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Statin Adherence: Does Gender Matter?

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Abstract
Purpose of Review Cardiovascular disease (CVD) continues to be the leading cause of death for men and women in the USA. Statins have contributed significantly to noted declines in cardiovascular-related mortality in the last decade; however, the benefit of statins is inequitable across genders. Women continue to be less likely to take statins and to meet target LDL goals than men. As a possible contributing factor to this disparity, we explore the evidence for gender-based differences in provision of, and adherence to statins.
Recent Findings Compared with men, women are less likely to adhere to statins. Potential reasons for this gender difference in use of statins can be observed across all phases of adherence including both intentional and unintentional non-adherence. Notable gender-specific contributing factors for statin non-adherence include decreased provider and patient awareness of CVD risk among women, higher risk of statin intolerance among women, and competing demands associated with family caregiving responsibilities. Similar to limitations in the broader CVD literature, there is inadequate inclusion of gender-specific analyses in statin-related trials.
Summary Gender-based disparities in statin adherence can be linked to both provider level, psychosocial, and medication intolerance factors. Interventions designed to improve statin adherence should take gender-specific challenges into consideration such as women being older at the time of increased CVD risk, higher rates of statin intolerance, and potentially greater caregiving responsibilities.

Keywords Medication adherence · Medication persistence · Gender · Statin medications

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Introduction

Cardiovascular disease (CVD) causes one in every three deaths in the USA [1]. Recent clinical advances in the care of acute coronary syndrome, as well as primary and secondary CVD prevention, have led to declines in the death rate due to ischemic heart disease (IHD); however, men and women have not benefited equally. Rather, the decline in CVD has been seen primarily among older adults, while younger adults, particularly women, face a rise in CVD mortality [2, 3]. Reasons for this gender disparity are likely multifactorial.

Gender-based differences in heart disease have also become a focus of clinical and research entities. Recent scientific statements by the American Heart Association (AHA) outline the growing evidence for sex-based differences in cardiovascular physiology including variances in risk, pathology, and

clinical presentations of acute and chronic CVD [4••, 5••]. Notable differences include that women generally experience onset of CVD 10 years later than men [6], though the risk for ischemic heart disease rises in parallel after age 55 years for women and 45 years for men [4••]. Women experience increased attributable risk from some traditional CVD risk factors such as diabetes [7] and smoking [8]. They face multiple gender-specific risk factors such as gestational diabetes, polycystic ovarian syndrome, and hormone-based therapies (e.g., oral contraceptives and hormone therapy for menopause related symptoms) [4••, 9]. Compared with men, women are more likely to have atypical symptoms of acute myocardial infarction (AMI), such as unusual fatigue or epigastric pain [5••]. Women are also more likely to present with atypical chest pain, which may be explained by higher rates of non-obstructive coronary disease or coronary microvascular dysfunction [4••, 5••, 6]. Women are also less likely to receive guideline-concordant care in the acute setting [10] and experience higher in-hospital mortality [11, 12]. After acute myocardial infarction, women are more likely to have complications such as bleeding and arrhythmias [5••] and less likely to be referred to cardiac rehabilitation [13].

The use of statins, or HMG-CoA reductase inhibitors, is another area of CVD prevention where gender-based differences are noteworthy. Current treatment guidelines for lipid management recommend use of statins for primary prevention of CVD in high-risk patients regardless of gender [14, 15]. In many situations, however, women are less likely to be prescribed statins than men [4••, 10, 16], including after a myocardial infarction [10, 17]. Gender differences in statin prescription occurs despite the fact that high triglycerides and low high-density lipoprotein incur a greater risk among women than men [18, 19]. Previous concerns about the clinical effectiveness of statins in women have been addressed by recent studies showing that, compared with men, women receive similar benefits for primary [20, 21•] and secondary prevention [21•, 22]. In clinical trials, women experience the same low-density lipoprotein (LDL) reductions on statins [22] and possibly greater atherosclerotic regression on statins per unit LDL reduction [23]. However, in practice, women taking statins are less likely to achieve desired LDL goals [24, 25] pointing to a difference between women's adherence and subsequent clinical impact of statins in a controlled research setting vs. in the real world. There is limited data on gender differences since hyperlipidemia management guidelines shifted to focus on the prescription of a specific intensity of statin rather than LDL levels. However, prior to the guideline change, women were less likely to receive a moderate- or high-intensity statin compared with men [24, 26, 27].

In sum, the reasons for gender differences in lipid management and outcomes have not been fully explained. As biological response to statins does not appear to play a significant role in gender differences, the more significant factors are likely related to access and adherence. Once a lipid-lowering medication has been prescribed, there are numerous gender-specific factors that can influence adherence, such as comorbid health conditions and psychosocial experiences. Gender-based differences in adherence to lipid-lowering medications have not been fully investigated. Thus, we aim to explore potential areas of gender differences in statin adherence.

Adherence to Statins

As noted by the former US Surgeon General Dr. C. Everett Koop, "drugs don't work in patients who don't take them" [28]. Current estimates suggest that consistent adherence to statins across genders is in the range of 36.4 to 44 % [29, 30]. Attempts at clarifying the reasons for low adherence to this effective medication have been unable to account for the majority of non-adherence. Thus, understanding reasons for non-adherence has led to the need to consider factors that might be more difficult to measure, such as patient-doctor interactions and patient engagement in the decision-making process [29]. Statin adherence appears to be worse among women compared with men [16, 29–32, 33••, 34, 35]. A recent systematic review that pooled gender-specific adherence data found an odds of non-adherence for women at 1.10 (95 % CI, 1.07, 1.13) [33••].

