The Prediction of Atherosclerotic Cardiovascular Disease in Type 1 Diabetes Mellitus

Do We Just Stop Here?

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Type 1 diabetes mellitus (T1D) is well recognized to be associated with a higher incidence and prevalence of atherosclerotic cardiovascular disease (ASCVD). However, randomized clinical trials in which risk factors for ASCVD (blood pressure, lipids, glycemia) have been modified are nonexistent for T1D patients. Thus, any model that is developed must be based on observational data only. The Steno Risk Engine, as described in this issue of *Circulation,* is the second attempt at estimating ASCVD risk in T1D patients and differs somewhat in design and application from that previously created from the Swedish National Diabetes Register (NDR).

The Swedish NDR study was based on a model derived from 3661 T1D patients, with >90% having no history of ASCVD over a 5-year interval wherein 197 fatal/nonfatal ASCVD events (myocardial infarction or stroke) occurred. Nonfatal coronary heart disease was defined as nonfatal myocardial infarction, unstable angina, percutaneous coronary intervention, and/or coronary artery bypass grafting, whereas stroke was defined as fatal or nonfatal cerebral infarction or subarachnoid hemorrhage, or was unspecified. In the Swedish study, the hazard ratios for significant predictors of an ASCVD event were previous cardiovascular disease, 3.51; diabetes duration, 2.76; smoking, 1.76; macroalbuminuria (>200 μg/min), 1.52; age of onset of T1D, 1.47; log ratio total cholesterol:high-density lipoprotein cholesterol, 1.26; log hemoglobin A1c (HbA1c), 1.19; and log systolic blood pressure, 1.17. With the use of all 8 variables, the predicted 5-year risk was 5.4±7.9% with a C-statistic of 0.83.

In contrast, the Steno Risk Engine was entirely a primary prevention model of first fatal/nonfatal cardiovascular disease (CVD) events that included ischemic heart disease, ischemic stroke, heart failure, and peripheral arterial disease from 4306 T1D patients, and it included ASCVD risk factors similar to the Swedish study + lifestyle. Over a median follow-up of 6.8 years, a much higher percentage of patients experienced an event, 793 or 18.4% of the cohort. The predictive model for ASCVD after postestimate shrinkage identified risk factors similar to the Swedish T1D Study (Table) with significant predictor rate ratios estimated for macroalbuminuria (2300 mg/g creatinine), 2.09; microalbuminuria (30–299 mg/g creatinine), 1.55; age, 1.50; estimated glomerular filtration rate age <40 years; 1.50; estimated glomerular filtration rate age ≥40 years, 1.41; male sex, 1.26; no regular exercise, 1.26; smoking, 1.23; diabetes duration, 1.14; HbA1c, 1.13; low-density lipoprotein cholesterol, 1.09; and systolic blood pressure, 1.06 with an overall C-statistic of 0.826.

Of importance and interest was the superiority of the Steno Risk Engine C-statistic in predicting the 5-year risk of fatal/nonfatal ASCVD in the Steno cohort in comparison with the same population from the Swedish NDR (0.794) and with 2 predictors not typically used in T1D, the United Kingdom Prospective Diabetes Study type 2 diabetes mellitus risk engine (0.766)* and the ASCVD risk equation (0.748).* It is noteworthy that only the Steno Risk Engine included heart failure and peripheral arterial disease, yet the number of T1D patients for each of these outcomes was not stated, but likely was much less than ischemic heart disease and stroke. Yet, when heart failure and peripheral arterial disease were eliminated, the Steno Risk Engine C-statistic fell to 0.814 and the Swedish risk score improved slightly to 0.796. This suggests that not all of these differences were because of these outcome dissimilarities.

Important in the generation of risk predictors is validation, present in both the Swedish NDR and Steno studies. The Funen cohort in Denmark was quite different than that at the Steno Diabetes Center. The Funen population had many fewer smokers (29.4% versus 64.1%) and more patients on antihypertensive (40.4% versus 28.8%) and lipid-altering (41.0% versus 9.8%) medications, yet the C-statistic for 2119 T1D patients was similar, 0.803. It remains unclear as to whether these differences in risk factor–related medications and the time on therapy were optimally assessed by the analytic approaches used.

Despite the added value of the Steno Risk Engine for predicting ASCVD events in T1D patients, several additional issues need to be clarified to determine the generalizability and clinical impact of these findings. The age of the cohort ranged from 18 to 90 years, yet the mean age at diagnosis was 20.8 years with the 95th percentiles at 11.8 and 33.1. Thus, there must have been very few T1D patients with a diagnosis in early childhood. Another concern is the confirmation of T1D in patients >30 years, almost one-third of the population assessed. Is an absolute need for insulin therapy in patients with a low C-peptide or GAD65-positive antibodies sufficient.

*The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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to define T1D? Not infrequently, type 2 diabetes mellitus results in insulinopenia with inadequate basal insulin secretion (low C-peptide) and the need for insulin therapy, and GAD65-positive autoantibodies alone are less diagnostic for T1D than the presence of 2 to 4 autoantibodies. In addition, an inquiry relates to the reliability of spot versus 24 urine collections to assess the quantity of proteinuria. Although a spot urine is reasonably accurate in the microalbuminuric range, the reliability becomes less when protein excretion is in the higher range; herein, 5.2% of the cohort had macroalbuminuria. Despite the limitations of assessing lifestyle at 1 point in time on future events, the Steno group deserves credit in addressing levels of physical activity in addition to alcohol consumption and tobacco. Unfortunately, nutrient intake patterns, an important part of ASCVD prevention, were not evaluated. What was so surprising was the relatively small risk ratio of tobacco use on ASCVD events (1.23 with 64.1% current smokers), in particular, in comparison with the Swedish cohort (1.76 with 24.4% smokers).

Another risk that differed between the 2 studies was the duration of T1D with the Steno and Swedish studies quite discrepant, 1.14 versus 2.76, respectively. The average duration of diabetes mellitus in the Swedish study, however, was much longer (mean, 28.0 years) than in the Steno study (mean, 15.6 years). This is of interest in that the means for age were not different, 44.6 versus 42.2, respectively, for the Swedish and Steno studies. Importantly, this builds on a previous point, there were many more patients in the Swedish study that differed between the 2 studies, and more aggressive control of blood pressure and lipids/lipoproteins in the prevention of ASCVD events and related mortality in patients with T1D.

**Disclosures**

None.
References


