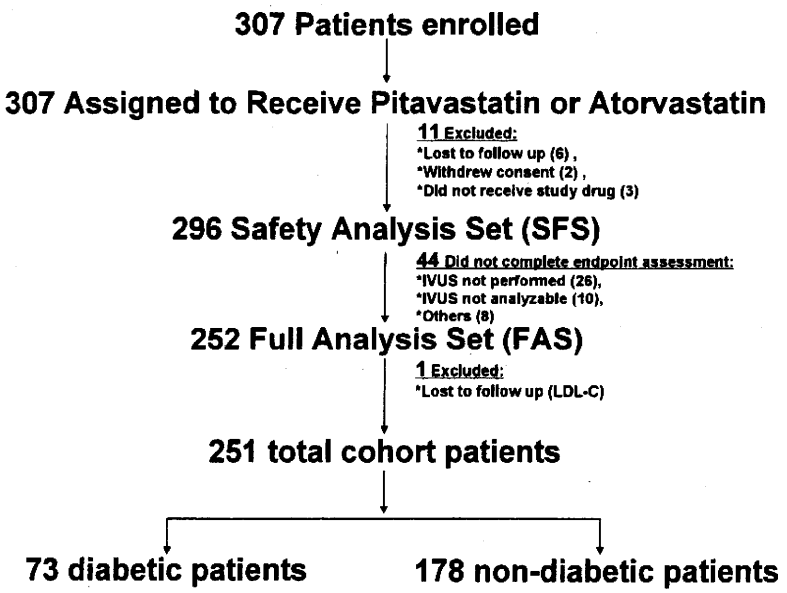

Fig. 1. Characteristics of Patients in JAPAN-ACS.

Scientific, Natik, USA) was used, and a motorized pullback device withdrew the transducer at 0.5 mm/sec. The consoles used were the ClearView or Galaxy 2 system (Boston Scientific, Natik, USA). The same imaging system with the same type of IVUS catheter was used for both the baseline and follow-up examinations

Two independent experienced investigators performed the quantitative IVUS analysis at the central laboratory. The target segment for analysis was identified as a non-PCI site of the culprit vessel (>5 mm proximal or distal to the PCI site) based on reproducible indices. Manual tracing was performed in every 0.1 mm cross-section and the software (echoPlaque2; INDEC systems Inc., Santa Clara, USA) automatically interpolated the tracings of 5 cross-sections between two manually traced images; therefore, the volume was calculated from each of the 0.017 mm-interval segments.

Blood Examination

Blood examinations for lipid levels were performed at baseline and 8–12 months follow-up. Lipid profiles were measured at SRL Co, Ltd. (Tokyo, Japan).

Statistical Analysis

We used the full analysis set (FAS) of data for primary analyses. Patient data were included in FAS if patients had ACS and measurable IVUS both at enrollment and follow-up. Because non-inferiority was shown between pitavastatin and atorvastatin, we combined the data of both groups and performed this subanalysis. LDL-cholesterol, non-HDL-cholesterol, LDL-C/HDL-C ratio, and apolipoprotein B (apo B) at the end of the study were divided into quartiles and the percentage change in PV in each quartile was compared in total and diabetic patients by ANOVA or *t* test when appropriate. The chi-square test was used for categorical variables. We also analyzed the association of baseline and follow-up HDL-cholesterol (over or equal to 40 mg/dL or less than 40 mg/dL) with the rate of restenosis in this cohort. The significance level was 5% two-sided (2.5% one-sided) and all statistical analyses were performed using the SAS System Release 9.1 (SAS institute, Cary, USA).

Results

Patient Population

The characterstics of patients in the present study are shown in **Fig. 1**. Between November 1, 2005 and October 31, 2006, 307 patients were enrolled at 33 centers in Japan, and 153 patients were randomly assigned to receive pitavastatin and 154 to atorvastatin. IVUS images qualifying for evaluation both at baseline and follow-up were obtained in 125 patients (82%) in the pitavastatin group and in 127 patients (82%) in the atorvastatin group. The median follow-up time with intraquartile range in the pitavastatin group was 9.3 (8.5–10.3) months and 9.6 (8.6–10.5) months in the atorvastatin group, respectively.

The details of baseline demographics and characteristics in this study have been reported elsewhere[9]. Among 251 total cohorts, 73 patients were diabetic.

There were no differences in the percent change of PV and LDL-cholesterol reduction between pitavastatin and atorvastatin groups in patients with or without diabetes. In diabetic patients, the percent change of PV was $-13.7 \pm 15.1\%$ ($p<0.001$, from baseline) in the pitavastatin group ($n=36$) and $-12.0 \pm 13.9\%$ ($p<0.001$, from baseline) in the atorvastatin group ($n=38$) ($p=0.7$, pitavastatin vs. atorvastatin). The percent change of PV was $-18.1 \pm 13.2\%$ ($p<0.001$, from baseline) in the pitavastatin group ($n=89$) and $-20.7 \pm 13.6\%$ ($p<0.001$, from baseline) in the atorvastatin group ($n=89$) in non-diabetic patients ($p=0.2$, pitavastatin vs. atorvastatin), while in diabetic patients, the percent change of LDL-cholesterol was $-35.7 \pm 21.1\%$ ($p<0.001$, from baseline) in the pitavastatin group ($n=35$) and $-37.6 \pm 22.6\%$ ($p<0.001$, from baseline) in the atorvastatin group ($n=38$) ($p=0.7$, pitavastatin vs. atorvastatin). The percent change of LDL-cholesterol was $-36.4 \pm 19.0\%$ ($p<0.001$, from baseline) in the pitavastatin ($n=89$) group and $-34.9 \pm 23.1\%$ ($p<0.001$, from baseline) in the atorvastatin group ($n=87$) in non-diabetic patients ($p=0.7$, pitavastatin vs. atorvastatin).

Table 1. Median and interquartiles of lipid profiles in total and diabetic patients

total cohort ($n=251$)			
Quartile	25%	50%	75%
LDL-C (mg/dL)	66	79	98
non HDL-C (mg/dL)	84	99	124
Apo B (mg/dL)	60	72	86
LDL-C/HDL-C	1.32	1.77	2.23
diabetic patients ($n=73$)			
Quartile	25%	50%	75%
LDL-C (mg/dL)	56.5	75	101.5
non HDL-C (mg/dL)	82	95	125.5
Apo B (mg/dL)	57	70	88
LDL-C/HDL-C	1.14	1.75	2.37

Association of Percent Change in Plaque Volume with Quartiles of Lipid Parameters

Table 1 shows 25th and 75th percentiles and medians in each lipid parameter in total and diabetic populations. According to these numbers we divided the total and diabetic patients into quartiles and compared the percent change of PV in each group (**Table 2**). Decreasing LDL-cholesterol, non-HDL-cholesterol, apo B, and LDL-C/HDL-C ratio quartiles were associated with a progressively larger percent change of PV

Table 2. Association of % change in plaque volume with quartile of lipid parameters

		quartile at follow up	1st	2nd	3rd	4th	p value
LDL-C	total	mean (range) [mg/dL]	53.2 (<66)	71.4 (66-79)	87.7 (79-98)	117.2 (98<)	
		% change in plaque volume (SD) [%]	-15.4 (12.7)	-20.3 (14.4)	-20 (13.0)	-14.2 (15.2)	0.03
	DM	mean (range) [mg/dL]	48.7 (<56.5)	69.1 (56.5-75)	88.6 (75-101.5)	119.4 (101.5<)	
		% change in plaque volume (SD) [%]	-16.5 (13.6)	-16.9 (14.5)	-10.6 (13.0)	-6.7 (15.2)	0.1
nonHDL-C	total	mean (range) [mg/dL]	70.0 (<84)	90.1 (84-99)	109.6 (99-124)	143.9 (124<)	
		% change in plaque volume (SD) [%]	-15.6 (12.8)	-18.5 (12.7)	-21.4 (14.0)	-14.0 (15.6)	0.01
	DM	mean (range) [mg/dL]	63.9 (<82)	87.4 (82-95)	111.6 (95-125.5)	149.9 (125.5<)	
		% change in plaque volume (SD) [%]	-16.2 (14.0)	-15.3 (14.6)	-12.4 (13.3)	-6.9 (15.4)	0.2
apoB	total	mean (range) [mg/dL]	50.5 (<60)	65.6 (60-72)	78.5 (72-86)	99.2 (86<)	
		% change in plaque volume (SD) [%]	-16.1 (12.4)	-19.2 (15.2)	-21.3 (11.7)	-13.2 (15.6)	0.006
	DM	mean (range) [mg/dL]	47.4 (<57)	62.6 (57-70)	78.8 (70-88)	99.6 (88<)	
		% change in plaque volume (SD) [%]	-16.3 (13.2)	-15.9 (14.3)	-14.6 (11.4)	-5.3 (15.9)	0.049
LDL-C/HDL-C	total	mean (range) [mg/dL]	1.02 (<1.32)	1.54 (1.32-1.77)	1.95 (1.77-2.23)	2.75 (2.23<)	
		% change in plaque volume (SD) [%]	-16.7 (14.5)	-19.5 (14.1)	-20.1 (13.1)	-13.6 (13.8)	0.03
	DM	mean (range) [mg/dL]	0.86 (<1.14)	1.48 (1.14-1.75)	1.95 (1.75-2.37)	2.86 (2.37<)	
		% change in plaque volume (SD) [%]	-18.6 (14.8)	-13.7 (14.6)	-14.2 (12.6)	-4.1 (13.0)	0.02

Table 3. Baseline characteristics of total cohort with quartiles of follow up LDL-cholesterol

