Alcohol Intake and the Risk of Coronary Heart Disease Mortality in Persons With Older-Onset Diabetes Mellitus

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A recent meta-analysis and reported in subsequent articles, numerous prospective epidemiological studies conducted with selected cohorts and general populations and subgroups have reported a nearly consistent pattern of a beneficial effect of modest levels of alcohol consumption, with reductions in the risk of coronary heart disease (CHD) or death ranging from 20% to 60%. Some mechanisms cited for the protective effect of moderate alcohol intake include its antiatherogenic role in increasing the levels of high-density lipoprotein cholesterol (HDL-C), its hemostatic effects by decreasing platelet aggregation and increasing fibrinolytic activity, and its possible association with beneficial changes in insulin and glucose metabolism.

Despite nutrition information and guidelines that advise against depriving diabetic patients of the potential benefit of moderate alcohol intake against cardiovascular events, the association between alcohol consumption and risk of cardiovascular outcomes in diabetic individuals has not been determined.

Objective To examine the relationship between alcohol intake and coronary heart disease (CHD) mortality in persons with older-onset diabetes.

Design Population-based, prospective cohort study conducted from 1984 through 1996, with a follow-up of up to 12.3 years.

Setting and Participants A total of 983 older-onset diabetic individuals (mean [SD] age, 68.6 [11.0] years; 45.2% male; 98.5% white) were interviewed about their past-year intake of alcoholic beverages during the 1984-1986 follow-up examination of a population-based study of diabetic persons in southern Wisconsin.

Main Outcome Measure Time to mortality from CHD by category alcohol intake.

Results Alcohol use was inversely associated with risk of CHD mortality in older-onset diabetic subjects. The CHD mortality rates for never and former drinkers were 43.9 and 38.5 per 1000 person-years, respectively, while the rates for those with alcohol intakes of less than 2, 2 to 13, and 14 or more g/d were 25.3, 20.8, and 10.0 per 1000 person-years, respectively. Compared with never drinkers and controlling for age, sex, cigarette smoking, glycosylated hemoglobin level, insulin use, plasma C-peptide level, history of angina or myocardial infarction, digoxin use, and the presence and severity of diabetic retinopathy, former drinkers had a relative risk (RR) of 0.69 (95% confidence interval [CI], 0.43-1.12); for those who drank less than 2 g/d (less frequent than 1 drink a week), the RR was 0.54 (95% CI, 0.33-0.90); for 2 to 13 g/d, it was 0.44 (95% CI, 0.23-0.84); and for 14 or more g/d (about 1 drink or more a day), it was 0.21 (95% CI, 0.09-0.48). Further adjustments for blood pressure, body mass index, education, physical activity, diabetes duration, hypertension history, overt nephropathy, peripheral neuropathy, lipid measures, or intake of medications such as aspirin and antihypertensive agents did not change the associations observed.

Conclusion Our results suggest an overall beneficial effect of alcohol consumption in decreasing the risk of death due to CHD in people with older-onset diabetes.

For editorial comment see p 279.
dence for the cardioprotective role of moderate alcohol intake in general populations. Coronary heart disease remains the leading cause of death in persons with type 2 diabetes, accounting for about 40% of all deaths. It may be possible that the level of protection, if any, from coronary events differs from that seen in generally healthier cohorts because of the presence of more coexisting medical problems, including the macrovascular and microvascular complications commonly seen in diabetes, and the different exposures to medications used for such conditions. The purpose of this study was to examine the association between alcohol consumption and mortality due to CHD in persons with older-onset diabetes using a population-based prospective study design.

METHODS

Study Cohort and Procedures

The Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) has been described in detail in earlier publications. Briefly, WESDR is a population-based study of diabetic persons that began in 1980 by working with 99% of 457 physicians providing primary care for diabetic patients in an 11-county area of southern Wisconsin. A total of 10,135 diabetic persons were identified, of which a representative sample of 2990 was selected for the baseline examination. This sample included all 1210 younger-onset diabetic patients (diabetes diagnosed before age 30 years) and a probability sample of 1780 older-onset diabetic persons (diabetes diagnosed after age 30 years), 824 of whom were taking insulin. Follow-up interviews and/or examinations were conducted in 1984-1986, 1990-1992, and 1995-1996 to update information on potential risk factors and relevant clinical events. The subject of this study was the older-onset group, of which 1370 participated in the baseline examination from 1980 to 1982. Of these, 1.5% refused to participate in the 1984-1986 follow-up examination, while 1.2% had an interview only, 0.4% were lost to follow-up, and 24.8% of the original cohort had died. The analyses in this article were performed for the remaining 987 subjects who returned for the follow-up examination done in 1984-1986, when information on alcohol intake was first obtained. We excluded 4 individuals who had missing information on alcohol consumption, leaving 983 older-onset diabetic persons in the study cohort, 98.5% of whom were white, with characteristics shown in Table 1.

