The Relationship Between Alcohol Consumption and Vascular Complications and Mortality in Individuals With Type 2 Diabetes

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OBJECTIVE

Moderate alcohol consumption has been associated with a reduced risk of mortality and coronary artery disease. The relationship between cardiovascular health and alcohol use in type 2 diabetes is less clear. The current study assesses the effects of alcohol use among participants in the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified-Release Controlled Evaluation (ADVANCE) trial.

RESEARCH DESIGN AND METHODS

The effects of alcohol use were explored using Cox regression models, adjusted for potential confounders. The study end points were cardiovascular events (cardiovascular death, myocardial infarction, and stroke), microvascular complications (new or worsening nephropathy or retinopathy), and all-cause mortality.

RESULTS

During a median of 5 years of follow-up, 1,031 (9%) patients died, 1,147 (10%) experienced a cardiovascular event, and 1,136 (10%) experienced a microvascular complication. Compared with patients who reported no alcohol consumption, those who reported moderate consumption had fewer cardiovascular events (adjusted hazard ratio [aHR] 0.83; 95% CI 0.72–0.95; *P* = 0.008), less microvascular complications (aHR 0.85; 95% CI 0.73–0.99; *P* = 0.03), and lower all-cause mortality (aHR 0.87; 96% CI 0.75–1.00; *P* = 0.05). The benefits were particularly evident in participants who drank predominantly wine (cardiovascular events aHR 0.78, 95% CI 0.63–0.95, *P* = 0.01; all-cause mortality aHR 0.77, 95% CI 0.62–0.95, *P* = 0.02). Compared with patients who reported no alcohol consumption, those who reported heavy consumption had dose-dependent higher risks of cardiovascular events and all-cause mortality.

CONCLUSIONS

In patients with type 2 diabetes, moderate alcohol use, particularly wine consumption, is associated with reduced risks of cardiovascular events and all-cause mortality.

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The prevalence of type 2 diabetes is increasing and is greatly influenced by lifestyle factors, such as consumption of high-calorie diets and sedentary behavior, with a resultant rise in excess weight (1). Alcohol use, another major factor of lifestyle, is also prevalent in established market economies, e.g., in the U.S. over 51% of people over the age of 18 years are regular drinkers (2) but not in Southeast Asia where lifetime abstention from alcohol is prevalent, reaching up to 90% (3).

The association between alcohol use and mortality or coronary artery disease in the general population has best been described by a U-shaped curve (4), favoring moderate drinking. In people with type 2 diabetes, much less is known about the association between alcohol use and vascular outcomes, particularly microvascular complications, or death. Alcohol consumption may have favorable effects on atherogenic factors such as inflammation, dyslipidemia, and insulin resistance (5). Several of these may be of particular benefit in patients with type 2 diabetes. However, alcoholic beverages have complex, and often detrimental, effects on blood glucose levels (6). Similarly, alcohol consumption may also be associated with other behaviors, such as smoking and participation in physical activity, and social factors that influence vascular risk. These confounding factors may be of particular relevance in patients with lifestyle-related diseases, such as type 2 diabetes.

Prior studies have reported an association between alcohol consumption and a decreased risk of nonfatal myocardial infarction and coronary heart disease mortality in subjects with diabetes (7–9). These were, however, performed in relatively homogeneous populations (female nurses (7) and male health professionals (8,9) in the U.S.), and incident events were relatively rare, with limited adjustment for potential confounding factors (7–9). In contrast to the relationship described in the general population, none of these studies report a U-shaped curve in the risks related to alcohol consumption. Instead, increasing levels of alcohol consumption were associated with a reduced risk of coronary heart disease events and mortality. None of these studies explored the relationship between alcohol consumption and the risk of microvascular complications in type 2 diabetes mellitus.

Most cohort studies in general populations do not report an association between the type of alcoholic drink consumed and risk of coronary artery disease. Nevertheless, the combination of high saturated fat intake, wine consumption, and lower coronary artery disease mortality, described as the "French paradox" (10), may, at least in part, be explained by the beneficial effects of wine consumption. Red wine, in particular, is associated with a reduction of several cardiovascular risk factors (11). However, it has also been suggested that the benefits associated with wine consumption are related more to favorable drinking patterns, when compared with the consumption of other forms of alcohol (12). The data relating the type of alcohol consumed to the risks of vascular events and death are extremely limited in patients with type 2 diabetes (8).

