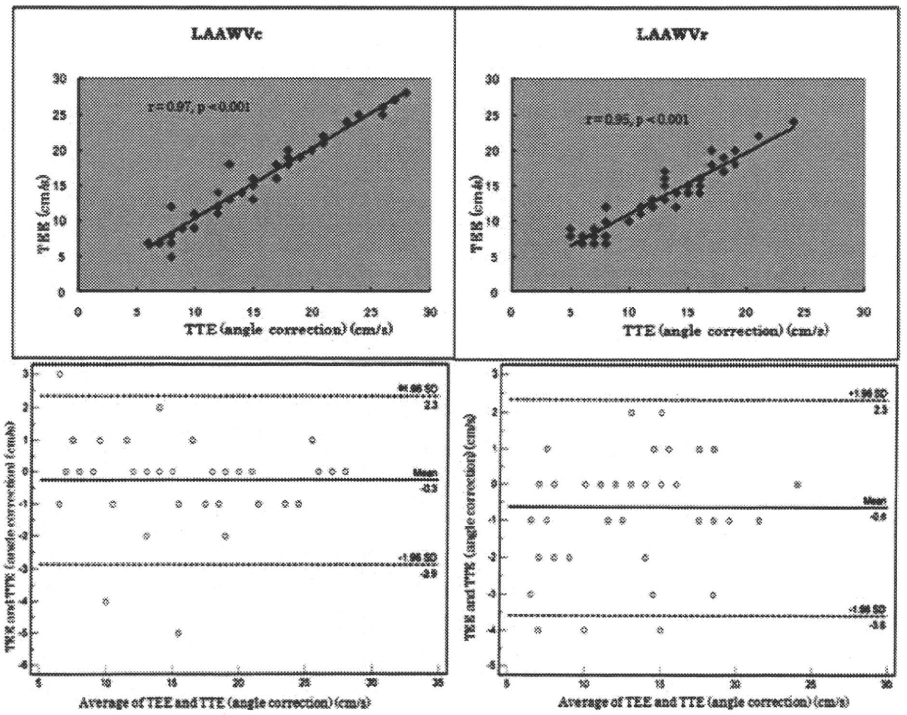

Figure 5. Regression analysis (left upper panel) and Bland-Altman plot (left lower panel) for LAA wall velocity during contraction (LAAWVc) measured by TEE and TTE when angle correction was applied for the Doppler beam in TTE. Regression analysis (right upper panel) and Bland-Altman plot (right lower panel) for LAA wall velocity during relaxation (LAAWVr) measured by TEE and TTE when angle correction was applied for the Doppler beam in TTE.

respectively) and LAAWVr (3.3% and 4.7%, respectively) measured using TTE.

Assessment of LAA Contraction and Relaxation in Healthy Individuals using TTE:

We were able to record and measure LAAWVc and LAAWVr using TTE in 105 of the 110 healthy subjects (95%). The heart rate and gender did not significantly affect LAAWVc or LAAWVr values obtained by the angle correction method (Table IV).

LAAWVc obtained by the angle correction method remained unchanged with aging, whereas LAAWVr obtained by the angle correction method significantly decreased with aging ($r = -0.48$, $P < 0.001$) (Tables III and IV). LAAWVr obtained by the angle correction method negatively correlated with LAD ($r = -0.33$, $P < 0.001$), A ($r = -0.38$, $P < 0.001$), and A′ ($r = -0.43$, $P < 0.001$) and positively correlated with E ($r = 0.28$, $P = 0.002$) and E′ ($r = 0.26$, $P = 0.004$). In contrast, LAAWVc obtained by the angle correction method did not significantly correlate with LAD, E′, A, or A′ (Table IV). A one-way ANOVA showed significant changes with aging in LAAWVr ($P < 0.001$), A ($P < 0.001$), E ($P < 0.001$), A′ ($P < 0.001$), E′ ($P < 0.001$), and LAD ($P = 0.001$). However, LAAWVc did not significantly change with aging (Table V and Fig. 6).

Discussion:

Analysis of LAA Function by Transthoracic Echocardiography:

Recently, the development of second harmonic TTE enables determination of LAA flow velocity for various heart diseases, including atrial

TABLE III

Pearson Correlation Coefficients between Age and Other Parameters in Healthy Individuals

Variables	Correlation coefficient	P-value
LAAWVc (cm/sec)	−0.09	0.494
LAAWVr (cm/sec)	−0.48	<0.001*
A (cm/sec)	0.66	<0.001*
E (cm/sec)	−0.58	<0.001*
A′ (cm/sec)	0.63	<0.001*
E′ (cm/sec)	−0.65	<0.001*
LAD (mm)	0.31	0.001*

*Statistically; refer to the footnote to Tables I and II for additional abbreviations.

