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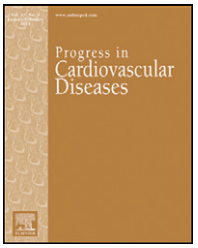

Advances in Lipid Therapy: The Role of Lipid Treatment in Women in Primary Prevention ☆

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ABSTRACT

Cardiovascular disease (CVD) remains the leading cause of death for women. Given the overall prevalence of CVD and its risk factors in women, primary prevention is an important focus. In 2013, the American College of Cardiology and the American Heart Association released guidelines for men and women on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk (ASCVD) in adults based on randomized-controlled trials. Fixed and appropriate intensity of a statin based on calculation of an individual's risk of ASCVD or in diabetics or those with severely elevated low-density lipoprotein cholesterol patients for primary prevention is recommended rather than cholesterol level goals. A more recent consensus statement regarding the role of non-statin therapies has been released, but like the prior guidelines released in 2013, there were no sex-specific recommendations. An evidence-based approach to ASCVD prevention should be used in women.

Cardiovascular disease (CVD) remains the leading cause of death women in the United States (US), with an estimated 398,068 women dying from CVD in 2013.[1,2] Although there have been noted reductions in mortality from CVD in women from better treatment of CVD, this has resulted in more women living with CVD and its potential consequences. An approach that focuses on treating CVD, rather than preventing CVD, is expensive and will result in an increase in risk factor burden on the population. In addition, studies continue to show an increased risk of in-hospital mortality in young women presenting with an acute myocardial infarction (MI), compared with men of the same age.[3,4] For these reasons, a focus of primary prevention of CVD is necessary to not only reduce mortality, but also reduce the overall impact of CVD on the health of the nation and its economic burden on the healthcare system.

Identifying and treating CVD risk factors have become a focus of the American Heart Association (AHA) in order to reduce the burden of CVD in the US.[5] There is significant evidence showing that controlling CVD risk factors is far from optimal. Based on the National Health and Nutrition Examination Surveys (NHANES) III study, less than 7.5% of the population met 6 of the 7 key CVD health metrics (Including not smoking, eating a healthy diet, being physically active, having a normal weight, blood pressure, glucose and cholesterol level).[6] In addition, a large analysis of 18 studies from the US showed that in 257,384 participants, only 3% of persons had their key CVD risk factors optimally managed.[7] By focusing on identification and treatment of CVD risk factors, the impact on CVD will be greater because of the ability to prevent (rather than treat) CVD.

☆ Statement of Conflict of Interest: see page XX.

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Abbreviations and Acronyms

ACC = American College of Cardiology

AHA = American Heart Association

ALT = Alanine aminotransferase

ASCVD = Atherosclerotic cardiovascular disease

ATP = Adult Treatment Program

CHD = Coronary heart disease

CVD = Cardiovascular disease

DM = Diabetes mellitus

FH = Familial hypercholesterolemia

HDL-C = High-density lipoprotein cholesterol

hs-CRP = High sensitivity C-reactive protein

LDL-C = Low-density lipoprotein cholesterol

MI = Myocardial infarction

NHANES = National Health and Nutrition Examination Surveys

US = United States

In 2013, a joint task force from the American College of Cardiology (ACC) and the AHA released evidence-based guidelines on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk (ASCVD) in adults.[8] These guidelines apply to both women and men, and changed their approach away from targeting cholesterol levels, but rather focusing on a fixed intensity of a statin based on estimated ASCVD risk. In primary prevention, the high-risk groups include those with elevated levels of low-density lipoprotein cholesterol (LDL-C) on a primary basis or those with diabetes ages 40–75 and LDL-C 70–189 mg/dl. Those in a lower risk primary prevention but with a 10-year estimated ASCVD risk is ≥7.5 are also shown to benefit, but membership in this group does not equate with statin treatment. This occurs only after a clinician–patient risk/benefit discussion that addresses other risk factors and optimal lifestyle, the potential for benefit versus the potential for adverse effects or drug–drug interactions with statin therapy and includes an informed patient preference. The guidelines emphasize statin therapy over other lipid lowering treatments and have eliminated past recommendations to treat to a specific LDL-C or non-high-density-lipoprotein cholesterol (HDL-C) goal. There were no specific sex differences in the guidelines released. Nonetheless, the data on which these guidelines were made were influenced by many trials that had relatively few women and did not often report sex-specific results when women were included but more recent trials have included more women and impacted the recommendation of the lipid guidelines (Tables 1A, 1B).

Table 1A – Women in primary prevention randomized control trials of statins.

Study	Number of Women Enrolled	Total Enrolled Studied	Percent Women (%)	Mean Age (Years)	Drug Name
ACAPS	445	919	48	61	Lovastatin
AFCAPS/ TexCAPS	997	6605	15	62	Lovastatin
HPS	1816	5963	30	NA	Simvastatin
ALLHAT	5051	10,355	49	NA	Pravastatin
ASCOT	1942	10,305	30	NA	Atorvastatin
MEGA	5356	7832	69	60	Pravastatin
PROSPER	1894	3239	58	75	Pravastatin
JUPITER	6801	17,802	38	68	Rosuvastatin

Does the ASCVD risk assessment overestimate risk in women?

Critics of the new guidelines on cholesterol management have suggested that the ASCVD risk score calculator recommended in the guidelines overestimates risk. Nonetheless, the ASCVD risk calculator was based on more than one population and is a pooled cohort equation that was developed and validated on Caucasian and African American men and women.[9] The pooled cohorts included participants from several large NHLBI-sponsored cohort studies that were both geographically and racially diverse and included the ARIC (Atherosclerosis Risk in Communities) study,[10] the Cardiovascular Health Study,[11] the CARDIA (Coronary Artery Risk Development in Young Adults) study,[12] the Framingham[13] and the Framingham Offspring Study.[14] Subsequent reports have validated the ASCVD risk calculator, including its accuracy in women.[15,16] Nevertheless, given the populations on which these were developed, these may over-estimate risks in Hispanic-Americans and East-Asian-Americans and under-estimate risks in South Asian-Americans, but this limitation was admitted by the guidelines' authors. Unfortunately, there have been very limited data on other racial groups, so no specific adjustment has been made in the current risk score assessment and the ASCVD risk score's validity beyond Caucasian and African Americans is unknown.

One study has suggested the ASCVD risk calculator overestimated risk by 75%–150%.[17] The three cohorts they used to demonstrate this included the Nurses' Health Study, The Women's Health Initiative and the Physicians' Health Study. In all of these studies, it should be noted that risk factors were self-reported and not measured or confirmed. The first study and the later study are not representative of

Table 1B – Women in secondary prevention randomized control trials of statins.

Study	Number of Women	Total Enrolled Studied	Percent Women (%)	Mean Age (Years)	Drug Name
4S	827	4444	19	61	Simvastatin
PLACII	22	151	15	62	Pravastatin
CARE	576	4159	14	61	Pravastatin
LIPID	1516	9014	17	62	Pravastatin
HPS	3266	14,573	22	NA	Simvastatin
PROSPER	1106	2565	43	76	Pravastatin
SPARCL	1908	4731	40	64	Atorvastatin

(Reproduced from Trends Cardiovasc Med. 2015 Feb.;25(2):84–94 by authors (Tables 1A/1B).

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