ASCVD Risk Assessment in Pre- and Post-menopausal Women: Is it All About Age?

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Disclosures

• None
Total Deaths in Women in USA 2013: 1,236,003

Cardiovascular Disease: 398,068
Chronic Lung Disease: 75,422
Lung Cancer: 70,542
Breast Cancer: 40,861

Prevalence of CVD in US Women: • 42,700,000
Prevalence of Breast Cancer in US Women: • 2,899,726

Centers for Disease Control and Prevention, and National Cancer Institute; 2015
ASCVD Risk Score

• Released in November 2013
• “Treat to target” goals for LDL-C and non-HDL-C were no longer recommended
• Treatment is focused on intensity of statin, (high and moderate intensity), virtually eliminating low dose statin therapy
• ASCVD definition now includes stroke in addition to coronary heart disease and peripheral arterial disease
• 4 major treatment groups were identified
• Marked reduced emphasis on non-statin therapies
• No guidelines are provided for treatment of triglycerides
Atherosclerotic Cardiovascular Disease (ASCVD) Risk Calculator

- 10 year risk: 40-79 years
- Lifetime risk: 20-59 risk estimator provides lifetime risk estimate
- Internal/External Validation in diverse populations
- This is intended to drive discussions of greater adherence to heart-healthy lifestyle in addition to determining who would benefit from lipid-lowering therapy
- Sex Specific Risk Factors?

http://tools.cardiosource.org/ASCVD-Risk-Estimator/
4 Major Treatment Groups

1. Individuals with Clinical ASCVD

2. Individuals with LDL-C $\geq 190$ mg/dL

3. Individuals with diabetes aged 40–75, LDL-C 70–189 mg/dL without clinical ASCVD

4. Individuals aged 40–75, LDL-C 70–189 mg/dL, without ASCVD but estimated 10 yr CVD risk of $\geq 7.5\%$
10-Year ASCVD Risk by Varying Single Risk Factor Levels in Women

10-Year ASCVD Risk by Varying Single Risk Factor Levels in Women: Examination of the ASCVD Tool

10-year predicted risks for ASCVD by varying levels of single risk factors in a hypothetical non-Hispanic white woman (A-D) and AA woman (E-H) at selected ages: individually varied total cholesterol, HDL, untreated SBP, or treated SBP with all other risk factors held constant at approximate age-adjusted national means (including nondiabetic and nonsmoking)
10-Year ASCVD Risk by Varying Single Risk Factor Levels in Women

In a hypothetical man who was a nonsmoker and did not have diabetes, 10-year estimated ASCVD risk exceeded 7.5% at every level entered for total cholesterol, HDL cholesterol, and treated SBP after 65 years of age regardless of race. In a similar hypothetical woman, this occurred at 75 years of age regardless of race.

Risk varied curvilinearly with HDL for all ages in a AA & non-Hispanic white man but only up to 70 years of age for a non-Hispanic white woman & 60 years of age for an African-American woman.

Linear Variation Greatest for SBP (tx/untx)
10-Year ASCVD Risk in Diabetic Patients by Race-Sex Group

**Men:** average risk factors & untreated SBP, smoking or DM led to 10-year ASCVD risk ≥7.5% at 55y non-Hispanic WM/ 45y for AA man (50y & 40y, respectively, if tx SBP)

**Women:** average risk factors, smoking or DM led to 10-year risk ≥7.5% at 60y WW and 55y AA woman (60y & 50y, respectively, if tx SBP).

In all 4 race-sex groups, the presence of diabetes appeared to have a slightly more prominent effect on predicted risk than smoking.
Risk Assessment in Women: ATP III vs ASCVD

- **ATP III**: Intrinsic properties of ATP III demonstrated that few women exceeded treatment thresholds set by ATP III (predicting CHD endpoint)
  - Nondiabetic man with average risk factor levels could reach the 10% intermediate-risk category when > 60 y. A woman remained in a low-risk category at all eligible ages.
  - Moreover, unlike a man, who could exceed the 10% intermediate-risk threshold with modestly elevated risk factors at 45y, a woman could only reach this risk threshold with extreme risk factor levels after 70y

- **ASCVD**: The inclusion of stroke in the Pooled Cohort Equations & emphasis on absolute risk, independent of LDL targets, results in the identification of many more women who may benefit from consideration of statin treatment. Because stroke constitutes a much greater proportion of CVD events in women (many of whom are <75 y), these changes in risk assessment may hold important public health implications.
So Is It “All About The Age”?

