Trends in Cardiovascular Complications of Diabetes

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MARKED REDUCTIONS IN cardiovascular disease (CVD) mortality have occurred over the last 50 years.1-11 It has been reported that adults with diabetes have experienced less decline in CVD mortality than those without diabetes.12-15 Adults with diabetes are at a 2- to 4-fold increased risk of CVD events relative to those without diabetes.16-20 and are at about a 60% increased risk of early mortality.21 However, it is uncertain whether the lack of decline in risk among diabetes patients actually exists, as conclusions drawn from current data are methodologically limited due to use of self-reported diabetes status,12,13 limited time span of data collection,12 and assessment of cause of death via death certificate.12,13

Given the importance of understanding whether CVD risk reduction has differentially affected adults with and without diabetes, we sought to test whether differences in CVD events have developed over the past several decades among those with and without diabetes in the Framingham Heart Study original and offspring cohorts. The Framingham Heart Study provides a unique setting in which this question can be answered because of long-term follow-up, standardized CVD event ascertainment, and careful documentation of concomitant risk factors.

METHODS

Study Design
Participants for this study were drawn from the Framingham Heart Study. Selection criteria and study design have been described previously.22,23 The standard clinic examination included an interview, physical examination, and laboratory tests. Cardiovascular events were documented throughout follow-up, standardized CVD event ascertainment, and careful documentation of concomitant risk factors.

Context Despite reductions in cardiovascular disease (CVD) mortality over the past few decades, it is unclear whether adults with and without diabetes have experienced similar declines in CVD risk.

Objective To determine whether adults with and without diabetes experienced similar declines in incident CVD in 1950-1995.

Design, Setting, and Participants Participants aged 45-64 years from the Framingham Heart Study original and offspring cohorts who attended examinations in 1950-1966 (“earlier” time period; 4118 participants, 113 with diabetes) and 1977-1995 (“later” time period; 4063 participants, 317 with diabetes). Incidence rates of CVD among those with and without diabetes were compared between the earlier and later periods.

Main Outcome Measures Myocardial infarction, coronary heart disease death, and stroke.

Results Among participants with diabetes, the age- and sex-adjusted CVD incidence rate was 286.4 per 10000 person-years in the earlier period and 146.9 per 10000 in the later period, a 49.3% (95% confidence interval [CI], 16.7%-69.4%) decline. Among participants without diabetes, the age- and sex-adjusted incidence rate was 84.6 per 10000 person-years in the earlier period and 54.3 per 10000 person-years in the later period, a 35.4% (95% CI, 25.3%-45.4%) decline. Hazard ratios for diabetes as a predictor of incident CVD were not different in the earlier vs later periods.

Conclusions We report a 50% reduction in the rate of incident CVD events among adults with diabetes, although the absolute risk of CVD is 2-fold greater than among persons without diabetes. Adults with and without diabetes have benefited similarly during the decline in CVD rates over the last several decades. More aggressive treatment of CVD risk factors and further research on diabetes-specific factors contributing to CVD risk are needed to further reduce the high absolute risk of CVD still experienced by persons with diabetes.

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We selected participants aged 45 to 64 years from 4 original cohort examinations, approximately 12 years apart (1950-1955, 1962-1966, 1977-1979, and 1986-1990), and 2 offspring examinations, 12 years apart (1979-1983 and 1991-1995). Participants could contribute information at more than 1 examination provided they reached the next examination free of a CVD event. For example, a 50-year-old participant with diabetes attending an examination in 1950 could contribute follow-up information for the next 12 years. If this participant was free of CVD in 1962, he/she could provide additional follow-up information for the assessment of CVD events.

Study participants were classified as belonging to 2 groups: an earlier period (examinations attended in the 1950s and 1960s) and a later period (examinations attended in the 1970s, 1980s, and 1990s). These 2 periods formed the basis for comparison of CVD incidence rates among participants with and without diabetes. Participants were followed up for CVD events for up to 12 years. The early period contributed 4118 participants (55385 person-years of follow-up) and the later period contributed 4063 participants (44073 person-years of follow-up). A total of 779 original cohort participants were part of the later period. Cardiovascular disease events were accrued until December 31, 2000.

The Boston Medical Center Institutional Review Board approved the study, and all participants gave written informed consent.