Pertinent procedures in the 1984-1986 examination included standardized methods for measuring height, weight, and blood pressure, dilating the pupils and taking stereoscopic color fundus photographs of 7 standard fields for determining the presence and severity of diabetic retinopathy; administering a structured interview for information on risk factors; taking urine samples for a

Table 1. Characteristics of Older-Onset Diabetic Persons Who Reported Information on Alcohol Intake in the 1984-1986 Examination of the Wisconsin Epidemiologic Study of Diabetic Retinopathy

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total (N = 983)</th>
<th>Never Drinkers (n = 107)</th>
<th>Former Drinkers (n = 322)</th>
<th>Drinkers, Average Alcohol Intake, g/d</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>&lt;2 (n = 340)</td>
<td>2-13 (n = 117)</td>
<td>14-28 (n = 60)</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>68.6 (11.0)</td>
<td>73.2 (9.3)</td>
<td>71.3 (9.8)</td>
<td>67.0 (11.8)</td>
</tr>
<tr>
<td>Male, %</td>
<td>45.2</td>
<td>42.6</td>
<td>42.4</td>
<td>42.4</td>
</tr>
<tr>
<td>Ever cigarette smoker, %</td>
<td>46.6</td>
<td>46.6</td>
<td>46.7</td>
<td>48.7</td>
</tr>
<tr>
<td>Current cigarette smoker, %</td>
<td>12.9</td>
<td>12.9</td>
<td>12.7</td>
<td>12.7</td>
</tr>
<tr>
<td>Systolic blood pressure, mean (SD), mm Hg</td>
<td>143.0 (23.1)</td>
<td>142.7 (24.3)</td>
<td>143.9 (23.2)</td>
<td>142.4 (23.9)</td>
</tr>
<tr>
<td>Diastolic blood pressure, mean (SD), mm Hg</td>
<td>75.3 (12.3)</td>
<td>71.5 (12.0)</td>
<td>73.7 (12.8)</td>
<td>75.9 (11.7)</td>
</tr>
<tr>
<td>Body mass index, mean (SD), kg/m²</td>
<td>29.1 (6.0)</td>
<td>28.8 (6.2)</td>
<td>29.3 (5.8)</td>
<td>29.4 (6.6)</td>
</tr>
<tr>
<td>Education ≥12 y, %</td>
<td>58.5</td>
<td>43.8</td>
<td>51.2</td>
<td>62.4</td>
</tr>
<tr>
<td>Regularly active ≥3 times per week, %</td>
<td>20.0</td>
<td>16.0</td>
<td>16.5</td>
<td>19.5</td>
</tr>
<tr>
<td>Taking insulin, %</td>
<td>56.4</td>
<td>61.7</td>
<td>57.3</td>
<td>54.7</td>
</tr>
<tr>
<td>Taking oral glucose-lowering agent, %</td>
<td>34.0</td>
<td>30.8</td>
<td>34.0</td>
<td>37.6</td>
</tr>
<tr>
<td>Diabetes duration, mean (SD), y</td>
<td>15.3 (8.0)</td>
<td>15.6 (8.3)</td>
<td>15.8 (8.1)</td>
<td>14.6 (7.4)</td>
</tr>
<tr>
<td>Glycosylated hemoglobin level, mean (SD), %</td>
<td>9.3 (1.9)</td>
<td>9.3 (1.9)</td>
<td>9.2 (1.9)</td>
<td>9.5 (1.9)</td>
</tr>
<tr>
<td>Plasma C-peptide level, mean (SD), nmol/L</td>
<td>1.02 (0.92)</td>
<td>1.07 (0.99)</td>
<td>1.11 (0.93)</td>
<td>1.02 (0.96)</td>
</tr>
<tr>
<td>History of angina or myocardial infarction, %</td>
<td>27.1</td>
<td>28.8</td>
<td>32.2</td>
<td>25.7</td>
</tr>
<tr>
<td>History of hypertension, %</td>
<td>66.5</td>
<td>75.2</td>
<td>70.4</td>
<td>63.9</td>
</tr>
<tr>
<td>Diabetic proliferative retinopathy, %</td>
<td>11.0</td>
<td>10.6</td>
<td>13.1</td>
<td>9.8</td>
</tr>
<tr>
<td>Overt nephropathy, %</td>
<td>19.7</td>
<td>24.0</td>
<td>22.9</td>
<td>16.5</td>
</tr>
<tr>
<td>Peripheral neuropathy symptoms, %</td>
<td>33.0</td>
<td>29.5</td>
<td>34.0</td>
<td>36.0</td>
</tr>
</tbody>
</table>