Rates of statin non-adherence for women are higher when measured by self-report compared with claim-based data sources [33••]; a difference that suggests a discrepancy between what is prescribed and what is actually taken. This discrepancy is surprising because self-report measures usually overestimate adherence-related behaviors [36]. The importance of adherence to statins is growing as guidelines around CVD prevention and the treatment of hyperlipidemia shift away from targeting a specific LDL goal and, instead, focus on providing patients with the appropriate dose of medication [14]. The removal of specific LDL goals means that providers no longer can rely on failure to meet treatment goals to trigger statin adherence counseling. Guidelines suggest intermittent LDL assessment as part of treatment to evaluate for adherence; however, intermittent LDL assessment is likely insufficient given the complexity of behaviors involved in proper medication adherence.

To explore potential gender differences in statin adherence, we must define key concepts of medication adherence. Multiple terms have been used to refer to the appropriate and inappropriate taking of medications. These terms include compliance, concordance, and persistence, among others [37]. Here, we use the term medication adherence, which is the process by which patients take their medications as prescribed [37]. Importantly, because adherence to a medication requires a complex series of behaviors, adherence should not be viewed as a dichotomous variable (i.e. "adherent" or "non-adherent"); instead, adherence should be considered along a continuum of time and behaviors. Vrijens et al. [37] refers to three key phases

of medication adherence: initiation, implementation, and discontinuation (see Fig. 1). Initiation refers to the point at which the patient not only receives and fills a prescription but actually takes the first dose of a medication. The next phase of adherence is implementation. Implementation occurs throughout the time when the patient takes their medication. It compares the pattern and amount of medication that a patient actually takes with what is prescribed. Finally, discontinuation occurs when the patient takes the last dose of a medication. Discontinuation may occur under the guidance of a patient's provider or a patient may independently discontinue a medication. Another important concept is whether non-adherence is intentional (an active decision not to take a medication as prescribed) or unintentional (never receiving a prescription or passively not taking a medication as prescribed, perhaps due to forgetfulness) [38, 39].

Initiation

Before a patient can be adherent, they must actually receive a prescription. Gender differences in prescription of statins differ by indication. There are conflicting findings about gender differences in the primary prevention of CVD with some studies reporting that women receive fewer statin prescriptions than men [40–42] and others report more such prescriptions for women [24, 43–45]. Intensification of lipid-lowering regimens appears similar between genders [46], though evidence suggests that older women with diagnosed CVD are treated less aggressively [27]. It is clear, however, that in case of secondary prevention, women are less likely than men to be prescribed statin medications, in particular in the setting of acute myocardial infarction [12, 17, 26, 40, 44, 47–50].

Lack of awareness of women's CVD risk among clinicians likely contributes to gender differences in statin prescriptions. In one study, physicians were presented with clinical scenarios of acute chest pain where the clinical history varied only by gender. Physicians were more likely to attribute the patient's chest pain to a cardiac etiology and prescribe appropriate treatment to male vs. female patients [51], despite approximately 50 % of participating physicians being female themselves. Similarly, in the PROMISE trial, providers were more likely to determine female patients to be at low-risk compared with male patients despite women having higher prevalence of traditional CVD risk factors [52]. Moreover, women are more likely to present with non-obstructive CAD, a condition that many providers may not recognize as warranting a statin prescription [6]. Providers may be further biased by early trial results which suggested a lower efficacy of statins among women, a likely side effect of lower rates of trial participation by women [22]. Finally, provider bias is also compounded by current risk stratification tools which often underestimate risk in women [24, 52, 53].

Provider perceptions of gender-specific clinical benefits of statins likely play out in the context of patient-provider communication. One survey of current and former statin users of both genders found that former users reported being less satisfied with discussions about statins with their providers [54]. It is unlikely that lack of opportunity for risk counseling contributes significantly to primary non-adherence, given that women are more likely than men to access and use preventive primary care resources than men [55]. However, women have been found to be less likely to get recommended LDL testing when compared with men [16] and only 48 % of US women report discussing heart disease with their provider [56]. Women may also be less likely to have appropriate conversations about stopping cholesterol medications. After the FDA issued a warning about the lack of effectiveness of Ezetimibe (Zetia), women were less likely than men to have this medication discontinued [57]. Finally, those patients with gender concordant providers may have better statin adherence; a finding that could point to an area of patient-provider communication that warrants further exploration [29].

Even those providers who appropriately assess and discuss CVD risk for female patients, concerns about potential

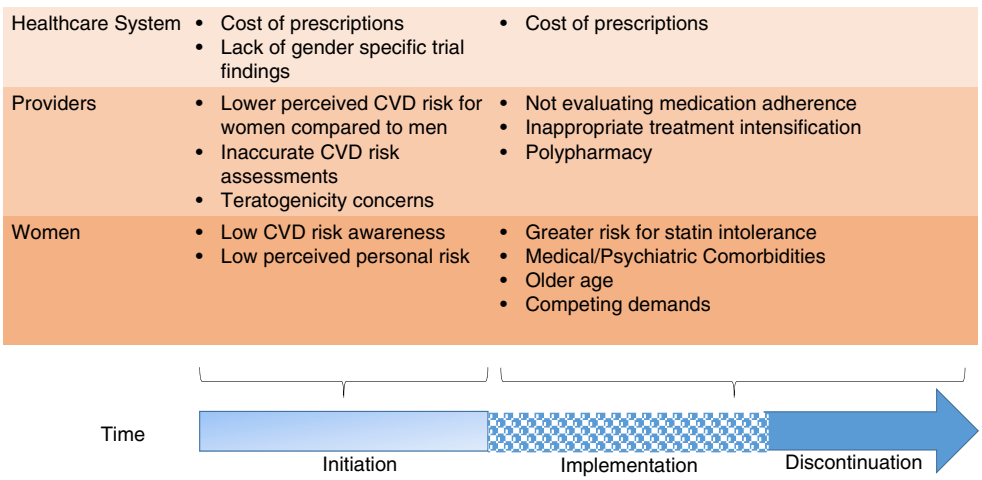

Fig. 1 Barriers to statin adherence for women

teratogenicity may present another barrier to prescription. Statins are considered teratogenic and recommended to be discontinued prior to conception [58, 59]. Studies of women on category X medications (those that are contraindicated during pregnancy) show that they have significant levels of non-adherence to contraception and are no more likely to adhere to contraception than women not on known teratogenic agents [60]. A better understanding of the risks of statins and effective contraception use in reproductive age women at risk for CVD would assist patient-provider decision making.