**Outcome Ascertainment**

Cardiovascular disease events were defined as recognized myocardial infarction, coronary heart disease death, and stroke. A panel of 3 physicians reviewed each CVD event according to preestablished criteria.²⁴

**Diabetes Diagnosis**

Diabetes was diagnosed as either fasting plasma glucose level of at least 126 mg/dL (7.0 mmol/L) (offspring examinations), nonfasting plasma glucose level of at least 200 mg/dL (11.1 mmol/L) (cohort examinations), or treatment with insulin or an oral hypoglycemic agent. Participants with a history of ketoacidosis or age at onset of younger than 30 years were excluded (n=16).

**Statistical Analysis**

Age- and sex-adjusted incidence rates for CVD events (per 10000 person-years) were calculated for each period; standard errors and 95% confidence intervals (CIs) were computed using the bootstrap bias-corrected and accelerated method,²⁵using SAS software, version 8.2.²⁶ Period-specific incidence rates were compared by calculating the percentage decline among participants with and without diabetes between the earlier and later periods. Proportional hazards models were used to examine whether the hazard ratio for diabetes as a CVD risk factor changed by period and included adjustment for age, sex, systolic blood pressure, hypertension treatment, current smoking, total cholesterol level, and body mass index. Time periods were pooled in the proportional hazards models and the interaction of time period and diabetes was used to test the null hypothesis of a constant hazard ratio for diabetes among time periods (ie, no interaction between the time period and diabetes). Secondary analyses were performed by sex and age. A 2-tailed P<.05 was considered statistically significant for all analyses.

Since diabetes was defined differently in the offspring and original Framingham cohorts, a sensitivity analysis was performed to examine the effect of changing the offspring cohort’s diabetes definition (fasting glucose level ≥126 mg/dL) to at least 140 mg/dL and at least 160 mg/dL.

To reduce the influence of aging in our closed cohort and to ensure that the age distributions across all decades overlapped, we restricted our analysis to participants between ages 45 and 64 years at index examinations.

**RESULTS**

There were 4005 nondiabetic participants in the earlier time period and 113 participants who had diabetes, compared with 3746 and 317 participants without and with diabetes in the later time period. Participants with diabetes tended to be older, have higher blood pressure, and were more likely to be obese. In the early compared with the later period, participants with and without diabetes both experienced significant declines in systolic blood pressure and total cholesterol level (Table 1).

In the earlier period, the age- and sex-adjusted incidence rate for CVD among participants with diabetes was 286.4 per 10000 person-years compared with 146.9 in the later period, a 49.3% decline (Table 2). Among participants without diabetes, the age- and sex-adjusted incidence rate for CVD in the earlier period was 84.6 per 10000 person-years compared with 54.3 in the later period, a 35.4% decline. Participants with diabetes experienced a greater absolute decline than those without diabetes (13.9%), but the 95% CI (−21.6% to 37.1%) suggests that the decline was not significantly different among those with and without diabetes. Women with diabetes experienced a 52.9% decline in CVD incidence rates (95% CI, 17.2%-88.6%) compared with a 48.4% decline (95% CI, 33.4%-63.3%) among women without diabetes. Similar trends were observed among men: those with diabetes experienced a 45.8% decline in CVD incidence rate (95% CI, 8.2%-83.5%) and those without diabetes experienced a 29.6% decline (95% CI, 17.5%-41.7%).

Period-specific hazard ratios for diabetes as a CVD risk factor were computed (Table 3). The multivariable-adjusted hazard ratio for diabetes as a CVD risk factor decreased slightly from the earlier to the later period (2.68 to 1.96). However, the interaction terms between time period and diabetes were not significant (P=.15). Results were similar when sex-specific analyses were performed (data not shown).
Table 1. Characteristics of Participants Aged 45 to 64 Years, With and Without Diabetes, by Time Period

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No Diabetes</th>
<th>Diabetes</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Earlier Period (n = 4005)†</td>
<td>Later Period (n = 3746)‡</td>
<td></td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>54 (5)</td>
<td>56 (6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Female</td>
<td>56 (2240)</td>
<td>54 (2030)</td>
<td>.04</td>
</tr>
<tr>
<td>Systolic blood pressure, mean (SD), mm Hg</td>
<td>137 (23)</td>
<td>127 (18)</td>
<td>&lt;.001</td>
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<tr>
<td>Hypertension</td>
<td>42 (1670)</td>
<td>33 (1251)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hypertension treatment</td>
<td>5 (186)</td>
<td>17 (631)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Current smoking</td>
<td>45 (1785)</td>
<td>26 (984)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Total cholesterol, mean (SD), mg/dL</td>
<td>245 (45)</td>
<td>215 (39)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Cholesterol-lowering medications¶</td>
<td>0.2 (8)</td>
<td>4 (157)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>BMI, mean (SD)#</td>
<td>26.1 (4.0)</td>
<td>26.8 (4.6)</td>
<td>.001</td>
</tr>
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<td>Total cholesterol, mean (SD), mg/dL</td>
<td>245 (45)</td>
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<tr>
<td>Female</td>
<td>56 (2240)</td>
<td>54 (2030)</td>
<td>.04</td>
</tr>
</tbody>
</table>

