Clinical and Population Studies

Light to Moderate Alcohol Consumption Is Associated With Lower Risk of Aortic Valve Sclerosis

The Study of Health in Pomerania (SHIP)

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Objective—In developed countries, sclerotic and calcific degeneration of the aortic valve is a common disorder showing pathophysiologic similarities with atherothrombotic coronary disease. Light to moderate alcohol consumption has been associated with a lower risk for atherothrombotic coronary disease and mortality. Whether alcohol consumption affects the development of aortic valve sclerosis (AVS) is not well known. In the present study, we aim to analyze the cross-sectional association between average daily alcohol consumption and AVS in the general population.

Approach and Results—We analyzed cross-sectional data from 2022 men and women, aged 45 to 81 years, from the population-based Study of Health in Pomerania. We used a computer-assisted interview that included beverage-specific questions about quantity and frequency of alcohol over the last 30 days to calculate the average quantity of alcohol consumption (in grams of ethanol per day). AVS was ascertained by echocardiography. The prevalence of AVS was 32.3%. Average daily alcohol intake displayed a J-type relation with AVS (fully adjusted P value: 0.005). Compared with individuals with an average consumption of 10 g of alcohol per day, multivariable-adjusted odds ratios were 1.60 (95% confidence interval, 1.19–2.14) among current abstainers and 1.56 (95% confidence interval, 1.01–2.41) among individuals with an average consumption of 60 g per day.

Conclusions—Our findings indicate that light to moderate alcohol consumption was associated with a lower odd of having AVS. Prospective data need to address whether alcohol consumption and related changes over time in several biological markers affect the progression of AVS. (Arterioscler Thromb Vasc Biol. 2015;35:1265-1270. DOI: 10.1161/ATVBAHA.114.304831.)

Key Words: alcohol consumption; aortic valve, calcification of; atherosclerosis; epidemiology; risk factors

In developed countries, sclerosis and calcification of the aortic valve is a relatively common valve disorder,1,2 affecting between 21% and 31% of adults over 65 years of age in the population.1,3–5 Usually, affected individuals are asymptomatic as the majority of these persons have just minor focal valve thickening or aortic valve sclerosis (AVS), without major compromise of the valve function. However, this condition also confers an increased risk for incident cardiovascular disease and mortality.1 Indeed, a moderate proportion of individuals, ranging from 2% to 5% in population-based samples, have a more evolved disease, resulting in stenosis of the aortic valve with a consequent obstruction of the left ventricular outflow3,6,7 and subsequent cardiovascular symptoms and even death if a replacement of the aortic valve is not performed.2 The pathophysiologic mechanisms and risk factors leading to the initial sclerosis and subsequent calcification of the aortic valve are incompletely understood, but show some similarities with the atherosclerotic disease process.3–10 Traditional risk factors,3,5,11,12 as well as inflammatory markers, seem to play a role, as supported by the presence of inflammatory cells in compromised valves and high levels of circulating C-reactive protein in individuals with AVS.13 For clinical assessment and
Association Between Alcohol Consumption and AVS

In adjusted regression models, average alcohol consumption (modeled as a continuous trait) was significantly correlated with AVS. Table 2 displays odds ratios for AVS according to select percentiles of average alcohol consumption using an average consumption of 10 g/d as the reference. After adjustment for age and sex, current abstainers had odds ratios for the association with AVS of 1.73 (95% confidence interval [CI], 1.30–2.30), whereas individuals consuming on average 20 g of pure alcohol per day had 1.09 (95% CI, 0.96–1.25; overall P value <0.001; model 1, Table 2). Greater amounts of alcohol consumption per day were associated with greater odds ratios for AVS. This pattern persisted after additional adjustment for educational level, smoking, physical inactivity, and waist-to-height ratio (model 2, Table 2). In the fully adjusted model (model 2, Table 2), the odds ratios for AVS associated with current abstaining was 1.60 (95% CI: 1.19–2.14), whereas for the consumption of 60 g of alcohol per day, it was 1.56 (95% CI: 0.101–2.41; overall P value =0.005). The results of the model 2 are also presented in Figure. We also ran a model that included supplementary adjustment for systolic blood pressure and glycohemoglobin (model 3, Table 2) because these variables may be considered cofounders or, alternatively, intermediate pathways in the mechanisms involved in the alcohol protection against cardiovascular diseases. In general, light to moderate drinking were associated with lower odds than abstention, whereas at high-risk amounts (ie, >60/70 g of alcohol per day25) were not different from abstainers (Figure).