Medication beliefs are known to be a common cause of non-adherence [61] and, similar to providers, women demonstrate a lack of awareness and concern of their own risk of CVD [62]. Only 54 % of women are aware that CVD is the leading cause of death in the USA [56], and many women still see CVD as a "man's disease" [63]. Even among those who are aware of the risk of CVD for women generally, many women still do not have an accurate perception of their individual risk [64]. CVD-specific beliefs among women may translate to a lack of appreciation for the importance of statins in primary and secondary prevention.

Medication cost may also be a driver of primary non-adherence. Lemstra et al. conducted a systematic review of factors predicting statin non-adherence and noted that medication copayment and lower income status were two of the six variables significantly associated with non-adherence [65], findings that have been seen elsewhere [35, 66]. Increasing income has been shown to decrease the risk of poor adherence, a finding that is most evident in men aged 40–65 and women 65 years and older [45]. The out-of-pocket cost for prescriptions is generally higher for women though this is not necessarily the case for chronic medications such as statins [16]. Regardless, statin non-adherence due to costs is reported more often among women than men (32.7 vs 24.2 %, $p = 0.02$) [46], consistent with findings seen in oncology where women on oral anti-cancer medications are more likely to experience cost-related non-adherence [67]. While cost was likely a more significant factor prior to increases in the availability of off-patent statins in most retail prescription formularies, it may still be a notable influence for many patients.

Implementation

Overall, statin intolerance is the most commonly reported cause of statin non-adherence [68]; it is also a primary cause of non-adherence during implementation. While there is no universal definition of statin intolerance, it has been described as the discontinuation of a statin medication due to "the occurrence of adverse symptoms perceived by the patient to be unacceptable, and/or laboratory abnormalities suggesting undue risk" [69]. While there is a range of adverse symptoms that have been reported by patients on statins, the most common are statin-associated muscle symptoms (SAMS) followed by abnormal liver enzymes [68, 70]. Statin associated muscle symptoms represents a wide range of clinical manifestations from mild muscle cramps to rhabdomyolysis. Incidence of SAMS varies by source with estimates of 5 % in clinical trials [71] and up to 29 % in observational studies [68].

Women are more likely to experience adverse drug reactions generally and for cardiovascular medication in particular with an odds ratio of 1.92 (95 % CI, 1.15–3.19) [72]. Moreover, female gender is a known risk factor for statin intolerance as are multiple conditions which are more common among women or more likely among women on statins (see Fig. 2) [68, 69, 73]. Women are more likely to report non-adherence due to side effects compared with men with an adjusted odd ratio of 1.35 (95 % CI, 1.04–1.74) [46]. Elderly women, an age group most likely to meet criteria for statin treatment, are particularly vulnerable to muscle-related side effects due to statins [71]. As noted, complaints of muscle-related side effects are lower in randomized controlled trials than in registries and other patient reported data sources [68], which complicate assessment of gender differences in side effects given the lower numbers of women in CVD trials.

Misinformation may contribute to the perceived risk of statin side effects given increases in media coverage of this issue [68]. Perceived risk of statin side effects are likely amplified by easy access to both accurate and inaccurate information on-line, potentially explaining the finding that former statin users are more likely than current users to report using the internet to research statins [54]. A recent study from the United Kingdom found a higher rate of statin discontinuation after a period of intense media coverage of statin side effects [74]. Recent efforts by national CVD organizations to disseminate high quality information about women's cardiovascular risk [75–77] may improve both CVD risk perceptions and an understanding of the role of statin medications.

For women who are not adherent due to bothersome symptoms, intolerance may be further compounded by inappropriate dosing increases. Conflicting information exists around whether or not women are more likely to have statin regimens

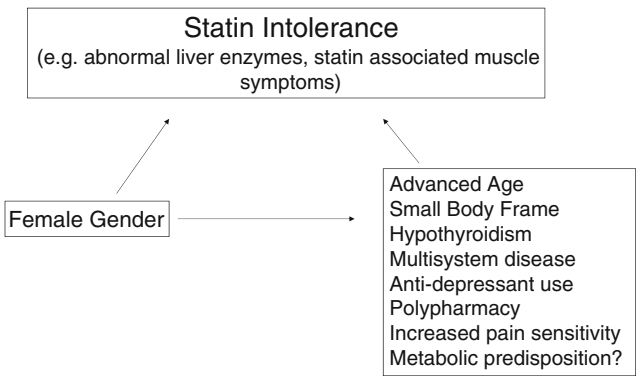

Fig. 2 Gender-specific factors associated with statin intolerance [68, 69, 71, 73]

intensified [24, 27, 43, 78]; however, patients with lower adherence to statins were more likely to receive dose intensification [43]. Regimen intensification has been found to be associated with worse adherence particularly among women [46]. If women are less likely to take statin medications due to medication side effects, but their poor adherence is perceived as treatment failure, regimen escalation to achieve treatment goals could further worsen intolerance and future treatment non-adherence.

