (MI) (RR 0.61; 95% CI, 0.22–1.68), revascularization (RR 0.87; 95% CI, 0.33–2.31), or CHD events (RR 0.87; 95% CI, 0.69–1.09) in women. However, this meta-analysis was limited in power with a very low number of CV events. In addition, the average length of follow-up was only 4.6 years [23]. The long-term benefits of statins beyond the relatively short duration of any trial must be considered. In another large meta-analysis from 2010 ($N = 44{,}992$; 39% women), statin therapy for primary prevention reduced CHD events in men but not women, even with inclusion of the MEGA (Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese) study in which a large proportion of women (total $N = 7{,}832$; 69% women) were enrolled [24, 25]. Nonetheless, both meta-analyses have significant limitations as sex-specific data were not available for several trials. Also, both aforementioned meta-analyses included the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack (ALLHAT-LLT) trial which had several limitations as demonstrated by an 11% reduction of LDL-C in the placebo group, whereas other trials usually observe little or no cholesterol reduction with placebo. In addition, the ALLHAT-LLT trial lacked adequate power to discriminate reductions in mortality and CHD events due to failure of achieving adequate reduction in LDL-C in the treatment group [26]. Therefore,

Table 1 Select lipid-lowering efficacy trials and meta-analyses which included sex-specific analysis

Trial Name (Year)—type of prevention	Total participants/women (%)	Patient population	Intervention (follow-up time)	Endpoint	Sex-specific results for endpoint
I. Meta-analyses					
Mora S et al. (2010)—primary [27]	13,154	• 3 trials—AFCAPS/TexCAPS. MEGA, JUPITER	Statin vs. placebo	Primary CV events	Women (RR 0.63; 95% CI 0.49–0.82, $p<0.001$ p for heterogeneity = 0.56
Petretta M et al. (2010)—mostly primary [24]	44,992/17,610 (39%)	• 7 randomized trials in men, 6 trials in women—AFCAPS, ASCOT LLA, ALLHAT, HPS, MEGA, PROSPER	Statin vs. placebo (3.9 years)	CHD events	Women (RR 0.89; 95% CI 0.79–1.00; $p = 0.05$) Men (RR 0.59; 95% CI 0.48–0.74; $p = 0.0001$) Excluding mixed prevention trials: Women (RR 0.95; 95%CI 0.78– 1.16; p= 0.562; heterogeneity $p = 0.39$); Men (RR 0.55; 95% CI 0.41–0.75; $p = 0.0001$; heterogeneity $p = 0.0001$)
Gutierrez J et al. (2012)—secondary [38]	43,193/8,897 (21%)	• 11 trials—ASCOT-LLA, LIPID, PROSPER, 4S, CARE, PLAC-I, SPARCL, MIRACL, FLORIDA, Fluvastatin, CCAIT	Statin vs. placebo	CV events	Women (RR 0.81; 95% CI 0.74–0.89) Men (RR 0.82; 95% CI 0.78–0.85) All-cause mortality in women (RR 0.92; 95% CI 0.76-1.13) vs. men (RR 0.79; 95% CI, 0.720.87); stroke in women (RR 0.92; 95% CI 0.76–1.10) vs. men (RR 0.81; 95% CI 0.72–0.92)
Walsh et al. (2004)—mixed [23]	Primary: 36,425/11,435 (31%) Secondary: 33,698/8,722 (26%)	• 6 primary prevention—Colestipol Study, ACAPS, AFCAPS/TEXCAPS, HPS, ALLHAT, ASCOT-LLA • 8 secondary prevention – Scottish Society of Physicians, Physicians of Newcastle upon Type Region, NHLBI Type II, 4S, PLAC-II, CARE, LIPID, HPS	Colestipol or statin or clofibrate or cholestyramine vs. placebo (4.6 years)	Total mortality, CHD mortality, nonfatal MI, revascularization, CHD events	-Primary: Total mortality (RR 0.95; 95% CI 0.62–1.46), CHD mortality (RR 1.07; 95% CI 0.47–2.40), nonfatal MI (RR 0.61; 95% CI 0.22–1.68), revascularization (RR 0.87; 95% CI 0.33–2.31), or CHD events (RR 0.87; 95% CI 0.69–1.09). -Secondary: Total mortality (RR 1.00; 95% CI 0.77–1.29), CHD mortality (RR 0.74; 95% CI 0.55–1.00), non-fatal MI infarction (RR 0.71; 95% CI 0.58–0.87), revascularization (RR 0.70; 95% CI 0.55–0.89), and total CHD events (RR 0.80; CI 0.71–0.91).
Kostis W et al. (2012)—mixed [31]	141,235/40,275 (29%)	• 18 trials—4S, AF-TEXCAPS, ALLHAT-LLT, ASCOT-LLA, AURORA, CARE, CORONA, GISSI-P, GREACE, HPS, JUPITER, LIPID, MEGA, A to Z, PROSPER, PROVE-IT, TNT, SEARCH	Statin vs. control (low-dose statin, placebo, usual care) (4 years)	CV event rate	Women (OR 0.81; 95% CI 0.75 to 0.89; p 0.0001) Men (OR 0.77; 95% CI 0.71 to 0.83; p <0.0001)
Cholesterol Treatment Trialists' (CTT) Collaboration (2015)—mixed [32]	174,149/44,675 (27%)	• 27 trials—4S, WOSCOPS, CARE, Post-CABG, AFCAPS/TexCAPS, LIPID, GISSI, LIPS, HPS, PROSPER, ALLHAT-LLT, ASCOT-LLA, ALERT, CARDS, ALLIANCE, 4D, ASPEN, MEGA, JUPITER, GISSI-HF, AURORA, CORONA, PROVE-IT, A to Z, TNT, IDEAL, SEARCH	22 trials: statin vs. control; 5 trials: intensive statin vs. less-intensive statin (4.9 years)	Reductions in major vascular events per 1.0mmol/L reduction in LDL cholesterol	Women (RR 0.84; 99% CI 0.78–0.91) Men (RR 0.78; 99% CI 0.75–0.81 Adjusted p value for heterogeneity by sex = 0.33 All-cause mortality in women (RR 0.91; 99% CI 0.84–0.99) vs. men (RR 0.90; 99% CI 0.86–0.95; adjusted heterogeneity $p = 0.43$)
II. Trials					
Statins					
ASCOT (2003)—primary [145]	10,305/1,942 (30%)	• Age 40–79 years with at least 3 other CV risk factors • Non-fasting TC ≤ 6.5 mmol/L	Atorvastatin 10mg vs. placebo (5 years)	Non-fatal MI, including silent MI and fatal CHD	Women (HR 1.10; 95% CI 0.57–2.12), $p = 0.7692$ Men (HR 0.59; 95% CI 0.44–0.77), $p = 0.0001$

Table 1 (continued)

Trial Name (Year)—type of prevention	Total participants/women (%)	Patient population	Intervention (follow-up time)	Endpoint	Sex-specific results for endpoint
MEGA (2006)—primary [146]	7,832/5,356 (69%)	• Men and postmenopausal women age 40–70 years in Japan with a bodyweight ≥ 40 kg and hypercholesterolemia • TC 5.69–6.98 mmol/L	Pravastatin 10–20mg vs. placebo (5.3 years)	First occurrence of CHD, fatal and non-fatal MI, angina, cardiac and sudden death, and coronary revascularization	Women (HR 0.71; 95% CI 0.44–1.14) Men (HR 0.63; 95% CI 0.42–0.95) *p* for heterogeneity = 0.71
JUPITER (2010)—primary [27]	17,802/6,801 (38%)	• Women age ≥60 years and men age ≥50 years without prior history of coronary disease, stroke, or diabetes mellitus • LDL-C <130 mg/dL and hsCRP ≥2.0 mg/L	Rosuvastatin 20mg vs. placebo (5 years)	Occurrence of a first major CV event (nonfatal MI, nonfatal stroke, hospitalization for UA, arterial revascularization, or confirmed CV death)	Relative risk reduction: Women (HR 0.54; 95% CI 0.37 to 0.80; p=0.002) Men (HR 0.58; 95% CI 0.45 to 0.73; p<0.001)
CARE (1996)—secondary [147]	4,159/576 (14%)	• Age 21 to 75 years, with acute MI between 3 and 20 months • TC < 240 mg/dL, LDL-C 115 to 174 mg/dL fasting TG < 350 mg/dL	Pravastatin 40mg vs. placebo (5 years)	CHD death or nonfatal MI	% risk reduction Women 43% (95% CI 4–66), p = 0.035 Men 21% (95% CI 4–35), p = 0.017
LIPID (1998)—secondary [39]	9,014/1,516 (17%)	• Age 31-75 years, with prior MI or UA in the previous 3-36 months	Pravastatin 40mg vs. placebo (6.1 years)	Rate of CHD death or nonfatal MI	Relative risk reduction: Women 11% (95% CI 18–33), p = 0.42 Men 26% (95% CI 17–35), p<0.01 Total 24% (95% CI 15–32), p <0.01
PROVE IT-TIMI 22 (2004)—secondary [37]	4,162/911 (21.9%)	• Hospitalized for ACS, not previously on lipid-lowering therapy • TC (measured within 24 hours of ACS event) < 240 mg/dL, and those on long-term lipid-lowering therapy < 200 mg/dL	Intensive statin (atorvastatin 80 mg) vs. standard therapy (pravastatin 40 mg) (2 years)	Death, MI, UA, revascularization (occurring after 30 days) or stroke	Women 6.7% absolute reduction in events and a 25% relative risk reduction (RRR) in hazard over standard statin therapy (p=0.04) Men 3.2% absolute reduction in events and 14% RRR in hazard (p=0.04). p-interaction for primary endpoint = 0.38
TNT (2005)—secondary [148]	10,001/1,902 (19%)	• Clinically evident CHD, defined as previous MI, previous or present angina with objective evidence of atherosclerotic CHD, and/or those who underwent a coronary revascularization procedure	Atorvastatin 10 mg/day vs. 80 mg/day (4.9 years)	Time to the first occurrence of a major CV event, defined as CHD death, non-fatal non-procedure-related MI, resuscitated cardiac arrest, and fatal or non-fatal stroke	Women relative and absolute reductions were 27% and 2.7%, respectively (HR 0.73; 95% CI 0.54–1.00, p = 0.049) Men, the corresponding rate reductions were 21% and 2.2% (HR 0.79; 95% CI 0.69-0.91, p = 0.001).
SPARCL (2006)—secondary [149]	4,731/908 (40%)	• Age ≥18 years, who had had an ischemic or hemorrhagic stroke or a TIA (diagnosed by a neurologist within 30 days after the event) 1 to 6 months before randomization	Atorvastatin 80mg vs. placebo (4.9 years)	Time from randomization to a first nonfatal or fatal stroke	Women (HR 0.84; 95% CI 0.63 - 1.11) Men (HR 0.84; 95% CI 0.68 -1.02) *p* value for treatment x sex interaction P =0.99
PROSPER (2002)—mixed [150]	5,804/3,000 (52%)	• Age 70–82 years, with either pre-existing vascular disease (coronary, cerebral, or peripheral) or raised risk of such disease because of smoking, hypertension, or diabetes • TC 4.0–9.0 mmol/L and TG < 6.0 mmol/L	Pravastatin 40mg vs. placebo (3.2 years)	Combined endpoint of definite or suspect death from coronary heart disease, non-fatal MI, and fatal or non-fatal stroke	Women (HR 0.96; 95% CI 0.79–1.18) Men (HR 0.77; 95% CI 0.65–0.92) *p* for interaction = 0.13
HPS (2003)—mixed [151]	20,536/5,082 (25%)	• Age 40–80 years, with TC ≥135 mg/dL and substantial 5-year risk of death from CHD because of a past medical history of coronary disease or occlusive disease of non-coronary arteries, carotid endarterectomy, or diabetes mellitus	Simvastatin 40mg vs. placebo (5 years)	First major vascular event	Event rate ratio: Female 14.4% simvastatin vs. 17.7% placebo Male 21.6% simvastatin vs. 27.6% placebo *p* for heterogeneity = 0.76