Characteristic	1st ($n=62$)	2nd ($n=62$)	3rd ($n=64$)	4th ($n=63$)	p value
Age (years)	66.4±9.9	61.4±11.0	61.6±10.6	60.4±12.1	0.01
Male (%)	81	92	81	73	0.042
BMI (kg/m^2)	24.3±3.5	24.7±3.3	23.9±3.6	24.5±3.7	0.6
Waist circumference (cm)	86.7±8.6	88.1±7.7	86.3±9.0	87.2±10.6	0.7
Diabetes (%)	35	27	20	33	0.2
Hypertension (%)	65	69	59	57	0.5
Family history of CAD (%)	23	19	16	14	0.6
Smoking (%)	34	50	58	46	0.054
Alcohol drinker (%)	68	52	38	35	0.001
Culprit vessel (%)					
RCA	31	21	42	33	0.1
LAD	53	68	48	48	
LCx	16	11	8	19	
LMT	0	0	2	0	
BMS (%)	63	69	67	63	0.6
DES (%)	37	27	30	33	
Other than stent (POBA) (%)	0	3	3	3	
TC (mg/dL)	184.3±30.1	184.8±27.7	203.7±30.4	216.7±43.5	<0.0001
LDL-C (mg/dL)	117.2±27.7	122.2±23.9	138.3±27.3	152.2±37.3	<0.0001
TG (mg/dL)	106.0 (72.5, 139.8)	111.5 (67.0, 141.3)	120.0 (76.8,157.8)	106.0 (80.5, 154.5)	0.4#
HDL-C (mg/dL)	46.1±9.1	43.0±9.7	44.4±9.9	44.2±10.3	0.3
non-HDL-C (mg/dL)	137.3±27.9	142.0±26.0	159.3±29.2	171.4±38.4	<0.0001
LDL-C/HDL-C	2.6±0.8	3.0±0.8	3.3±0.9	3.5±0.8	<0.0001
Apo A-I (mg/dL)	116.3±20.0	106.8±17.3	111.2±18.9	109.3±20.6	0.047
Apo B (mg/dL)	92.6±20.4	97.6±18.3	110.6±20.1	116.0±26.2	<0.0001
Apo E (mg/dL)	4.3±1.4	4.0±1.1	4.1±1.0	4.3±1.1	0.4
Apo B/Apo A-I	0.82±0.22	0.93±0.22	1.02±0.23	1.08±0.25	<0.0001

TG is expressed as median and interquartile range, #: Wilcoxon/Kruskal-Wallis test

in total and diabetic patients. The difference was significant in all parameters of the total cohort, while the difference was significant only in apo B and LDL-C/HDL-C in diabetic patients. We also analyzed baseline demographics of each quartile according to follow-up LDL-cholesterol (**Table 3**). The mean age and the prevalence of alcohol drinkers were higher in the first quartile than the other quartiles, which might affect less PV change in the first quartile. Total cholesterol, LDL-cholesterol, non-HDL-cholesterol, apo B, and apo B/apo AI were higher in the third and fourth quartiles than the others.

Because we noticed a smaller percent change of PV in the fourth quartile than the others, we compared the percent change of PV between the combined data from the first to third quartiles and the fourth quartile in each lipid parameter (**Fig. 2**). There was a significant difference between the two groups by t test in all the lipid parameters, indicating that the fourth quartile had less plaque regression than the others.

Next, we compared the percent change of PV in diabetic patients. The baseline characteristics of diabetic patients according to the quartiles of follow-up LDL are shown in **Table 4**. There was no significant difference in age, sex, BMI, waist circumference, or the prevalence of hypertension, family history of coronary artery disease, smoking, and alcohol drinking in this cohort, while total cholesterol, LDL-cholesterol, non-HDL-cholesterol, LDL-C/HDL-C ratio, apo B, apo B/apo AI ratio were higher in the third and fourth quartiles than the others. When we performed the same analysis with the total cohort, a significant difference was found between the combined data from the first to third quartiles and the fourth quartile, except non-HDL-cholesterol (**Fig. 3**). Because further

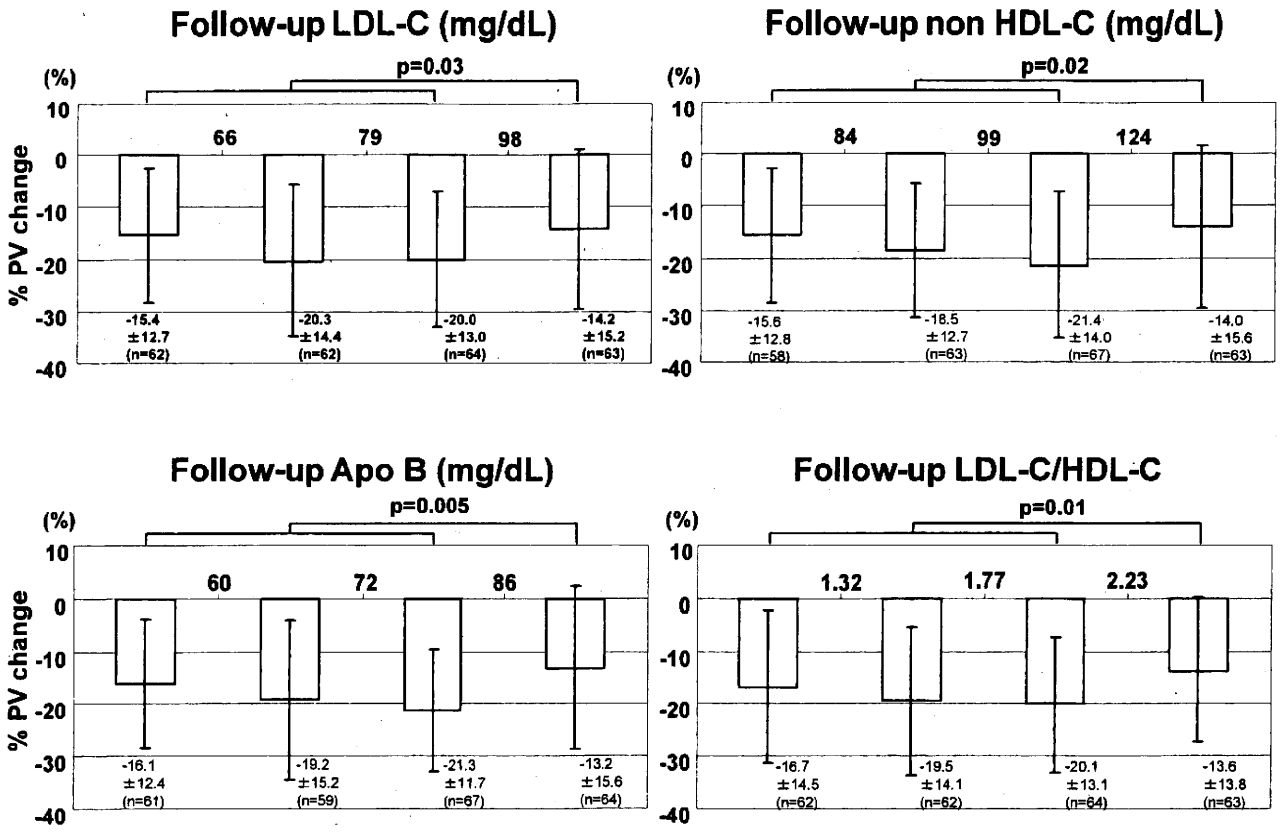

Fig. 2. Percent change of PVin each quartile of follow-up lipid parameters in the total cohort.

reduction of lipid profiles seemed to result in further reduction of PV in diabetic patients, we also compared the percent PV change after dividing them into 2 groups according to the median. As shown in **Fig. 4**, a significant difference was found between the two groups, except in non-HDL-cholesterol. However, the *p* value was smaller in LDL-cholesterol when we used the median as a cutoff value, while it was larger in apo B. Although we did not find significant differences in non-HDL-cholesterol, a *p* value of 0.028 was obtained when we used a cutoff of 100 mg/dL for non HDL-cholesterol.

Effect of HDL-Cholesterol Levels on Major Adverse Cardiovascular Events

To examine the effect of HDL-cholesterol levels on major adverse cardiovascular events (MACE), such as target lesion revascularization (TLR) and target vessel revascularization (TVR), we compared their incidence in the total cohort according to baseline and follow-up HDL-cholesterol levels (≥40 mg/dL or <40 mg/dL). As shown in **Table 5**, patients with lower HDL-cholesterol at baseline or follow-up showed a significantly higher incidence of TLR, but not of TVR or other vessel revascularization. The baseline characteristics of the two groups according to the levels of follow-up HDL-cholesterol levels are shown in **Table 6**. There was no significant difference in demographic characteristics between the two groups. As expected, HDL-cholesterol and apo AI were higher and the LDL-C/HDL-C ratio and apo B/AI were lower in patients with higher HDL-cholesterol. A similar finding was observed when we divided the patients according to baseline HDL-cholesterol levels (data not shown).