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semiquantitative determination of urinary proteins (Labstix, Ames Division, Miles Inc, Elkhart, Ind); and taking blood samples for standardized measurements of glycosylated hemoglobin and plasma C-peptide levels for the whole cohort and serum total cholesterol and HDL-C levels for a subset of the cohort. All procedures were performed in a mobile van in or near the city in which the participants lived. The study was approved by the institutional review board of the University of Wisconsin Medical School, Madison.

Ascertainment and Computation of Alcohol Intake
During the 1984-1986 and 1990-1992 follow-up examinations, participants were asked about their intake of alcoholic beverages. Questions included whether participants had ever had any beer, wine, or liquor at any time during their lives; whether they had at least 1 drink of beer, wine, or liquor in the past year; and, if so, about how often they drank an alcoholic beverage. Additional questions were asked about the number of servings consumed during the average week of 12-oz (355-mL) bottles or cans of beer, 4-oz (118-mL) glasses of wine, and 1.5-oz (44-mL) shots of liquor. From these, we computed the average total amount of absolute alcohol consumed in grams per day, using an equation based on a published national survey of alcohol consumption: average alcohol intake (grams per day) = 1/7 × (0.04B × 12) + (0.15W × 4) + (0.45L × 1.5) oz × 28.35 g/oz, where B, W, and L are the numbers of servings consumed during an average week of beer, wine, and liquor, respectively. Although we did not directly validate the alcohol intake data, the rank correlations between our calculated levels of alcohol intake using this equation and serum levels of HDL-C were statistically significant in both examinations (1984-1986 and 1990-1992).

Identification of Deaths
Deaths were ascertained from regular contact with study participants and their relatives, designated contact persons, or physicians and from reviews of daily newspaper obituaries. Identified deaths were confirmed with annual requests for death certificate information made to the Section of Vital Statistics of the Wisconsin Center for Health Statistics. The names of persons who had been lost to follow-up, who had moved out of Wisconsin, or who were suspected to be deceased were submitted for matching against Wisconsin death records and the National Death Index. For each match made, a copy of the death certificate was obtained from the appropriate state. Only deaths confirmed by death certificates were included in the definition of CHD death. Persons who were thought to be deceased but for whom a death certificate could not be located were considered to be alive as of the last contact date they were known to be alive. Medical conditions on the Wisconsin death certificates were coded by trained nosologists in the Wisconsin Division of Health using the International Classification of Diseases, Ninth Revision (ICD-9). Out-of-state certificates were coded and processed in the same manner. Participants were considered to have died of CHD if the underlying cause of death was assigned to ICD-9 codes 410 through 414.9. Although we did not validate this coding, other studies have observed a relatively high validity of death certificates that stated CHD as the cause of death. No codes for sudden death or other ill-defined and unknown causes were included in our definition of CHD mortality.

Statistical Analysis
Participants were grouped into the following categories based on the amount of absolute alcohol they consumed in the past year, as reported in the 1984-1986 examination: 0 g/d (all nondrinkers), less than 2 g/d (less frequent than 1 drink per week), 2 to 13 g/d (at least 1 drink per week), 14 to 28 g/d (1-2 drinks per day), and more than 28 g/d (more than 2 drinks per day). Due to the possibility that abstainers of alcohol could have stopped drinking because of the presence of comorbid conditions, persons with an alcohol intake of 0 were further divided into 2 categories: lifetime abstainers or never drinkers, who were used as the reference category, and former drinkers.