Table 1 (continued)

Trial Name (Year)—type of prevention	Total participants/women (%)	Patient population	Intervention (follow-up time)	Endpoint	Sex-specific results for endpoint
Ezetimibe					
IMPROVE-IT (2015)—secondary [41]	18,144/4,416 (24%)	• Age >50 years with ACS and LDL-C of 50- 125 mg/dL for patients not receiving prior prescription lipid-lowering therapy and 50–100 mg/d for those on lipid-lowering	Ezetimibe 10mg/simvastatin 40mg vs. placebo/simvastatin 40mg (6 years)	CV death, MI, hospitalization for UA, coronary revascularization ≥30 days, and stroke.	Women 12% risk reduction (HR 0.88; 95% CI 0.79–0.99) Men 5% reduction for men (HR 0.95; 95% CI 0.90–1.01)$p = 0.26$ for interaction
PCSK9 Inhibitors					
FOURIER (2017)—secondary [42]	27,564/6,769 (25%)	• Age 40–85 years, with stable ASCVD (MI, non-hemorrhagic stroke, or symptomatic peripheral artery disease) and additional risk factors • LDL-C ≥ 70 mg/dL or HDL-C ≥ of 100 mg/dL, while taking an optimized lipid-lowering regimen including a high or moderate intensity statin, with or without ezetimibe	Evolocumab 140 mg subcutaneous every 2 weeks or 420 mg monthly vs. placebo (2.2 years)	CV death, MI, stroke, hospitalization for UA or coronary revascularization	Women relative risk reductions 0.81 (95% CI 0.69–0.95) Men 0.86 (95% CI 0.80–0.94) P interaction = 0.48
ODYSSEY (2018)—secondary [43]	18,924/4,762 (25%)	• ACS 1 to 12 months earlier • LDL-C level ≥70 mg/dL, a non−HDL-C ≥ 100 mg/dL or apo B level of ≥80 mg/dL and were receiving statin therapy at a high-intensity dose or at the maximum tolerated dose	Alirocumab subcutaneously 75 mg every two weeks vs. placebo (2.8 years)	Composite of death from CHD, non-fatal MI, fatal or nonfatal ischemic stroke, or UA requiring hospitalization	Relative risk reductions in women 9% vs. 17% in men P interaction = 0.35
Fibrates					
FIELD (2005)—mixed [45, 46]	9,795/3,657 (37.3%)	• Age 50–75 years with type 2 diabetes and not using a statin • 22% of population had previous CVD	Fenofibrate 200mg vs. placebo (5 years)	First occurrence of nonfatal MI or death from coronary heart disease	Women (HR 0.80; 95% CI 0.64–0.99; $p = 0.04$) Men (HR 0.92; 95% CI 0.81–1.05; $p = 0.2$) p for difference by sex = 0.3
ACCORD (2010)—mixed [44]	5,518/1,694 (31%)	• Age 40–79 years with clinical CVD, or 55–79 years of age with subclinical CVD or ≥ 2 additional risk factors	Fenofibrate 160mg + simvastatin, average dose 22.3mg vs. placebo + simvastatin, average dose 22.4mg (4.7 years)	First occurrence of major CV event, including nonfatal MI, nonfatal stroke, or death from CV causes	Women: event rate 9.05% fenofibrate vs. 6.64% placebo Men: event rate 11.18% fenofibrate vs. 13.30% placebo $p = 0.01$ for difference by sex
Niacin					
HPS2-THRIVE (2014)—secondary [47]	25,673/4,444 (17%)	• Age 50–80 years, with a history of MI, cerebrovascular disease, PAD, or diabetes with evidence of symptomatic coronary disease	Niacin 2g + laropiprant 40mg+ simvastatin 40mg vs. placebo + simvastatin 40mg (3.9 years)	Major vascular events (nonfatal MI, death from coronary causes, stroke of any type, or coronary or non-coronary revascularization)	Women: event rate 13.4% niacin +laropiprant vs. 12.3% placebo Men: event rate 13.2% niacin +laropiprant vs. 14.0% placebo $p = 0.07$ for difference by sex
Omega-3 fatty acids					
JELIS (2007)—mixed [49]	18,645/12,786 (69%)	• Men age 40–75 years and postmenopausal women age < 75 years with hypercholesterolemia, with or without CAD • TC > 6.5 mmol/L, which corresponded to a LDL cholesterol > 4.4 mmol/L	EPA-only omega-3 fatty acid 1.8 g/day + statin vs. statin alone (5 year)	Major coronary events, including SCD, fatal and nonfatal MI, UA, angioplasty, stenting, or CABG	Women (HR 0.87; 95% CI 0.68–1.13) Men (HR 0.76; 95% CI 0.62–0.94) $p = 0.43$ for difference by sex

Table 1 (continued)

Trial Name (Year)—type of prevention	Total participants/women (%)	Patient population	Intervention (follow-up time)	Endpoint	Sex-specific results for endpoint
REDUCE-IT (2019)—mixed [52]	8,179/2,357 (26%)	• Age ≥ 45 years, established CVD or age ≥ 50 with diabetes and ≥ 1 additional risk factor • Fasting TG level from 135-499 mg/dL; LDL-C from 41 and 100 mg/ dL • Stable dose of statin for ≥4 weeks	Icosapent ethyl (EPA) 4 g/day + statin vs. statin alone (4.9 years)	Composite of CV death, nonfatal MI, nonfatal stroke, coronary revascularization, or UA in a time-to-event analysis	Women (HR 0.82; 95% CI 0.66–1.01) Men (HR 0.73; 95% CI 0.65–0.82) $p = 0.33$ for interaction
STRENGTH (2020)—mixed [53]	13,078/4,568 (35%)	• Age ≥ 18 years considered at high risk for a future CV event, either presence of established ASCVD, diabetes with age ≥ 40 years for men and ≥ 50 years for women with ≥ 1 additional risk factor or high-risk primary prevention patients aged ≥ 50 years for men or ≥ 60 years for women with ≥ 1 additional risk factor	4 g/day of omega-3 carboxylic acid formulation of EPA and DHA vs. placebo of corn oil (1.75 years)	Composite of CV death, nonfatal MI, nonfatal stroke, coronary revascularization, and hospitalization for UA	Women (HR 0.94; 95% CI 0.78–1.14) Men (HR 1.01; 95% CI 0.90–1.13) p for interaction = 0 .54
OMEMI (2020)—secondary [54]	1,027/294 (29%)	• 70–82 years old patients with recent (2-8 weeks) AMI.	1.8 g n-3 PUFA (930 mg EPA and 660 mg DHA) vs. placebo of corn oil (2 years)	Composite of non-fatal AMI, revascularization, stroke, all-cause death, HF hospitalization after 2 years	p for interaction by sex = 0.53