Discussion

In this post-hoc analysis of the JAPAN-ACS study we have shown that diabetic patients had more regression by targeting lower levels of LDL, non-HDL cholesterol, and LDL-C/HDL-C with intensive lipid-lowering therapy in Japanese; however, our data may indicate that the same target can be used for apo B in diabetic or non-diabetic ACS patients. We also found that patients with lower HDL-cholesterol had a higher

Table 4. Baseline characteristics of diabetic patients with quartiles of follow-up LDL-C

Characteristic	1st (n=18)	2nd (n=18)	3rd (n=19)	4th (n=18)	p value
Age (years)	64.2±10.8	62.0±9.7	60.6±10.8	64.2±11.3	0.7
Male (%)	83	94	84	67	0.2
BMI (kg/m^2)	24.4±3.6	25.9±3.1	24.8±3.8	24.4±4.4	0.6
Waist circumference (cm)	87.1±7.4	89.1±6.0	89.4±8.0	88.4±10.7	0.9
Hypertension (%)	67	78	74	67	0.8
Family history of CAD (%)	28	11	16	17	0.6
Smoking (%)	39	39	63	50	0.4
Alcohol drinker (%)	67	61	47	39	0.3
Culprit vessel (%)					
RCA	28	22	47	44	
LAD	44	61	32	39	0.5
LCx	28	17	21	17	
LMT	0	0	0	0	
BMS (%)	44	72	74	72	
DES (%)	56	22	21	28	0.2
Other than stent (POBA) (%)	0	6	5	0	
TC (mg/dL)	186.4±33.8	187.1±25.0	201.5±23.0	217.3±48.7	0.03
LDL-C (mg/dL)	115.9±30.0	123.5±21.3	138.7±17.0	149.1±44.3	0.006
TG (mg/dL)	112.0 (76.0, 153.0)	117.0 (77.0, 140.5)	127.0 (107.0, 173.0)	134.0 (76.3, 191.3)	0.6#
HDL-C (mg/dL)	48.6±9.7	42.7±6.3	41.3±13.3	45.9±12.1	0.2
non-HDL-C (mg/dL)	134.5±28.6	144.4±24.1	160.2±19.4	170.6±43.4	0.004
LDL-C/HDL-C	2.4±0.8	3.0±0.7	3.6±0.9	3.3±0.9	0.0004
Apo A-I (mg/dL)	123.6±21.3	107.4±16.3	106.4±26.5	109.1±23.6	0.09
Apo B (mg/dL)	92.4±20.9	96.9±18.5	111.8±14.9	115.7±27.3	0.003
Apo E (mg/dL)	4.3±1.2	4.3±1.0	4.2±1.0	4.4±1.0	0.95
Apo B/Apo A-I	0.76±0.20	0.92±0.23	1.10±0.26	1.09±0.26	0.0001

TG is expressed as median and interquartile range, #: Wilcoxon/Kruskal-Wallis test

risk for target lesion revascularization, and should be considered for additional therapy to prevent restenosis.

IVUS provides a precise evaluation of the vascular wall and has been shown to be the most sensitive and reliable technique for measuring coronary atherosclerosis progression and regression[15]. Several IVUS trials have shown that intensive lipid-lowering therapy is associated with a decrease of atherosclerosis progression or regression of plaque burden[6]. In the JAPAN-ACS we found much more regression of coronary atheroma after statin therapy than these studies in US[6, 7]. Consistent with our findings, Okazaki *et al.* also showed similar regression with 20 mg atorvastatin after ACS[8]. These data may indicate that Japanese patients are more susceptible to statin therapy in terms of atheroma regression; however, Takayama *et al.* have recently shown that rosuvastatin can induce significant regression of coronary PV (−5.1%) in Japanese patients with stable CAD[16], consistent with the findings by Nissen *et al.*[6, 7]. Taken together, the differences in regression rates between ours and those of Nissen *et al.* might be derived from the patient population; stable CAD and ACS patients. It is still difficult to investigate non-culprit coronary arteries by IVUS in Japan, which might also explain the difference between Japanese and US studies.

The National Cholesterol Education Program currently recommends an optional target LDL-cholesterol of <70 mg/dL for patients at high risk of cardiovascular events, including those with an ACS event[17], while the Japanese guideline recommends an LDL-cholesterol target <100 mg/dL for secondary prevention[18]. However, this study might provide a rationale for more aggressive lipid lowering, targeting LDL-cholesterol of <75 or 70 mg/dL in diabetic patients after ACS, while non-diabetic patients can be treated to reach LDL-cholesterol of <100 mg/dL. Our data also support non-HDL-cholesterol as an additional target

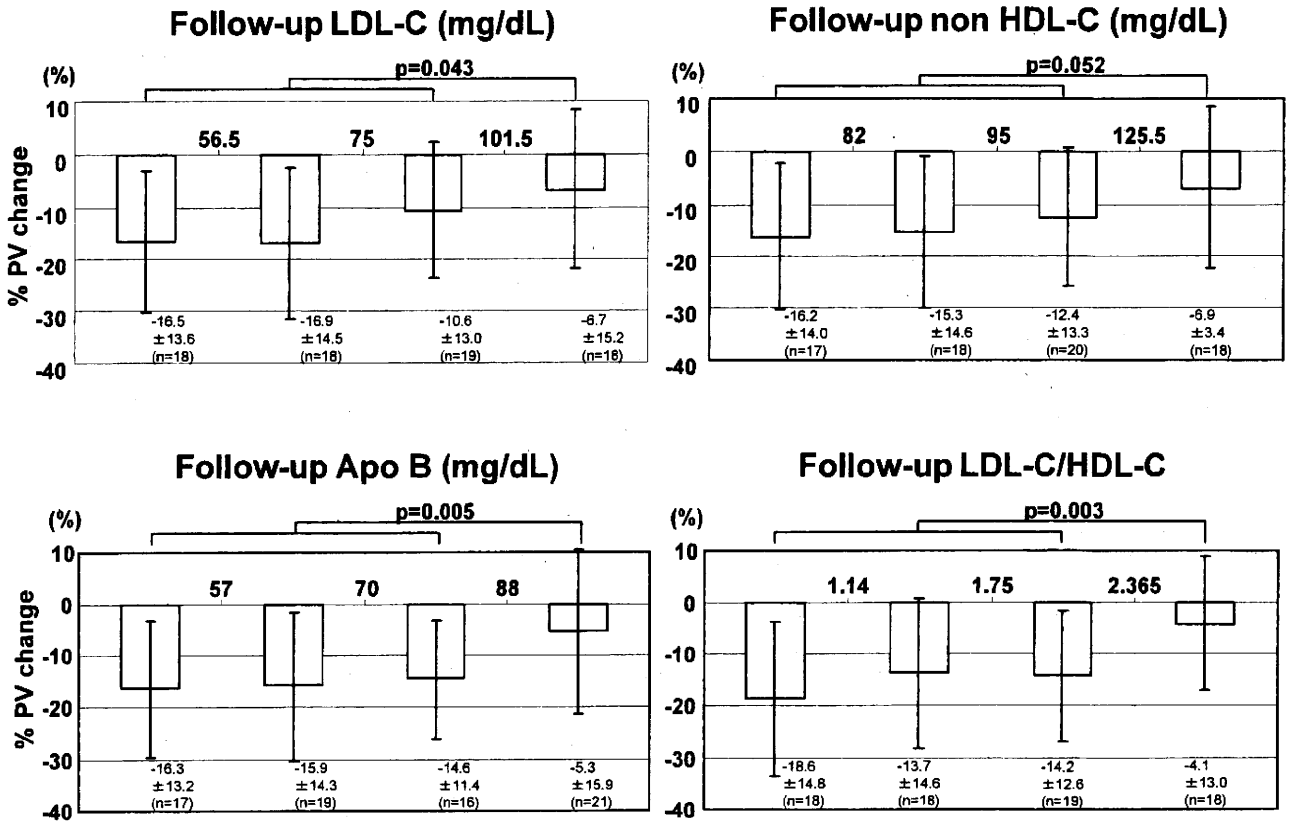

Fig. 3. Percent change of PV in each quartile of follow-up lipid parameters in diabetic patients.

for the management of ACS patients. Although the median cutoff did not result in a significant difference, a significant difference was observed when we used 100 mg/dL for the cutoff, which is consistent with the guidelines of the National Cholesterol Education Program for very high-risk patients. In terms of apo B, we obtained a smaller *p* value when we used a cutoff of 88 mg/dL than 70 mg/L in diabetic patients, which was almost the same in the total cohort. We showed less regression of coronary atheroma in diabetic patients after intensive statin treatment even though the mean LDL-cholesterol levels were almost the same in diabetic and non-diabetic patients. Considering that diabetic patients tend to have small dense LDL, the data on apo B might indicate that LDL particle number should be reduced to a certain level to obtain the maximum effects for plaque regression in diabetic patients. Further study is required to develop a rationale for aggressive lipid-lowering therapy in Japanese.

In this sub-analysis, we showed that low HDL-cholesterolemia <40 mg/dL was associated with increased TLR after ACS. As shown in **Table 6**, there was no demographic difference between the two groups except apo A1 and the ratio of LDL to HDL-cholesterol and the apo B to apo A1 ratio, indicating that low levels of HDL-cholesterol are a powerful predictor of major cardiovascular events even in patients treated with the maximum dose of statins. Previous studies have also shown that HDL-cholesterol levels during statin treatment are independently predictive of major cardiovascular events even in patients with LDL-cholesterol levels less than 70 mg/dL[11, 12]. Recently, Taylor *et al.* have shown that the use of extended-release niacin causes significant regression of carotid intima-media thickness when combined with a statin[19]; therefore, additional treatment might be required to raise HDL-cholesterol to prevent major cardiovascular events in patients with low HDL-cholesterolemia.