The association between alcohol consumption and AVS did not differ significantly by sex and was not modified by age or smoking (P values for interaction >0.05).

We performed a sensitivity analysis with a statistical model adjusted for age, sex, educational level, smoking, physical inactivity, body mass index, triglycerides, high-density lipoprotein, low-density lipoprotein, and diabetes mellitus and obtained similar results (data not shown). In addition, we split the group of abstinence into 2 groups: lifetime (n=69) and 30 days abstainers, but former drinkers (n=392). We did not find a significant difference (P=0.915) in the association between alcohol consumption and AVS between these 2 groups.

Discussion

Our findings indicate a cross-sectional J-shaped association between alcohol consumption and AVS in an adult general population. Individuals with light to moderate alcohol consumption displayed the lowest odds of having AVS when compared with current abstainers and heavy drinkers. This association persisted after further adjustment for various cardiovascular and metabolic risk factors. To the best of our knowledge, this is the first study showing a correlation between light to moderate alcohol consumption and AVS.

In the Context of Published Literature

Multiple individual studies22–27 and meta-analyses20,28–31 demonstrated a protective effect of light to moderate alcohol consumption on different cardiovascular traits and outcomes. Combining data from 34 prospective studies with 1 015 835 individuals, Costanzo and colleagues30 concluded that light levels of alcohol consumption were inversely associated with all-cause mortality in both men and women. Similarly, a comprehensive review and meta-analysis based on 84 prospective studies20,28–31 demonstrated a protective effect of light to moderate alcohol consumption in patients with overt cardiovascular disease27,32 and on cardiovascular risk factors like diabetes mellitus.14 In line with these data, we observed that light to moderate alcohol consumption is associated with lower odds of AVS, whereas heavy alcohol drinking was associated with higher odds of AVS. Therefore, it is recommended to assess alcohol consumption as a continuous variable in future studies.
consumption was associated with a lower prevalence of AVS in our general population sample, as compared with current abstainers and compared with individuals with higher alcohol consumption (>40 g/d).

However, the potential cardioprotective effect of alcohol consumption is not universally accepted, and it is still a topic of controversy and debate. A recent Mendelian Randomization analysis, using the genetic variant rs1229984 as a proxy for alcohol consumption, reported that individuals with a genetic predisposition for lower alcohol consumption have lower odds for cardiovascular diseases. Although these data are intriguing and partially contradict observations from epidemiological studies, it has to be kept in mind that Mendelian Randomization analyses are based on important assumptions, as detailed by Hernan and Robins, one of them being that the genetic variant under study affects cardiovascular diseases risk only through alcohol consumption (and not directly or through other indirect effects). Thus, pleiotropy is considered
one of the key limitations of Mendelian Randomization experiments. In this context, it is noteworthy that the rs1229984 A-allele is associated with a broad spectrum of traditional risk factors, including blood pressure, inflammatory markers, adiposity measures, and non–high-density lipoprotein cholesterol.

It is well accepted that as the individuals get older, they are likely to decrease their alcohol consumption. Furthermore, individuals with high average amount of alcohol consumption show the strongest decrease in their drinking habits or even converting to abstainers over time. Thus, the group of current abstainers is heterogeneous, including lifetime abstainers and former drinkers who quit for any one of several reasons. If all these former drinkers are analyzed jointly as current abstainers, they would probably have a worse cardiovascular prognosis when compared with the individuals with light to moderate alcohol consumption. Consistent with this concept, we observed a worse cardiovascular risk profile in current abstainers as compared with individuals consuming between 0 and 20 g alcohol per day.