Abbreviation: NA, not applicable.
SI conversion: To convert total cholesterol to mmol/L, multiply by 0.0259.
*Data are reported as No. (%) unless otherwise noted.
¶P value for participants without diabetes, comparing time periods, obtained from analysis of variance or logistic regression after adjustment for age and sex; age is sex-adjusted and sex is age-adjusted.
*P value for baseline characteristics in participants with diabetes, comparing time periods, obtained from analysis of variance or logistic regression after adjustment for age and sex; age is sex-adjusted and sex is age-adjusted.
†Adjusted for age, sex, systolic blood pressure, hypertension treatment, current smoking, total cholesterol, and body mass index.
‡Data on cholesterol-lowering medications are not available for the 1950-1955 examination. Data refer to 1962-1966 examination for the earlier period.
§Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Obesity was defined as BMI greater than 30.

Table 2. Incidence Rates of Cardiovascular Disease Among Participants Aged 45 to 64 Years, With and Without Diabetes, by Time Period

<table>
<thead>
<tr>
<th></th>
<th>No Diabetes</th>
<th>Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular events, No.†</td>
<td>451</td>
<td>53</td>
</tr>
<tr>
<td>Incidence rate per 10,000 person-years‡</td>
<td>84.6</td>
<td>146.9</td>
</tr>
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</table>

Abbreviations: CI, confidence interval; NA, not applicable.
*Percentage decline = incidence rate (early) − incidence rate (late)/incidence rate (early).
†Cardiovascular events include recognized myocardial infarction, coronary heart disease death, and stroke.

Table 3. Hazard Ratios for Risk of Cardiovascular Disease Among Participants Aged 45 to 64 Years, With and Without Diabetes, by Time Period

<table>
<thead>
<tr>
<th></th>
<th>Early Period</th>
<th>Later Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age- and sex-adjusted</td>
<td>2.98 (2.10-4.24)</td>
<td>2.48 (1.84-3.34)</td>
</tr>
<tr>
<td>Multivariable-adjusted†</td>
<td>2.68 (1.88-3.82)</td>
<td>1.96 (1.44-2.66)</td>
</tr>
</tbody>
</table>

*P < .001 vs without diabetes for all hazard ratios.
†Adjusted for age, sex, systolic blood pressure, hypertension treatment, current smoking, total cholesterol, and body mass index.

**COMMENT**

Adults with diabetes have experienced a 50% reduction in the rate of incident CVD, although persons with diabetes have remained at a consistent, approximate 2-fold excess for CVD events compared with those without diabetes. Adults without diabetes have had a smaller but statistically similar 35% reduction in CVD event rates. Patients with diabetes have benefited in a similar manner to those without diabetes during the decline in CVD rates in the US population over the last several decades. Although gains have been made, substantial opportunity remains for additional progress to reduce the high absolute risk of CVD events in persons with diabetes.

The results of our study differ from those previously published, which have suggested that adults with diabetes have experienced less declines in CVD risk than those without diabetes. Differences in our findings may be attributed to the longer duration of follow-up, and comparison groups composed of older as well as more contemporary data and a different outcome measure. For instance, Gu et al compared CVD mortality rates between 1971-1975 and 1982-1984. Our earlier time period contains data from the 1950s, and our later time period uses data collected as recently as 2000, allowing a much longer period over which to detect declines in

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CVD event rates. In addition, other studies have relied on self-reported physician diagnosis of diabetes\textsuperscript{23,25} or medical record review for mention of diabetes,\textsuperscript{14} whereas our diabetes diagnosis is derived from routine screening by use of glucose measures and direct questioning of participants. In addition, other studies that have reported less declines in CVD risk for those with diabetes have relied on death certificates to obtain cause of death.\textsuperscript{12-15} Death certificates have been shown to overestimate deaths attributed to coronary heart disease by more than 24%.\textsuperscript{27} Furthermore, reporting of diabetes on death certificates is not random.\textsuperscript{28,29} Thus, if a death certificate of a descendent with diabetes is more likely to record a CVD death, the risk of CVD death among persons with diabetes may be inflated. Since coding practices of death certificates change over time, heightened awareness of diabetes as a CVD risk factor may have led to increases in the attribution of CVD deaths to diabetes in more recent periods.