The current study has some limitations. The first is that LDL-cholesterol was determined by a direct method, not by a Friedwald equation because the equation could not be applied for blood samples from some patients. Recently, Nakamura *et al.* have shown that the direct measurement of LDL-cholesterol is still poor in terms of accuracy and stability[20]; however, even when we used the equation, we found similar

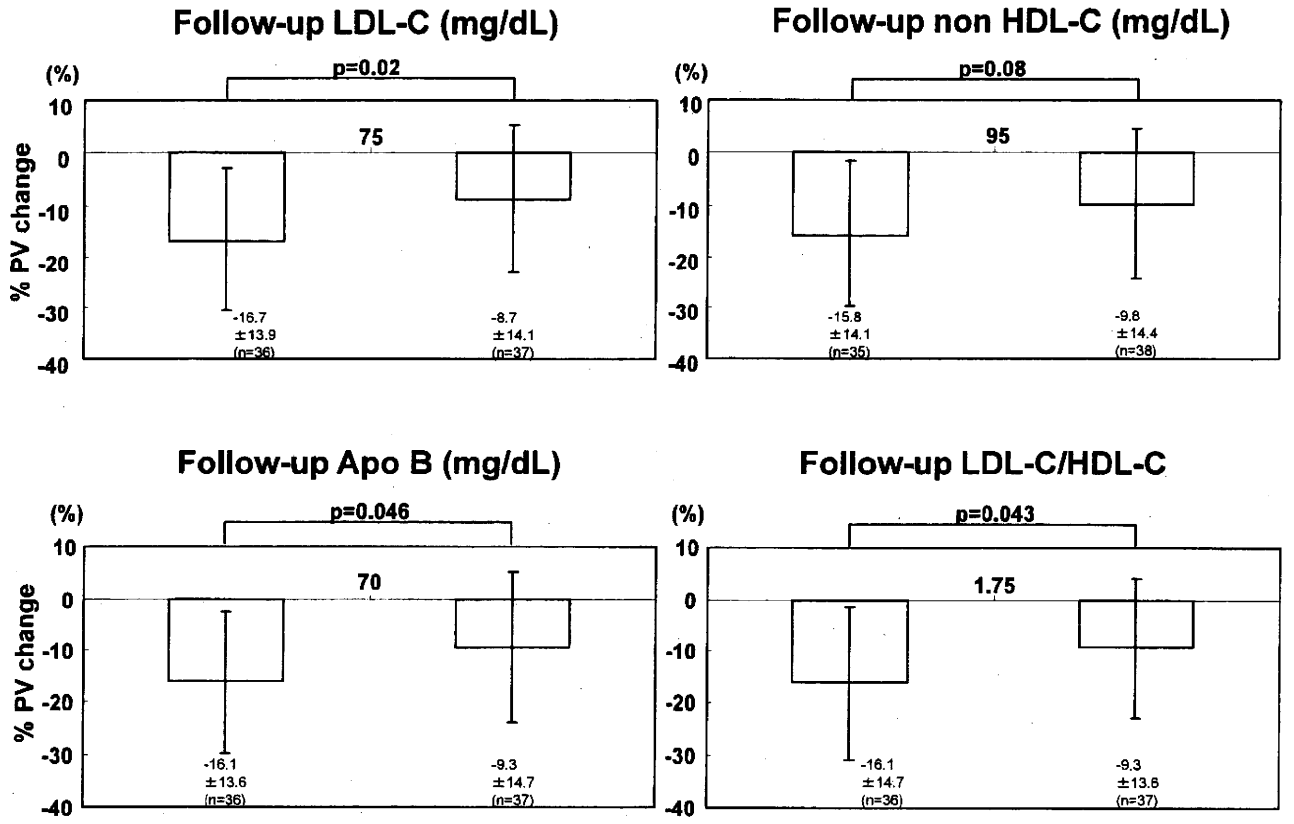

Fig. 4. Percent change of PV according to the median of follow-up lipid parameters in diabetic patients.

Table 5. Relationship between baseline and follow-up HDL-C levels with major adverse cardiovascular events (MACE)

baseline HDL-C	HDL-C < 40 mg/dL (n = 85)	HDL-C ≧ 40 mg/dL (n = 164)	p value
MACE	21 (24.7)	32 (19.5)	0.9
TLR	16 (18.8)	13 (7.9)	0.01
TVR (non-TLR)	3 (3.5)	11 (6.7)	0.3
Other vessel revascularization	6 (7.1)	10 (6.1)	0.09
follow-up HDL-C	HDL-C < 40 mg/dL (n = 64)	HDL-C ≧ 40 mg/dL (n = 187)	p value
MACE	15 (23.4)	38 (20.3)	0.6
TLR	12 (18.8)	17 (9.1)	0.046
TVR (non-TLR)	3 (4.7)	11 (5.9)	0.7
Other vessel revascularization	5 (7.8)	11 (5.9)	0.6

MACE: Major Adverse Cardiac Events
TLR: Target Lesion Revascularization
TVR: Target Vessel Revascularization

n (%)

results with this analysis (data not shown). The second is that this study lacked a control group receiving a placebo or less-intensive lipid-lowering therapy because the JAPAN-ACS study was designed to prove the non-inferiority of pitavastatin against atorvastatin. In this sub-analysis we combined the data on both statins; however, we deemed it ethically unacceptable to give a placebo to patients with ACS. The third is that the diagnosis of diabetes mellitus was made by the attending physicians, and no oral glucose tolerance

Table 6. Baseline characteristics of total cohort with HDL-C

Characteristic	follow-up HDL-C < 40 mg/dL (n = 64)	follow-up HDL-C ≧ 40 mg/dL (n = 187)	p value
Age (years)	62.8 ± 10.6	62.2 ± 11.3	0.7
Male (%)	89	79	0.064
BMI (kg/m^2)	24.4 ± 3.4	24.4 ± 3.6	0.99
Waist circumference (cm)	88.4 ± 8.9	86.6 ± 9.1	0.2
Diabetes (%)	25	30	0.4
Hypertension (%)	61	63	0.8
Family history of CAD (%)	22	17	0.3
Smoking (%)	52	45	0.4
Alcohol drinker (%)	45	49	0.6
Culprit vessel (%)			
RCA	25	34	0.4
LAD	61	52	
LCx	14	13	
LMT	0	0	
BMS (%)	70	64	0.6
DES (%)	28	33	
Other than stent (POBA) (%)	2	3	
TC (mg/dL)	189.9 ± 28.6	200.0 ± 37.8	0.052
LDL-C (mg/dL)	130.9 ± 27.3	133.0 ± 33.9	0.6
TG (mg/dL)	119.0 (85.3, 155.5)	105.0 (74.0, 143.0)	0.09#
HDL-C (mg/dL)	37.5 ± 6.5	46.8 ± 9.6	< 0.0001
non-HDL-C (mg/dL)	152.3 ± 27.7	152.5 ± 35.2	0.98
LDL-C/HDL-C	3.6 ± 0.9	2.9 ± 0.8	< 0.0001
Apo A-I (mg/dL)	98.0 ± 14.8	115.4 ± 18.9	< 0.001
Apo B (mg/dL)	105.2 ± 20.1	103.9 ± 24.3	0.7
Apo E (mg/dL)	3.9 ± 1.1	4.2 ± 1.2	0.057
Apo B/Apo A-I	1.09 ± 0.22	0.92 ± 0.24	< 0.0001

TG is expressed as median and interquartile range, #: Wilcoxon/Kruskal-Wallis test

test was performed to confirm diabetes, which is why we did not analyze non-diabetic patients.

In conclusion, early intensive statin therapy in Japanese patients after ACS resulted in the marked regression of coronary PV in total and diabetic patients. Diabetic patients can obtain more benefit from intensive lipid-lowering therapy with lower target levels of LDL, non-HDL-cholesterol, and LDL-C/HDL-C in Japanese. These lipid profiles may be related to the coronary plaque burden in statin-treated patients. On the other hand, low HDL-cholesterol levels are related to major cardiovascular events; therefore, patients with lower HDL-C are recommended for more intensive and comprehensive management to prevent the recurrence of coronary events.

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Appendices

Steering Committee

Takafumi Hiro, MD, Katsumi Miyauchi, MD, Yoshihisa Nakagawa, MD, Masakazu Yamagishi, MD, Yukio Ozaki, MD (working members, respectively), Takeshi Kimura, MD, Hiroyuki Daida, MD (co-principal investigators, respectively), Masunori Matsuzaki,

MD (principal investigator).

Independent Event Assessment Committee

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Independent Statistician

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Alcohol Consumption and Risk of Atrial Fibrillation

A Meta-Analysis

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Objectives The purpose of this meta-analysis is to summarize the estimated risk of atrial fibrillation (AF) related to alcohol consumption.

Background Results from observational studies examining the relationship between alcohol consumption and AF are inconsistent.

Methods A systematic electronic search of Medline (January 1966 to December 2009) and Embase (January 1974 to December 2009) databases was conducted for studies using key words related to alcohol and AF. Studies were included if data on effect measures for AF associated with habitual alcohol intake were reported or could be calculated. The effect measures for AF for the highest versus lowest alcohol intake in individual studies were pooled with a variance-based method. Linear and spline regression analyses were conducted to quantify the relationship between alcohol intake and AF risk.

Results Fourteen eligible studies were included in this meta-analysis. The pooled estimate of AF for the highest versus the lowest alcohol intake was 1.51 (95% confidence interval: 1.31 to 1.74). A linear regression model showed that the pooled estimate for an increment of 10 g per day alcohol intake was 1.08 (95% confidence interval: 1.05 to 1.10; R^2 = 0.43, $p < 0.001$). A spline regression model also indicated that the AF risk increased with increasing levels of alcohol consumption.

Conclusions Results of this meta-analysis suggest that not consuming alcohol is most favorable in terms of AF risk reduction. (J Am Coll Cardiol 2011;57:427–36) © 2011 by the American College of Cardiology Foundation

Atrial fibrillation (AF) is the most common sustained arrhythmia, representing a growing epidemic, and is accompanied by serious complications. Atrial fibrillation accounts for 45% of all embolic strokes and has a deleterious impact on longevity, with an approximate doubling of all-cause mortality (1). Although the etiology of AF is not fully understood, many epidemiological associations with AF, including both cardiac (e.g., valvular disease, cardiomyopathy, coronary artery disease) (2) and noncardiac conditions (e.g., aging, obesity, sleep apnea, diabetes mellitus, metabolic syndrome, heavy alcohol consumption) (3) have been vigorously investigated.

