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**ORIGINAL CONTRIBUTIONS**

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**Alcohol Consumption and Myocardial Infarction: A Case-Control Study in France and Northern Ireland**

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The effect of alcohol consumption was assessed in 561 men with myocardial infarction and 643 healthy controls recruited from France and Northern Ireland between 1988 and 1991 in the ECTIM Study (Enquête Cas-Témoins de l'Infarctus du Myocarde). In total, patients consumed less wine than did controls, while non-wine-derived alcohol consumption did not differ significantly. After adjustment for cardiovascular risk factors and country of recruitment by logistic regression, alcohol consumption displayed a protective effect against myocardial infarction, the magnitude of which was comparable in both countries. This effect, which was essentially due to wine consumption in France and to nonwine consumption in Northern Ireland, was largely attenuated by the introduction of high density lipoprotein cholesterol into the model. Thus, both wine and nonwine consumption appear to exert a protective effect against myocardial infarction which is partly mediated through an increase in high density lipoprotein cholesterol. *Am J Epidemiol* 1996;143:1089-93.

alcohol drinking; alcohol, ethyl; apolipoproteins; case-control studies; lipoproteins; myocardial infarction; wine

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Moderate alcohol consumption has been shown to be inversely related to risk of coronary artery disease. These findings have been observed repeatedly in ecologic (1), case-control (2, 3), prospective (4, 5), and angiographic studies (6). All of the accumulated data appear to be most compatible with a causal protective

effect of alcohol (see the paper by Klatsky (7) for a discussion). Recently, much attention has been focused on the possibly superior protective effect of wine consumption relative to that of other alcoholic beverages (8, 9). It has been suggested that this putative specific effect, at least for red wine, might be attributable to antioxidizing or antiplatelet activity of some components of wine (10, 11). Conversely, other epidemiologic data suggest that alcoholic beverages are equally protective against coronary disease (12, 13). Using data from the ECTIM Study (Enquête Cas-Témoins de l'Infarctus du Myocarde), which involved two countries (Northern Ireland and France) with very different drinking habits, we examined the role of wine- and non-wine-derived alcohol consumption in myocardial infarction.

**MATERIALS AND METHODS**

**Patients**

Full details on the populations studied have been published elsewhere (14, 15). Briefly, 1,204 men aged

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Received for publication December 5, 1994, and in final form March 21, 1996.

Abbreviations: ECTIM, Enquête Cas-Témoins de l'Infarctus du Myocarde, HDL, high density lipoprotein; LDL, low density lipoprotein; MONICA, Monitoring of Trends and Determinants in Cardiovascular Disease.

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25–64 years were recruited between 1988 and 1991 from three MONICA (Monitoring of Trends and Determinants in Cardiovascular Disease) registers, one in Northern Ireland (Belfast) and two in France (Toulouse and Strasbourg) (14–16). The subjects had to reside within the relevant department, and their parents and grandparents had to have been born in the region and in Europe, respectively (for the French centers) or in the historical entity of Ulster (for Northern Ireland). Controls were randomly selected from electoral rolls in France and from lists of general practitioners in Northern Ireland. Stratification by age permitted an approximate match of the age distribution of cases and controls. Patients were selected from the MONICA registers of each center 3–6 months after having a myocardial infarction. Informed consent was obtained from all subjects.

In Northern Ireland, subjects were invited to come to a clinic, while French participants were visited in their homes by specially trained medical staff. All subjects completed a questionnaire on medical history, medication use, smoking status, and alcohol consumption. Patients were asked to report their cigarette and alcohol consumption prior to the myocardial infarction, while controls were asked about current consumption. Alcohol drinking was assessed as usual weekly intake of wine, beer, cider, and spirits (liquor), reported by each subject through a standardized interview which focused on different days of the week and different periods within the day. Daily intake of alcohol was estimated from the average number of grams of ethanol in a typical serving of each type of alcoholic beverage (9.6–12 g for wine, 12–21 g for beer, 3.8 g for cider, and 3.2–19.2 g for spirits).

A blood sample was obtained from each subject after at least 10 hours' fast and was centrifuged at room temperature within 4 hours. After addition of preservative, the plasma was stored at 4°C for no longer than 6 days and was shipped at 4°C to the Central Laboratory in Lille, France, for immediate lipid measurement.