After examining the frequency distribution of all variables, the association of alcohol intake with possible confounders was assessed by χ2 analysis and analysis of variance. Mortality rates were calculated as the number of deaths from CHD divided by the total number of person-years accrued for each cohort member, based on the length of follow-up (computed as the number of days from the date of the 1984-1986 examination to the date of death, date of last contact, or December 31, 1996, whichever was earliest). The relation of alcohol consumption level and subsequent mortality due to CHD was examined with Kaplan-Meier analysis. The log-rank test was used to evaluate whether mortality differed by groups of alcohol intake. Cox proportional hazards regression was used to assess associations adjusted for age (as a continuous measure) and sex as well as those further controlled by factors that could affect the risk of coronary events and those potentially related to both mortality and alcohol intake. These included cardiovascular risk factors, such as cigarette smoking (classified as never, former, current), systolic and diastolic blood pressure, body mass index (calculated as weight in kilograms divided by the square of height in meters), education (<12, 12, or >12 years), and physical activity (defined as engaging in regular physical activity ≥3 times per week); and diabetes-related variables, such as use of insulin, intake of oral glucose-lowering agents, duration of diabetes, and levels of glycosylated hemoglobin (grouped as <8.0%, 8.0%-9.9%, and ≥10.0%) and plasma C-peptide (categorized as undetectable, 0.03-0.29, 0.30-0.89, 0.90-1.49, and ≥1.50 nmol/L). Other comorbid conditions (or their markers) examined included history of hyper-
tension (defined as systolic blood pressure of ≥160 mm Hg or diastolic of ≥95 mm Hg, or taking antihypertensive medications), intake of antihypertensive agents, history of angina or myocardial infarction, intake of digoxin, intake of aspirin, the presence and severity of diabetic retinopathy (grouped into none, mild to early nonproliferative, moderate to severe nonproliferative, and proliferative retinopathy, based on fundus photographs graded in masked fashion using a modified Airli House Classification system\textsuperscript{36,30,31}), presence of peripheral neuropathy symptoms (defined as loss of tactile sensation in hands or feet or decreased ability to feel the hotness or coldness of things touched), and presence of overt nephropathy (defined as having a urinary protein concentration of ≥0.30 g/L as measured by a reagent strip, or a history of dialysis or renal transplantation). Variables were progressively entered in the regression models, which included age and sex, starting from cardiovascular factors, to diabetes-related variables, and finally to comorbid conditions or their markers. Variables that remained independently related to CHD mortality were retained in the final model.

To examine the presence of effect modification, stratified analyses were performed on subgroups of participants defined by specific variables, including age (<69.6 vs ≥69.6 years, the median age for the cohort), sex, cigarette smoking (never vs ever), insulin use, glycosylated hemoglobin level (<9.1% vs ≥9.1%, the median value), aspirin intake, history of hypertension, history of angina or myocardial infarction, and presence of retinopathy, peripheral neuropathy symptoms, and overt nephropathy. Likelihood ratio tests\textsuperscript{32} were used to check for interactions in the proportional hazards models, which included cross-product terms for these variables and each alcohol intake level.

Serum lipid levels are important risk factors for coronary events and might influence our findings. Therefore, for the subset of the study cohort for whom we had measurements of HDL-C, total cholesterol, and the ratio of total cholesterol to HDL-C (n = 451), we repeated our multivariate analyses including each of these variables.

The assumption of proportionality for the Cox regression models was tested and met. Hazard ratios were reported as relative risks (RRs) with 95% confidence intervals (CIs). All P values were 2-tailed, with values of .05 or less indicating statistical significance. The analyses were performed using SAS Version 6.12 (SAS Institute Inc, Cary, NC).

RESULTS

Of the 983 persons eligible for follow-up, 10.9% were lifetime abstainers; 32.8% were former drinkers; and 34.6%, 11.9%, 6.1%, and 3.8% had alcohol intakes of less than 2, 2 to 13, 14 to 28, and more than 28 g/d, respectively.

Not all potential risk factors were evenly distributed among the alcohol intake groups (Table 1). Persons with higher alcohol consumption were more likely to be younger, male, and smokers, and to have higher diastolic blood pressure and education. Compared with nondrinkers, drinkers were less likely to be sedentary and to be taking insulin and tended to have relatively lower plasma C-peptide levels. No clear patterns were observed for the other variables, although the rates of comorbid conditions or complications (eg, history of CHD and hypertension, presence of proliferative retinopathy and overt nephropathy) from nondrinkers as a group to drinkers with increasing alcohol intake levels suggested V- or J-shaped patterns (Table 1).

During follow-up of up to 12.3 years (7004 person-years), we identified 198 CHD deaths, 100 from acute myocardial infarction (ICD-9 code 410) and 98 from coronary atherosclerosis or chronic ischemic heart disease (ICD-9 codes 414.0-414.9). The overall CHD mortality rate for the study cohort was 28.3 per 1000 person-years. The rates for never drinkers and former drinkers were 43.9 and 38.5 per 1000 person-years, respectively, while the rates for those with alcohol intakes of less than 2, 2 to 13, 14 to 28, and more than 28 g/d were 25.3, 20.8, 9.8, and 10.4 per 1000 person-years, respectively. Because of the small number of cases and the similar coronary mortality rates for moderate (14-28 g/d) and heavy (>28 g/d) drinkers, we merged these 2 categories in subsequent analyses.