The association of episodic heavy alcohol use with the onset of AF has been recognized as "holiday heart syndrome" for a long time (4). Recently, it has been hypothesized that not only episodic but also habitual heavy alcohol consumption is associated with the risk of AF (5). However, results from epidemiological studies that aim to confirm this hypothesis have been inconsistent, although high alcohol consumption has been associated with several major disease groups such as neoplasms and cardiovascular diseases (6). It is also important to clarify the overall impact of any degree of alcohol intake on AF risk given that moderate alcohol consumption has been associated with a lower risk of cardiovascular disease (7) or all-cause mortality (8). Therefore, our aim of this meta-analysis of observational studies is to review the risk of AF in relation to alcohol consumption, focusing on determining if there is a dose-response relation-

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Abbreviations and Acronyms

AF = atrial fibrillation
CI = confidence interval
OR = odds ratio
PAF = paroxysmal atrial fibrillation
RR = relative risk

ship between any degree of alcohol consumption and the risk of AF as well as AF risk in relation to heavy alcohol drinking.

Methods

Search strategy. Electronic literature searches (Medline, January 1966 to December 2009; and Embase, January 1974 to December 2009) to identify studies describing alcohol intake and AF were conducted using medical subject headings related to alcohol (alcohol drinking OR alcohol related disorders OR alcoholism OR alcoholic beverage OR ethanol) and AF (arrhythmias OR atrial fibrillation). Reference lists from the identified articles were manually examined for relevant new articles. This process was repeated until no additional articles could be identified. No language restriction was imposed.

For inclusion, a study had to fulfill the following criteria: 1) have a cohort or case-control design; 2) identify AF as an outcome variable of interest separate from other arrhythmias; and 3) provide or allow calculation of the effect measure (i.e., relative risk [RR] in a prospective study or odds ratio [OR] in a retrospective study) with its corresponding confidence interval (CI). As an exception, because of the overlap between AF and atrial flutter, studies in which AF and atrial flutter were combined as a study outcome were also included. However, when data on risk of both AF only and the combination of AF and atrial flutter were provided simultaneously in 1 study, we used data on the risk of AF only. We excluded studies wherein alcohol consumption was classified as "yes" or "no" because the degree of daily alcohol consumption could not be ascertained through such a response.

Data extraction. Two of our investigators (S.K. and H.S.) independently reviewed all relevant articles and identified eligible studies. Discrepancies were resolved by group discussion. We extracted the following data from each publication: first author's name, year of publication, geographic region, design of the observational study (i.e., cohort or case-control), selection of study population (i.e., hospital-based or population-based), participants' characteristics (i.e., age [mean or range], proportion of men, and whether participants with heart disease that influenced AF risk were excluded), characteristics of outcome (i.e., onset or recurrence, dominantly paroxysmal atrial fibrillation [PAF] or dominantly chronic [persistent] AF, and whether atrial flutter was included in the study outcome), methods of assessment of alcohol consumption (i.e., questionnaire, interview, or reviews of medical records and registries), methods for ascertainment of AF (i.e., electrocardiogram screening, registries, or participant's report), category of alcohol intake, number of participants and cases, and study-specific controlled variables.

The effect measure in each study was extracted or, if the effect measure for AF was not provided, it was calculated based on data on the number of cases and noncases in referent and exposed groups. In principle, we defined the lowest alcohol intake category or no drinking as the referent group and the other category as the exposed group. When a study classified >2 alcohol intake categories, we extracted or calculated all available effect measures for AF. If a study provided several effect measures, such as unadjusted and adjusted effect measures, the most completely adjusted effect measure was used.

The effect measures were transformed to their natural logarithm (log OR/RR). Fundamentally, the standard error (SE) was calculated from the corresponding CI. In some studies (9–11), the SE corresponding to the log OR/RR was not provided. Then we directly calculated the SE corresponding to the log OR/RR using data on the number of cases and noncases in the exposed and referent groups in each comparison as follows:

$$SE^2 = \frac{1}{C_1} + \frac{1}{N_1} + \frac{1}{C_0} + \frac{1}{N_0}$$

(in case of log OR) (9,11) or:

$$SE^2 = \frac{1}{C_1} - \frac{1}{C_1 + N_1} + \frac{1}{C_0} - \frac{1}{C_0 + N_0}$$

(in case of log RR) (10), where C_1 and N_1 indicate the number of cases and noncases in the exposed group, respectively, and C_0 and N_0 indicate the number of cases and noncases in the referent group, respectively. If necessary, the effect measure and its corresponding SE were approximated from figures in the manuscripts using an image scanner (CanoScan LiDE 500F [resolution 600 dpi], Canon, Inc., Tokyo, Japan).

To standardize alcohol intake, we used a common scale (grams per day) for ethanol consumption. When a study used the number of drinks per day as a unit of alcohol intake, the unit was transformed into grams of ethanol according to the study-specific methods for estimating the amount of ethanol per drink. If the amount of ethanol per drink was not specified, the unit was considered equivalent to 12 g ethanol (12).

For each study, data on the mean level of daily alcohol intake for each category were extracted or calculated as point estimates of ethanol consumption. When this information was not provided, we assigned the mid-point of the upper and lower boundaries in each category as the average intake. If the highest category had an open upper boundary, mean alcohol intake was estimated to be 1.2 times the lower boundary (13).

Data synthesis. To summarize the association of habitual heavy alcohol consumption with the risk of AF, the effect measures were pooled for the highest versus lowest alcohol intake category. Based on the definition of heavy alcohol

drinking by the National Institute on Alcohol Abuse and Alcoholism (12), we limited this analysis to studies in which the highest alcohol intake category was defined as consumption of 2 or more drinks per day for men, 1 or more drinks per day for women, and 1.5 or more drinks per day for the combination of men and women. Subjects described as "alcohol abusers" and "alcoholics" were also considered to be heavy drinkers. The pooled estimate was calculated by averaging the log OR/RRs weighted by the inverse of variance based on a fixed- or random-effects model. We used the results from the random-effects model if between-study heterogeneity, which was assessed by Q statistics and I-squared (14), was significant (15). Because daily alcohol consumption in heavy alcohol drinkers varied from study to study, we conducted stratified analysis according to the degree of "heavy" drinking. Analyses were also stratified by the pre-specified study characteristics. We also conducted meta-regression analyses to assess the influence of study characteristics on study results.

The possibility of publication bias was assessed primarily by visual inspection of a funnel plot in which the effect measure in the individual study was plotted against its corresponding SE. The funnel plot is expected to be symmetrical with respect to the overall estimate if publication bias is absent. We secondarily assessed the possibility of publication bias by 2 formal tests: the Begg's adjusted rank correlation test (16) and the Egger's regression asymmetry test (17). If publication bias was statistically suspected, we also followed the Duval and Tweedie "trim and fill" procedure (18) for further estimation of the possible effect of the publication bias. This method considers the possibility of hypothetical unpublished studies that would have allowed a funnel plot to be symmetrical and recalculates a pooled estimate after imputation of the effect measures of the hypothetical studies as though they actually existed.

We primarily used weighted, least-squared regression models (19) to explore the dose-response relationship between alcohol intake and the risk of AF by regressing the log OR/RR of AF on the alcohol dose. To further investigate the shape of the relationship between the level of alcohol consumption and the risk of AF, we used restricted cubic splines with knots at the 25th, 50th, and 75th centiles of the distribution of alcohol consumption. These analyses were limited to data from studies with a referent category whose mean alcohol consumption was reported or estimated to be less than 1 drink per day, so that overlapping of alcohol intake of exposed and referent groups could be avoided as much as possible. Two-sided p values of ≤ 0.05 were considered statistically significant except for tests of publication bias for which the recommended level is p value ≤ 0.10 (20). Data were analyzed using STATA software version 10 (STATA Corp., College Station, Texas).

Results

Study characteristics. Figure 1 shows details of the literature search. Our electronic literature search resulted in retrieval of 1,754 citations (591 from Medline and 1,163 from Embase). Of these, 1,673 citations were excluded after the first screening. Eighty-one papers as well as 20 additional papers identified by manual search were left for full-text review. After this review, of the 101 papers, 87 were excluded for the reasons shown in Figure 1. Finally, 14 studies (9–11,21–31), which comprised 130,820 participants and 7,558 cases, were included in this meta-analysis.