Because women develop CVD later in life than men, women may have increased rates of polypharmacy and drug-drug interactions, both known risk factors for statin intolerance [68]. In practice-based observational studies, women on statins have been noted to have higher CVD risk with more comorbidities [24]; therefore, they are presumably more likely to be on multiple medications which could further increase risk of statin intolerance and side effects.

Comorbidity may also influence statin adherence. Women receiving active treatment for breast cancer are less likely to be at their LDL goal and less likely to be adherent to statin medications [79]. This finding is particularly concerning given that women with a history of breast cancer may be at increased risk of CVD, particularly those treated with earlier radiation regimens [80–82]. In general, women are more likely to take multiple medications than men [16] further increasing the cost burden for women [83]. One study of Australian women found that those taking additional chronic medications in addition to statins report challenges to covering the costs of multiple pills [83].

Complex comorbidity and medication interaction may also arise from mental health diagnoses. Depression and anxiety are associated with risk of non-adherence among patients with IHD in general [84], and women have higher rates of depression compared with men [85]. The impact of comorbid mental health on adherence has been noted in diabetes for both genders [61] and among women with respect to contraception [86]. Additionally, depression increases risk of IHD among women [87], and the risk of death particularly in younger women [88]. The impact of mental health on statin adherence may be an area of future exploration.

Increasing age itself is another predictor of poor statin adherence. Mann et al. report that there is a U-shaped effect on adherence with respect to age such that the youngest and oldest patients have worse adherence for both men and women [35]. Among elderly Medicare beneficiaries with or at risk for CVD, women were 21 % less likely to use statins than men [41] and less than a third of this difference was attributable to individual-level characteristics. A study by Carey et al. in the UK, found that men had higher initiation and continuation of statins after a myocardial infarction, but that most of this difference was explained by the younger age of the included male population [47].

Finally, statin implementation among women may be adversely impacted by competing demands as caregivers. For adherence generally, practical social support is associated with better adherence, and patients from a cohesive family situation experience 1.74 times greater adherence [89]. However, women often consider their own health as less of a priority than the health of their family [63]. Women with known heart disease report less support for self-care and disease management than men [90]. Even having assistance may not be as helpful for women compared with men. Receipt of informal caregiving is only associated with reaching LDL goals in men not women [25]. Between 22 and 31 % of women caregivers report that caregiving has a negative impact on their own health and 51 % of women note that family responsibilities and caregiving is a top barrier to CVD prevention [56].

Discontinuation

Many of the reasons that patients do not adhere to statin regimens are seen with discontinuation or the permanent stopping of a statin medication. According to a survey of current and former statin users, the primary reasons for statin discontinuation were side effects (62 %), cost (17 %), and lack of efficacy (12 %) [54]. Comorbid medical problems likely also contribute to discontinuation of statins as suggested by women undergoing treatment for breast cancer are more likely to discontinue statin medications [79].

Remaining Questions About Statin Adherence

Multiple areas of uncertainty remain about gender-based differences in statin adherence. For example, do gender-based differences in adherence vary by racial and ethnic subgroups? Differences in risk of CVD between racial groups has been recognized with African-Americans being at the highest risk [1, 4••]. African-American veterans have worse control of lipids than white veterans though these differences are only significant among male patients [91]. Turner et al. found that black women received higher-intensity treatment with statins than black men, white women, and white men but were still less likely to have their LDL at goal [78]. Compared with white patients, non-white individuals have been found to have higher rates of non-adherence [33••]. Differences between racial/ethnic groups have also been seen in statin adherence post-MI [92] and after intensification of regimens [93]. A better understanding of the interaction between racial and gender differences in statin adherence is needed [4••, 92], as adequate consideration of the diversity of the patient population is necessary for the equitable delivery of care [15].

Limitations of Current Literature

While the existing literature provides information about multiple areas where there may be gender-based differences in statin adherence, there are limitations. First, as often seen in the wider literature on adherence, the method of adherence assessment is not always well defined or is limited to having an assessment of active prescription. This approach to adherence measurement likely omits non-adherence that is unrelated to refill patterns (e.g., missing dosages, taking at the wrong time of day). Second, many articles report on LDL goal attainment rather than adherence to the statin medication. This is an understandable reflection of the focus of previous lipid treatment guidelines. However, with a newer focus on matching the statin dose intensity to the correct risk patient, statin adherence literature may be more effective by targeting how providers can ensure that patients are taking the correct statin dosing. It will be important to monitor the impact of this guideline transition on gender differences in statin use and management of hyperlipidemia. Common to statin trials and the larger cardiovascular literature in general, there have been fewer women included as participants (approximately 20 %) [16, 20, 22]. This lack of inclusion of women in clinical trials likely explains the weaker evidence supporting use of statins in primary prevention among women [94•] and translates to a limited ability to fully inform how trial findings translate into sex and gender-specific tolerance of statins and guideline recommendations more generally. Even when adequate numbers of women have been included in statin-related studies, gender-specific analyses are rarely included or published. Instead, investigators often statistically control for gender or sex effects in analyses if considered explicitly at all. The pursuit of "big data" has been put forth as a potential opportunity to resolve some lingering questions around areas of gender-based differences and disparities [95].

Conclusions

There is evidence of gender-based differences in statin adherence across initiation, implementation, and discontinuation. With initiation or primary adherence, providers and patients are less aware of the risks of CVD and thus put a lower emphasis on the role of statins for women. For both adherence implementation and discontinuation, greater side effects, comorbid physical and mental illness, and competing social demands for women compared with men likely impact statin adherence. Including women in greater numbers in statin trials and the conduction of gender-specific analyses would support additional clarification of gender-based differences.