Notwithstanding these considerations, in our analyses, we obtained no evidence that the association between alcohol consumption and AVS was modified by age or that the strength of association with AVS differed between lifetime abstainers and 30 days abstainers, but former drinkers.

### Potential Mechanisms for the Observed Association

The precise mechanisms how light to moderate alcohol consumption leads to a lower risk for cardiovascular disease and mortality are still not clear. The effects of alcohol consumption on cardiovascular risk might be mediated by changes on lipid and adipocyte hormone levels, insulin sensitivity, abdominal obesity, hemostatic factors, as well as further markers involved in the systemic inflammation and endothelial cell function, as detailed elsewhere. Some potentially relevant biomarkers are discussed more comprehensively in the next paragraph.

In a recent meta-analysis, alcohol consumption was associated with increased levels of high-density lipoprotein cholesterol, apolipoprotein A1, and adiponectin as well lower levels of fibrinogen, making these biomarkers potential mediators for the association between alcohol and AVS. In this context, the beneficial effects of high-density lipoprotein cholesterol for the cardiovascular system are well established. On a parallel note, recombinant apolipoprotein A1 Milano reversed aortic valve stenosis and positively affected valve remodeling in experimental settings. In line with these data, a recent proteomic study revealed that apolipoprotein A1 and fibrinogen were significantly enriched in the valves of patients submitted to aortic valve replacement as compared with normal aortic valves. Although the presence of apolipoprotein A1 might be a protective mechanism against increased levels of low-density lipoprotein cholesterol, lipoprotein (a), and triglycerides on the aortic valve surface, the presence of fibrinogen seems...
to be implicated in the inflammatory process of the aortic valve calcification.43

On a similar note, in patients with periodontal disease, plasma fibrinogen levels were positively associated with AVS.44 Fibrinogen has a significant role in atherogenesis and thrombogenesis, fibrinolysis, and inflammation.45,46 Besides the decrease in the plasma levels of fibrinogen, it seems that alcohol also affects the stability of the fibrinogen, leading to a loosening of its structure.45 Adiponectin, which levels also increase with the consumption of alcohol,20 has insulin-sensi-
tizing, anti-inflammatory, antithrombotic, and antiatherogenic effects.47 Low levels of adiponectin were associated with increased valvular inflammation and neovascularization and faster evolution of stenosis in individuals with calcific aortic stenosis.47

Study Limitations
Some limitations of this study should be mentioned. First, the study sample consisted of middle-aged Europeans; it is not known whether our findings are also applicable to other ethnicities and age-groups. Second, our data are cross-sectional; therefore, we cannot draw any temporal conclusions concerning cause and effect. Third, our data regarding the last 30 day of alcohol consumption only approximate long-term average alcohol consumption over the past years or decades. Chronic alcohol consumption is likely to be more relevant for the development of AVS than short-term alcohol consumption. However, the 30 day-beverage-specific quantity-frequency index (the one we used) has been validated and widely used in Germany and other European countries,48 and alcohol consumption obtained over different reference periods have been shown to correlate reasonably well.48 Besides that, we did not have data to differentiate sick-quitters from lifetime and other abstainers. Fourth, although we have incorporated numerous metabolic and cardiovascular risk factors in our multivariable model, we cannot exclude the possibility of further residual confounding. Besides that, for our definition of physical inactivity, we used 2 items regarding hours of exercise in summer and winter with limited validity and reliability. Finally, there are some pathophysiological pathways, for example, lifestyle, that could partially explain the observed association between alcohol consumption and AVS, but for which we had no specifically measured variable in our sample.

Regardless of these limitations, our study has also a few strengths, including the population-based setting, the large number of individuals, the use of standardized data collection methods, and the capacity to perform adjustment for a variety of clinical risk factors.

Conclusions
In conclusion, the study findings indicate that light to moderate alcohol consumption was associated with a lower risk of having AVS in men and women. Our findings require replication in independent samples, and the exact molecular mechanisms explaining this association warrant further inves-
tigations. Prospective data need to address whether alcohol consumption and changes in the above mentioned biological markers over time affect the progression of AVS.