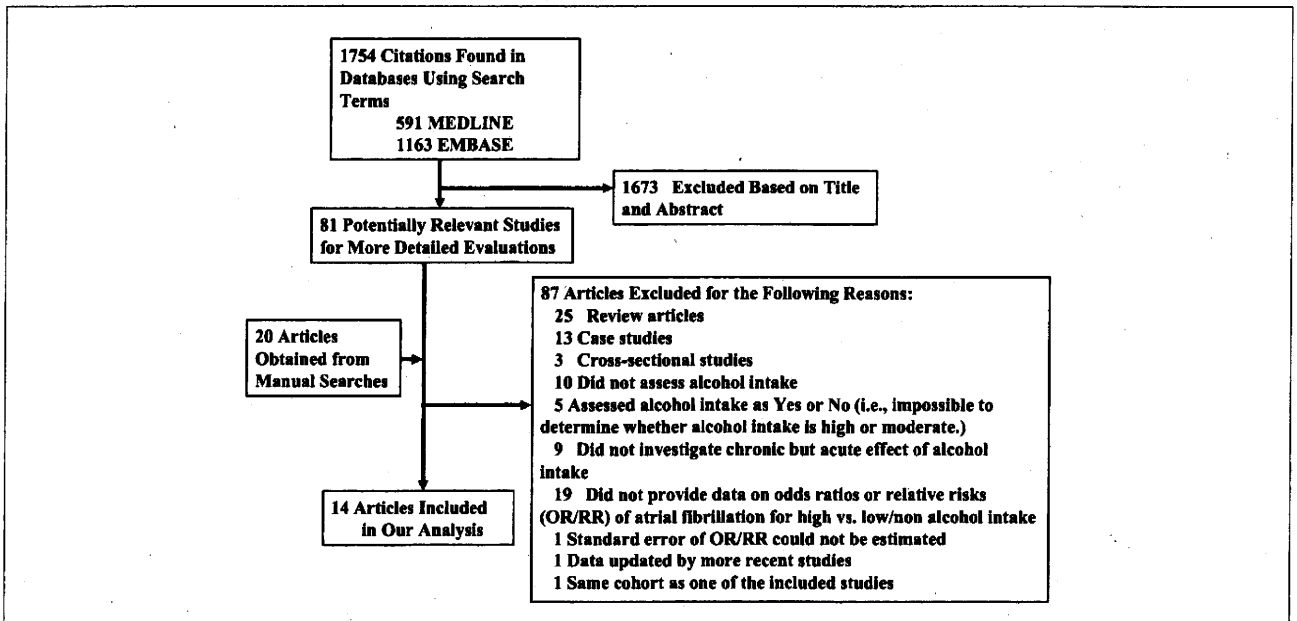

Figure 1 **Study Flow Chart of Meta-Analysis**

Table 1 Characteristics of Studies Included in the Meta-Analysis

Authors (Ref. #)		Year of Publication	Design	Selection of Population	Country	Age (yrs), Range (Mean)	% Men
Rich et al. (9)		1985	Case-control	Hospital-based	U.S.	18–70	76
Cohen et al. (10)		1988	Cohort	Population-based	U.S.	NA	NA
Krahn et al. (21)		1995	Cohort	Population-based	Canada	18–62 (31)	100
Wilhelmsen et al. (22)		2001	Cohort	Population-based	Sweden	47–55	100
Ruigomez et al. (23)		2002	Case-control	Hospital-based	Sweden	40–89	46
Djousse et al. (24)	Men	2004	Cohort	Population-based	U.S.	28–62	100
	Women						0
Frost and Vestergaard (25)	Men	2004	Cohort	Hospital-based	Denmark	50–64	100
	Women						0
Mattioli et al. (11)		2005	Case-control	Population-based	Italy	54	74
Mukamal et al. (26)	Men	2005	Cohort	Population-based	U.S.	26–75 (51)	100
	Women					26–73 (52)	0
Ruigomez et al. (27)	PAF	2005	Case-control	Hospital-based	Sweden	40–89	47
	Chronic		Cohort	Hospital-based		40–89	49
Planas et al. (28)		2006	Cohort	Hospital-based	Spain	53	64
Mukamal et al. (29)		2007	Cohort	Population-based	U.S.	≥65	42
Conen et al. (30)		2008	Cohort	Population-based	Switzerland	≥45 (53)	0
Marcus et al. (31)		2008	Case-control	Both	U.S.	53	75

		Were Patients With Heart Disease Excluded?	PAF Dominant or Chronic-AF Dominant	Was Method to Distinguish PAF From Chronic AF Described?	Onset or Recurrent AF	Was Atrial Flutter Among AF Events Included?	Method of Ascertaining AF	Method for Assessment of Exposure
Rich et al. (9)		Yes	PAF	Yes	Onset	No	Medical records	Medical records
Cohen et al. (10)		No	Chronic	No	Onset	No	Medical records	Questionnaires
Krahn et al. (21)		No	Chronic	No	Onset	No	ECG screening or physicians' report	Medical records
Wilhelmsen et al. (22)		No	Chronic	No	Onset	No	Registries	Questionnaires
Ruigomez et al. (23)		No	Chronic	Yes	Onset	No	Registries	Medical records
Djousse et al. (24)		No	Chronic	No	Onset	Yes	ECG screening	Questionnaires
Frost and Vestergaard (25)		Yes	Chronic	No	Onset	Yes	Registries	Questionnaires
Mattioli et al. (11)		Yes	PAF	Yes	Onset	No	Medical records	Questionnaires
Mukamal et al. (26)		Yes	Chronic	No	Onset	Yes	ECG screening, medical records, Registries	Interviews
Ruigomez et al. (27)	PAF	No	PAF	Yes	Onset	No	Registries	Medical records
	Chronic	No	Chronic		Recurrent	No	Registries	
Planas et al. (28)		Yes	PAF	Yes	Recurrent	No	ECG screening	Medical records
Mukamal et al. (29)		No	Chronic	No	Onset	Yes	ECG screening, medical records, Registries	Questionnaires
Conen et al. (30)		Yes	Chronic	No	Onset	No	Participants' reports	Questionnaires
Marcus et al. (31)		No	PAF	No	Onset	No	Medical records	Interviews

Continued on next page

Characteristics of the 14 included studies are shown in Table 1. Nine studies used a cohort design, 4 studies used a case-control design, and 1 study reported data from both case-control and cohort designs. All studies were conducted in Western countries (7 in Europe and 7 in North America).

For assessing daily alcohol consumption, only 4 of the 14 studies (25,26,29,31) validated methods to assess alcohol intake. All effect measures were controlled for age and sex, and most of the included reports (10 studies) made adjustments for heart disease, which potentially elevates the risk of AF, or excluded participants with heart disease. Only 3 studies (10,29,31) considered racial differences among the participants.

Risk of AF through heavy alcohol consumption. The lowest amount of alcohol consumed in the highest category in each study ranged from 1.5 to 6 drinks per day. Consequently, in all 14 studies, the criteria for heavy alcohol drinking as previously defined were met (12). Three studies reported separate results according to sex. One study analyzed 2 populations separately according to age (≤60 years or >60 years), and 1 study indicated 2 risk measures (1 for PAF and another for the progression from an AF episode to permanent AF). Finally, 19 effect measures were analyzed to

Table 1 Continued

		Category of Alcohol Intake (Ethanol Consumption)	No. of Cases	No. of Participants	Duration (yrs)*
Rich et al. (9)		>70 ml/day or not	58	116	—
Cohen et al. (10)		6 or more drinks/day or <1 drink/day	28	3,966	—
Krahn et al. (21)		Self- and physician-reported alcoholism or not	299	3,983	44
Wilhelmsen et al. (22)		Alcohol abuse or not	754	7,495	25.2
Ruigomez et al. (23)		None, 1–5, 6–15, 16–42, >42 U/week (1 U = 10 ml)	1,035	6,035	—
Djousse et al. (24)	Men	None, 0.1–12, 12.1–24, 24.1–36, >36 g/day	544	2,921	≥24
	Women		511	2,806	
Frost and Vestergaard (25)	Men	Quintile (4.1, 12.1, 20.0, 36.1, 68.7 g/day)	374	22,528	5.7
	Women	Quintile (1.1, 4.6, 9.4, 15.6, 38.8 g/day)	182	25,421	5.8
Mattioli et al. (11)		0, 1–20, 21–50, >50 ml/day	116	232	—
Mukamal et al. (26)	Men	<1, 1–6, 7–13, 14–20, 21–27, 28–34, >34 drinks/week (1 drink = 12 g)	548	7,588	16.3
	Women	<1, 1–6, 7–13, 14–20, >20 drinks/week (1 drink = 12 g)	523	8,827	18.8
Ruigomez et al. (27)	PAF	None, 1–7, 8–21, 21 U/week (1 U = 10 ml)	525	5,525	—
	Chronic		70	418	2.7
Planas et al. (28)		>40 g/day or not (men); >20 g/day or not (women)	32	115	2.5
Mukamal et al. (29)		None, former, <1, 1–6, 7–13, >13 Drinks/week (1 drink = 13.3 g)	1,232	5,609	9.1
Conen et al. (30)		None, <1, 1–2, >2 drinks/day (1 drink = 15 g)	653	34,175	12.4
Marcus et al. (31)		>1.5 drinks/day or not	74	260	—

		Age/Sex	Smoking	Study BMI or WC	Confounders SBP or HT	Heart Disease†	Other Control Variables	Total No. of Control Variables
Rich et al. (9)		✓				✓		2
Cohen et al. (10)		✓	✓				Race	3
Krahn et al. (21)		✓						1
Wilhelmsen et al. (22)		✓						1
Ruigomez et al. (23)		✓				✓		2
Djousse et al. (24)		✓			✓	✓		3
Frost and Vestergaard (25)		✓	✓	✓	✓	✓		5
Mattioli et al. (11)		✓				✓		2
Mukamal et al. (26)		✓	✓	✓	✓	✓	Education, income, diabetes, physical activity, respiratory function	10
Ruigomez et al. (27)	PAF	✓						1
	Chronic							
Planas et al. (28)		✓			✓	✓		3
Mukamal et al. (29)		✓		✓	✓	✓	Race, income, diabetes, use of psychoactive medication	8
Conen et al. (30)		✓	✓	✓	✓	✓	Diabetes	6
Marcus et al. (31)		✓		✓	✓	✓	Race	5

*Duration is the duration between the time point of alcohol consumption and subsequent observation. †Cardiac function (e.g., left ventricular end-systolic volume, left atrial size) was involved in heart disease.

AF = atrial fibrillation; BMI = body mass index; ECG = electrocardiogram; HT = hypertension; NA = not available; PAF = paroxysmal atrial fibrillation; SBP = systolic blood pressure; WC = waist circumference.

summarize the risk of AF in relation to heavy alcohol intake. The pooled estimate of OR/RR for the highest category of alcohol consumption compared with the lowest category in individual studies was 1.51 (95% CI: 1.31 to 1.74) (Fig. 2).

There was significant between-study heterogeneity in the effect measures (Q-squared, 33.2; I-squared, 45.8%; p = 0.02). Table 2 shows results of stratified and meta-regression analyses across a number of key study characteristics to explore causes of the study heterogeneity. On the whole, a positive association between AF risk and heavy alcohol consumption was consistently found in all stratified analyses.