The aim of this study was to examine the associations between alcohol consumption and the risk of vascular events and death in patients with type 2 diabetes, with special reference to microvascular outcomes, level of alcohol consumption, and the predominant type of alcoholic drink.

RESEARCH DESIGN AND METHODS

The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified-Release Controlled Evaluation (ADVANCE) study (clinical trial reg. no. NCT00145925, clinicaltrials.gov) was a randomized, factorial, controlled trial conducted in 20 countries that recruited 11,140 patients with type 2 diabetes mellitus (13). Participants were defined eligible for the study if they were at least 55 years old, had been diagnosed with type 2 diabetes after the age of 30 years, and had a history of major macrovascular or microvascular disease or at least one additional cardiovascular risk factor. The study had two treatment arms, one comparing intensive and standard glycemic control and another comparing active and placebo blood-pressure-lowering treatment. The study outcomes consisted of major cardiovascular events (death from cardiovascular disease, nonfatal stroke, or nonfatal myocardial infarction), microvascular complications (new or worsening renal disease or diabetic eye disease, as previously described [14]), and all-cause mortality. The study participants provided written informed consent, and approval was obtained from the local ethics committee in all participating centers. Detailed study eligibility criteria and study methods (13) as well as the main results (15,16) have been previously published.

Alcohol consumption was ascertained by self-report. At the baseline study visit, the current average number of standard drinks of alcohol consumed within a week was recorded. Standard drink sizes were specified as a half a pint (0.28 L) of beer, 125 mL of wine, and one drink or shot containing approximately 25 mL of spirits. The type of alcoholic beverage consumed was further specified as wine, beer, or spirits. Similar data were also collected at the 24-month follow-up visit and the final study visit. Participants were also asked were also asked whether they were a regular drinker of alcohol (defined as drinking alcohol during most weeks in the year) prior to the diagnosis of diabetes and the average number and type of standard drinks per week in the year prior to being diagnosed with diabetes. These latter data, on the consumption of alcohol at 24 months, final study visit, and in the year prior to the diagnosis of diabetes, were, however, used only to establish the stability of alcohol consumption. The primary analyses presented relate to the level of alcohol consumption recorded at the baseline study visit.

Alcohol consumption at baseline was grouped as nil, moderate, or heavy. Using the Royal College of Physicians' criteria, heavy consumption was defined as >21 standard drinks weekly for men and >14 standard drinks for women, and moderate consumption was defined as ≤ 21 drinks weekly for men and ≤ 14 drinks for women (17).

For the primary analyses, the effect of baseline alcohol consumption on cardiovascular events, microvascular complications, and all-cause mortality was examined by *1*) comparing any alcohol use to abstinence and *2*) examining the effect of alcohol use in a dose-dependent manner per alcohol drink consumed in separate groups of moderate and heavy drinkers. For subsequent analyses, the association between the

type of alcoholic beverage consumed at outset of the trial and vascular events and mortality was examined. Specifically, the effects of wine drinking were compared with other alcoholic drinks. From a sum of all alcoholic drinks consumed within the week, those who drank half or more as wine were considered wine drinkers and compared with those who drank mainly beer and spirits. The effects of alcohol consumption on outcomes in participants from different regions of the world were also examined using the following geographic and economic partition: Asia (China, India, Malaysia, and the Philippines), Eastern Europe (the Czech Republic, Estonia, Hungary, Lithuania, Poland, Russia, and Slovakia), and established market economies (Australia, Canada, France, Germany, Ireland, Italy, the Netherlands, New Zealand, and the U.K.) (18). The stability of alcohol consumption was assessed by comparing the self-reported alcohol intake of participants at their baseline study visit (the level used for all other analyses) with that reported during follow-up visits (24 months and end of study) and in the year prior to the diagnosis of diabetes.