Blood pressure measurements were made according to the recommendations of the British Hypertension Society (17), using a random-zero sphygmomanometer. All measurements were taken to the nearest 2 mmHg and were performed in duplicate. Hypertension was defined as a systolic blood pressure of  $\geq 160$  mmHg or a diastolic blood pressure of  $\geq 95$  mmHg upon examination, or use of antihypertensive medication.

Subjects were considered hyperlipidemic if they were on hypolipidemic therapy or if their low density lipoprotein (LDL) cholesterol level was higher than 200 mg/dl. Diabetes mellitus was assumed if the sub-

ject reported that a physician had ever told him he was diabetic.

### Lipid determinations

Plasma total cholesterol and triglycerides were measured by enzymatic methods (Boehringer, Mannheim, Germany) adapted to a Hitachi 705 analyzer (Hitachi Sales Corporation, Lyndhurst, New Jersey). Cholesterol was measured in the very low density lipoprotein fraction after it was separated by ultracentrifugation, and in the high density lipoprotein-containing supernatant after sodium phosphotungstate/magnesium chloride precipitation (Boehringer, Mannheim, Germany). LDL cholesterol was determined by subtraction.

### Statistical analysis

Statistical analysis was performed using SAS software (Statistical Analysis System; SAS Institute, Cary, North Carolina). Univariate comparisons were made using the chi-squared test for categorical variables, the *t* test for approximate normal and lognormal variables, and the Wilcoxon signed-rank test for alcohol and cigarette consumption. The role of alcohol intake in myocardial infarction risk was analyzed after multivariate adjustment by logistic regression. Odds ratios are given with 95 percent confidence intervals.

## RESULTS

### Subjects' characteristics

In total, 561 cases and 643 controls were studied. Their characteristics are shown in table 1. In France, cases were significantly older, presented more frequently with hypertension and dyslipidemia, and smoked significantly more cigarettes than controls, while no significant difference was found for body mass index or diabetes. A significant difference was also found for smoking status in Northern Ireland. Patients had significantly lower levels of high density lipoprotein (HDL) cholesterol than did controls, while no difference was found for total cholesterol and LDL cholesterol. In Northern Ireland, cases had higher triglyceride levels than controls, while no difference was found in France.

Total alcohol consumption did not differ significantly between the two groups. On the contrary, in Northern Ireland, controls reported a higher intake of wine than did cases, while nonwine consumption did not reach statistical significance. French subjects consumed mainly wine (26.3 g of alcohol per day), while Northern Irish subjects consumed mostly nonwine beverages (34.6 g/day).

**TABLE 1. Clinical characteristics of 561 myocardial infarction patients and 643 healthy controls drawn between 1988 and 1991: The ECTIM Study**

	France					Northern Ireland				
	Cases (n = 359)		Controls (n = 422)		p value	Cases (n = 359)		Controls (n = 422)		p value
	Mean	SD*	Mean	SD		Mean	SD	Mean	SD	
Age (years)	54.0	8.2	51.9	8.9	0.001	54.0	8.0	54.2	7.8	0.84
Body mass index†	26.9	3.2	26.9	3.9	0.96	26.2	3.6	25.8	3.7	0.29
Diabetes mellitus (%)	15		12		0.30	6		3		0.10
Hyperlipidemia (%)	39		15		0.0001	20		15		0.15
Hypertension (%)	35		22		0.0001	22		25		0.48
Smoking (cigarettes/day)	10.6	14.7	5.2	10.2	0.0001	15.9	20.0	5.1	10.6	0.0001
Cholesterol (g/liter)	2.23	0.41	2.28	0.46	0.13	2.42	0.41	2.38	0.43	0.26
Triglycerides (g/liter)	1.57	0.98	1.62	1.56	0.08	2.05	1.43	1.64	0.92	0.001
HDL* cholesterol (g/liter)	0.43	0.11	0.50	0.13	0.0001	0.42	0.13	0.51	0.15	0.0001
LDL* cholesterol (g/liter)	1.53	0.34	1.51	0.39	0.38	1.65	0.37	1.59	0.40	0.09
Alcohol (g/day)	32.6	33.5	35.7	35.5	0.17	34.2	48.9	37.2	54.2	0.88
Wine	24.9	27.7	27.4	27.9	0.12	0.5	2.0	1.7	8.0	0.002
Nonwine	7.7	16.3	8.3	20.2	0.29	33.7	49.1	35.5	53.7	0.65

\* SD, standard deviation; HDL, high density lipoprotein; LDL, low density lipoprotein.