- The incorporation of diabetes into quantitative risk assessment is another shift from ATP III, in which diabetes was considered a “risk equivalent” condition.
- Age Effect: Strong age effect on 10-year multivariable risk assessment was once again demonstrated. Even among individuals with optimal risk factors, 10-year ASCVD risk ≥7.5% was reached by 65y in a non-Hispanic WM, 70y in AA man, 75y in a non-Hispanic WW, and 70 y in an AA woman.
- Unfortunately, very few individuals with all optimal risk factors actually exist in the United States, as data from National Health and Nutrition Examination Surveys (NHANES) estimate a prevalence of 2.4% of all optimal risk factors in U.S. adults ≥60y.
What About Those at Optimal Risk?

- Very few Americans with Optimal Risk based on NHANES sample
- Thus, the clinical and public health significance of this feature of the equations is minimal.
What About Those at Optimal Risk?

- From a clinical perspective, the recommended clinician-patient discussion should facilitate shared decision making regarding the potential use of statins in these individuals with optimal risk factors. Conversely, young individuals 40 to 50 years of age may not reach a 10-year predicted ASCVD risk of 7.5% or even the moderately recommended risk threshold of 5% to <7.5% 10-year ASCVD risk in spite of significant risk factor burden.
- These findings highlight the importance of engaging in a clinician-patient discussion before statin prescription to review the specific components that contribute to the patient’s CVD risk and potential modifiable factors that could mitigate that risk.
- They also underscore the importance of the recommendation to assess longer-term risk in younger individuals (age ≤50 years of age) who may have substantial risk factor burden but low short-term risk, *primarily because of their age*. 
Limitations: ASCVD Risk Assessment

- **Older Adults**: virtually absent in the RCT data that informed the guideline
- Except for PROSPER (Prospective Study of Pravastatin in the Elderly at Risk)- 8,804 patients 70-82 y, & SAGE (Study Addressing Goals in the Elderly)- 893 patients 65-85 y, ~20-30% of 1° & 2° prevention lipid trial participants >70 y
- Statin treatment-risk paradox: despite high attributable risk of hypercholesterolemia & statin-associated reduction in all-cause mortality in elderly, statin use declines sharply at elderly age
- Despite SAGE & PROSPER demonstration of greater benefit in older patients with statin (High vs mod; statin vs placebo; respectively), paucity of data resulted only in 2° recommendation
Limitations: ASCVD Risk Assessment

• The PINNACLE registry data offer little further elucidation. The mean PINNACLE patients’ age was 65.2 years, and only 29.9% were in the Medicare category.
• The Pooled Cohort Equations provide no ASCVD estimate for those older than age 75 years, who have the highest absolute ASCVD event risk, nor did its antecedent, the Framingham Risk Score.
• The 2004 update to the National Cholesterol Education Program ATPIII guideline explicitly confirmed that older persons benefit from therapeutic LDL-C lowering
• Matters for aging population, specifically women
Limitations: ASCVD Risk Assessment

- **Race**: Pooled Cohort Equations provide guidance only for non-Hispanic whites & blacks. Data lacking for South Asians (high risk group) and any other race.

- **Vulnerable populations** merit special attention where observational studies or expert opinion may be all that is currently available.

- Avoid suggesting that these high-risk populations await their 40th birthdays for risk assessment and interventions.

- **Age-based discrimination at both ends** of the spectrum poses a potentially serious challenge.
So What Is Missing for Risk Assessment for Women When We Rely on ASCVD?
“Baby Weight” and Risk of Heart Disease and Diabetes

• Followed 305 Patients for 1 year post partum
• Women who maintained excess pounds between 3-12 months postpartum had elevated risk factors for diabetes and cardiovascular disease
• Women who didn't lose weight had higher blood pressure, higher levels of LDL, apo B and greater resistance to insulin (25% of cohort)
• Indirect Evidence that women who don’t lose their “baby weight” are at greater risk for heart disease

Kew S et al. Diabetes Care 2014
Preterm Delivery (PTD) and CVD Hospitalizations

Cohort (N=47,908): women who delivered preterm (<37 weeks' gestation) [N=5992 (12.5%)] vs. Normal term birth at the same period

