Diabetes Mellitus in Women Can be RUTHless
Lessons From the Raloxifene Use for The Heart (RUTH) Trial
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Since 1998, when Haffner et al reported that adults from Finland with type 2 diabetes mellitus (DM) were at the same risk for future myocardial infarction as adults with previous myocardial infarction, guidelines have increasingly advocated that people with DM are cardiovascular disease (CVD) risk equivalents and should be treated as secondary prevention. However, since that time, mixed results have been obtained by evaluating other cohorts, with several results not being able to demonstrate that adults with DM achieve a 20% 10-year risk. This concept of cardiac risk equivalency with DM has come under scrutiny.

The investigators of the Raloxifene Use for the Heart (RUTH) trial thus evaluated a very large cohort of women and followed them up for CVD events and all-cause mortality to evaluate this premise. This trial demonstrated that women with DM without known coronary heart disease (CHD) had a lower risk of nonfatal CHD and CVD events compared with women without DM and with CHD, but their risk of CHD mortality, CVD mortality, and all-cause mortality was similar to the risk of those with CHD and no DM. These results support the hypothesis that women with DM are at increased risk but do not achieve secondary prevention targets as a whole. In this very large study, Daniels et al evaluated almost 7000 women with a mean age of 67.3 years and a median follow-up of 5.6 years. Of these, 3672 women had a history of DM without known CHD, and 3265 women had a history of CHD without known DM. Cox proportional hazard models were used to compare cardiovascular outcomes in these 2 groups. This study demonstrated that all-cause mortality trended higher in those people with DM (hazard ratio, 1.18; 95% confidence interval, 0.98–1.42; P=0.08) but CVD events were lower in those with DM by 39% (P<0.0001). This suggests that DM may be affecting more than the coronaries, and their risk is multifactorial, but DM alone does not impart equivalent CVD risk to women with known CHD.

Despite the conclusions of Daniels et al, the RUTH study demonstrated that all women with DM are not CVD equivalents, with almost 40% lower risk than CHD patients. This is supported by other large studies of people with DM. Malik et al, in the Multi-Ethnic Study of Atherosclerosis (MESA), demonstrated that people with DM, without further stratification, do not achieve a 2% per year (10-year 20% rate) of CVD events.

Like most studies published since the study of Haffner et al, the RUTH trial confirmed that people with DM are not quite equivalent to those people with known CHD. Nonetheless, the presence of DM conveys an elevated risk, but there is marked heterogeneity among people with DM, even to the extent that it could affect treatment recommendations. Thus arises the dilemma: Do we continue to treat all women with DM as CHD risk equivalents (although many do not achieve that risk status), or do we further stratify to better align intensity of therapy with levels of CV risk?

The American College of Cardiology/American Heart Association guidelines for the assessment of cardiovascular risk in asymptomatic adults support that the concept of further stratification of people with DM is useful. These guidelines suggest that coronary artery calcium (CAC) scanning is useful for cardiovascular risk assessment in asymptomatic adults with DM 40 years of age and older (Class IIa recommendation). These recommendations are based on studies that demonstrate that not all people of DM have equal CV risk and that the CAC score has been found to be predictive beyond conventional risk factors in several DM cohorts. A study performed CAC measurement in 716 asymptomatic patients with DM and no CHD. During 8 years of follow-up, 40 patients had myocardial infarction, and 36 additional patients experienced cardiac death. The CHD event rate was 5.6% per year for patients with DM with scores of >400 compared with 0.7% per year for those with lower scores. The area under the receiver operating characteristic curve with CAC was significantly higher (0.77) for prediction of myocardial infarction than the Framingham Risk Score (0.63). This concept of DM risk stratification with CAC was further reinforced by the MESA study. MESA demonstrated that overall annual CHD event rates were 1.5% for people with DM and no congestive heart failure. They concluded that individuals with DM have low risks for CHD when CAC or carotid intima–media thickness is not increased. Those with DM who had CAC scores >100 had annual CHD rates of 2% or higher, whereas CAC scores of 0 were associated with annual rates <1.0%. The MESA study established that prediction of CHD and CVD events is improved by CAC more than by carotid intima–media thickness and supports the latest recommendations about CAC screening in those with DM.

As per the American Heart Association guidelines for women, low-density lipoprotein–lowering drug therapy is recommended simultaneously with lifestyle therapy...
in women with CHD to achieve a low-density lipoprotein-cholesterol >100 mg/dL (Class I; Level of Evidence A) and is also indicated in women with other atherosclerotic CVD or DM or 10-year absolute risk >20% (Class I; Level of Evidence B). Other American College of Cardiology/American Heart Association Guidelines also continue to advocate that DM imparts secondary prevention risk, and these guidelines have focused on statin therapy for higher-risk patients, rather than targeting low-density lipoprotein levels. The implications from the guidelines are that DM imparts a 10-year absolute risk of >20%. The RUTH study, as well as the MESA study, demonstrates that DM is not a true CVD risk equivalent in women but certainly supports the hypothesis that these women deserve extra attention and lipid-lowering therapy, if they have multiple CVD risk factors or CAC present. Nonetheless, whether one relies on the Finnish study or the results of MESA and RUTH, the conclusions by Daniels et al are prudent that women with DM are at increased risk compared with those without DM, and both patient and physician need further education related to CV risk assessment and possible pharmacological and lifestyle therapies.

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**References**


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