A key question raised by prior studies is whether the presence of diabetes reduces the benefit of advances in CVD prevention and treatment. Our data do not support this claim. When comparing CVD risk factors from the earlier vs the later period, we demonstrate significant declines for important CVD risk factors, including systolic blood pressure and total cholesterol. These findings occur in the setting of data from clinical trials demonstrating significant benefits of CVD risk factor reduction among diabetics. The UK Prospective Diabetes Study showed that blood pressure control reduced the risk of death from diabetes.\textsuperscript{30} Results from the Heart Outcomes Prevention Evaluation (HOPE) and MICRO-HOPE studies showed that ramipril reduced CVD events by 25% among diabetics.\textsuperscript{31} A multifaceted intervention regarding CVD risk factor reduction among patients with type 2 diabetes reduced CVD events by 50%.\textsuperscript{32} Among large clinical trials, subgroup analyses of patients with diabetes have demonstrated higher absolute reductions in CVD outcomes compared with those without diabetes, including blood pressure\textsuperscript{33} and lipid control.\textsuperscript{34,35} Thus, data from clinical trials provide the mechanism by which adults with and without diabetes can experience reductions in CVD incidence.

Despite significant declines in CVD risk associated with diabetes, adults with diabetes are still at an approximately 2-fold risk of CVD events compared with those without diabetes. Ongoing efforts remain necessary to promote aggressive CVD risk reduction among adults with diabetes. Data from the Third National Health and Nutrition Examination Survey show that adults with diabetes are not treated optimally.\textsuperscript{36} Eighteen percent of participants had poor glycemic control (hemoglobin A\textsubscript{1c} >9.5%), 34.3% had blood pressure greater than 140/90 mm Hg, and 58% had low-density lipoprotein cholesterol levels greater than 130 mg/dL. Given that the prevalence of diabetes is increasing,\textsuperscript{37,41} it is critical that efforts be made to implement findings from clinical trials to promote CVD risk factor reduction.

Some limitations in our data exist. Our study sample is not nationally representative, nor is it ethnically diverse. However, the relations of risk factors to cardiac outcomes observed in Framingham have been validated in several ethnically and geographically diverse cohorts and were found to be applicable.\textsuperscript{33,44} We were unable to rely on a standard definition of diabetes in both of our study periods. The earlier period is composed of participants with diabetes diagnosed predominantly by nonfasting glucose samples, whereas the later period consists of diabetes diagnoses made by both nonfasting and fasting glucose samples. We have tried to circumvent this issue by conducting a sensitivity analysis. Given that our data are not substantially different, we do not believe that this difference in diabetes diagnosis can fully account for our findings.

We report a 30% reduction in the rate of incident CVD events among adults with diabetes. Adults with and without diabetes have benefited similarly during the decline in CVD rates in the US population over the last several decades. However, the absolute risk of CVD among those with diabetes remains 2-fold greater compared with persons without diabetes. Both aggressive treatment of conventional CVD risk factors and further research on diabetes-specific factors contributing to CVD risk are needed to further reduce the high absolute risk of CVD still experienced by persons with diabetes.

Author Contributions: Dr Fox had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Fox, Sorlie, Savage. Acquisition of data: Levy, D’Agostino, Wilson. Analysis and interpretation of data: Fox, Coady, Sorlie, Meigs, D’Agostino, Wilson, Savage. Drafting of the manuscript: Fox. Critical revision of the manuscript for important intellectual content: Coady, Sorlie, Levy, Meigs, D’Agostino, Wilson, Savage. Statistical analysis: Fox, Coady, Sorlie, D’Agostino, Wilson. Obtained funding: Levy. Administrative, technical, or material support: Meigs, D’Agostino, Savage. Study supervision: Levy, Meigs, Wilson.

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Role of the Sponsor: Drs Fox, Sorlie, and Savage and Mr Coady, as employees of the National Heart, Lung, and Blood Institute, contributed to the design and conduct of the study, the collection, analysis, and interpretation of the data, and the preparation, review, and approval of the manuscript.

REFERENCES