Abbreviations

AFCAPS/TexCAPS Air Force/Texas Coronary Atherosclerosis Prevention Study, *MEGA* Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese, JUPITER Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin Study Group, CV cardiovascular, RR relative risk, ASCOT-LLA The Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm, *ALLHAT-LLT* The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack, *HPS* Heart Protection Study, *PROSPER* Prospective Study of Pravastatin in the Elderly at Risk, *CHD* coronary heart disease, *LIPID* Long-Term Intervention with Pravastatin in Ischaemic Disease, *4S* Scandinavian Simvastatin Survival Study, *UA* unstable angina, *CARE* Cholesterol and Recurrent Events trial, *PLAC-I* Pravastatin Limitation of Atherosclerosis in the Coronary Arteries trial, *SPARCL* Stroke Prevention by Aggressive Reduction in Cholesterol Levels Study, *MIRACL* Myocardial Ischemia Reduction With Aggressive Cholesterol Lowering Study, *FLORIDA* Fluvastatin on Risk Diminishment After Acute Myocardial Infarction, *CCAIT* Canadian Coronary Atherosclerosis Intervention Trial, *ACAPS* Asymptomatic Carotid Artery Progression Study, *MI* myocardial infarction, AURORA A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: an Assessment of Survival and Cardiovascular Events, *CORONA* Controlled Rosuvastatin Multinational Trial in Heart Failure, *GISSI-P* Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico Prevention, *GREACE* Greek Atorvastatin and Coronary Heart Disease Evaluation, *PROVE-IT* Pravastatin or Atorvastatin Evaluation and Infection Therapy, *TNT* Treating to New Targets, *SEARCH* Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine, *LDL* low density lipoprotein, *TC* Total cholesterol, *hsCRP* high sensitivity C-reactive protein, *TG* triglycerides, *ACS* acute coronary syndrome, *TIA* transient ischemic attack, *ASCVD* atherosclerotic cardiovascular disease, *WOSCOPS* West of Scotland Coronary Prevention Study, *LIPS* Lescol Intervention Prevention Study, *ALERT* Assessment of Lescol in Renal Transplantation, *CARDS* Collaborative Atorvastatin Diabetes Study, *ALLIANCE* Aggressive Lipid-Lowering Initiation Abates New Cardiac Events, *ASPEN* Aggressive Lipid-Lowering Initiation Abates New Cardiac Events, *IDEAL* Incremental Decrease in End Points Through Aggressive Lipid Lowering Study Group, IMPROVE-IT Improved Reduction of Outcomes: Vytorin Efficacy International Trial, FOURIER Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk, *HDL* high-density lipoprotein, *ODYSSEY* Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab, *FIELD* Fenofibrate Intervention and Event Lowering in Diabetes, *ACCORD* Action to Control Cardiovascular Risk in Diabetes, *HPS2-THRIVE* Heart Protection *Study* 2-Treatment of HDL to Reduce the Incidence of Vascular Events, *PAD* peripheral artery disease, *JELIS* Japan EPA Lipid Intervention Study, *REDUCE-IT* Reduction of Cardiovascular Events With Icosapent Ethyl–Intervention Trial, *STRENGTH* Study to Assess Statin Residual Risk Reduction With Epanova in High CV Risk Patients With Hypertriglyceridemia, *PUFA* polyunsaturated fatty acids, *DHA* docosahexaenoic acid, *EPA* eicosapentaenoic acid, *OMEMI* OMega-3 fatty acids in Elderly with Myocardial Infarction

the lack of lipid-lowering benefit with statin treatment in ALLHAT-LLT may have contributed to the lack of event reduction seen in these older meta-analyses.

On the contrary, the landmark JUPITER (Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin) trial (N = 17,802; 38% women), in which patients with normal LDL-C and elevated high-sensitivity C-reactive protein (hs-CRP) were randomized to rosuvastatin 20 mg or placebo, demonstrated that rosuvastatin used for primary prevention reduced CV events in women with a relative risk reduction similar to that in men. A sex-specific post hoc analysis of JUPITER from 2010 resulted in similar and significant proportional reductions in the primary endpoint for both women (46%; p=0.002) and men (42%; p<0.001). It is particularly remarkable that absolute event rates were lower in women as they were older (median age of 68 years in women and 63 years in men) and generally had more CV risk factors than men, including higher prevalence of hypertension and metabolic syndrome. Women had a significantly greater reduction compared with men in revascularization/unstable angina (UA), while men had a greater reduction in stroke [27]. The authors of this study also conducted a meta-analysis of 13,154 women, incorporating JUPITER along with other exclusively primary prevention trials including MEGA. Their findings demonstrated that statin therapy in women significantly reduced cardiovascular disease (CVD) events by about one-third, but there was no significant effect on total mortality [27]. The discrepancy of statin efficacy in women from older meta-analyses may be a result of inadequate number of events as most of these previous analyses were conducted before the publication of the JUPITER trial.

A meta-analysis from 2010 of 11 trials (N = 65,229) that included JUPITER and specifically focused on all-cause mortality did not show any evidence for the benefit of statin therapy among high-risk men and women for primary prevention. Unfortunately, this study had insufficient data to analyze the effects of statins in women versus men and had a relatively short average follow-up period of 3.7 years [28]. Meta-analyses have suggested that the relative risk reduction with respect to coronary events may become greater with longer duration of statin therapy [29]. It is also important to remember the constraints of meta-analyses as they are retrospective in nature and are subject to limitations related to heterogeneity of analysis in included studies [30].

Meta-analyses that combine primary and secondary prevention trials have shown more consistent benefit of statins in women. In one meta-analysis of 18 randomized clinical trials (RCTs) (N = 141,235; 29% women), the benefit of statins in lowering CV events and all-cause mortality was statistically significant in both sexes [31]. These results were consistent with the Cholesterol Treatment Trialists' Collaboration meta-analysis from 2015 which included 27 RCTs (N = 174,149; 27% women), both primary and secondary prevention showing that statin therapy had similar efficacy in men and women at an equivalent risk of CVD for the prevention of major vascular events [32].

Secondary Prevention

The use of statins in women for secondary prevention has more evidence than primary prevention, in terms of both lipid-lowering as well as hard CV outcomes (Table 1). Studies investigating CV outcomes have demonstrated statins to be as effective in women as in men for secondary prevention. This includes the Heart Protection Study of high-risk individuals in the UK (N = 20,536; 25% women), which demonstrated that CV events were reduced by simvastatin in women (event rate ratio 14.4% in simvastatin and 17.7% in placebo) as well as in men (event rate ratio 21.6% in simvastatin and 27.6% in placebo) (interaction p-value of 0.76) [33]. Furthermore, in the Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) study (N = 9,014; 17% women) conducted in 2003, pravastatin did not show different treatment effect for the risk of CV events in women with previous MI or UA and a baseline LDL-C 155–271 mg/dL compared to that in men (p value for heterogeneity > 0.05). However, statin therapy significantly reduced CV outcomes in men but not in women which may be attributed to the fact that this trial was not adequately powered to show separate effects in women who only comprised 17% of the study population [34]. Interestingly, the Study of Coronary Atheroma by Intravascular Ultrasound: Effect of Rosuvastatin Versus Atorvastatin (SATURN) (N = 1,039; 26.4% women), which utilized serial intravascular ultrasound measures of coronary atheroma volume in patients treated with rosuvastatin versus atorvastatin for 24 months, revealed greater atheroma regression in women than men following treatment. After treatment, women had higher HDL-C and CRP but similar LDL-C as compared to men in this study. Both sexes demonstrated comparable plaque regression rates when the treatment LDL-C values were ≥70 mg/dL; however, women had significantly greater coronary atheroma regression than their male counterparts for LDL-C levels <70 mg/dL [35]. This study suggested that specific LDL-C targets may be important, especially in women.

A secondary analysis of the Treating to New Targets (TNT study) (N = 10,001; 19% women) proved that the benefits of intensive (atorvastatin 80 mg) versus standard (atorvastatin 10 mg) lipid-lowering therapy were equally applicable to women. The relative and absolute reductions in major CV events with intensive statin therapy in women were 27% and 2.7%, respectively [hazard ratio (HR) 0.73; 95% CI, 0.54–1.00, p=0.0490], compared to the corresponding event rate reductions in men 21% and 2.2% (HR 0.79; 95% CI, 0.69–0.91, p=0.001) [36]. Similarly, a subgroup

analysis of The Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22) trial ($N = 4,162$; 21.9% women) demonstrated that both women and men derived significant benefit from intensive statin therapy with high-dose atorvastatin 80 mg versus standard-dose pravastatin 40 mg following acute coronary syndrome (ACS). In fact, intensive statin therapy proved to have a stronger clinical impact in women. The mean LDL-C reduction needed in women to observe a 1% reduction in events was 1.0 mg/dL vs. 2.4 mg/dL in men. Women had a higher absolute reduction (6.7% women vs 3.2% men) and relative risk reduction (25% women vs 14% men) in the primary composite endpoint of death from any cause or a major CV event. Given the dramatic benefit of intensive statin therapy observed in both sexes, the authors concluded that gender should not play a role in determining who should be treated with intensive statin therapy for secondary prevention [37].

Meta-analyses of secondary prevention trials have also consistently demonstrated statins to be of equal benefit in women compared to men. A meta-analysis of 8 secondary prevention trials ($N = 33,698$; 26% women) revealed that the number needed to treat to prevent one CV event in women was 26, comparable to 24 in men [23]. Another meta-analysis of 11 RCTs ($N = 43,193$; 21% women) compared the protective effect of statins between sexes and determined that statin therapy was an effective intervention in the secondary prevention of CV events in both sexes. Statin therapy was associated with reduced CV events in all outcomes for women; however, there was no benefit on stroke (RR, 0.92 [95% CI, 0.76–1.10] vs RR, 0.81 [95% CI, 0.72–0.92]) and all-cause mortality (RR, 0.92 [95% CI, 0.76–1.13] vs RR, 0.79 [95% CI, 0.72–0.87]) in women as compared to men [38]. Although, it is important to consider that in two of the trials, LIPID [39] and CARE [40], antiplatelet agent use was lower in women, which raises the concern that women were undertreated for guideline-directed medical therapy for CVD. Additionally, women were older and had more hypertension compared with men, and these differences in co-morbidities could have influenced the results of these analyses [38].

Non-statins

While statins remain the foundation of pharmacologic CV risk factor reduction, other agents such as ezetimibe and PCSK9 inhibitors can be combined with statins to further address LDL-C lowering and CV event risk reduction. Furthermore, it is important to determine whether this LDL-C lowering with non-statin agents affects clinical outcomes similarly in both women and men and whether treatment of non-LDL atherogenic lipid particles provides additional benefit.

Ezetemibe

Insight from IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) ($N = 18,144$; 24% women) demonstrates the benefit of adding ezetimibe to statin therapy after an ACS event in both women and men. The overall higher baseline risk of CV events in women compared to men appeared to translate into a greater absolute reduction in first and total CV events, with a greater risk reduction in women (12%) than men (5%) for the primary composite endpoint when ezetimibe was added to simvastatin. The benefit of adding ezetimibe in secondary prevention for women appeared to be most apparent in the reduction of MI (women [HR 0.78; 95% CI 0.66–0.91)] vs. men [HR 0.90; 95% CI 0.82–1.00]) [41].