† Weight (kg)/height<sup>2</sup> (m<sup>2</sup>).

### Multivariate analysis

The importance of total alcohol consumption in discriminating between patients and controls was assessed by logistic regression analysis using different models (table 2). After adjustment for study center, age, cigarette smoking, hyperlipidemia, hypertension status, body mass index, and diabetes, a significant protective effect for alcohol consumption was observed (model 1). When analyses were performed separately for each country, similar results were obtained (consumption of 50 g/day: odds ratio = 0.78 (95 percent confidence interval 0.64–0.95) for Northern

Ireland and odds ratio = 0.74 (95 percent confidence interval 0.61–0.90) for France). The introduction of HDL cholesterol into the model sharply decreased the magnitude of the protective effect of alcohol consumption (model 2). Introducing quadratic terms for alcohol consumption into the model did not significantly improve the results (data not shown).

Similar results were observed when total alcohol consumption was broken down into wine and nonwine intake (table 3). In particular, both components dis-

**TABLE 2. Effect of total alcohol intake in logistic regression of selected predictors on myocardial infarction: The ECTIM Study, 1988–1991**

Predictor variable*	Model 1		Model 2	
	Odds ratio	95% CI†	Odds ratio	95% CI
Age (years)	1.31	1.12–1.53	1.34	1.14–1.56
Alcohol (g/day)	0.80	0.66–0.97	0.90	0.74–1.10
Smoking (cigarettes/day)	1.60	1.45–1.76	1.52	1.35–1.71
Body mass index‡	0.96	0.68–1.36	0.64	0.44–0.93
Hyperlipidemia	2.57	1.91–3.46	2.48	1.83–3.37
Diabetes mellitus	1.35	0.91–2.02	1.36	0.89–2.06
Hypertension	1.36	1.02–1.80	1.32	0.98–1.78
HDL† cholesterol (g/liter)			0.63	0.56–0.70

\* Adjusted for study center. Continuous variables were entered in the units noted. Odds ratios based on continuous variables were calculated for the following variations: 10 years of age, 50 g of alcohol/day, 10 cigarettes/day, 10 units of body mass index, and 0.10 g/liter of HDL cholesterol. Odds ratios based on dichotomous variables were computed using the following reference categories: dyslipidemia, no; diabetes, no; hypertension, no.

† CI, confidence interval; HDL, high density lipoprotein.

‡ Weight (kg)/height<sup>2</sup> (m<sup>2</sup>).

**TABLE 3. Effect of wine-derived and non-wine-derived alcohol intake in logistic regression of selected predictors on myocardial infarction: The ECTIM Study, 1988–1991**

Predictor variable*	Model 1		Model 2	
	Odds ratio	95% CI†	Odds ratio	95% CI
Age (years)	1.31	1.12–1.53	1.35	1.15–1.58
Alcohol (g/day)				
Wine	0.74	0.55–0.99	0.86	0.64–1.15
Nonwine	0.82	0.67–0.99	0.90	0.74–1.10
Smoking (cigarettes/day)	1.60	1.45–1.76	1.52	1.35–1.71
Body mass index‡	0.96	0.68–1.37	0.67	0.46–0.97
Hyperlipidemia	2.58	1.92–3.47	2.48	1.83–3.37
Diabetes mellitus	1.36	0.91–2.03	1.36	0.89–2.07
Hypertension	1.36	1.02–1.81	1.32	0.98–1.78
HDL† cholesterol (g/liter)			0.63	0.56–0.70

\* Adjusted for study center. Continuous variables were entered in the units noted. Odds ratios based on continuous variables were calculated for the following variations: 10 years of age, 10 g of wine- or non-wine-related alcohol/day, 10 cigarettes/day, 10 units of body mass index, and 0.10 g/liter of HDL cholesterol. Odds ratios based on dichotomous variables were computed using the following reference categories: dyslipidemia, no; diabetes, no; hypertension, no.

† CI, confidence interval; HDL, high density lipoprotein.

‡ Weight (kg)/height<sup>2</sup> (m<sup>2</sup>).

played a protective effect, the effect of wine consumption being comparable to that of nonwine. Again, both effects became nonsignificant when HDL cholesterol was taken into account (model 2).