Statistical Analyses

Baseline variables are summarized as the mean and SD for normally distributed continuous variables and as median and interquartile range (IQR) if skewed. Categorical variables are reported as numbers and percentages. The differences between the groups of alcohol drinkers and abstainers were tested by the Student *t* test for normally distributed continuous variables, the Mann–Whitney *U* test for skewed continuous variables, and the χ^2 test for categorical variables. The correlations between alcohol consumption at baseline and at other time points were determined using Spearman ρ test. Adjusted Cox models were derived, including possible confounding factors. The final model included age, sex, BMI, randomized treatment groups, glycated hemoglobin (HbA_{1c}), duration of diabetes, history of cardiovascular disease, HDL cholesterol, LDL cholesterol, triglycerides, creatinine clearance, systolic blood pressure, heart rate, any blood pressure medication, any lipid-lowering medication, any antiplatelet agent, current smoking, any regular exercise, and higher education (age at the time of finishing highest level of education >17 years). The risk reduction is described as percentages: (1 − hazard ratio) × 100. Adjusted hazard ratios (aHRs) and 95% CIs are also reported. Analyses were performed using SAS version 9.3 (SAS Institute Inc., Cary, NC) or SPSS version 21 (IBM, Armonk, NY).

RESULTS

The characteristics of the study population in general and by alcohol consumption are described in Table 1. Compared with alcohol abstainers, alcohol drinkers were older, predominantly men, had higher BMI, had shorter duration of diabetes, had lower LDL cholesterol, and smoked more (Table 1) (all $P < 0.01$). Of note, there were no significant differences in HDL cholesterol levels or in the prevalence of cardiovascular disease. Supplementary Tables 1 and 2 show the baseline characteristics of patient according to their drinking habits and the predominant type of alcohol consumed.

Outcomes

The median follow-up of 11,140 patients in the study was 5 years, during which 1,147 (10%) participants experienced a major cardiovascular event, 1,131 (10%) experienced a microvascular complication, and 1,031 (9%) died (Table 2).

Alcohol Use

Alcohol use at baseline was reported by 3,389 (30%) patients, with 413 (4%) reporting heavy consumption. Of patients drinking alcohol, 1,335 primarily drank wine (median consumption of 5, IQR 2–10, drinks per week), while 2,054 primarily drank beer and spirits (median consumption of 7, IQR 3–14, drinks per week).

Alcohol Use at Baseline and Study Outcomes

Compared with abstainers, any alcohol use was associated with a 17% lower risk of cardiovascular events, a 15% lower risk of microvascular complications, and a 13% lower risk of all-cause mortality (Fig. 1). These benefits were predominantly observed among participants who consumed moderate amounts of alcohol (Table 2 and Supplementary Fig. 1), though the number of participants drinking heavily was low and the crude event rates were similar (Table 2). The benefits of alcohol consumption were consistent across almost all subgroups and end points studied (Supplementary Figs. 2–4).

Moderate Versus Heavy Alcohol Consumption

When moderate and heavy alcohol consumption were examined separately, for moderate drinkers, there was no significant relationship between the amount of alcohol consumed (per standard drink) and the incidence of any of the study outcomes (Fig. 2, upper section). By contrast, for heavy drinkers, each drink consumed was associated with a higher risk of cardiovascular events and all-cause mortality (Fig. 2, lower section), and a similar trend was observed for microvascular complications.

Type of Alcohol Predominantly Consumed

When alcohol use was evaluated by the type of alcoholic beverage consumed, those who reported primarily drinking wine had a 22% lower risk of cardiovascular events and 23% lower risk of all-cause mortality when compared with participants who drank no alcohol, but with no significant reduction in microvascular complications (Table 3). In contrast, the drinking of beer and spirits was not associated with significantly lower risks of any of the study outcomes (Table 3). When the outcomes of those who drank primarily wine were directly compared with those who drank mainly beer and/or spirits, there were no significant differences in cardiovascular (aHR 0.84; 95% CI 0.66–1.06; $P = 0.15$) or microvascular (aHR 1.05; 95% CI 0.81–1.35; $P = 0.73$) events, though a trend toward reduced mortality was observed (aHR 0.79; 95% CI 0.61–1.01; $P = 0.06$).

Regional Differences in Alcohol Consumption

The consumption of alcohol varied considerably between regions. In Asia, only 9.8% of participants drank alcohol (7.7% moderate and 2.1% heavy drinkers) compared with 23.7% (22.9% moderate and 0.7% heavy) in Eastern Europe and 50.9% (44.5% moderate and 6.4% heavy) in the established market economies. However, analyses stratified by regional subgroup, comparing those who consumed any alcohol with those who were abstinent, demonstrated no interaction between region and any of the study outcomes (Supplementary Fig. 5).