Compared with never drinkers, drinkers had significantly lower risks

\textbf{Figure.} Survival Curves for Coronary Heart Disease Mortality According to Alcohol Intake in 983 Older-Onset Diabetic Persons, Wisconsin Epidemiologic Study of Diabetic Retinopathy, 1984-1996

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure}
\caption{Survival Curves for Coronary Heart Disease Mortality According to Alcohol Intake in 983 Older-Onset Diabetic Persons, Wisconsin Epidemiologic Study of Diabetic Retinopathy, 1984-1996}
\end{figure}
for death due to CHD (Figure). The age- and sex-adjusted RRs progressively decreased across increasing levels of alcohol intake (Table 2). Additional adjustments for significant cardiovascular factors, diabetes-related variables, and comorbid conditions or markers, which included cigarette smoking, insulin use, glycosylated hemoglobin level, plasma C-peptide level, history of angina or myocardial infarction, digoxin use, and diabetic retinopathy severity, showed that the associations for alcohol users remained significant. The RRs were 0.54 (95% CI, 0.33-0.90), 0.44 (95% CI, 0.23-0.84), and 0.21 (95% CI, 0.09-0.48) for those with intake levels of less than 2, 2 to 13, and 14 or more g/d, respectively (Table 2). Further control for the presence of overt nephropathy (also significantly related to CHD mortality in this cohort in the presence of all variables in the earlier model) had little effect on the significant associations observed. Results were also essentially unchanged with inclusions of other factors not independently related to CHD death, such as blood pressure, body mass index, education, physical activity, diabetes duration, hypertension history, peripheral neuropathy symptoms, or intake of aspirin, antihypertensive drugs, or oral hypoglycemic agents (data not shown). In all multivariate-adjusted models, the RRs for former drinkers were generally 15% to 30% lower than lifetime abstainers, although these data were not statistically significant (Table 2).

We examined variables, including age, sex, smoking status, insulin use, glycosylated hemoglobin level, aspirin intake, and hypertension history, for their potential to modify the negative associations between alcohol intake and fatal CHD. None were statistically significant (P > 0.05 for all) as interaction variables. In earlier studies of general cohorts, there were concerns that current abstainers were more likely to have other comorbid conditions such that a protective effect of modest alcohol intake was not apparent among those who had no coexisting disease or history of serious illnesses. We tested this hypothesis in our cohort of older-onset diabetic persons and found no significant differences in the alcohol–CHD mortality relationship between persons who had and did not have the diabetic complications of overt nephropathy, any grade of retinopathy, symptoms of peripheral neuropathy, any grade of angina or myocardial infarction (Table 3). Although some subgroup RRs were not statistically significant because of smaller numbers, all RRs for alcohol drinkers compared with never drinkers still showed lower risks, regardless of disease status.

Because serum lipid levels might have influenced our findings, we performed similar analyses for 451 dia-

### Table 2. Mortality Rates and RRs for Death Due to CHD According to Alcohol Intake in 983 Older-Onset Diabetic Persons, WESDR*

<table>
<thead>
<tr>
<th>Variables</th>
<th>Never Drinkers (n = 107)</th>
<th>Former Drinkers (n = 322)</th>
<th>&lt;2 (n = 340)</th>
<th>2-13 (n = 117)</th>
<th>≥14 (n = 97)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of deaths from CHD</td>
<td>27</td>
<td>76</td>
<td>66</td>
<td>21</td>
<td>8</td>
</tr>
<tr>
<td>CHD mortality per 1000 person-years</td>
<td>43.9</td>
<td>38.5</td>
<td>25.3</td>
<td>20.8</td>
<td>10.0</td>
</tr>
<tr>
<td>Age- and sex-adjusted RR (95% CI)</td>
<td>1.00 (Reference)</td>
<td>0.84 (0.54-1.31)</td>
<td>0.68 (0.43-1.08)</td>
<td>0.52 (0.29-0.94)</td>
<td>0.26 (0.12-0.60)</td>
</tr>
<tr>
<td>Multivariate model 1 RR (95% CI)†</td>
<td>1.00 (Reference)</td>
<td>0.77 (0.48-1.23)</td>
<td>0.60 (0.37-0.99)</td>
<td>0.45 (0.24-0.85)</td>
<td>0.27 (0.12-0.62)</td>
</tr>
<tr>
<td>Multivariate model 2 RR (95% CI)‡</td>
<td>1.00 (Reference)</td>
<td>0.69 (0.43-1.12)</td>
<td>0.54 (0.33-0.90)</td>
<td>0.44 (0.23-0.84)</td>
<td>0.21 (0.09-0.48)</td>
</tr>
</tbody>
</table>