Compliance with Ethical Standards

Conflict of Interest Karen M. Goldstein, Leah L. Zullig, and Lori A. Bastian declare that they have no conflict of interest. Hayden B. Bosworth declares grant support from Johnson & Johnson, Improved Patient Outcomes, and Takeda and personal fees from Genetech, Walgreens, and CVS Caremart.

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References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, et al. Heart disease and stroke statistics—2016 update: a report from the American Heart Association. Circulation. 2016;133(4):e38–60.
2. Ford ES, Capewell S. Coronary heart disease mortality among young adults in the U.S. from 1980 through 2002: concealed leveling of mortality rates. J Am Coll Cardiol. 2007;50(22):2128–32.
3. Wagner A, Arveiler D, Ruidavets JB, Bingham A, Montaye M, Ferrieres J, et al. Gender- and age-specific trends in coronary heart disease mortality in France from 2000 to 2007: results from the MONICA registers. Eur J Prev Cardiol. 2014;21(1):117–22.
4.•• McSweeney JC, Rosenfeld AG, Abel WM, Braun LT, Burke LE, Daugherty SL, et al. Preventing and experiencing ischemic heart disease as a woman: state of the science: a scientific statement from the American Heart Association. Circulation. 2016;133(13):1302–31. **This is a recent update from the AHA about sex and gender-based differences in CVD**.
5.•• Mehta LS, Beckie TM, DeVon HA, Grines CL, Krumholz HM, Johnson MN, et al. Acute myocardial infarction in women: a scientific statement from the American Heart Association. Circulation. 2016;133(9):916–47. **This is a recent update from the AHA about sex and gender-based differences in CVD**.
6. Sanghavi M, Gulati M. Sex differences in the pathophysiology, treatment, and outcomes in IHD. Curr Atherosclerosis Rep. 2015;17(6):511.
7. Ballotari P, Ranieri SC, Luberto F, Caroli S, Greci M, Giorgi Rossi P, et al. Sex differences in cardiovascular mortality in diabetics and nondiabetic subjects: a population-based study (Italy). Int J Endocrinol. 2015;2015:914057.
8. Mucha L, Stephenson J, Morandi N, Dirani R. Meta-analysis of disease risk associated with smoking, by gender and intensity of smoking. Gender Med. 2006;3(4):279–91.
9. Mehta PK, Wei J, Wenger NK. Ischemic heart disease in women: a focus on risk factors. Trends Cardiovasc Med. 2015;25(2):140–51.