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Disclosures
None.

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in developed countries, scoliotic and calcific degeneration of the aortic valve is a common disorder showing pathophysiologic similarities and joint risk factors with atherothrombotic coronary disease. Light to moderate alcohol consumption has been associated with a lower risk for atherothrombotic coronary disease and mortality. In the present study, we analyzed cross-sectional data of the population-based Study of Health in Pomerania (1035 men and 987 women; aged 45–81 years) and assessed the association between average daily alcohol consumption and aortic valve sclerosis. Average daily alcohol intake displayed a J-type relationship with aortic valve sclerosis. Thus, compared with individuals with a consumption of 10 g of alcohol per day, multivariable-adjusted odds ratios were 1.60 among current abstainers and 1.56 among individuals with a consumption of 60 g per day. Our findings indicate that light to moderate alcohol consumption was associated with a lower risk of having aortic valve sclerosis.
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Materials and Methods

Study sample

The Study of Health in Pomerania (SHIP)

The Study of Health in Pomerania (SHIP)\(^1\) is a population-based study conducted in West Pomerania, the north-east area of Germany. A more detailed description of the study design and recruitment has been previously described elsewhere.\(^2\) The net sample (without migrated or deceased persons) comprised 6,265 eligible individuals with 4,308 (response 68.8%) of them taking part in the study performed between October 1997 and May 2001. At the baseline examination, echocardiography was restricted to 2,578 individuals (1,274 women, 49.4%) who were 45 years or older. For the present analysis, we excluded participants with missing values for aortic valve sclerosis in the echocardiogram (n=226), for alcohol intake (n=170) or any of the covariables (n=240), as well individuals with reported history of aortic stenosis (n=23) or aortic valve replacement (n=6). The final analytical sample compromised 2,022 (987 women; 48.8%) subjects. All study participants gave written informed consent. The study was approved by the ethics committee of the University of Greifswald\(^3\) and complies with the Declaration of Helsinki.

Interview, medical and laboratory examination

Data on socio-demographics, alcohol consumption, smoking habits, physical activity, and medication use were gathered by trained and certificated medical staff during a standardized computer-assisted interview.\(^2\) The following demographic variables were assessed: age, gender and school educational attainment (in years of education completed). Alcohol consumption was assessed using a beverage-specific quantity-frequency measure: number of days with alcohol consumption (beer, wine,
and spirits) and average daily alcohol consumption for such a day over the last 30 days. Average alcohol consumption (in grams per day) was calculated by multiplying frequency and amount of alcohol from beer, wine, and spirits, respectively, using a standard ethanol content of 4.8 percent (by volume) in beer, 11 percent (by volume) in wine, and 33 percent (by volume) in spirits for conversion. Abstainers were defined as individuals who did not consume alcohol during the last 30 days. As current abstainers are a heterogeneous group of lifetime teetotalers and individuals refraining from alcohol due to ill health or other reasons, we also used alternative definitions of abstaining for the sensitivity analyses: (a) lifetime abstaining; (b) 30 days abstainers, but former drinkers. Smoking status was categorized as never, past only, current. Individuals who did not take part in leisure-time physical activity during summer or winter for at least one hour per week were classified as being physically inactive. Information on medication was categorized according to the World Health Organization Anatomical Therapeutic Chemical (ATC) Classification System code.