PCSK-9 Inhibitors

The Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) trial ($N = 27,564$; 25% women) proved that the efficacy and safety of PCSK9 inhibitor evolocumab was similar between women and men across a broad range of ages. Among patients with clinically evident atherosclerotic CVD randomized to evolocumab in addition to statin therapy vs placebo, women and men had similar relative risk reductions in the primary endpoint which included CV death, MI, stroke, hospitalization for UA, or coronary revascularization (0.81; 95% CI 0.69–0.95 women vs. 0.86; 95% CI 0.80–0.94 men). In this trial, women had a lower 3-year primary endpoint event rate than men (12.5 vs. 15.3%, respectively, $p < 0.001$) [42]. Results from Evaluation of Cardiovascular Outcomes after an Acute Coronary Syndrome During Treatment with Alirocumab (ODYSSEY) ($N = 18,924$; 25% women) showed that reduction in the primary endpoint was similar in women (HR 0.91; 95% CI, 0.77–1.08) and men (HR 0.83; 95% CI, 0.74–0.92) treated with alirocumab (p interaction = 0.35) [43]. Overall, the trials of non-statin agents including PCSK9 inhibitors have shown comparable efficacy in both sexes.

Fibrates

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study ($N = 5,518$; 31% women) investigated whether statin plus a fibrate reduced risk of CVD in patients with type 2 diabetes as compared to statin monotherapy. Prespecified subgroup analysis demonstrated an interaction by sex favoring men: women had higher CV event rate with the addition of fenofibrate to statin. The primary outcome (first occurrence of non-fatal MI, non-fatal stroke, or death from CV causes) for men was 11.2% in the fenofibrate group versus 13.3% in the placebo group, whereas the rate for women

was 9.1% in the fenofibrate group versus 6.6% in the placebo group ($p = 0.01$ for interaction) [44]. This trial raised questions about the safety and possible harm of fenofibrates in women with diabetes.

Contrary to the ACCORD study, the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study ($N = 9,795$; 37.3% women) demonstrated fenofibrate efficacy and safety in women. This study determined that fenofibrate improved the lipoprotein profile more in diabetic women than men. The primary endpoint of non-fatal MI plus coronary death was not significantly reduced; however, the secondary endpoint of total CV events including CV death, fatal and non-fatal stroke, and carotid and coronary revascularization was reduced. When adjusted for covariates, fenofibrate reduced total CV outcomes by 30% in women (95% CI 8–46%, p=0.008) and 13% in men (95% CI 1–24%, p=0.07) [45]. The dissimilar results of ACCORD and FIELD may be due to several factors. CV event rates among women in the control arm of FIELD were nearly 50% higher than in the ACCORD trial, probably because the patients in FIELD had higher baseline risk, as fewer than one-third received statin therapy in the FIELD trial compared to the ACCORD trial in which all participants were on statins. Furthermore, FIELD appeared to have greater power than ACCORD due to the higher event rate combined with including more female participants [46].

Niacin

In the Heart Protection Study 2–Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) trial ($N = 25,673$; 17% women), patients with vascular disease were randomized to niacin and laropiprant vs. placebo. Niacin-laropiprant did not have any significant effect on major vascular events, and actually led to increase in serious adverse effects associated with the gastrointestinal system (4.8% vs. 3.8%, p<0.001, musculoskeletal system (3.7% vs. 3.0%, p<0.001), and skin (0.7% vs. 0.4%, p=0.0003). Furthermore, pre-specified sub-analyses based on sex showed a trend ($p = 0.07$) towards worse CV outcomes in women treated with niacin [47]. Another large niacin trial, AIM-HIGH, which showed no benefit in clinical outcomes, included less than 15% women and did not report sex-specific results [48].

Omega-3 Fatty Acids

In the Japan EPA Lipid Intervention Study (JELIS) trial ($N = 18,645$; 69% women), eicosapentanoic acid (EPA) treatment reduced the frequency of major coronary events in both women and men. A subgroup analysis revealed no interaction in outcomes by gender [49]. In addition, in the ANCHOR trial, icosapent ethyl was shown to be safe and effective in reducing TG in adults on stable statin therapy and with TG 200–400mg/dL. A post hoc analysis of the ANCHOR trial found that in 146 women with diabetes at high CVD risk with persistently high TG on statins, icosapent ethyl 4 g/day significantly reduced TG (−21.5%, p<0.0001) without increasing LDL-C and lowered other potentially atherogenic parameters including oxidized-LDL and lipoprotein-associated phospholipase A_2 (Lp-PLA_2) [50]. This study is of particular importance because in women as compared to men, diabetes confers a greater relative increase in risk of CVD development [51].

Finally, the more contemporary and landmark outcomes trial of icosapent ethyl, REDUCE-IT (Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial) ($N = 8,179$; 26% women), demonstrated that among patients with elevated TG despite statin use, the risk of ischemic events including CV death was significantly lower among those who received 2 g of icosapent ethyl twice daily as opposed to placebo. Similar treatment effect was observed in both women and men, though the female subgroup did not meet statistical significance with a hazard ratio for the primary end point of 0.82 in women (95% CI 0.66–1.01) and 0.73 (95% CI 0.65-0.82) in men, p for interaction = 0.33 [52].

A number of the recent omega-3 fatty acid trials have failed to show benefit in men or women. The recent Long-Term Outcomes Study to Assess Statin Residual Risk with Epanova in High Cardiovascular Risk Patients with Hypertriglyceridemia (STRENGTH) trial ($N = 13,078$; 35% women) did not show a significant difference in the composite outcome of major CV events in the omega-3 fatty acid arm as compared to a placebo of corn oil in statin-treated adults with high CV risk. In this analysis, pre-specified subgroups demonstrated no heterogeneity based on sex (p value for interaction = 0.54). In contrast to the previously discussed trials which used purified EPA, this study consisted of a combined formulation of EPA and docosahexaenoic acid (DHA) [53]. In addition, the OMega-3 fatty acids in Elderly with Myocardial Infarction (OMEMI) trial (N = 1,027; 29% women) was comprised of older patients with recent MI randomized to n-3 polyunsaturated fatty acids (PUFAs), a combination of EPA and DHA, vs. placebo and did not establish any benefit with respect to primary outcomes of composite CV events; these results were similar in both female and male pre-specified groups (p for interaction = 0.53) [54]. Of note, the dose of EPA in these two trials was much lower than that in REDUCE-IT, and each of these trials assessed the combination of DHA/EPA as opposed to EPA alone.

Sub-Optimal Dyslipidemia Control in Women—Rationale and Challenges

Cholesterol/LDL-C Goals Are Not Achieved

The multi-center EUROASPIRE series by the European Society of Cardiology (ESC) investigated gender-related differences in management and risk factor control of patients with heart disease and determined that less women than men met their target LDL-C (17.3% vs 22.3%, respectively) without a difference in lipid-lowering medication or compliance [55]. One study of over 9,000 patients (51.9% women) with concomitant hypertension and dyslipidemia found that women, particularly obese women, had decreased likelihood of achieving LDL-C goal (OR 1.347, p=0.004) [56]. A similar study assessing demographics of a primary care practice demonstrated that women were less likely to achieve cholesterol goals [odds ratio (OR) 0.82 95% CI 0.70–0.95] despite having more prescriptions for statins (48% vs 39%, p <0.001). Furthermore, women on a high-intensity statin were only half as likely to attain their LDL-C goal as their male counterparts [57]. This study seems to argue that when all else is equal, the cholesterol profile of a woman is less responsive to medical therapy than that of a man. As was previously discussed, there appear to be inherent sex-related biological differences in lipid metabolism that may also play a role. Another plausible explanation is that women have a worse CV risk profile that requires more aggressive therapy to address [55].

Other studies illustrate that lack of achievement of lipid targets in women compared to men may stem from a combination of biological and behavioral factors such as lower statin prescription/utilization, non-adherence, lower awareness of CVD risk, and worse side effect profile. A retrospective analysis of cardiology outpatient electronic health records investigating gender differences in lipid goal attainment in nearly 10,000 patients with coronary artery disease (CAD) identified that only 30.6% of women achieved target LDL-C goal of <70 mg/dL compared to 38.4% of men (p<0.001), and women were less likely to achieve a non-HDL-C goal of <100 mg/dL (37.1% vs 48.2%, p <0.001). However, this discrepancy can be explained by the fact that women were undertreated in this study. Far less women were on statin therapy (16.9% vs 11.6%, p <0.001) or any lipid-lowering therapy (12.8% vs 7.8%, p <0.001), and women were also less likely to be on high-potency statin (14.9% vs 18.0%, p <0.001) [58].

It is apparent that women have worse control of dyslipidemia than their male counterparts; however, whether the etiology of this disparity is biologic, behavioral, or a combination of the two is unclear. Further insight into why the treatment of dyslipidemia is less aggressive in women will be detailed extensively herein.

Lower Statin Prescription/Utilization

It has been demonstrated numerous times that women use statins less frequently than their male counterparts. A world-wide systematic review and meta-analysis of 43 studies including more than 2 million patients in a primary care setting at high risk or with established CAD found that the prevalence of statin prescription was lower in women than men (60% vs 63%) with pooled women-to-men prevalence ratio 0.90 (95% CI 0.85–0.95) [59]. Similar trends within community practice are observed on a national level as evidenced by a contemporary study of nearly 6,000 statin-eligible patients in which females were prescribed statins less frequently than males (67.0% vs. 78.4%, respectively, p<0.001) and less frequently received statins at the guideline-based intensity (36.7% vs. 45.2%, p<0.001). Furthermore, a higher proportion of females reported having previously never been offered statin therapy (18.6% vs. 13.5%, p<0.001) [60]. While there is conflicting data regarding gender differences in statin use for primary prevention, what remains clear is that women receive less aggressive treatment for dyslipidemia in the setting of secondary prevention.

Large-scale observations from the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines) National Quality Improvement Initiative of roughly 40,000 patients with non-ST-segment elevation ACS identified that women were less likely to receive statin therapy upon discharge (55.9% women vs 63.4% male; adjusted OR 0.92) [61]. A retrospective cohort study of over 88,000 US adults discharged from the hospital post MI came to similar conclusions several years later regarding the sex disparities that exist in secondary prevention. Less women filled a prescription for a high-intensity statin than men (47% of women vs 56% of men) with an adjusted risk ratio of 0.91 (95% CI 0.90–0.92) in the total population. Women were less likely to fill their prescription within all subgroups analyzed particularly among extremes of age [62]. Furthermore, younger women have demonstrated that they are significantly less likely to remain on statin therapy one year after hospital discharge from AMI, a disparity which appears to be mostly driven by treatment initiation [63]. This is particularly concerning, as younger women stand to gain the most potential benefit of statin therapy, and older women are among the highest risk warranting more aggressive treatment.