10. Kumbhani DJ, Steg PG, Cannon CP, Eagle KA, Smith Jr SC, Hoffman E, et al. Adherence to secondary prevention medications and four-year outcomes in outpatients with atherosclerosis. Am J Med. 2013;126(8):693–700.e1.
11. El-Menyar A, Ahmed E, Albinali H, Al-Thani H, Gehani A, Singh R, et al. Mortality trends in women and men presenting with acute coronary syndrome: insights from a 20-year registry. PLoS ONE. 2013;8(7), e70066.
12. Shehab A, Al-Dabbagh B, AlHabib KF, Alsheikh-Ali AA, Almahmeed W, Sulaiman K, et al. Gender disparities in the presentation, management and outcomes of acute coronary syndrome patients: data from the 2nd Gulf Registry of Acute Coronary Events (Gulf RACE-2). PLoS ONE. 2013;8(2), e55508.
13. Colbert JD, Martin BJ, Haykowsky MJ, Hauer TL, Austford LD, Arena RA, et al. Cardiac rehabilitation referral, attendance and mortality in women. Eur J Prev Cardiol. 2015;22(8):979–86.
14. Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;129(25 Suppl 2):S1–45.
15. Mosca L, Benjamin EJ, Berra K, Bezanson JL, Dolor RJ, Lloyd-Jones DM, et al. Effectiveness-based guidelines for the prevention of cardiovascular disease in women—2011 update: a guideline from the American Heart Association. Circulation. 2011;123(11):1243–62.
16. Manteuffel M, Williams S, Chen W, Verbrugge RR, Pittman DG, Steinkellner A. Influence of patient sex and gender on medication use, adherence, and prescribing alignment with guidelines. J Women's Health (2002). 2014;23(2):112–9.
17. Buja A, Boemo DG, Furlan P, Bertoncello C, Casale P, Baldovin T, et al. Tackling inequalities: are secondary prevention therapies for reducing post-infarction mortality used without disparities? Eur J Prev Cardiol. 2014;21(2):222–30.
18. Lu W, Resnick HE, Jablonski KA, Jones KL, Jain AK, Howard WJ, et al. Non-HDL cholesterol as a predictor of cardiovascular disease in type 2 diabetes: the strong heart study. Diabetes Care. 2003;26(1):16–23.
19. Shai I, Rimm EB, Hankinson SE, Curhan G, Manson JE, Rifai N, et al. Multivariate assessment of lipid parameters as predictors of coronary heart disease among postmenopausal women: potential implications for clinical guidelines. Circulation. 2004;110(18):2824–30.
20. Kostis WJ, Cheng JQ, Dobrzynski JM, Cabrera J, Kostis JB. Meta-analysis of statin effects in women versus men. J Am Coll Cardiol. 2012;59(6):572–82.
21.• Fulcher J, O'Connell R, Voysey M, Emberson J, Blackwell L, Mihaylova B, et al. Efficacy and safety of LDL-lowering therapy among men and women: meta-analysis of individual data from 174,000 participants in 27 randomised trials. Lancet (London, England). 2015;385(9976):1397–405. **This is a paper describing data from the Cholesterol Treatment Trialists' Collaboration that demonstrates the similar efficacy of statin in women compared to men**.
22. Gutierrez J, Ramirez G, Rundek T, Sacco RL. Statin therapy in the prevention of recurrent cardiovascular events: a sex-based meta-analysis. Arch Intern Med. 2012;172(12):909–19.
23. Puri R, Nissen SE, Shao M, Ballantyne CM, Barter PJ, Chapman MJ, et al. Sex-related differences of coronary atherosclerosis regression following maximally intensive statin therapy: insights from SATURN. J Am Coll Cardiol Img. 2014;7(10):1013–22.
24. Schoen MW, Tabak RG, Salas J, Scherrer JF, Buckhold FR. Comparison of adherence to guideline-based cholesterol treatment goals in men versus women. Am J Cardiol. 2016;117(1):48–53.
25. Hammond G, Mochari-Greenberger H, Liao M, Mosca L. Effect of gender, caregiver, on cholesterol control and statin use for secondary prevention among hospitalized patients with coronary heart disease. Am J Cardiol. 2012;110(11):1613–8.
26. Virani SS, Woodard LD, Ramsey DJ, Urech TH, Akeroyd JM, Shah T, et al. Gender disparities in evidence-based statin therapy in patients with cardiovascular disease. Am J Cardiol. 2015;115(1):21–6.
27. Vimalananda VG, Miller DR, Hofer TP, Holleman RG, Klamerus ML, Kerr EA. Accounting for clinical action reduces estimates of gender disparities in lipid management for diabetic veterans. J Gen Intern Med. 2013;28 Suppl 2:S529–35.
28. Ho PM, Bryson CL, Rumsfeld JS. Medication adherence: its importance in cardiovascular outcomes. Circulation. 2009;119(23):3028–35.
29. Chan DC, Shrank WH, Cutler D, Jan S, Fischer MA, Liu J, et al. Patient, physician, and payment predictors of statin adherence. Med Care. 2010;48(3):196–202.
30. Newby LK, LaPointe NM, Chen AY, Kramer JM, Hammill BG, DeLong ER, et al. Long-term adherence to evidence-based secondary prevention therapies in coronary artery disease. Circulation. 2006;113(2):203–12.
31. Bermingham M, Hayden J, Dawkins I, Miwa S, Gibson D, McDonald K, et al. Prospective analysis of LDL-C goal achievement and self-reported medication adherence among statin users in primary care. Clin Ther. 2011;33(9):1180–9.
32. Lilly SM, Mortensen EM, Frei CR, Pugh MJ, Mansi IA. Comparison of the risk of psychological and cognitive disorders between persistent and nonpersistent statin users. Am J Cardiol. 2014;114(7):1035–9.
33.•• Lewey J, Shrank WH, Bowry AD, Kilabuk E, Brennan TA, Choudhry NK. Gender and racial disparities in adherence to statin therapy: a meta-analysis. Am Heart J. 2013;165(5):665–78.e1. **This is the most recent systematic review of gender disparities in statin adherence**.
34. Kautzky-Willer A, Stich K, Hintersteiner J, Kautzky A, Kamyar MR, Saukel J, et al. Sex-specific-differences in cardiometabolic risk in type 1 diabetes: a cross-sectional study. Cardiovasc Diabetol. 2013;12:78.
35. Mann DM, Woodward M, Muntner P, Falzon L, Kronish I. Predictors of nonadherence to statins: a systematic review and meta-analysis. Ann Pharmacother. 2010;44(9):1410–21.
36. Stirratt MJ, Dunbar-Jacob J, Crane HM, Simoni JM, Czajkowski S, Hilliard ME, et al. Self-report measures of medication adherence behavior: recommendations on optimal use. Translat Behav Med. 2015;5(4):470–82.
37. Vrijens B, De Geest S, Hughes DA, Przemyslaw K, Demonceau J, Ruppar T, et al. A new taxonomy for describing and defining adherence to medications. Br J Clin Pharmacol. 2012;73(5):691–705.
38. Lehane E, McCarthy G. Intentional and unintentional medication non-adherence: a comprehensive framework for clinical research and practice? A discussion paper. Int J Nurs Stud. 2007;44(8):1468–77.
39. Molloy GJ, Messerli-Burgy N, Hutton G, Wikman A, Perkins-Porras L, Steptoe A. Intentional and unintentional non-adherence to medications following an acute coronary syndrome: a longitudinal study. J Psychosom Res. 2014;76(5):430–2.
40. Koopman C, Vaartjes I, Heintjes EM, Spiering W, van Dis I, Herings RM, et al. Persisting gender differences and attenuating age differences in cardiovascular drug use for prevention and treatment of coronary heart disease, 1998–2010. Eur Heart J. 2013;34(41):3198–205.
41. Bhattacharjee S, Findley PA, Sambamoorthi U. Understanding gender differences in statin use among elderly Medicare beneficiaries: an application of decomposition technique. Drugs Aging. 2012;29(12):971–80.
42. Naicker K, Liddy C, Singh J, Taljaard M, Hogg W. Quality of cardiovascular disease care in Ontario's primary care practices: a