## DISCUSSION

Although the inverse association between moderate alcohol use and coronary artery disease is now well established, the protective effect of different types of alcoholic beverages is still a matter of debate. Some studies have found red wine to be superior (8), and the lower incidence of myocardial infarction in France as compared with other industrialized countries has been attributed to a higher consumption of wine, particularly red wine, in that country (9). Conversely, other studies have found beer or spirits consumption to be protective (5, 18). Nevertheless, most epidemiologic studies have failed to detect any differences between the various types of alcoholic beverages. In addition, few epidemiologic studies have been carried out in Southern Europe, where there has traditionally been a high level of drinking wine on a regular basis. To our knowledge, this is the first case-control study of alcohol consumption and myocardial infarction that has been performed in France.

Case-control studies, however, might suffer from a number of pitfalls, particularly from exposure biases due either to reporting of current or past habits by the subjects themselves or (especially for coronary disease) to measurement of post-illness biologic factors.

Even though information on alcohol drinking was not obtained by self-questionnaire but through detailed interview by a trained technician, reported alcohol consumption in this study may have tended to underestimate actual intake. Hence, it is possible that cases in this study might have underestimated their alcohol intake prior to myocardial infarction, thus introducing exposure bias. Such a bias could also be due to the fact that persons with high consumption of alcoholic beverages who suffer myocardial infarction are less likely to survive (19). Nevertheless, previous reports have shown that underreporting occurs mainly among heavy, problem drinkers, while teetotallers or subjects who consume moderate amounts of alcohol probably report their alcohol intakes accurately (20, 21).

Myocardial infarction patients were recruited 3–9 months after the event, and they were taking various medications at the time of examination, which might have directly or indirectly modified their blood pressures and lipid levels. Changes in life habits after myocardial infarction, especially dietary changes, might have also contributed to these alterations. For all of these reasons, very broad and conservative defini-

tions of hyperlipidemia, hypertension, and diabetes were used in the present analysis. Results from a comprehensive analysis of lipids and lipoproteins in the ECTIM Study have been reported elsewhere (14), and the importance given to HDL cholesterol measurements in comparison with LDL cholesterol in discriminating between cases and controls is discussed. As can be seen in table 1, the HDL cholesterol level is dramatically decreased in cases, and it is conceivable that some of the case-control difference might be due to postinfarction changes in the cases. As a consequence, the confounding effect of HDL cholesterol on the myocardial infarction-alcohol relation might have been inflated. However, some residual negative association, though not significant, does exist in accordance with recent studies (22, 23).

In this study, both wine-derived and non-wine-derived alcohol were found to be inversely related to coronary artery disease after adjustment for major confounding factors. This was due to the strong relation between cigarette smoking and alcohol consumption (Spearman correlation coefficient = 0.18,  $p < 0.0001$ ), which obscured the negative relation between alcohol consumption and myocardial infarction in univariate analysis. Hence, our data do not support the hypothesis that wine is superior to other alcoholic beverages in terms of protection against coronary artery disease.

Various mechanisms have been proposed to explain the lower coronary artery disease risk observed among moderate drinkers. Moderate alcohol consumption has been shown to increase HDL cholesterol levels (22) and plasma fibrinolytic activity (24). Alcohol consumption has also been shown to decrease platelet activation (25, 26), and phenolic substances present in red wine inhibit low density lipoprotein oxidation, with a possible protective effect against atherosclerotic plaque progression (11). In contrast, other studies have found decreased levels of plasma beta-carotene in men drinking 20 g of alcohol per day relative to nondrinkers (27). In this study, the protective effect of alcohol, whether consumed as wine or nonwine, was completely abolished by the introduction of HDL cholesterol into the model. Thus, increased HDL cholesterol appears to provide most of the protective effect of alcohol consumption.

Finally, some recently published articles have advocated moderate alcohol drinking as a preventive measure for protection against coronary heart disease (28). Considering the potentially harmful effects of heavy drinking on health, and not knowing whether the decrease in coronary heart disease will outweigh the increase in alcohol-associated disease, the current authors cannot recommend such a policy. At most, the

results indicate that moderate drinkers at risk for coronary artery disease do not need to abstain from alcohol or switch to wine.

## ACKNOWLEDGMENTS

This study was supported by grants from the Squibb (Paris, France), Sanofi (Paris, France), and Parke-Davis (Courbevoie, France) Laboratories; the Mutuelle Générale de l'Éducation Nationale; the British Heart Foundation; and the Institut National de la Santé et de la Recherche Médicale (INSERM).

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