Anthropometric measurements included height, weight and waist circumference. Waist-to-height ratio was calculated as the waist circumference divided by height measured in centimeters. After a 5 minutes rest period, systolic and diastolic blood pressures were measured three times at the right arm of seated participants using a digital blood pressure monitor (HEM-705CP, Omron Corporation, Tokyo, Japan) with a 3 minutes interval between consecutive measurements. The present analysis used the average of the second and third blood pressure measurement. Arterial hypertension was defined as systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg and/or current self-reported use of antihypertensive medication.
A non-fasting venous blood sample was obtained from all study participants between 07:00 a.m. and 04:00 p.m. while sitting. Glycated hemoglobin was determined by high-performance liquid chromatography (Bio-Rad Diamat Analyzer, Munich, Germany). Diabetes mellitus was defined as self-reported and/or use of antidiabetic medication defined by the ATC code (A10) and/or glycated hemoglobin ≥ 6.5% and/or non-fasting glucose ≥ 11.1 mmol/l. High-density lipoprotein cholesterol (HDL-C) was measured after precipitation of the apoB-containing lipoproteins with phosphotungstic acid/MgCl2 (EPOS 5060; Boehringer Ingelheim, Mannheim, Germany). Serum concentrations of apolipoprotein A1 were measured with commercially available reagents on a BN II analyzer (Dade Behring, Eschborn, Germany). Lipid-lowering medication was defined by the ATC code (C10). Carotid plaques were defined as stenosis >0% in left or right internal carotid artery. Antiplatelet medication was defined by the ATC code (B01AC). Plasma fibrinogen concentrations were assayed according to Clauss (Electra 1600 analyzer; Instrumentation Laboratory, Barcelona, Spain).

**Echocardiography**

Two-dimensional, M-Mode and Doppler echocardiography were performed using the Vingmed CFM 800A system (GE Medical Systems, Waukesha, USA). The aortic valve was scanned from the parasternal short and long axis as well as from the apical three and five chamber views. An abnormal irregular thickening and a focal or diffuse increase of the echogenicity of the leaflets with or without reduced systolic opening was defined as AVS. Aortic stenosis was present if calcification of the leaflets with a reduced systolic opening and a Doppler gradient of at least 15 mm Hg were found. The examiners were blinded to any clinical data from the patient.
including the presence of murmurs. Certification examinations revealed an agreement measurements between observers of >90%.\textsuperscript{10}

**Statistical analysis**

Data on quantitative characteristics are expressed as median (25th, 75th percentile). Data on qualitative characteristics are expressed as percent values. For descriptive purposes, average alcohol consumption was grouped as: 30 days abstainer, consumption of >0 to <20 g/day, 20 to <40 g/day, 40 to <60 g/day, ≥60 g/day (Table 1). Next, the association between alcohol consumption and AVS was estimated using a logistic regression model with average daily alcohol consumption being modeled as a continuous trait. To fully explore and test potential nonlinear associations, we modeled average alcohol consumption using multivariable fractional polynomials, taking the ‘spike at zero’ into account.\textsuperscript{12} Results of the adjusted logistic regression models were displayed by plotting adjusted OR for AVS against average alcohol intake. We plotted these odds ratios on a continuous scale in Figure 1, using an average daily alcohol consumption of 10 g as reference.\textsuperscript{13} Furthermore, in Table 2 we display the OR for AVS for selected percentiles of alcohol consumption, (modeled as a continuous trait)\textsuperscript{14} compared to an average alcohol intake of 10 g/day.\textsuperscript{13}

Three models were estimated accounting for different covariates. The first model was adjusted for age and sex. The second model added educational level, smoking, physical inactivity and waist-to-height ratio. We preferred this variable instead of body mass index or waist-to-hip ratio since a previous analysis\textsuperscript{15} of our group revealed that waist-to-height ratio was a better predictor for cardiovascular risk and mortality than body mass index or waist-to-hip ratio in our sample. The third model also included systolic blood pressure and glycated hemoglobin. In separate
models, we tested multiplicative interaction terms of alcohol consumption with sex, age, and smoking status, while adjusting for the other covariates of model 2. We performed a sensitive analysis with an extra model adjusted for age, sex, educational level, smoking, physical inactivity, BMI, triglycerides, HDL, LDL and diabetes. We also tested whether the magnitude of the association differed between subgroups of lifetime teetotalers or 30 days abstainers, and former drinkers.

In model 2, 21.7% of the sample cases had to be excluded due to missing values. Therefore we performed regression analyses using multiple imputation via chained equations using 20 imputed datasets. However, point estimates and confidence intervals were similar to complete-case analysis and we reported estimates from complete-case analysis.

Analyses were performed using Stata/MP4 13.1 (Stata Corp., College Station, TX, USA).

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