cross sectional study examining differences in guideline adherence by patient sex. BMC Fam Pract. 2014;15:123.
43. Pittman DG, Fenton C, Chen W, Haffner S, Pendergrass M. Relation of statin nonadherence and treatment intensification. Am J Cardiol. 2012;110(10):1459–63.
44. Sheppard JP, Fletcher K, McManus RJ, Mant J. Missed opportunities in prevention of cardiovascular disease in primary care: a cross-sectional study. Br J Gen Pract: J Royal Coll Gen Pract. 2014;64(618):e38–46.
45. Wallach-Kildemoes H, Andersen M, Diderichsen F, Lange T. Adherence to preventive statin therapy according to socioeconomic position. Eur J Clin Pharmacol. 2013;69(8):1553–63.
46. Billimek J, Malik S, Sorkin DH, Schmalbach P, Ngo-Metzger Q, Greenfield S, et al. Understanding disparities in lipid management among patients with type 2 diabetes: gender differences in medication nonadherence after treatment intensification. Women's Health Issues: Off Publ Jacobs Inst Women's Health. 2015;25(1):6–12.
47. Carey IM, DeWilde S, Shah SM, Harris T, Whincup PH, Cook DG. Statin use after first myocardial infarction in UK men and women from 1997 to 2006: who started and who continued treatment? Nutr, Metab Cardiovasc Dis: NMCD. 2012;22(5):400–8.
48. Pereira M, Araujo C, Dias P, Lunet N, Subirana I, Marrugat J, et al. Age and sex inequalities in the prescription of evidence-based pharmacological therapy following an acute coronary syndrome in Portugal: the EURHOBOP study. Eur J Prev Cardiol. 2014;21(11):1401–8.
49. Ferrari R, Abergel H, Ford I, Fox KM, Greenlaw N, Steg PG, et al. Gender- and age-related differences in clinical presentation and management of outpatients with stable coronary artery disease. Int J Cardiol. 2013;167(6):2938–43.
50. Johansen ME, Hefner JL, Foraker RE. Antiplatelet and statin use in US patients with coronary artery disease categorized by race/ethnicity and gender, 2003 to 2012. Am J Cardiol. 2015;115(11):1507–12.
51. Abuful A, Gidron Y, Henkin Y. Physicians' attitudes toward preventive therapy for coronary artery disease: is there a gender bias? Clin Cardiol. 2005;28(8):389–93.
52. Hemal K, Pagidipati NJ, Coles A, Dolor RJ, Mark DB, Pellikka PA, et al. Sex differences in demographics, risk factors, presentation, and noninvasive testing in stable outpatients with suspected coronary artery disease: insights from the PROMISE Trial. JACC Cardiovascular Imaging. 2016.
53. Agrawal S, Van Eyk J, Sobhani K, Wei J, Bairey Merz CN. Sex, myocardial infarction, and the failure of risk scores in women. J Women's Health (2002). 2015;24(11):859–61.
54. Cohen JD, Brinton EA, Ito MK, Jacobson TA. Understanding statin use in America and gaps in patient education (USAGE): an internet-based survey of 10,138 current and former statin users. J Clin Lipidol. 2012;6(3):208–15.
55. Vaidya V, Partha G, Karmakar M. Gender differences in utilization of preventive care services in the United States. J Women's Health (2002). 2012;21(2):140–5.
56. Mosca L, Mochari-Greenberger H, Dolor RJ, Newby LK, Robb KJ. Twelve-year follow-up of American women's awareness of cardiovascular disease risk and barriers to heart health. Circ Cardiovasc Qual Outcomes. 2010;3(2):120–7.
57. Shrank WH, Choudhry NK, Tong A, Myers J, Fischer MA, Swanton K, et al. Warnings without guidance: patient responses to an FDA warning about ezetimibe. Med Care. 2012;50(6):479–84.
58. Godfrey LM, Erramouspe J, Cleveland KW. Teratogenic risk of statins in pregnancy. Ann Pharmacother. 2012;46(10):1419–24.
59. Kusters DM, Hassani Lahsinoui H, van de Post JA, Wiegman A, Wijburg FA, Kastelein JJ, et al. Statin use during pregnancy: a systematic review and meta-analysis. Expert Rev Cardiovasc Ther. 2012;10(3):363–78.
60. Steinkellner A, Chen W, Denison SE. Adherence to oral contraception in women on category X medications. Am J Med. 2010;123(10):929–34.e1.
61. Gellad WF, Grenard JL, Marcum ZA. A systematic review of barriers to medication adherence in the elderly: looking beyond cost and regimen complexity. Am J Geriatr Pharmacother. 2011;9(1):11–23.
62. Biswas MS, Calhoun PS, Bosworth HB, Bastian LA. Are women worrying about heart disease? Women's Health Issues: Off Publ Jacobs Inst Women's Health. 2002;12(4):204–11.
63. Emslie C. Women, men and coronary heart disease: a review of the qualitative literature. J Adv Nurs. 2005;51(4):382–95.
64. Kling JM, Miller VM, Mankad R, Wilansky S, Wu Q, Zais TG, et al. Go Red for Women cardiovascular health-screening evaluation: the dichotomy between awareness and perception of cardiovascular risk in the community. J Women's Health (2002). 2013;22(3):210–8.
65. Lemstra M, Blackburn D. Nonadherence to statin therapy: discontinuation after a single fill. Can J Cardiol. 2012;28(5):567–73.
66. Watanabe JH, Kazerooni R, Bounthavong M. Association of copayment with likelihood and level of adherence in new users of statins: a retrospective cohort study. J Manag Care Pharm: JMCP. 2014;20(1):43–50.
67. Lee M, Khan MM. Gender differences in cost-related medication non-adherence among cancer survivors. J Cancer Survivorship: Res Pract. 2016;10(2):384–93.
68. Stroes ES, Thompson PD, Corsini A, Vladutiu GD, Raal FJ, Ray KK, et al. Statin-associated muscle symptoms: impact on statin therapy—European Atherosclerosis Society Consensus Panel Statement on Assessment, Aetiology and Management. Eur Heart J. 2015;36(17):1012–22.
69. Stulc T, Ceska R, Gotto Jr AM. Statin intolerance: the clinician's perspective. Curr Atherosclerosis Rep. 2015;17(12):69.
70. Plakogiannis R, Arif SA. Women versus men: is there equal benefit and safety from statins? Curr Atherosclerosis Rep. 2016;18(2):6.
71. Bhardwaj S, Selvarajah S, Schneider EB. Muscular effects of statins in the elderly female: a review. Clin Interv Aging. 2013;8:47–59.
72. Zopf Y, Rabe C, Neubert A, Gassmann KG, Rascher W, Hahn EG, et al. Women encounter ADRs more often than do men. Eur J Clin Pharmacol. 2008;64(10):999–1004.
73. Ahmad Z. Statin intolerance. Am J Cardiol. 2014;113(10):1765–71.
74. Matthews A, Herrett E, Gasparrini A, Van Staa T, Goldacre B, Smeeth L, et al. Impact of statin related media coverage on use of statins: interrupted time series analysis with UK primary care data. BMJ (Clin Res Ed). 2016;353:i3283.
75. Hayes SN, Wood SF, Mieres JH, Campbell SM, Wenger NK. Taking a giant step toward Women's heart health: finding policy solutions to unanswered research questions. Women's Health Issues: Off Publ Jacobs Inst Women's Health. 2015;25(5):429–32.
76. American Heart Association. Woman-to-woman heart care. Hospitals & Health Networks. 2016 January 22.
77. American Heart Association. Go red for women 2016. Available from: https://www.goredforwomen.org/.
78. Turner BJ, Hollenbeak CS, Weiner M, Tang SS. A retrospective cohort study of the potency of lipid-lowering therapy and race-gender differences in LDL cholesterol control. BMC Cardiovasc Disord. 2011;11:58.
79. Calip GS, Boudreau DM, Loggers ET. Changes in adherence to statins and subsequent lipid profiles during and following breast cancer treatment. Breast Cancer Res Treat. 2013;138(1):225–33.
80. Hooning MJ, Botma A, Aleman BM, Baaijens MH, Bartelink H, Klijn JG, et al. Long-term risk of cardiovascular disease in 10-year survivors of breast cancer. J Natl Cancer Inst. 2007;99(5):365–75.