Stability of Alcohol Consumption

Both consumption of any alcohol and the number of alcoholic drinks consumed at baseline correlated with alcohol consumption at 24-month follow-up

Table 1—Patient characteristics in general and by alcohol use

	Total n = 11,140	No alcohol use n = 7,751	Alcohol users n = 3,389	P value
Age, years	65.8 (6.4)	65.6 (6.3)	66.1 (6.6)	<0.001
Female	4,733 (42.5)	4,140 (53.4)	593 (17.5)	<0.001
BMI, kg/m^2	28.3 (5.2)	28.0 (5.3)	29.1 (4.8)	<0.001
Current smoking	1,682 (15.2)	992 (12.8)	690 (20.4)	<0.001
History of cardiovascular disease	3,590 (32.2)	2,474 (31.9)	1,116 (32.9)	0.29
History of microvascular disease	1,155 (10.4)	843 (10.9)	312 (9.2)	0.008
Age at completion of highest level of education, years	18.4 (7.3)	18.2 (7.3)	18.9 (7.2)	<0.001
Systolic blood pressure, mmHg	145 (21.5)	144 (22)	147 (21)	<0.001
Diastolic blood pressure, mmHg	81 (11)	80 (11)	82 (11)	<0.001
Heart rate, bpm	74 (12)	75 (12)	72 (12)	<0.001
Total cholesterol, mmol/L	5.20 (1.19)	5.25 (1.21)	5.08 (1.14)	<0.001
HDL cholesterol, mmol/L	1.26 (0.35)	1.26 (0.35)	1.25 (0.35)	0.43
LDL cholesterol, mmol/L	3.11 (1.03)	3.16 (1.04)	3.00 (1.00)	<0.001
Triglycerides, mmol/L	1.61 (1.20–2.30)	1.63 (1.20–2.30)	1.60 (1.17–2.30)	0.16
HbA_{1c}, %	7.2 (6.4–8.2)	7.3 (6.5–8.4)	7.0 (6.4–7.9)	<0.001
HbA_{1c}, mmol/mol	55.2 (47.5–66.1)	56.3 (47.5–68.3)	53.0 (46.5–62.8)	<0.001
Any exercise (≥15 min duration) per week	9,531 (85.6)	6,511 (84.0)	3,020 (89.1)	<0.001
Creatinine clearance, mL/min	82.3 (28.6)	79.9 (28.6)	87.8 (27.7)	<0.001
Any blood pressure medication	8,365 (75.1)	5,846 (75.4)	2,519 (74.3)	0.22
Any lipid-lowering medication	3,934 (35.3)	2,458 (31.7)	1,476 (43.6)	<0.001
Any antiplatelet medication	5,199 (46.7)	3,554 (45.9)	1,645 (48.5)	0.009
Duration of diabetes, years	7 (3–11)	7 (3–12)	6 (2.5–11)	<0.001

Normally distributed continuous variables are presented as mean (SD) and compared using Student t test, skewed continuous variables are presented as median (IQR) and compared using Mann–Whitney U test, and categorical variables are presented as number (percentage) and compared using χ^2 test.

(Spearman ρ for any alcohol consumption = 0.70 [$P < 0.001$], and number of alcoholic drinks per week = 0.74 [$P < 0.001$]). The respective correlations at the end of study were 0.61 ($P < 0.001$) and 0.65 ($P < 0.001$). Among those drinking alcohol, the median number of standard drinks consumed per week was 6 (IQR 2–12) at 24 months and 6 (IQR 2–13) at the end of the study, compared with 6 (IQR 2–14) at baseline. The consumption of alcohol and number of standard drinks per week at baseline also correlated with previous consumption and number of drinks (in the year prior to the diagnosis of diabetes; Spearman ρ = 0.76 [$P < 0.001$] for both).

CONCLUSIONS

This study provides evidence that individuals with type 2 diabetes who report drinking alcohol in moderation have a lower risk of cardiovascular events, microvascular complications, and all-cause mortality within 5 years when compared with those who report that they do not drink alcohol at all. A possible U-shaped curve was observed between alcohol consumption and cardiovascular events and mortality, suggesting that heavy drinking reverses any benefits; though the number of heavy drinkers was relatively small. After extensive adjustment for other risk factors and potential confounding factors, a 17% lower risk of cardiovascular events and a 13% lower risk of all-cause mortality were observed in those who drank moderately. There was also a suggestion that these lower

Table 2—Study outcomes (crude event rates and aHRs) according to alcohol consumption