*RR indicates relative risk, as estimated by the hazard ratio using Cox proportional hazards regression, comparing each alcohol intake group with older-onset diabetic persons who were never drinkers; CHD, coronary heart disease; WESDR, Wisconsin Epidemiologic Study of Diabetic Retinopathy; and CI, confidence interval. †Multivariate model 1 was adjusted for age, sex, cigarette smoking, insulin use, glycosylated hemoglobin level, plasma C-peptide level, aspirin intake, and hypertension history. ‡Multivariate model 2 was as adjusted in multivariate model 1 and additionally adjusted for history of angina or myocardial infarction, use of digoxin, and the presence and severity of diabetic retinopathy.

### Table 3. Stratified Analysis: Mortality Rates and Multivariate-Adjusted RRs for Death Due to CHD According to Alcohol Intake and Subgroups of Older-Onset Diabetic Persons Defined by History of Angina or Myocardial Infarction at Baseline, WESDR*

<table>
<thead>
<tr>
<th>Variables</th>
<th>Never Drinkers (n = 704)</th>
<th>Former Drinkers (n = 478)</th>
<th>&lt;2 (n = 143)</th>
<th>2-13 (n = 126)</th>
<th>≥14 (n = 101)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of CHD deaths</td>
<td>15</td>
<td>41</td>
<td>39</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>CHD mortality per 1000 person-years</td>
<td>32.8</td>
<td>29.1</td>
<td>19.0</td>
<td>14.0</td>
<td>4.8</td>
</tr>
<tr>
<td>Multivariate RR (95% CI)</td>
<td>1.00 (Reference)</td>
<td>0.75 (0.39-1.45)</td>
<td>0.65 (0.33-1.28)</td>
<td>0.51 (0.22-1.21)</td>
<td>0.20 (0.06-0.77)</td>
</tr>
</tbody>
</table>

*RR indicates relative risk, as estimated by the hazard ratio using Cox proportional hazards regression, comparing each alcohol intake group with older-onset diabetic persons who were never drinkers, adjusted for age, sex, cigarette smoking, insulin use, glycosylated hemoglobin level, plasma C-peptide level, aspirin use, and the presence and severity of diabetic retinopathy, CHD, coronary heart disease; WESDR, Wisconsin Epidemiologic Study of Diabetic Retinopathy; and CI, confidence interval.
betic persons, a subset of the older-onset diabetic cohort who had complete information on HDL-C and total cholesterol levels. This subset, compared with those with no data on serum lipids, showed no significant difference (P > .05) in the means, ranks, and age- and sex-adjusted proportions for variables such as survival time, age, sex, cigarette smoking, education, physical activity, body mass index, insulin use, diabetes duration, glycosylated hemoglobin level, C-peptide level, blood pressure, proteinuria, peripheral neuropathy symptoms, presence and severity of diabetic retinopathy, hypertension, and history of angina, myocardial infarction, or stroke. Similar multivariate models that included either HDL-C, total cholesterol, or the ratio of total cholesterol to HDL-C still showed significantly lowered risks for the groups with higher alcohol intake (Table 4).

We also examined the alcohol–CHD mortality association using different alcohol intake categories as a reference, finding consistently protective associations with regular drinking. For example, using all abstainers (never and former drinkers combined) as the reference category, the multivariate-adjusted RRs were 0.73 (95% CI, 0.52-1.02), 0.59 (95% CI, 0.35-0.998), and 0.28 (95% CI, 0.13-0.60) for those with alcohol intakes of less than 2, 2 to 13, and 14 or more g/d, respectively (P for trend based on median value for each level = .002), with an overall effect associated with any amount of drinking compared with abstinence equal to 0.63 (95% CI, 0.46-0.86). Using infrequent drinkers (alcohol intake <2 g/d) as the reference, the adjusted RRs were 1.83 (95% CI, 1.11-3.02) for never drinkers, 1.27 (95% CI, 0.89-1.81) for former drinkers, 0.80 (95% CI, 0.47-1.37) for drinkers of 2 to 13 g/d, and 0.38 (95% CI, 0.18-0.81) for drinkers of 14 g/d or more.

