Intensive Diabetes Treatment and Cardiovascular Outcomes in Type 1 Diabetes Mellitus

Implications of the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study 30-Year Follow-up

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KEYWORDS

- Diabetes • Cardiovascular • Mortality • Risk • DCCT • EDIC

KEY POINTS

- The Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) study has effectively demonstrated that early intensive insulin therapy in type 1 diabetes mellitus (T1D) decreases cardiovascular mortality and several cardiovascular risk factors.
- Despite this, limited evidence exists for management of cardiovascular risk in T1D.
- Management of increased cardiovascular risk involves excellent glycemic, blood pressure, lipid control, and management of kidney disease.

INTRODUCTION

As the 100th anniversary of the discovery of insulin fast approaches, globally the prevalence of type 1 diabetes mellitus (T1D) is increasing.[1] T1D is a heterogeneous disorder characterized by autoimmune destruction of insulin-secreting pancreatic beta cells, and exogenous insulin replacement is crucial for metabolic optimization,

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typically achieved using insulin analogs and mechanical technologies. The actual prevalence of T1D is unknown, although one estimate by the Juvenile Diabetes Research Foundation (JDRF) suggests that there are up to 3 million individuals in the United States with T1D (http://www.jdrf.org/about/what-is-t1d/facts/).

Complications in T1D can be microvascular, neuropathic, or macrovascular. Atherosclerotic cardiovascular disease (CVD) is a long-term macrovascular complication that is a major concern when caring for individuals with T1D. It is now well established that T1D is associated with an accelerated risk of CVD compared with individuals without diabetes, leading to increased morbidity and mortality in both men and women.[2] In the past 2 decades, rates of complications in T1D have declined, with the largest relative declines in acute myocardial infarction (MI) and stroke.[3] Data from Canada and the United Kingdom document a 3% to 5% yearly decline in the rates of acute MI, stroke, cardiovascular mortality, and all-cause mortality in patients with diabetes since the early 1990s.[4,5] Despite a decline in mortality rates and consequent increase in life expectancy,[6] however, individuals with T1D still experience a 10-times higher cardiovascular risk than those without. Women are disproportionately affected,[7–9] and one estimate suggests that cardiovascular risk for young adults with childhood-onset T1D is increased more than 30-fold.[10] Thus the mortality burden remains high, and cardiovascular complications are the major contributor later in life.

The Diabetes Control and Complications Trial (DCCT) was a prospective randomized control trial comparing intensive versus standard glycemic control in individuals with recently diagnosed T1D.[11] This landmark study demonstrated that intensive blood glucose control with hemoglobin A_{1c} (HbA$_{1C}$) close to 7% reduced the incidence of microvascular complications of T1D. The long-term follow up trial Epidemiology of Diabetes Interventions and Complications (EDIC), which followed participants from the DCCT over 11 years for complications of T1D, demonstrated that early intensive therapy aimed at near-normal glycemia compared with conventional therapy decreased the risk of cardiovascular complications by 42%.[12] This article reviews the current evidence on CVD in T1D, primarily focusing on 30-year results from the DCCT/EDIC, and discusses implications for clinical care. CVD, for purposes of this review, is defined as coronary heart disease (CHD), cerebrovascular disease, and peripheral arterial disease.

EPIDEMIOLOGY OF CARDIOVASCULAR DISEASE IN TYPE 1 DIABETES MELLITUS

The prevalence of CVD in T1D in the EURODIAB IDDM Complications Study, which included 3250 patients from 16 European countries, was approximately 9% in men and 10% in women, increasing with age and duration of diabetes.[13] A large Finnish database report, which included 86 individuals with T1D, revealed that CVD mortality in T1D increases by 52% for every 1% increase in HbA$_{1C}$.[14]

When considered separately, CHD is the most common manifestation of CVD. CHD mortality rates are reported as between 6% and 8% and are higher in those over 40 years of age than in those under 40 years of age.[15] The reported average cumulative incidence of CHD ranges is approximately 15% over 15 years of follow-up.[16] Cerebrovascular disease occurs less commonly than CHD in T1D and, although incidence rates are low,[16] associated mortality is high.[17] The EURODIAB study reported an incidence of 0.74% per year, which is higher than the incidence in the general population.[13] A United Kingdom cohort study revealed increased hazard ratios for stroke in men and women with T1D.[18] PAD has been shown to be a predictor of CHD and cardiovascular mortality. Most available data in diabetes focus on lower extremity amputations. In a meta-analysis that included 5 studies of T1D patients, the risk of lower extremity amputation increased by 26% for every 1% increase in HbA$_{1C}$.[19]