Outcome	All participants n = 11,140	Abstinent n = 7,751	Moderate alcohol use n = 2,976	Heavy alcohol use n = 413
Cardiovascular events	1,147 (10.3%)	817 (10.5%) Reference category	292 (9.8%) aHR 0.82; 95% CI 0.71–0.95; P = 0.008	38 (9.2%) aHR 0.88; 95% CI 0.63–1.23; P = 0.46
Microvascular complications	1,131 (10.2%)	846 (10.9%) Reference category	247 (8.3%) aHR 0.83; 95% CI 0.72–0.97; P = 0.02	38 (9.2%) aHR 0.96; 95% CI 0.68–1.35; P = 0.81
All-cause mortality	1,031 (9.3%)	718 (9.3%) Reference category	276 (9.3%) aHR 0.86; 95% CI 0.74–0.99; P = 0.04	37 (9.0%) aHR 0.95; 95% CI 0.68–1.34; P = 0.77

aHRs were determined using Cox regression and adjusted for age, sex, BMI, randomized treatment groups, HbA_{1c}, duration of diabetes, history of cardiovascular disease, HDL cholesterol, LDL cholesterol, triglycerides, creatinine clearance, systolic blood pressure, heart rate, any blood pressure medication, any lipid-lowering medication, any antiplatelet agent, current smoking, any regular exercise, and higher education (age at the time of finishing highest level of education >17 years).

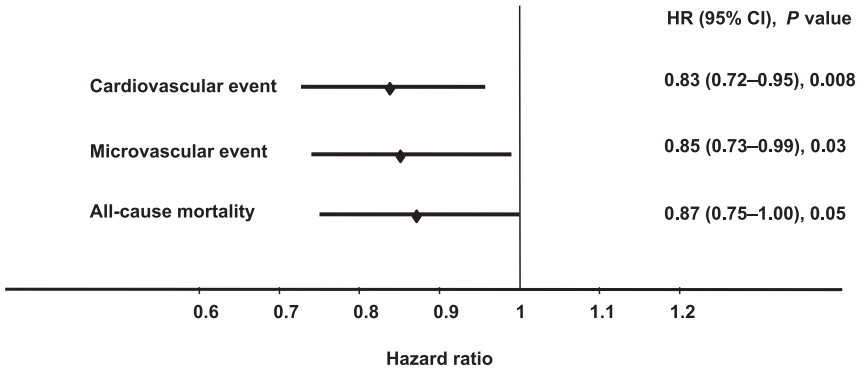

Figure 1—The association between any alcohol use and study outcomes. The models include age, sex, BMI, glucose and blood pressure treatment arms, current smoking, any regular exercise, education level, systolic blood pressure, heart rate, HbA_{1c}, duration of diabetes, HDL cholesterol, LDL cholesterol, triglycerides, creatinine clearance, lipid-lowering medication, blood pressure medication, antiplatelet medication, history of cardiovascular disease, and any alcohol consumption. HR, hazard ratio.

risks were predominantly associated with consumption of wine rather than other alcoholic drinks.

Previous Studies

The prevalence of alcohol consumption among adults with chronic medical conditions in the U.S. is ~31% (19). In our study of an ethnically diverse population of patients with type 2 diabetes, the level of alcohol consumption was similar.

Three smaller studies of patients with type 2 diabetes have reported an association between alcohol consumption and a reduced risk of myocardial infarction and fatal coronary heart disease in health care professionals in the U.S. (7–9). In female nurses (7), the adjusted relative risk of incident myocardial infarction or coronary death was reduced by 28% among participants who drank moderate amounts of alcohol and by 55% in those with a high alcohol intake (≥5 g/day) compared with those who drank no alcohol (7). Among male health professionals, the adjusted relative risk (compared with nondrinkers) of myocardial infarction was reduced by 38% in moderate drinkers (0.5–2 drinks per day) and 52% in those who consumed more than two standard drinks of alcohol per day (8). Male physicians with diabetes (type 1 or 2) who, on average, consumed ≥1 alcoholic drink per week but <1 drink per day had a 33% lower adjusted relative risk of coronary heart disease mortality, whereas those consuming at least one alcoholic drink per day had a 58% reduction in adjusted relative risk compared with those who rarely (<1 drink per month) or never drank alcohol (9). The current data, in a larger and more heterogeneous population, with more extensive adjustment for potential confounding factors, support a beneficial effect of alcohol consumption but, in contrast to these prior studies in patients with diabetes, suggest that any benefit may be negated by high alcohol consumption.