In the stratified analysis by mean alcohol intake in the highest intake group, the pooled estimates of AF for <4 drinks per day, or 48 g per day, and ≥4 drinks per day was 1.32 (95% CI: 1.15 to 1.50) and 1.74 (95% CI: 1.35 to 2.24), respectively. However, the difference was not significant (p = 0.17). When analyses were limited to the 6 studies that regarded nondrinkers as the referent group, the

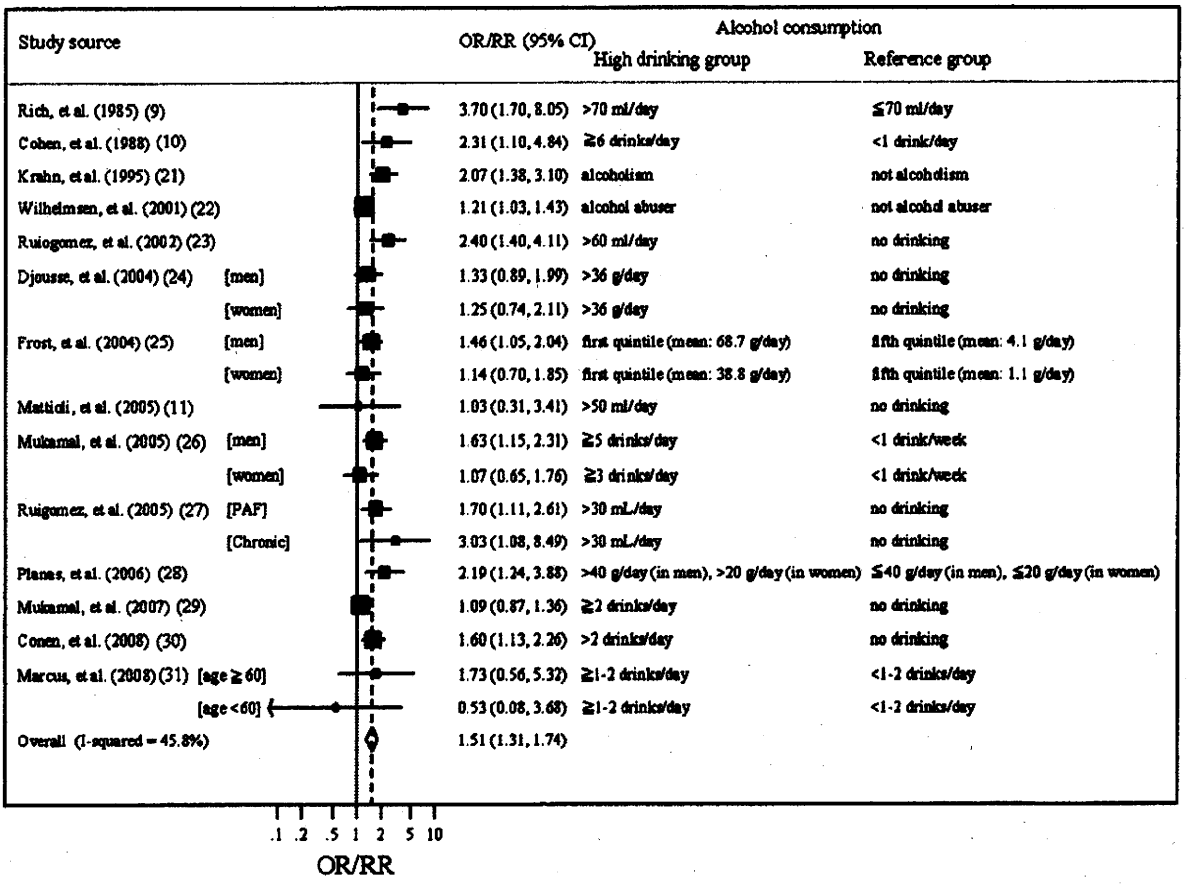

Figure 2 **OR/RR and 95% CI of AF by Alcohol Intake Group**

Odds ratio (OR) or relative risk (RR) and 95% confidence interval (CI) of atrial fibrillation (AF) for highest versus lowest alcohol intake groups. Size of **squares** reflects the statistical weight of each study. Overall estimate is indicated by **unshaded diamond**. PAF = paroxysmal atrial fibrillation.

pooled estimate for the highest category was 1.36 (95% CI: 1.18 to 1.57).

Stratified analysis by geographic region, participants' sex, or whether persons with heart disease were included did not show any significant difference in pooled estimates between strata. Using a case-control design seemed to produce a substantially larger AF risk (pooled estimates 1.98 [95% CI: 1.49 to 1.63]) compared with the use of other designs (pooled estimate 1.34 [95% CI: 1.22 to 1.47]). However, these differences were not borderline significant ($p = 0.06$). Selecting hospital-based participants produced a borderline significantly larger pooled estimate in comparison with population-based participants (pooled estimate 1.75 [95% CI: 1.45 to 2.11] vs. 1.30 [95% CI: 1.18 to 1.44]; $p = 0.049$).

Strong associations were observed when the type of AF end point in the study was PAF-dominant (pooled estimate 1.92 [95% CI: 1.44 to 2.56]) or AF recurrence (pooled estimate 2.37 [95% CI: 1.44 to 3.90]) whereas a significantly weaker association was observed in studies that included atrial flutter as a study end point (pooled estimate 1.25 [95% CI: 1.10 to 1.43]) than in those that did not (pooled estimate 1.83 [95% CI: 1.45 to 2.30]; $p = 0.02$).

The method for ascertainment of AF did not significantly affect the magnitude of the association between high alcohol consumption and AF risk. However, a significantly stronger association was observed when reviewed data on alcohol intake were based on medical records or registries (pooled estimate 2.17 [95% CI: 1.74 to 2.70]) compared with other methods of determining alcohol consumption, such as questionnaires or interviews (pooled estimate 1.28 [95% CI: 1.16 to 1.41]; $p < 0.001$). The influence of study adjustments for possible confounders was not significant, although AF effect measures were attenuated with adjustment for hypertension or blood pressure (pooled estimate 1.33 [95% CI: 1.17 to 1.50]).

Publication bias was visually suggested by the asymmetrical funnel plot of the reported results (Fig. 3), which was also statistically supported by Egger's test ($p = 0.03$) but not Begg's test ($p = 0.31$). We attempted to adjust for this publication bias using the trim and fill method (18). After 4

Table 2 Stratified Analyses of Pooled Relative Risk of Atrial Fibrillation for Highest Alcohol Intake Versus Lowest Alcohol Intake

Variable	No. of Data Units	Risk Estimates (95% CI)	Q Statistics	I-Squared	p Value of Heterogeneity	Meta-Regression*
Mean estimated alcohol intake of exposed group						
<4 drinks (48 g) per day	11	1.32 (1.15–1.50)	13.1	23.6%	0.22	Referent
≥4 drinks (48 g) per day or alcohol abuser	8	1.74 (1.35–2.24)	18.8	62.8%	0.009	0.16
Drinking status of referent group						
Nondrinkers	8	1.36 (1.18–1.57)	12.6	44.6%	0.08	Referent
Light drinkers	11	1.56 (1.27–1.91)	20.5	51.1%	0.03	0.73
Design						
Cohort	13	1.34 (1.22–1.47)	20.4	41.1%	0.06	Referent
Case-control	6	1.98 (1.49–2.63)	6.5	22.5%	0.26	0.06
Selection of study population						
Population-based	10	1.30 (1.18–1.44)	14.3	37.0%	0.11	Referent
Hospital-based	7	1.75 (1.45–2.11)	10.8	44.2%	0.10	0.06
Both population- and hospital-based	2	1.28 (0.49–3.39)	1.1	6.7%	0.30	0.88
Geographic region						
North America	10	1.50 (1.19–1.90)	19.5	53.7%	0.02	Referent
Europe	9	1.40 (1.25–1.58)	13.7	41.8%	0.09	0.76
Sex						
Men	4	1.32 (1.06–1.64)	2.3	—	0.51	Referent
Women	5	1.37 (1.21–1.55)	7.3	45.0%	0.12	0.47
Men/women	10	1.85 (1.33–2.56)	22.8	60.5%	0.007	0.32
Excluding participants with heart disease						
No	11	1.50 (1.24–1.82)	20.5	51.3%	0.03	Referent
Yes	8	1.53 (1.31–1.80)	10.6	34.1%	0.16	0.79
Was atrial flutter included as AF outcome?						
No	12	1.83 (1.45–2.30)	23.8	53.9%	0.01	Referent
Yes	7	1.25 (1.10–1.43)	5.1	—	0.52	0.02
Type of AF outcome						
Chronic AF dominant	14	1.43 (1.24–1.66)	22.0	45.4%	0.04	Referent
PAF dominant	6	1.92 (1.44–2.56)	6.0	17.2%	0.30	0.11
Was AF outcome the first episode or recurrence?						
First episode	17	1.46 (1.27–1.69)	28.5	43.8%	0.03	Referent
Recurrence	2	2.37 (1.44–3.90)	0.3	—	0.59	0.10
Methods for assessment of alcohol intake						
Questionnaires	9	1.26 (1.13–1.40)	7.4	—	0.50	Referent
Interviews	4	1.41 (1.07–1.85)	3.0	—	0.39	0.45
Historical data reviews	6	2.17 (1.74–2.70)	3.7	—	0.60	<0.001
Methods for ascertainment of AF						
ECG screening	3	1.47 (1.12–1.95)	2.5	20.0%	0.29	Referent
Medical records	5	2.14 (1.38–3.31)	5.5	27.6%	0.24	0.28
Registries	6	1.35 (1.19–1.54)	10.2	51.1%	0.07	1.00
Others†	5	1.43 (1.11–1.85)	10.8	62.9%	0.03	0.83
Study adjustment						
Smoking						
No	13	1.58 (1.29–1.95)	28.0	57.2%	0.005	Referent
Yes	6	1.47 (1.24–1.73)	4.6	—	0.46	0.68
Obesity (BMI or waist circumference)						
No	11	1.76 (1.40–2.21)	23.3	57.1%	0.01	Referent
Yes	8	1.29 (1.13–1.48)	7.9	10.9%	0.34	0.07
SBP or HT						
No	9	1.93 (1.40–2.64)	20.8	66.3%	0.004	Referent
Yes	10	1.33 (1.17–1.50)	11.0	9.4%	0.35	0.06
Heart disease						
No	5	1.74 (1.24–2.43)	11.3	64.4%	0.02	Referent
Yes	14	1.39 (1.24–1.56)	22.0	40.8%	0.06	0.44

*Represents test for significance of the study modification across strata. †Participants' report or using combination of registry with electrocardiographic screening.
CI = confidence interval; other abbreviations as in Table 1.