Finally, we analyzed the relationship of alcohol consumption and all-cause mortality. Controlling for the same variables (all independently related to total mortality) listed in Table 2, the RRs were 0.74 (95% CI, 0.56-0.98) for former drinkers and 0.64 (95% CI, 0.48-0.86), 0.47 (95% CI, 0.33-0.69), and 0.49 (95% CI, 0.33-0.74) for those with intake levels of less than 2, 2 to 13, and 14 or more g/d, respectively.

**COMMENT**

In this population-based, prospective study, older-onset diabetic persons who drank higher amounts of alcohol had a considerably reduced risk of death due to CHD compared with never drinkers. Despite the initial differences in some characteristics across alcohol intake groups at baseline, some of which were expected and seen in studies involving healthier populations, the reductions in risk were independent of and appeared similar across levels of known risk factors related to CHD, survival, and diabetes.

Bias appeared unlikely to substantially account for the observed associations. Differential follow-up was unlikely, given the uniform and regular vital status follow-up procedures used by staff masked to the exposure status in determining fatal events. Although misclassification in our outcome could have occurred with the use of death certificate data in assigning the underlying cause of death, such information was collected without knowledge of the alcohol intake levels reported in the study. Chance was possible but it appeared unlikely to materially affect our findings, given the strength of the relationships we found. The significant risk reductions among alcohol drinkers that remained from simpler multivariate models to those adjusting for several covariates made it less likely that the associations found were due to unmeasured factors. A strength of the study was our ability to measure (using objective and standardized procedures) and subsequently control for cardiovascular and diabetes-related factors associated with survival.

Because of the self-reported nature of our alcohol data and the lack of long-term information on alcohol intake (such as a history of lifetime drinking), misclassification of exposure status was possible. For example, the former drinkers group could have included former heavy drinkers, former moderate drinkers, and former infrequent drinkers who reported not having any alcohol in the past year. Diabetes-related and other comorbid conditions could also influence a patient’s decision to alter his/her drinking habits over time. We thus did similar analyses using updated informa-

**Table 4. Multivariate RRs for Death Due to CHD According to Alcohol Intake in a Subset of Older-Onset Diabetic Persons With Complete Data on HDL-C and Total Cholesterol (n = 451), Wisconsin Epidemiologic Study of Diabetic Retinopathy**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Nondrinkers</th>
<th>Drinkers, Average Alcohol Intake, g/d</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Never Drinkers</td>
<td>Former Drinkers</td>
</tr>
<tr>
<td>Multivariate RR (95% CI), additionally adjusted for HDL-C†</td>
<td>1.00 (Reference)</td>
<td>0.81 (0.39-1.71)</td>
</tr>
<tr>
<td>Total cholesterol‡</td>
<td>1.00 (Reference)</td>
<td>0.83 (0.40-1.71)</td>
</tr>
<tr>
<td>Ratio of total cholesterol to HDL-C§</td>
<td>1.00 (Reference)</td>
<td>0.87 (0.42-1.81)</td>
</tr>
</tbody>
</table>

*RR indicates relative risk, as estimated by the hazard ratio using Cox proportional hazards regression, comparing each alcohol intake group with older-onset diabetic persons who were never drinkers, adjusted for age, sex, cigarette smoking, insulin use, glycosylated hemoglobin level, plasma C-peptide level, history of angina or myocardial infarction, use of digoxin, and the presence and severity of diabetic retinopathy; CHD, coronary heart disease; HDL-C, high-density lipoprotein cholesterol; and CI, confidence interval.
†Quintiles of serum HDL-C were 12-30, 31-36, 37-42, 43-52, and ≥53 mg/dL (0.31-0.80, 0.81-0.95, 0.96-1.11, 1.12-1.37, and ≥1.38 mmol/L), respectively.
‡Quintiles of serum total cholesterol were 101-181, 182-204, 205-228, 229-255, and ≥256 mg/dL (2.6-4.6, 4.7-5.2, 5.3-5.9, 6.0-6.6, and ≥6.7 mmol/L), respectively.
§Quintiles of ratio of serum total cholesterol to HDL-C were 1.8-3.8, 3.9-4.7, 4.8-5.9, 6.0-7.4, and ≥7.5.
tion on alcohol intake and other potential confounders among 533 older-onset diabetic participants who were still alive and returned for the next follow-up examination in 1990-1992, finding consistently protective associations in alcohol drinkers compared with never drinkers (data not shown). Furthermore, using a subset of the cohort who had information on serum lipids, we observed a significant correlation between our calculated alcohol intake levels and serum HDL-C concentrations. We likewise found, as expected, strong and direct relationships with diastolic blood pressure and cigarette smoking, lending further credence to the participants’ reports of alcohol consumption.