Non-adherence to Lipid-Lowering Therapy

While consistent adherence to statins across all patients is low (36.4–44%) [64], numerous studies (63-64) have demonstrated that adherence is markedly lower among women. A comprehensive meta-analysis of 53 studies illustrating this point identified that compared to men, women had a 10% greater odds ratio of non-adherence to statin therapy [65]. As current lipid guidelines focus on treating above certain thresholds with expected reductions in LDL-C levels, but without a focus on a specific LDL-C goal, this may translate into less patient understanding of the residual burden of risk and the need for escalation of therapy [64]. The reason behind lower rates of adherence to statin therapy among women is likely multifactorial. Polypharmacy plays a role as we know that women on average take more medications than men which increases pill and cost burden [64, 66, 67]. Psychosocial factors are also important. Women have been shown to have higher rates of depression and anxiety and the risk for medication nonadherence in patients suffering from anxiety and depression has been shown to be up to 4.4 times higher compared to patients without symptoms [68]. Furthermore, women are more likely than men to be caregivers which have competing demands on their personal health. A standardized cross-sectional survey of 2,300 women in the USA about awareness of CV risk showed that at least half of women (51%) felt that caretaking responsibilities were a barrier to CVD prevention [69].

Lower Awareness, Underestimation of CVD Risk in Women

Another main reason that women are under-prescribed statins is that many clinicians underestimate the CVD risk of women. CVD has long been described as a "man's disease." The incidence of CVD in middle-aged women is about one-third of that of men, and CVD occurs earlier in men by one decade. This has led to the common misconception that women are at lower risk and do not need to be treated as aggressively [59]. Numerous studies have demonstrated that clinicians perceive women to be at lower risk. An interesting and shocking "attitude study" by Abuful et al. discovered that when considering a hypothetical case of a 58-year-old male vs postmenopausal female with identical clinical, lab and angiographic evidence of CAD, a majority of physicians considered the male patient to be at higher risk and prescribed lipid-lowering therapy more often for the male patient (67% vs 54%, p <0.07) [70]. Insights from the PROMISE (Prospective Multicenter Imaging Study for Evaluation of Chest Pain) trial revealed that women had a higher prevalence of traditional risk factors but were characterized as lower risk by a majority of providers [71]. According to the USAGE (Understanding Statin Use in America and Gaps in Education) survey, women reported that they were less likely to be educated about their risk of CVD [72]. As CVD risk is often under-estimated in women, it is no surprise that the risk of younger women is even further misjudged by providers. This is evident from the VIRGO study (Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients) study. Among a high-risk population of young women (ages 18–55) with acute MI, women were less likely than men to be told that they were at risk of heart disease (relative risk: 0.89; 95% CI 0.84 to 0.96) or to have a provider discuss risk modification (relative risk: 0.84; 95% CI 0.79 to 0.89) before their index acute MI event [73].

Unfortunately, the lack of awareness of CVD risk in women among physicians translates into a lack of self-awareness among female patients and lower health consciousness. Awareness of CVD as a leading cause of death among women has nearly doubled since 1997 but has more recently plateaued and remains suboptimal [74]. However, despite nationwide efforts and the ongoing Go Red for Women American Heart Association (AHA) campaign, more recent data demonstrates that patient self-awareness is now actually declining from 2009 to 2019, especially among Hispanic and non-Hispanic black women [75]. A contemporary study of sex differences in statin use within community practice by Nanna et al. demonstrated that females were more likely to decline statin therapy (3.6% vs. 2.0%, p<0.001), or discontinue statin therapy (10.9% vs. 6.1%, p<0.001). Females were also less likely to believe that statins were safe (47.9% vs. 55.2%, p<0.001) or effective (68.0% vs. 73.2%, p<0.001) [60].

Limited Treatment Options in Pregnancy

Management of dyslipidemia in pregnancy is particularly challenging. Statins have been traditionally contraindicated in pregnancy due to the theoretical concern about the role of cholesterol in the developing embryo and teratogenesis. Lipid levels increase during pregnancy which can further complicate management in an already vulnerable patient population. Statins are considered by the Food and Drug Administration (FDA) to be a category X drug as several animal studies have shown central nervous system and limb abnormalities with the use of high doses [76]. However, more recently, statin use in pregnancy is being revisited by the FDA and may change. The 2018 American College of Cardiology (ACC)/AHA Guideline on Management of Blood Cholesterol recommends that women who are considering pregnancy or who become pregnant should discontinue statin therapy [77]. However, a prior systematic review from 2016 found no clear relationship between congenital anomalies and statin use in pregnancy [78]. As women delay pregnancy which has been evidenced by an international trend

of advancing maternal age [79, 80], the prevalence of CAD and the subsequent need for statins also increase. Therefore, exploring the safety of statins in pregnancy becomes more prescient and needs to be further elucidated. In addition, there is inadequate data on the use of non-statin therapies including ezetimibe, PCSK9 inhibitors, bempedoic acid, fenofibrate, and icosapent ethyl. The only lipid-lowering therapy currently approved in pregnant women are bile acid sequestrants because they do not pass into systemic circulation and therefore do not pose a risk of congenital malformations [76]. In cases of extreme lipoprotein abnormalities during pregnancy, LDL apheresis can be used safely as well as gemfibrozil and omega-3 fatty acids for severely elevated triglycerides.

Side Effects of Lipid-Lowering Therapy

Women are disproportionally affected when it comes to adverse drug reactions (ADRs) from lipid-lowering medications. There are numerous sex-related physiologic, pharmacokinetic, and pharmacodynamic differences of CV pharmacologic agents, specifically lipid-lowering therapies that contribute to the different side effect profiles observed in women versus men. Numerous physiologic factors affect drug distribution among women. The most obvious of which is that women have a smaller volume of distribution owing to their lower body mass index (BMI) and smaller organ size. Women have a higher proportion of body fat which influences the distribution of lipophilic drugs including numerous statins. In addition, women on average have lower glomerular filtration rate. Hormonal factors also play a prominent role as menstrual cycle, pregnancy, and menopause result in variable sex steroid concentrations and alterations in total body water content which in turn affects renal blood flow and creatinine clearance. Intuitively, one would expect that CV pharmacologic agents should have recommended dose adjustments for women. Given the paucity of sex-specific analyses, that determination has not been made. In what little sex-specific CV pharmacologic literature exists, there does not appear to be a large discrepancy in sex-related statin pharmacokinetics, granted most of the literature that does exist has been obtained via retrospective, subgroup, post-hoc or meta-analyses [81].

Given the frequently higher plasma concentration of statins, women experience more side effects than men and are nearly twice as likely to discontinue statin therapy due to adverse effects [60]. Myopathy is perhaps the most well-known adverse effect of statins and occurs at a higher rate in women. One prospective Swedish study of 192 outpatients receiving statin therapy observed that the risk of myopathy was 50% higher in women than men [82]. Lower BMI, metabolism, plasma volume, and reduced muscle mass make women more susceptible to muscular ADRs. Female sex and advanced age are well known risk factors for statin ADRs [83]. In a cohort that stands to gain the most benefit from statin therapy, elderly females have been identified as being at higher risk by the ACC/AHA/NHLBI Clinical Advisory statement or guideline [84]. Cerivastatin, which has since been pulled from the market, was associated with unacceptably high rates of myopathy and rhabdomyolysis, especially in thin, elderly females. A subgroup analysis of women over 65 years assigned to either 0.8 mg or 0.4 mg of the drug demonstrated that myopathy incidence was 5.6% and 7.4%, respectively, well exceeding the average rate of myopathy in the overall study population which was consistently less than 2% [85, 86].

Statin therapy in women has also been shown to be associated with higher rates of diabetes. This is best exemplified in the JUPITER trial, where sex stratification revealed that the risk of developing diabetes in women was 49% as opposed to 14% in men. The authors concluded, however, that the benefit of statins in reducing CVD outweighed the risk of diabetes [27]. An investigation of postmenopausal women in the Women's Health Initiative (WHI) including over 150,000 women revealed similar disconcerting findings that statin use was associated with a nearly 50% increased risk of diabetes mellitus even after adjusting for other potential confounders (multivariate adjusted HR 1.48; 95% CI 1.38–1.59) [87].

The body of literature regarding sex-specific adverse effects of other lipid-lowering therapies is not nearly as robust as statin literature. RCTs assessing clinical effects of PCSK9 inhibitors have shown a favorable safety profile with a low rate of adverse events (AEs) overall; however, as with statins, the data is limited in women, especially regarding AEs. In a clinical setting, PCSK9 inhibitors are also well tolerated; the most common AEs include influenza-like illness, nasopharyngitis, myalgia, and injection site reactions. There appear to be no clinically relevant differences between genders [88].

Bempedoic acid, the newest lipid-lowering therapy to emerge on the market, also appears to be well tolerated, with no clear gender differences regarding AEs. Of particular interest is that this medication has been demonstrated to be a viable treatment option for patients with a history of statin intolerances, which disproportionately affects women. According to the phase 3, double-blind, placebo-controlled CLEAR (Cholesterol Lowering via Bempedoic acid, an ACL-inhibiting Regimen) Serenity study, patients with a history of intolerance to at least 2 statins who were randomized to bempedoic acid had a lower rate of myalgia than patients taking placebo (4.7% vs 7.2%). The study is notable for the large proportion of women (56%), which may be a function of the higher rate of statin intolerances observed in

women. Not only was LDL-C significantly reduced in the bempedoic acid arm, but so was hs-CRP (−24.3%; $p<0.001$ for all comparisons) [89]. Given the fact that women are more susceptible to statin-induced myalgias, and women have higher levels of inflammatory markers including hs-CRP, bempedoic acid emerges as a viable and very effective option for lipid-lowering therapy in women. In fact, a recent pooled analysis of 4 pivotal bempedoic acid RCTs signaled a greater reduction of LDL-C in women as opposed to men (placebo-corrected difference 21.2% women vs 17.4% men). At the very least, the efficacy among women and men of bempedoic acid merits further exploration [90].