There are few prior data exploring the relationship between alcohol consumption and the microvascular complications of diabetes. Two prospective

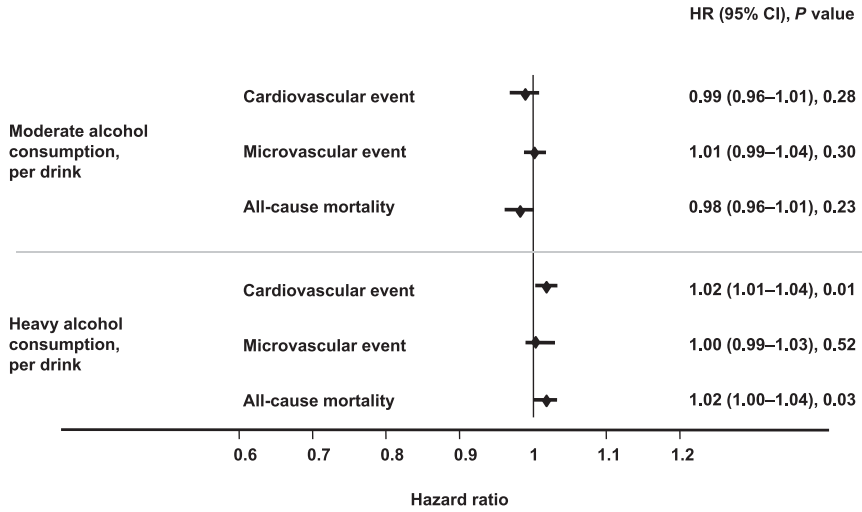

Figure 2—The association between moderate and heavy alcohol consumption (hazard ratio per drink) and study outcomes. Moderate alcohol consumption included up to 21 standard drinks in men and 14 standard drinks in women within a week. High consumption included >21 weekly drinks in men and >14 weekly drinks in women. The models include age, sex, BMI, glucose and blood pressure treatment arms, current smoking, any regular exercise, education level, systolic blood pressure, heart rate, HbA_{1c}, duration of diabetes, HDL cholesterol, LDL cholesterol, triglycerides, creatinine clearance, lipid-lowering medication, blood pressure medication, antiplatelet medication, history of cardiovascular disease, and any alcohol consumption. HR, hazard ratio.

Table 3—Study outcomes (crude event rates and aHRs) according to the predominant type of alcohol consumed

Outcome	All participants *n* = 11,140	Abstinent *n* = 7,751	Mainly wine consumption *n* = 1,335	Mainly other alcohol consumption *n* = 2,054
Cardiovascular events	1,147 (10.3%)	817 (10.5%) Reference category	118 (8.8%) aHR 0.78; 95% CI 0.63–0.95; *P* = 0.01	212 (10.3%) aHR 0.86; 95% CI 0.73–1.01; *P* = 0.07
Microvascular complications	1,131 (10.2%)	846 (10.9%) Reference category	105 (7.9%) aHR 0.85; 95% CI 0.68–1.04; *P* = 0.12	180 (8.8%) aHR 0.77; 95% CI 0.71–1.01; *P* = 0.07
All-cause mortality	1,031 (9.3%)	718 (9.3%) Reference category	108 (8.1%) aHR 0.77; 95% CI 0.62–0.95; *P* = 0.02	205 (10.0%) aHR 0.93; 95% CI 0.78–1.10; *P* = 0.38

aHRs were determined using Cox regression and adjusted for age, sex, BMI, randomized treatment groups, HbA_{1c}, duration of diabetes, history of cardiovascular disease, HDL cholesterol, LDL cholesterol, triglycerides, creatinine clearance, systolic blood pressure, heart rate, any blood pressure medication, any lipid-lowering medication, any antiplatelet agent, current smoking, any regular exercise, and higher education (age at the time of finishing highest level of education >17 years).

cohort studies have assessed the relationship between alcohol intake and the risk of diabetic retinopathy (20,21). The Wisconsin Epidemiologic Study of Diabetic Retinopathy found no association between the amount of alcohol consumed and either the incidence or the progression of diabetic retinopathy (20). In contrast, Young et al. reported that heavy alcohol consumption (defined as >1.9 standard drinks per day) was associated with a more than doubling of the risk of incident retinopathy (21). Data from the EURODIAB Prospective Complications study suggest, however, that in type 1 diabetes, moderate alcohol consumption does reduce a range of microvascular complications (22). The current data suggest comparable benefits in type 2 diabetes, presumably by similar mechanisms to those that protect against macrovascular complications (23,24).