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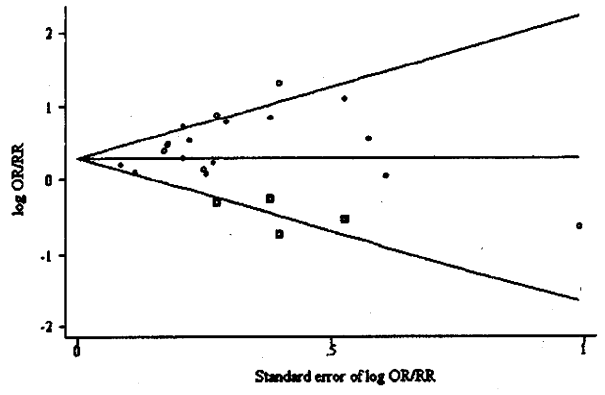

Figure 3 Funnel Plot of High Alcohol Consumption and AF

Funnel plot of high alcohol consumption and atrial fibrillation (AF) risk before and after adjustment for publication bias using trim and fill procedures. Hypothetical dummy studies indicated by **circles within squares** are added to the genuine studies indicated by **circles**. OR = odds ratio; RR = relative risk.

negative unpublished results were incorporated to produce a hypothetically symmetrical funnel plot, the pooled estimate of AF for heavy alcohol consumption was modestly attenuated to be 1.39 (95% CI: 1.19 to 1.62) but remained statistically significant ($p < 0.001$).

Dose-response relationship between alcohol intake and AF risk. Nine studies (10,11,23–27,29,30) involving 126,051 participants and 6,341 cases were eligible for analysis of the dose-response relationship between different categories of alcohol intake and AF risk. The alcohol dose in these studies ranged from 4.0 to 86.4 g per day. Figure 4 illustrates the linear and spline regression curves for AF risk related to daily alcohol intake. The linear dose-response curve showed a significant relationship between alcohol intake and AF risk ($R^2 = 0.43$, $p < 0.001$). The coefficient for the linear term was $7.4 \pm 1.3 \times 10^{-3}$, meaning that the incremental increase in relative risk of AF per 10 g alcohol consumption per day was $e^{10\times7.4\pm1.3\times10^{-3}} = 1.08$ (95% CI: 1.05 to 1.10). Also, in the spline regression model, AF risk significantly increased with larger daily alcohol consumption levels ($R^2 = 0.44$, $p < 0.001$). However, the fit of this model was not significantly different from that of the linear regression model ($p = 0.77$).

Discussion

Our study is the first to systematically review the literature on the association between alcohol consumption and the risk of AF. In this review, high alcohol intake was shown to be associated with a significant elevation in AF risk, both by overall analysis and across a number of stratified analyses based on key characteristics of study methods, although there was substantial study heterogeneity in the magnitude of AF risk, partly due to variability in study design and methodology. Even though, in principle, observational studies do not allow for proof of causality, there are several theoretically plausible speculations for the cause-effect relationship between high alcohol intake and the development of AF.

One speculation is based on biological findings that suggest a harmful effect of high alcohol intake on maintenance of normal heart rhythm, including the achievement of a hyperadrenergic state (32), impairment of vagal tone (33), direct effect on myocardial structure (34), and various electrophysiological changes in atrial cells (e.g., increase in intra-atrial conduction time represented by a length of the P-wave, reduction in the refractory period, negative inotropic effect through calcium-channel inhibition in ventricular cells) (31,35,36).

Another speculation is based on reports suggesting that the development of chronic heart failure accompanied by long-term excessive alcohol consumption may result in elevated AF risk (2). Particularly, dilated cardiomyopathy is typical of alcohol abusers with chronic heart failure. The average total lifetime alcohol consumption was reported to be significantly greater in patients with dilated cardiomyopathy than in a population-based control group (37). Moreover, alcoholics were found to have progressive dilated cardiomyopathy in proportion to the duration of heavy drinking even before the clinical appearance of chronic heart failure (38).

It remains to be established whether the dose-response relationship between daily alcohol consumption and AF risk is interpreted as linear or not (e.g., J-shaped curve, threshold curve). While we identified a linear association of daily alcohol consumption with the risk of AF, a J-shaped relation or threshold value was not observed from the

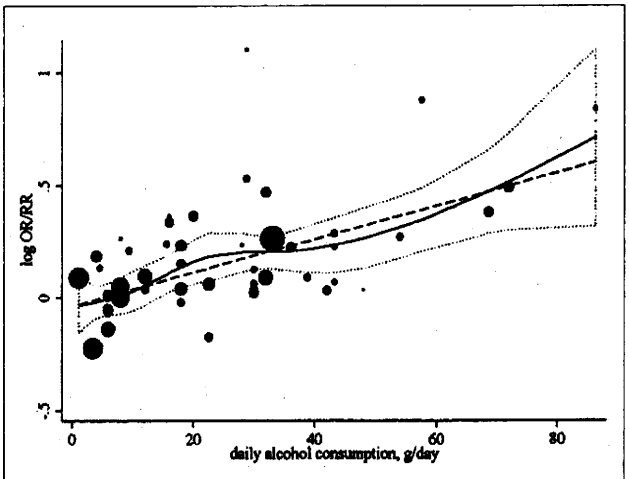

Figure 4 Regression of Natural Log OR/RR for Atrial Fibrillation on Daily Alcohol Consumption.

The **solid curve** and its accompanying area indicate the log odds ratio or relative risk (OR/RR) and its corresponding 95% confidence interval based on a restricted cubic spline regression model with knots at 8, 22.5, and 33.1 g/day of alcohol consumption. This model did not significantly improve the fit compared with the linear regression model expressed by the **dotted line**. The area of each data point is proportional to its statistical weight.

current spline regression curve. These regression analyses suggest no evidence that moderate alcohol consumption is beneficial in ameliorating the risk of AF, unlike that of cardiovascular disease (7). If anything, moderate alcohol drinkers may have a greater risk of AF than nondrinkers, although the AF risk is not as large as that for heavy drinkers.

Study limitations. First, the definition of heavy drinking is heterogeneous across studies. Second, the majority of the included studies did not state whether the method used for assessment of alcohol intake was validated. Third, few studies considered racial differences among participants. Differences in ethnicity or proportion of whites and nonwhites among different studies might have affected AF risk estimates. Fourth, asymptomatic PAF could have been missed in any of these studies. Given that heavy alcohol drinkers are likely to have experienced PAF, the risk of AF in relation to high alcohol intake would be underestimated in any of the examined studies. Fifth, no studies have investigated the effect of different types of alcoholic beverages on AF risk, although it has been reported that wine has a better effect on cardiovascular disease (39). Sixth, it could not be ruled out whether a particular drinking pattern, such as whether alcohol was consumed with a specific food or at meals, could have contributed to the AF risk irrespective of alcohol dosage. For example, alcohol is usually consumed during meals, as in Mediterranean countries (39), which might explain a beneficial effect.

A meta-analysis cannot completely solve problems with confounders that vary from study to study. Lack of adjustment for possible confounders could also produce a superficially strong association between high alcohol consumption and AF risk. For example, a weaker association between high alcohol consumption and AF risk was observed when studies included blood pressure values or the presence of hypertension among study confounders. In fact, hypertension was reported to be an independent risk factor for AF (2), and the risk of hypertension increases linearly with alcohol consumption (40). Possibly, the AF risk associated with high alcohol consumption is partly explained by an alcohol-related development of hypertension. In addition, other factors that could not be specified by this meta-analysis or were not specified in the individual included studies might contribute to residual confounding (e.g., objective sleep apnea [41], diabetes mellitus [42]).

Lastly, results that indicated risk of AF could be biased by study design and other methodological features. For example, larger AF risk estimates were observed in studies having a case-control design compared with studies having a cohort design or in hospital-based studies compared with population-based studies. The AF risk could have been overestimated by exaggeration of alcohol intake in patients with AF in studies with a case-control design (i.e., recall bias) or an unavoidable reduction in alcohol intake as a result of a control subject having an illness in a hospital-based setting (i.e., selection bias). However, underestimation of AF risk is possible if patients did not truthfully report the full extent of alcohol intake when completing questionnaires.

Conclusions

Habitual heavy alcohol drinking is associated with an increased risk of AF, although several study limitations exist and must be recognized. The relationship between daily alcohol consumption and the risk of AF was explained by a linear dose-response model, suggesting that not consuming alcohol at all is the most favorable behavior for avoiding AF rather than moderate alcohol consumption. Further investigation is needed to establish the extent to which this association is explained by a causal relationship.

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Key Words: alcohol ■ atrial fibrillation ■ meta-analysis.