Statins and Cancer Risk in Women

The relationship of statin and cancer is quite complex but warrants brief mention. The early CARE (Cholesterol and Recurrent Events) trial showed an alarming increased incidence of breast cancer in statin users [40]. Subsequently in other statin trials, however, this association has not been proven. An analysis of statin use and breast cancer in WHI showed no relationship between statin use and breast cancer [91, 92], and more recent literature has suggested that statins could actually have a possible protective effect among patients with cancer. More and more evidence has emerged that statin's pharmacologic effect extends beyond cholesterol reduction and that statins exhibit numerous protective properties that are involved in the pathogenesis of cancer including anti-inflammatory, anti-proliferative, anti-invasion, pro-apoptosis, and immunomodulation properties. A recent meta-analysis of 60 observational studies which included close to one million participants demonstrated that statin use could exhibit potential survival benefit in the prognosis of cancer patients [93]. This finding was confirmed by another meta-analysis from 2020 of 17 cohort studies that demonstrated statin use was significantly associated with a lower risk of breast cancer recurrence (adjusted HR 0.72, $p<0.001$) and breast cancer mortality (HR 0.80, $p<0.001$) [93]. While the association between statin use and cancer is unclear, further investigation is needed into this subject.

Other Factors Affecting Lipid Management

Stronger Potency of Traditional Risk Factors in Women

As CVD remains the leading cause of death in women, early recognition of risk factors is especially important in women. While it is not the focus of this review, it is important to recognize that "traditional risk factors" affect women differently. Numerous studies have demonstrated that diabetes confers a higher risk of CVD and vascular mortality in women as opposed to men [51, 94–97]. A more recent 2018 meta-analysis including nearly one million adults demonstrated that independent of other major risk factors, diabetes roughly doubled the occlusive vascular mortality risk in men but tripled the risk in women. Death rates due to diabetes were much higher in younger women ages 35–59 years and associated with 5- to 6-fold increased risk of occlusive vascular mortality [98]. A French study found that among very high-risk diabetic patients treated with statin, women were at higher risk of not achieving LDL-C target (OR 2.27; 95% CI 1.62–3.17) [99]. Furthermore, a more recent systematic review and meta-analysis of diabetes CV outcomes trials found that diabetic women receive suboptimal management of risk factors and they use statins less often (RR 0.90; 95% CI 0.86–0.93) among other preventative medications and have higher LDL-C (mean difference 0.34 mmol/L; 95% CI 0.29, 0.39) [100].

Women also have a different lipid profile than men as previously discussed, and targeting traditional goals for LDL-C may be missing the mark. Numerous studies have demonstrated that hypertriglyceridemia and low HDL-C are independent predictors of CV death in women [101, 102]. Additionally, the ratio of TG to HDL-C is a powerful predictor of all-cause mortality in women with suspected ischemia as demonstrated by a report from the Women's Ischemia Syndrome Evaluation (WISE) [103].

A few other traditional risk factors that have a higher potency in women that bear mentioning include smoking and obesity. Smoking is less prevalent in women; however, the rate of smoking cessation in women is less than half of that in men [104]. A meta-analysis of 2.4 million individuals identified that female smokers had a 25% greater risk of CVD than men [105]. In addition, smoking disproportionately increases the risk of obstructive CAD in women (RR 0.75 in smokers vs 0.50 in non-smokers) [106]. Obesity also confers a greater relative risk of CVD in women (64% in women vs 46% in men) as demonstrated by the Framingham Heart Study [107]. This is of particular importance as not only are obese women at higher risk of CVD, but they are also less likely to achieve LDL-C goals [56].

Risk Factors Unique to Women

Fortunately, the gender gap in risk stratification has gained more recent attention and shed light on numerous novel risk factors that are unique to women. Pregnancy-related disorders have been recognized as important risk factors in the development of CVD. This category encompasses a wide range of adverse pregnancy outcomes that include hypertensive disorders of pregnancy (HDP), small-for-gestational-age birth, preterm birth, and gestational diabetes mellitus. Women with a history of HDP have been shown to have numerous biochemical derangements postpartum including

higher glucose, insulin, triglycerides, total cholesterol, LDL-C, and lower HDL-C [108]. A more recent prospective cohort analysis of over one million women demonstrated that gestational diabetes was associated with an increased risk of heart disease 25 years after delivery, ischemic heart disease (HR 1.23; 95% CI 1.12–1.36), myocardial infarction (HR 2.14; 95% CI 1.15–2.47), coronary angioplasty (HR 2.23; 95% CI 1.87–2.65), and coronary artery bypass graft (HR 3.16; 95% CI 2.24–4.47) [109]. Spontaneous preterm delivery has been associated with a nearly three-fold increased risk of maternal CVD death later in life [110]. Endothelial dysfunction has emerged as a common underlying mechanism observed in numerous women with a history of adverse pregnancy outcomes and can explain at least in part a woman's predisposition to developing heart disease [111, 112]. It is important to understand that a woman's cardiovascular response to pregnancy is an early marker of future maternal CVD risk, and that an abnormal response may serve as a woman's first physiologic stress test [110].

Disruption or irregularity of ovulatory cycling including early menopause and polycystic ovarian syndrome (PCOS) has also been linked to increased risk of CV events. Numerous studies have demonstrated that early menopause is associated with an increased risk of coronary atherosclerosis and adverse CV events [113–116]. PCOS encompasses a clustering of cardiometabolic abnormalities and is also associated with an increased risk of CVD [117, 118].

Lastly, women are disproportionately affected by inflammatory-mediated autoimmune diseases which have been associated with higher risk of developing CVD such as rheumatoid arthritis and psoriasis. As more evidence emerges that atherosclerosis is a disease of chronic inflammation [119], it is of particular concern that women have higher levels of inflammatory markers including hs-CRP. Furthermore, the risk of future ischemic heart disease events increases proportionally with increasing levels of hs-CRP [120]. Hs-CRP independently predicts future vascular events regardless of LDL-C level as was demonstrated by Ridker et al. as rosuvastatin significantly reduced the incidence of major CV events in apparently healthy individuals without hyperlipidemia but with elevated hs-CRP levels in the JUPITER trial [121].

Shortcomings of Conventional Risk Calculators

Given the unique risk profile of women, it should come as no surprise that conventional risk assessment models perform poorly in female patients. Risk assessment tools were traditionally developed and validated in an older, predominantly white male population. Therefore, they often times both under- and over-estimate risk in women [122] (Table 2).

Traditional "coronary risk factors" were first coined by a group of investigators in Framingham, Massachusetts, in the 1950–1960s that include age, hypertension, smoking, diabetes, and hyperlipidemia. They have come to form the foundation of numerous risk assessment tools; however, a significant proportion of coronary events in women (~20%) occurs in the absence of these risk factors [123]. Notably, the Framingham Risk Score (FRS) does not include family history, pregnancy-related conditions, and numerous other emerging risk factors as outlined above so that it may severely underestimate risk in women [124]. The FRS frequently classifies women as low risk, even in the presence of significant subclinical atherosclerosis as was demonstrated by Michos et al. in their analysis of non-diabetic asymptomatic women where the majority of women (84%) with significant coronary artery calcium ≥ 75th percentile were classified as low risk by FRS [125]. The National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (NCEP/ATP III) adopted a modified version of the FRS that includes age, total and HDL-C, smoking status, and systolic blood pressure. However, this modification appears equally fraught among women. According to data from the Third National Health and Nutrition Examination Survey (NHANES III), >95% of US women less than 70 years of age are classified as "low risk" [126].

The Reynold's Risk Score (RRS) is a newer sex-specific model derived from and validated in a large cohort of women. In 2007, Ridker et al. assessed 35 novel and traditional risk factors among roughly 25,000 healthy US women, age 40 and older and followed them for an average of 10.2 years to evaluate for CV events. The new algorithms reclassified 40–50% of women predicted to be intermediate risk by current ATP-III prediction scores into higher or lower risk categories which greatly improved accuracy. This effect was present not only for the best-fitting model, but also for the simplified model which is now known as the RRS and is limited to age, systolic blood pressure, HbA1c, smoking status, total and HDL-C, hsCRP, and parenteral history of MI before age 60 years [123]. The RRS has been shown to be better calibrated than Framingham-based models in a large external validation cohort of the multi-ethnic Women's Health Initiative Observational Cohort which over-estimated risk for CHD and major CVD. RRS also showed improved discrimination overall and in black and white women [127].

The most recent ACC/AHA guidelines recommend the use of the 2013 Pooled Cohort Equation (PCE) which includes age, gender, total and HDL-cholesterol, systolic blood pressure, blood pressure treatment, smoking status, and diabetes mellitus. There does not appear to be a consensus on how this calculator discriminates risk in women. Numerous studies including the Rotterdam Study [128] and MESA (Multiethnic Study of Atherosclerosis) Study [129] among others [130, 131] have demonstrated that PCE overestimates risk across the general population.

The MESA study evaluated the PCE among a more ethnically diverse population and determined that it overestimated risk among men, women, and all racial/ethnic groups. Of note, however, the degree of over-estimation was lowest in white women [129]. On the contrary, other studies have shown good calibration and discrimination of the PCE. Among adults from the REGARDS study (Reasons and Geographic and Racial Differences in Stroke) for whom statin initiation was considered based on PCE, observed and predicted 5-year ASCVD risk were similar. Furthermore, PCE was well calibrated and demonstrated good discrimination not just in men, whites and blacks, but also in women [132]. More specifically, Mora et al. later evaluated the predictive accuracy of the 2013 PCE in the Women's Health Initiative (WHI) which included 16,180 multi-ethnic female participants. While the PCE models appeared to over-estimate risk among self-reported data, the risks were better aligned and discriminated well after including the Centers for Medicare and Medicaid Services (CMS) claims data at which point the PCE models discriminated well [133].

A 2018 meta-analysis applied four different risk prediction algorithms including the aforementioned FRS, PCE, RRS, and the European model Systematic COronary Risk Evaluation (SCORE) algorithm to data from 86 prospective studies which included over 350,000 participants without CVD at baseline. Gender differences included over-prediction of risk in younger women but under-prediction in older women using FRS. RRS underestimated risk somewhat in men, but on average was well calibrated in women. After adjustment for risk factors and CVD incidence, the performance was nearly equalized across all models [134].