In prior studies in general populations, concerns were raised\(^5\)\(^3\)\(^4\) that persons who reported abstaining from alcohol use, which usually formed the reference group used in comparing risks among groups of alcohol drinkers, did so because of coexisting medical conditions that could account for the higher risks among nondrinkers. This was unlikely in our study because we used the information on ever drinking to identify our reference group of lifetime abstainers. (Separate analyses using different subgroups as the reference category consistently showed lowered risks among drinkers, especially regular drinkers.) We also observed similar inverse associations for alcohol drinkers in subgroups defined by cardiovascular risk factor status, such as age and sex, and the presence of certain diabetic complications, with no evidence of interaction between alcohol consumption and any of the subgroup variables we studied (although the power to detect such interactions may be limited). Further analyses that excluded deaths occurring in the earlier (eg, first 5) years of follow-up showed that the inverse relationship between alcohol and fatal CHD remained (data not shown), refuting the argument that abstainers might have a greater burden of ill health than drinkers because of undiagnosed preexisting diseases. Overall, we found no strong evidence that the higher death rates in abstainers were due to misclassification of exposure status.

Our cohort did not exhibit a wide range of alcohol consumption. Most participants were either nondrinkers or infrequent (ie, less frequent than 1 drink per week) drinkers, with merely 1.8% of individuals drinking more than 42 g/d (more than 3 drinks per day). This restricted our evaluation to a relatively tight range of alcohol use, especially any inference regarding heavy drinking. However, despite the limited range and the greater proportion of abstainers found in our diabetic cohort compared with general populations, we were still able to consistently find protective, graded associations from infrequent drinkers to regular drinkers of about 1 drink or more per day. Regarding the apparent negative relationship with infrequent drinking (alcohol intake <2 g/d), the exact reasons for this observation are not known, given the lack of a strong biologic evidence for this association in diabetic patients. It is possible that infrequent drinking was a marker of other health-related behaviors or that some individuals in this subgroup underreported their consumption. The lack of information on the onset or duration of alcohol use and its possible relationship with the onset or duration of medical conditions prevented us from further differentiating the health status of regular drinkers, infrequent drinkers, former drinkers, and lifelong abstainers. It is also possible that regular drinkers were constitutionally healthier than never drinkers, regardless of the presence of any medical comorbidities. Another limitation was our inability to assess the role of diet, genetic determinants, and other lipid and hemostatic factors, which may modify or confound any relationship between alcohol and CHD mortality in diabetic individuals.

The consistency of our results with those of others who studied healthier populations, showing an apparent protective effect of moderate alcohol consumption on the risk of coronary events, is notable. Given the current lack of epidemiological data on the relationship of alcohol intake to CHD deaths in people with diabetes, our findings provide evidence of such a relationship in persons largely known to have more advanced atherosclerotic and other complications compared with nondiabetic individuals. Moreover, the lowered risk associated with increasing alcohol intake levels found in this diabetic cohort appear greater than those found in many general population studies (up to 80% vs 20%-60%). This may suggest a possibly greater synergism or potential of the antiatherogenic, hemostatic, and/or glucose metabolism-related effects of alcohol consumption in people with older-onset diabetes. This is also consistent with the perception that the benefit of alcohol seems greatest in individuals (such as those with type 2 diabetes) at higher risk of cardiovascular mortality.\(^2\)

Our results are not inconsistent with the current guidelines regarding alcohol consumption for people with diabetes, namely, “the same precautions regarding the use of alcohol that apply to the general public also apply to people with diabetes.”\(^2\)\(^5\)\(^6\)\(^1\) Daily intakes of no more than 1 drink for women and no more than 2 drinks for men have been recommended.\(^2\)\(^3\) Although our population-based cohort consisted of older-onset diabetic persons with characteristics that varied in terms of the presence of coexistent medical problems and diabetic complications, as well as use of insulin and other medications, we were not able to assess the acute risks (associated with higher alcohol consumption) of hyperglycemia, hypoglycemia, or other short-term complications in the presence of other medical problems seen in diabetes. More importantly, policies regarding long-term, moderate consumption of alcohol specifically for the prevention of CHD in older-onset diabetic patients cannot be made and should await the results of additional prospective studies, including those with a sizable number of newly diagnosed diabetic women and men and those using incident disease measures and multiple long-term assessments of alcohol
intake. Such results must also be carefully and thoroughly reviewed in the light of further findings on the possible risks of other noncardiac end points, such as stroke and hypertension, in people with diabetes.

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