81. Bradshaw PT, Stevens J, Khankari N, Teitelbaum SL, Neugut AI, Gammon MD. Cardiovascular disease mortality among breast cancer survivors. Epidemiol (Cambridge, Mass). 2016;27(1):6–13.
82. Darby SC, Ewertz M, McGale P, Bennet AM, Blom-Goldman U, Bronnum D, et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. N Engl J Med. 2013;368(11):987–98.
83. Stewart Williams JA, Wallick CJ, Byles JE, Doran CM. Assessing patterns of use of cardio-protective polypill component medicines in Australian women. Drugs Aging. 2013;30(3):193–203.
84. Dempe C, Junger J, Hoppe S, Katzenberger ML, Moltner A, Ladwig KH, et al. Association of anxious and depressive symptoms with medication nonadherence in patients with stable coronary artery disease. J Psychosom Res. 2013;74(2):122–7.
85. Pedersen CB, Mors O, Bertelsen A, Waltoft BL, Agerbo E, McGrath JJ, et al. A comprehensive nationwide study of the incidence rate and lifetime risk for treated mental disorders. JAMA Psychiatry. 2014;71(5):573–81.
86. Callegari LS, Zhao X, Nelson KM, Borrero S. Contraceptive adherence among women Veterans with mental illness and substance use disorder. Contraception. 2015;91(5):386–92.
87. Rutledge T, Linke SE, Johnson BD, Bittner V, Krantz DS, Cornell CE, et al. Relationships between cardiovascular disease risk factors and depressive symptoms as predictors of cardiovascular disease events in women. J Women's Health (2002). 2012;21(2):133–9.
88. Shah AJ, Ghasemzadeh N, Zaragoza-Macias E, Patel R, Eapen DJ, Neeland IJ, et al. Sex and age differences in the association of depression with obstructive coronary artery disease and adverse cardiovascular events. J Am Heart Assoc. 2014;3(3), e000741.
89. DiMatteo MR. Social support and patient adherence to medical treatment: a meta-analysis. Health Psychol: Off J Div Health Psychol, Am Psychol Assoc. 2004;23(2):207–18.
90. Thomas JR, Clark AM. Women with heart failure are at high psychosocial risk: a systematic review of how sex and gender influence heart failure self-care. Cardiol Res Pract. 2011;2011:918973.
91. Goldstein KM, Melnyk SD, Zullig LL, Stechuchak KM, Oddone E, Bastian LA, et al. Heart matters: gender and racial differences cardiovascular disease risk factor control among veterans. Women's Health Issues: Off Publ Jacobs Inst Women's Health. 2014;24(5):477–83.
92. Lauffenburger JC, Robinson JG, Oramasionwu C, Fang G. Racial/ethnic and gender gaps in the use of and adherence to evidence-based preventive therapies among elderly Medicare part D beneficiaries after acute myocardial infarction. Circulation. 2014;129(7):754–63.
93. Romanelli RJ, Segal JB. Predictors of statin compliance after switching from branded to generic agents among managed-care beneficiaries. J Gen Intern Med. 2014;29(10):1372–8.
94.• Wenger NK. Juggling multiple guidelines: a woman's heart in the balance. J Women's Health (2002). 2016;25(3):213–21. **This is a description of an expert cardiologists' interpretation of current evidence and guidelines as it applies to female patients and her approach to managing CVD risk and disease specifically for women**.
95. Joynt KE, Mega JL, O'Donoghue ML. Difference or disparity: will big data improve our understanding of sex and cardiovascular disease? Circ Cardiovasc Qual Outcomes. 2015;8(2 Suppl 1):S52–5.