Despite the importance of novel risk factors such as adverse pregnancy outcomes, their incorporation has not yet demonstrated improvements in current risk prediction models. An analysis by Stuart et al. of over 67,000 women free of prior CVD, and roughly 100,000 observations over the course of 10 years, found that additional inclusion of HDP and parity to an established risk score failed to improve discrimination or reclassification in this low-risk population [135]. A similar European study found that while a history of HDP or delivery of low birth weight offspring could identify women with increased risk of CVD mid-life, when considered with conventional risk factors, they did not significantly improve 10-year CVD risk prediction in women at least 50 years of age [136]. The HUNT study including over 18,000 Norwegian women came to similar conclusions as well: pre-eclampsia independently predicted CVD after controlling for established-risk factors (HR 1.60, 95% CI 1.16–2.17); however, the addition of pregnancy complications (pre-eclampsia, gestational hypertension, preterm delivery, or small for gestational age) to a conventional risk prediction model made only small improvements to CVD prediction [137]. While these conclusions are disappointing, they highlight the complexity of risk stratification in women. It is possible that because adverse pregnancy outcomes are associated with traditional risk factors that are already included in standard risk assessment models, there is not much additive benefit [138]. However, identification and incorporation of pregnancy-related risk factors may have greater value in predicting longer term or lifetime CVD risk in younger women, before traditional risk factors such as dyslipidemia have developed.

Coronary artery calcium (CAC) scoring has gained traction as a diagnostic modality that augments traditional risk stratification and has made its way into most primary prevention guidelines to help inform the decision to initiate statin therapy. One could argue that CAC scoring is particularly impactful in women, as this cohort will rarely reach an intermediate or high risk categorization as designated by FRS even if they have 1 major CHD risk factor throughout middle age [139]. An illuminating study by Lakoski et al. illustrated that roughly 30% of MESA (Multi-Ethnic Study of Atherosclerosis) women, classified as "low risk" by FRS, had prevalent CAC (score >0) and a small but not insignificant minority (5%) had advanced CAC (score ≥ 300). Women with CAC were at increased risk of CHD (HR 6.5; 95% CI 2.6–16.4) and CVD events (HR 5.2; 95% CI 2.5–10.8)[139]. Unfortunately, the ACC/AHA PCE appears to show a similar discordance with atherosclerotic plaque burden as does the FRS. A 2016 meta-analysis found that among nearly 7,000 "low risk" women per PCE (10-year ASCVD score <7.5%) from 5 large population-based cohorts, CAC was present in approximately one-third (36.1%) and associated with an increased risk of atherosclerotic CVD. Furthermore, addition of CAC to traditional risk factors led to modest improvement in prognostic accuracy [140].

Guidelines Comparing Management of Dyslipidemia in Women

The use of the aforementioned risk assessment algorithms provides the framework for primary and secondary prevention of CVD including the management of dyslipidemia among most international guidelines. The fact that these tools fail to discriminate between genders is becoming more readily recognized by international cardiology societies. Small modifications have been made to reflect this change but overall, guidelines across many countries still lack specific recommendations for women (Table 3).

The preferred risk assessment tool for the ACC/AHA remains the PCE since 2013. The ACC released new

Table 2 Overview of conventional cardiovascular disease risk calculators

Risk assessment model	Variables included	Performance in women
Framingham risk score (1998) [124]	• Age • Gender • Total cholesterol • LDL-C • HDL-C • Systolic BP • Diabetes Mellitus • Smoking status	Underestimates risk: 84% of non-diabetic asymptomatic women with CAC score >75th percentile were classified as low risk [125]
NCEP/ATP III (2002) [126]	• Age • Gender • Total cholesterol • HDL-C • Smoking status • Systolic BP • BP Treatment	Underestimates risk: >95% of women <70 y/o classified as "low risk" [126]
Reynold's Risk Score for Women (2007) [123]	• Age • Total cholesterol • HDL-C • Systolic BP • HbA1c • Smoking status • Parental history of MI < 60 years • Serum hs-CRP	Better calibrated than Framingham-based models in large external validation cohort of WHI Observational Cohort [127]
ACC/AHA Pooled Cohort Equation (2013)	• Age (validated only in patients 40 to 79 years of age) • Gender • Total Cholesterol • HDL-C • Systolic BP • BP treatment • Diabetes mellitus • Smoking status	Unclear performance but appears to discriminate well in WHI • The observed (predicted) risks for baseline 10-year risk categories < 5%, 5% to less than 7.5%, 7.5% to less than 10%, and >10% after including CMS claims data: 3.8 (4.3), 7.1 (6.4), 8.3 (8.7), and 18.9 (18.7) • Overall, the equations discriminated risk well (C statistic, 0.726; 95% CI, 0.714–0.738) [133]

Abbreviations

LDL-C low-density lipoprotein cholesterol, *HDL-C* high-density lipoprotein cholesterol, *BP* blood pressure, *CAC* coronary artery calcium, *NCEP* National Cholesterol Education Program, *ATP* Adult Treatment Panel, *y/o* years old, *HbA1c* hemoglobin A1c, *MI* myocardial infarction, *hs-CRP* high sensitivity C-reactive protein, NCET/ATP II: *WHI* Women's Health Initiative, *ACC* American College of Cardiology, *AHA* American Heart Association, *CMS* Centers for Medicare and Medicaid Services

primary prevention guidelines in 2019 which acknowledged several novel risk factors, called ASCVD "Risk Enhancers." These encompass "conditions specific to women" (e.g., pre-eclampsia, premature menopause), as well as inflammatory disease (especially psoriasis and rheumatoid arthritis) or hs-CRP ≥2.0 mg/L which is more prevalent in women. These "risk enhancers" should be considered in intermediate risk (≥7.5% to <20% 10-year ASCVD risk) or certain borderline-risk (5% to <7.5%) adults, and if present, favor the initiation or intensification of statin therapy. Furthermore, if the decision is still uncertain in the intermediate risk cohort, then the guidelines recommend measuring CAC in selected adults with a score ≥1 favoring statin therapy [141].

The ESC is on par with their American colleagues in recognizing and acknowledging certain female-specific risk enhancers. SCORE or QRISK are the 10-year risk assessment tools of choice in the UK. ESC guidelines emphasize the greater risk of developing sustained hypertension and/or diabetes mellitus in women with a history of obstetric complications. It also acknowledges certain "non-traditional risk factors" to consider including CAC; however, these recommendations are not as explicit as those of the ACC/AHA. It is also important to note that European guidelines emphasize the risk of inflammatory joint disease. The European League Against Rheumatism recommends multiplying the CVD risk score as obtained via standard risk prediction models by one and half to obtain a higher and more accurate risk prediction [142, 143]. Of note, within Europe, the British National Institute for Health and Care Excellence CVD risk assessment and reduction guidelines do not make mention of women at all [124].

Canadian Cardiovascular Society Guidelines (CCS) are similar to European and American regarding risk assessment calculation using a modified FRS.

Table 3 Comparison of international cardiology society guidelines specific to women

International cardiology society	Risk Assessment model	Guidelines specific to women
American College of Cardiology/American Heart Association (ACC/AHA 2018) [141]	Pooled Cohort Equation	• Consideration of specific "Risk Enhancers" such as premature menopause (age <40 years) and history of pregnancy-associated disorders (hypertension, preeclampsia, gestational DM, SGA, preterm deliveries) and inflammatory diseases (RA, psoriasis) that are more prevalent in women when discussing lifestyle intervention and potential benefit of statin • Sexually active women of child-bearing age on statin therapy should be counseled on reliable form of contraception • Statins contraindicated in pregnancy—Stop statin 1–2 mo. before pregnancy attempted (FDA currently reviewing Category X designation)
European Society of Cardiology (ESC 2019) [143]	SCORE or QRISK	• Statins recommended for 1° and 2° prevention in women with the same indications as men • No lipid-lowering drugs when pregnancy is planned, during pregnancy or breastfeeding. Consider bile acid sequestrants ± LDL apheresis for severe FH patients
Canadian Cardiovascular Society (CCS 2021) [144]	Modified FRS or Cardiovascular Life Expectancy Model (CLEM) to calculate CV age	• Screen for dyslipidemia in women regardless of age if postmenopausal or in women with a history of pregnancy-related disorders and inflammatory diseases (RA, psoriasis, etc.) • Recognition that pregnancy-related complications (pre-eclampsia, hypertensive disorders, gestational DM, placental abruption, preterm delivery, SGA) are associated with higher lifetime risk of developing overt CVD • Favor using CV age over 10-year risk calculators in this cohort • Advise against the use of statins in pregnancy, however, if necessary then hydrophilic statins are favored

Abbreviations

DM diabetes mellitus, *SGA* small for gestational age, *RA* rheumatoid arthritis, *mo* month, *1°* primary, *2°* secondary, *LDL* low-density lipoprotein, *FH* familial hypercholesterolemia, *FRS* Framingham Risk Score, *SCORE* Systematic Coronary Risk Evaluation, *CV* cardiovascular, *CVD* cardiovascular disease

Alternatively, CCS recommends using Cardiovascular Life Expectancy Model (CLEM) to calculate CV age. More recent guidelines for the management of dyslipidemia were released in March of 2021 that have several updates relevant to women. Regardless of age, screening for dyslipidemia is extended to postmenopausal women, women with inflammatory diseases (e.g., rheumatoid arthritis, Lupus etc.), and women with pregnancy-related disorders. These guidelines focus more specifically on pregnancy-related complications such as pre-eclampsia, hypertensive disorders, gestational diabetes, placental abruption, preterm delivery, stillbirth, and delivery of low birth weight infants and recognize that they are associated with higher lifetime risk of developing CV risk factors (e.g., dyslipidemia and hypertension) and overt ASCVD. As most women have a relatively minimal short-term risk of ASCVD immediately postpartum, CCS recommends favoring CV age over 10-year risk calculators in this cohort to assist with decisions about lipid-lowering pharmacotherapy. Individual discussions regarding treatment that carefully weigh risks versus benefits are important in guiding management as there is still insufficient evidence to guide decisions about the use of lipid-lowering therapy in women based on pregnancy factors alone. Effective birth control methods are recommended in women of reproductive age who are taking statins for primary prevention and women should interrupt therapy at the time of pregnancy. If statin therapy is to be continued, CCS suggests the use of hydrophilic compounds due to more difficult passage through the placenta. Similar to ACC/AHA guidelines, CAC screening can be considered for asymptomatic adults at least 40 years of age at intermediate risk (FRS 10–20%)

Table 4 Summary points from the review: challenges in lipid management in women.