During a follow-up period of >10 years, patients with PTD had higher rates of simple and complex cardiovascular events and higher rates of total cardiovascular-related hospitalizations.
Gestational Diabetes Mellitus and Risk of Maternal CVD

Nationwide: All births 2007-2008 in France: 7 year follow up; 1,518,990 deliveries with 62,958 with GDM

Hypertensive Disorders of Pregnancy (HDP) and Risk of Maternal CVD

<table>
<thead>
<tr>
<th>First Author, Year (Reference No.)</th>
<th>Relative Risk (95% CI)</th>
<th>Mean or Median Years of Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jónsdóttir, 1995 (67)</td>
<td>1.90 (1.02, 3.52)</td>
<td>Unknown</td>
</tr>
<tr>
<td>Hannaford, 1997 (66)</td>
<td>1.65 (1.26, 2.16)</td>
<td>Up to 26</td>
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<td>Irgens, 2001 (20)</td>
<td>3.61 (0.76, 17.18)</td>
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<td>Smith, 2001 (34)</td>
<td>2.10 (1.60, 2.60)</td>
<td>15–19</td>
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<td>Kestenbaum, 2003 (19)</td>
<td>2.55 (1.70, 3.83)</td>
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<tr>
<td>Wilson, 2003 (64)</td>
<td>1.95 (0.90, 4.22)</td>
<td>Unknown</td>
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<td>Funai, 2005 (65)</td>
<td>3.01 (2.18, 4.33)</td>
<td>30</td>
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<tr>
<td>Wikström, 2005 (21)</td>
<td>2.21 (1.56, 3.31)</td>
<td>19–28</td>
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<td>Lykke, 2009 (63)</td>
<td>1.82 (1.65, 2.00)</td>
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<tr>
<td>Mongraw-Chaffin, 2010 (39)</td>
<td>2.73 (1.78, 4.18)</td>
<td>37</td>
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<td>Skjaerven, 2012 (68)</td>
<td>1.90 (1.60, 2.20)</td>
<td>25</td>
</tr>
</tbody>
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Northern Finland Birth Cohort 1966: Risk For CVD, MI and MI Deaths in Women with Hypertension during Pregnancy.

Elevated BP during pregnancy, regardless of type, signals high risk of CVD, CKD and DM

Heart Disease Secondary to Breast Cancer Treatment

• Heart Disease and Breast Cancer Radiation:
  – Left vs Right Breast: Increased risk of CAD & MI
  – No Increase in cardiac death
• Heart Disease and Anthracyclines:
  – Reported 10-50% with some degree of heart failure in following 10 years
• Heart Disease and Herceptin (Tratuzumab):
  – Increased risk if age >50, use of hypertensive medications or low-normal heart function (3.8% vs 0.9% after 5 years)
  – In elderly (>70 y), much greater risk shown - higher rates in those with heart disease or with diabetes
• Heart Disease with Combination Chemotherapy:
  – 12,500 Women: 7X more likely to develop heart disease or CHF if received both anthracycline and Herceptin
  – 4X more likely to have heart disease or CHF received Herceptin alone

Harris et al. J Clin Oncology 2006:26:1390
Serrano et al. Annals of Oncology 2011
Bowles et al. Journal NCI. 2012;104:1293-1305
Risk of IHD after Radiation for Breast Cancer

Rates of Coronary events increased by 7.4%/Gy (P<0.001)
Avg radiation 1-2 Gy to Right Breast, usually higher in Left Breast
Risk of major coronary events began within 5 years after exposure

Darby et al. NEJM 2013;368:987-998
Future Considerations for ASCVD Risk Assessment in Women

- Women with Pregnancy-related CV Risks
- Women With PCOS
- Women with Breast Cancer
- Women with systemic autoimmune disorders (SLE/RA)
- Sex Hormones/HRT Use
- Race Specific: Need more data
- Age-Specific: Age-based discrimination at both ends of the spectrum; need more data on young and elderly

Must avoid suggesting that these high-risk populations await their 40th birthdays for risk assessment and interventions.
Approach

Assess ASCVD Risk
- Include FHx
- Consider MESA Risk Score

Inventory of Sex Specific Risk Factors
- Pregnancy CV Risks
- PCOS
- Breast Cancer/Chest Radiation
- HRT/Menopausal State

Assess Women Predominant Conditions
- SLE
- RA

Personalize for Patient
- Personalize/Precision Medicine