Wine and Other Alcoholic Beverages

In moderation, alcohol appears to lower the levels of inflammatory markers, decrease platelet aggregation (25), and increase HDL by 12% on average (26). Indeed, alcohol use is considered a more important determinant of HDL cholesterol levels that other lifestyle habits, including exercise (27). This effect is unlikely to account for our findings as, although there was a weak correlation between baseline HDL cholesterol levels and the number of alcoholic drinks consumed per week (Spearman ρ 0.06; $P < 0.001$), the baseline HDL cholesterol levels did not differ between alcohol consumers and abstainers. Wine drinkers have been reported to be less overweight, exercise more, and drink with meals (28), which offers plausible explanations for the observed differences between the studied types of drinks. Additionally, previous studies have suggested that certain components in red wine may improve endothelial function (29,30).

Strengths and Limitations

The current study is one of the largest to explore the relationship between alcohol consumption and vascular outcomes and mortality in patients with type 2 diabetes. The participants in the study cohort were well characterized, and the study outcomes had been prespecified and were independently adjudicated. Baseline differences between individuals who do and do not drink alcohol complicate, and potentially confound, all analyses of the cardiovascular impact of alcohol consumption. This is an inevitable limitation of all observational studies addressing this issue. One of the major strengths of the current study is, however, its size and very careful characterization of the study participants at baseline. This enables extensive multivariable adjustment and allows us to estimate the independent effects of alcohol consumption with as much confidence as possible.

The current study also has limitations. Although detailed data on alcohol use were collected prospectively in the ADVANCE trial, the current study is a retrospectively performed (post hoc) analysis. The current analyses are based on the consumption of alcohol at the time of randomization in the ADVANCE trial. This may not have accurately captured the prior or subsequent behavior of the participants, and we are unable to assess the duration of alcohol consumption. In contrast to most other studies exploring the effects of alcohol, we have, however, reported the stability of alcohol consumption (both prior and subsequent). It is possible that those who drank no alcohol at the time of randomization were abstinent due to health concerns, what has been termed the "sick quitter" effect (31). Furthermore, alcohol use was self-reported, and the accuracy of recall was not assessed. Some participants may have underestimated their consumption, both in terms of the number and alcohol content (size) of the drinks consumed. Any underestimation of alcohol consumption is unlikely to be a factor in those who declare themselves to be abstainers. Many of the participants drank a range of alcoholic beverages. The analyses based on the predominant type of alcohol consumed (wine or beer and spirits) may, therefore, oversimplify a more complex relationship. Given the purported benefits, those subjects pursuing a healthy lifestyle in general may tend to drink moderately. Although the large cohort allows extensive adjustment, it is impossible to correct for all potential confounders. Likewise, the number of participants reporting heavy alcohol consumption was relatively low, and the findings related to this subgroup should be interpreted with appropriate caution.

Conclusion

This study demonstrates an association between moderate alcohol consumption and reduced vascular events and death in patients with type 2 diabetes. These findings do not appear to be explained by other coassociated lifestyle and risk factors. This does not, however, establish causality, and any potential benefits must be weighed against the potential detrimental effects of alcohol, such as an increased risk of hypoglycemia, an

increased risk of hepatic complications, and an increased incidence of certain cancers (32). In light of these caveats, it would be premature to make any firm clinical recommendations regarding alcohol consumption by patients with type 2 diabetes. Nevertheless, the current study finds no grounds to discourage mild to moderate alcohol consumption, at least in terms of its vascular effects.

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Author Contributions. J.I.B. designed this substudy, undertook the statistical analyses, and wrote the initial drafts of the paper. S.Z., C.K.C., and M.W. revised the initial drafts of the paper for scientific content. J.C., G.M., N.P., B.W., S.H., B.N., and A.P. collected the data and revised the initial drafts of the paper for scientific content. Q.L. undertook the statistical analyses and revised the initial drafts of the paper for scientific content. G.S.H. designed this substudy, undertook the statistical analyses, and revised the initial drafts of the paper for scientific content. J.I.B. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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