1. There are physiologic differences in lipid metabolism in women and men, mediated mostly by hormonal influences, with changes in lipoprotein profiles throughout the lifespan of a woman.
2. Women are under-represented in clinical CV trials which may stem from multiple reasons including disproportionate inclusion/exclusion criteria, less awareness of CV risk, and implicit bias.
3. Existing data suggests that statins and other lipid-lowering medications are equally effective in women and men for both primary and secondary prevention.
4. Under-utilization of statins in women is due to a variety of factors, including lower statin prescription, higher rates of non-adherence, CV risk underestimation, limited treatment options in pregnancy, and worse side effect profile.
5. Traditional risk factors such as diabetes, smoking, and obesity have been demonstrated to confer a higher relative risk of CV disease in women.
6. Unique CV risk factors in women are under-recognized such as adverse pregnancy outcomes (hypertensive disorders, small for gestational age, gestational diabetes, preterm delivery); disruption or irregularity of ovulatory cycling (e.g., early menopause, PCOS); and women are disproportionately affected by inflammatory-mediated autoimmune diseases that are associated with higher risk of developing CV disease.
7. Conventional CV risk calculators are derived from male-dominated cohorts, and mostly do not consider the aforementioned unique risk factors and therefore perform poorly in women.
8. International guidelines regarding dyslipidemia management are largely deficient in female-specific recommendations.

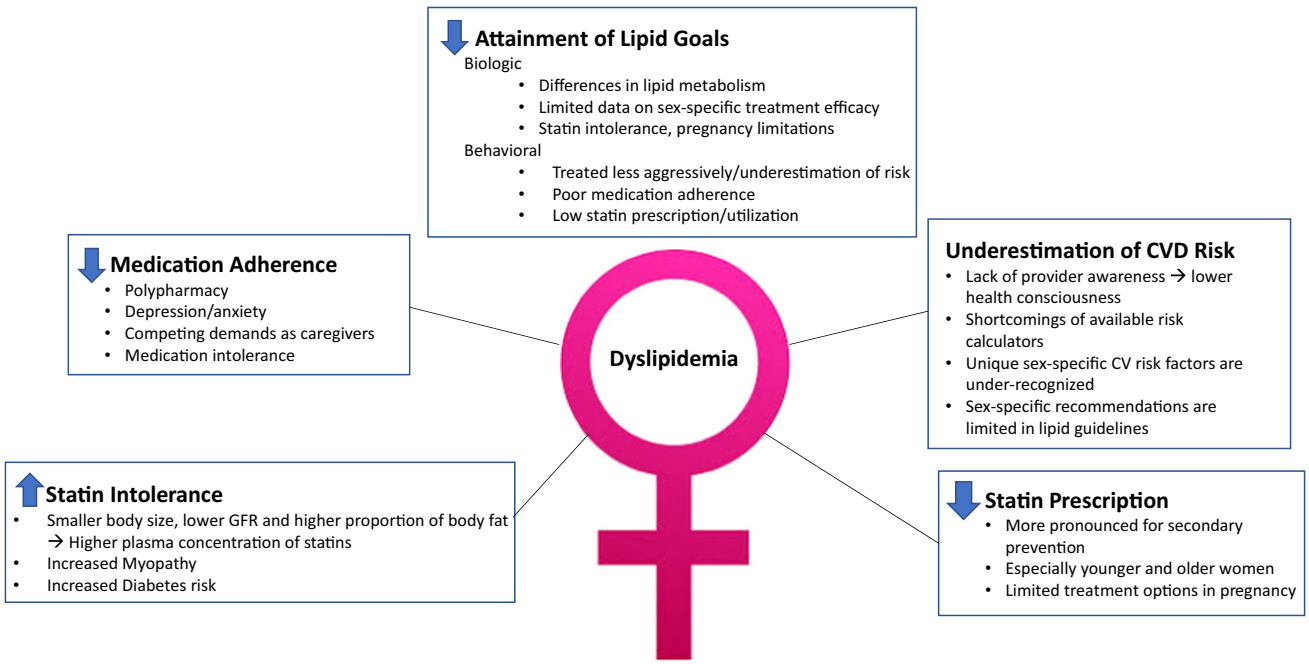

Figure 1 Barriers to optimal dyslipidemia management in women

when treatment decisions with lipid-lowering therapy are uncertain [144].

Conclusion

While the practical management of dyslipidemia in women does not differ significantly from men, it is important to consider the nuances and unique sex-specific challenges that we have reviewed (Table 4, Figures 1 and 2). There is a paucity of data regarding lipid management specific to women. This stems mostly from the fact that women are largely under-represented in clinical trials of lipid-lowering therapy, the most important of which is statin therapy. Assuming that women should be treated in a similar fashion as men ignores the fact that lipid control is influenced by differences in biology and behavior between sexes. Unfortunately, this has translated into worse control of dyslipidemia in women. It is therefore imperative for clinicians to address medication adherence and statin intolerance which will help to eliminate differences in attainment of lipid goals in women. Furthermore, clinicians should be aware of their own biases and failure

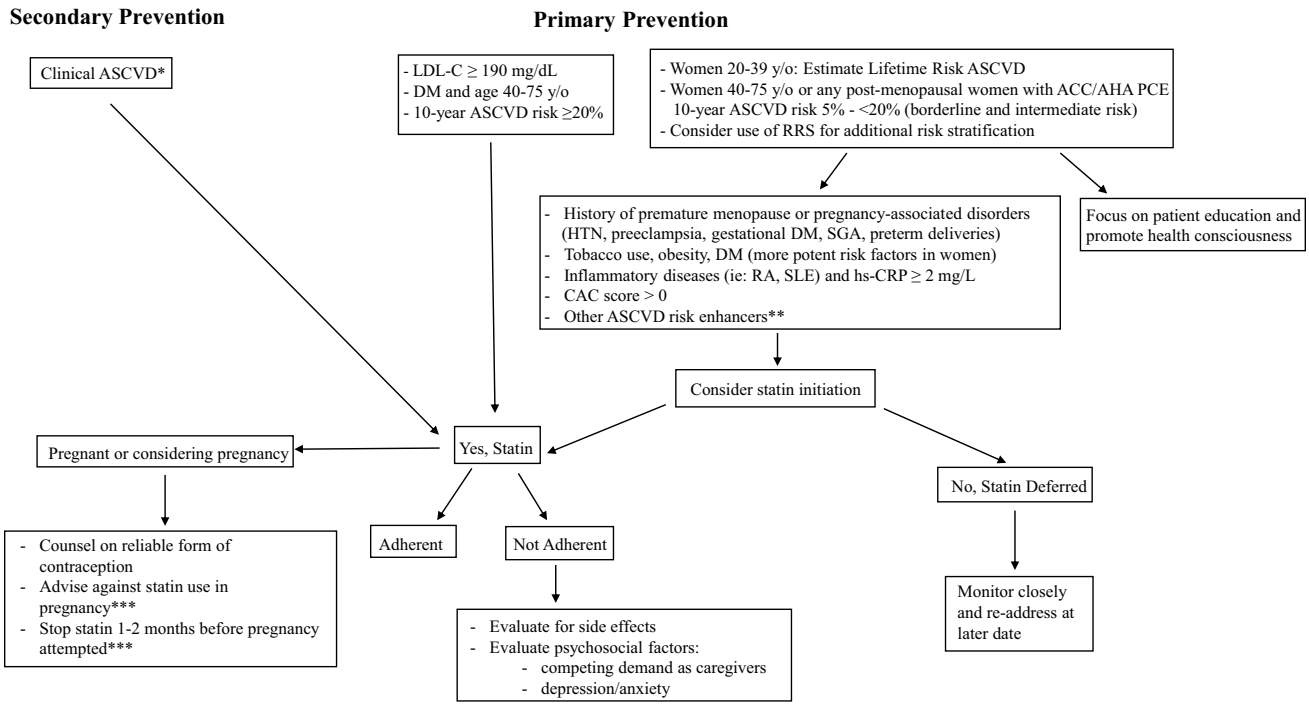

Figure 2 Proposed Algorithm on Management of Blood Cholesterol in Women to Supplement 2018 ACC/AHA Guideline. *ACS, history of MI, stable or unstable angina or coronary or other arterial revascularization, stroke, TIA or PAD including aortic aneurysm, all of atherosclerotic origin. **ASCVD Risk Enhancers: family history of premature ASCVD, persistently elevated LDL-C ≥160 mg/dL, Chronic kidney disease, metabolic syndrome, ethnicity (e.g. South Asian ancestry), persistently elevated triglycerides ≥175 mg/dL, Lipoprotein (a) >50 mg/dL, ankle-brachial index (ABI) <0.9. ***This recommendation is currently being revisited by the FDA. ACS indicates acute coronary syndrome; MI, myocardial infarction; TIA, transient ischemic attack; PAD, peripheral arterial disease; ASCVD, Atherosclerotic Cardiovascular Disease; LDL-C, low density lipoprotein cholesterol; DM, diabetes mellitus; y/o, years old; ACC/AHA PCE, American College of Cardiology/American Heart Association Pooled Cohort Equation; RRS, Reynold's Risk Score; HTN, hypertension; SGA, small for gestational age; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; hs-CRP, high-sensitivity C reactive protein; CAC, coronary artery calcium

to recognize their female patients' true risk of atherosclerotic CVD which leads to lack of patient education, awareness, and initiation of appropriate treatment. While female-specific lipid guidelines are not available, the recognition of unique risk factors in current guidelines is an important step in the right direction which will hopefully lead to more progress in closing the gender gap of dyslipidemia.

Availability of Data and Material Not applicable.

Code Availability Not applicable.

Declarations

Competing Interests Dr. Sidhu reports Scientific Advisory Board service Astra Zeneca in 2019 & Sanofi-Regeneron in 2019. Dr. Gianos reports Educational Grant from Astra Zeneca (diabetes initiative), site principal investigator for HERITAGE and HORISON trials from Novartis, and VESALIUS trial from Amgen; non-promotional speaker honorarium from Kaneka (lipid-lowering medications).

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