TABLE IV

Pearson Correlation Coefficients between LAAWVr or LAAWVc and Other Parameters in Healthy Individuals

	LAAWVr		LAAWVc	
Variables	Correlation coefficient	P-value	Correlation coefficient	P-value
Age	−0.48	<0.001*	−0.09	0.191
Rate (bpm)	0.00	0.496	−0.01	0.448
Men	−0.03	0.377	0.08	0.215
A (cm/sec)	−0.38	<0.001*	0.05	0.303
E (cm/sec)	0.28	0.002*	0.16	0.045*
A′ (cm/sec)	−0.43	<0.001*	0.02	0.399
E′ (cm/sec)	0.26	0.004*	−0.03	0.375
LAD (mm)	−0.33	<0.001*	−0.07	0.242

*Statistically; refer to the footnote to Tables I and II for additional abbreviations.

fibrillation, and these values correlate well with those obtained by TEE.[6,7,9] However, some limitations remain in measuring the flow velocity using a transthoracic approach. Detection rate of measurable flow velocities ranged from 62% to 88% for various heart diseases with sinus rhythm or atrial fibrillation.[6,7] On the other hand, the intravenous contrast injection allows better visualization of the LAA and assessment of blood flow velocities.[10] In this study, TTE enabled detection of flow velocities <30 cm/sec with a sensitivity of 88% and specificity of 81%; TTE had higher sensitivity and specificity as compared with TEE. However, the contrast agent is expensive and this method is complicated to require an injection, therefore this method is not popular.

The usefulness of transesophageal TDE for the assessment of LAA function has been well described.[11–16] Transesophageal TDE patterns of LAA were reproducible and similar to those of Doppler flow, and peak TDE velocities correlated well with flow velocity and the LAA functions were evaluated in the patients with mitral stenosis or atrial fibrillation.[11–16] Recently, Uretsky et al. demonstrated that transthoracic TDE could be used to analyze LAA function and detect decreased LAA wall velocity in patients with atrial fibrillation.[8] In the present study, including patients who underwent TEE, we showed transthoracic TDE of the LAA wall velocities had significant correlations with transesophageal Doppler flow velocities in the LAA. We also demonstrated the feasibility of transthoracic TDE in assessing LAA contraction and relaxation function. The present results indicated that LAAWV measured using transthoracic TDE had a very high correlation with transesophageal TDE measurements. One of the reasons for the high correlation between parameters of TTE and TEE may be depression of autonomic nervous system by intravenous injection of diazepam and intramuscular administration of glucagon. The values were almost equal when angle correction by our method was applied for the Doppler beam, while making three-dimensional angle corrections was very difficult and was not accomplished. In addition, the intraobserver and interobserver variabilities for LAAWVc and LAAWVr tissue Doppler

TABLE V

Characteristics of Each Age Decade in Healthy Individuals

Age (Decade)	Second	Third	Fourth	Fifth	Sixth	Seventh	Eighth	Ninth	P-value
Number	13	11	15	13	13	15	14	11	–
Men	8	6	8	7	8	9	8	7	–
LAAWVc (cm/sec)	22 (3)	22 (4)	22 (4)	22 (3)	22 (3)	22 (3)	22 (3)	22 (3)	0.977
LAAWVr (cm/sec)	23 (3)	22 (5)	21 (3)	20 (4)	19 (3)	17 (3)	17 (4)	17 (4)	<0.001*
A (cm/sec)	50 (15)	48 (10)	55 (15)	62 (4)	66 (15)	78 (16)	83 (13)	80 (12)	<0.001*
E (cm/sec)	112 (27)	91 (18)	82 (14)	79 (12)	73 (12)	68 (21)	70 (13)	72 (11)	<0.001*
A′ (cm/sec)	5 (2)	7 (2)	7 (2)	10 (2)	10 (2)	10 (2)	10 (2)	11 (2)	<0.001*
E′ (cm/sec)	17 (3)	15 (4)	14 (2)	13 (4)	11 (2)	10 (2)	9 (2)	8 (2)	<0.001*
LAD (mm)	29 (3)	30 (4)	31 (4)	31 (4)	32 (4)	33 (3)	34 (3)	32 (3)	0.001

*Statistically; refer to the footnote to Tables I and II for additional abbreviations.

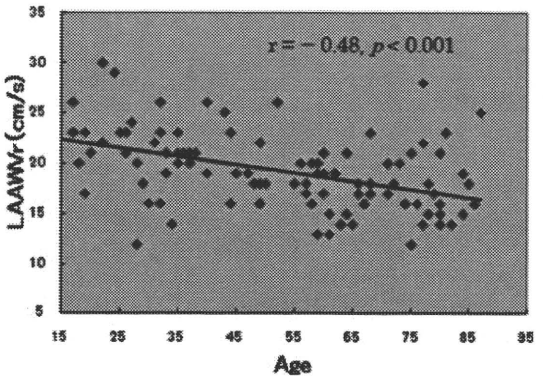

Figure 6. LAAWVr plotted against age in healthy subjects.

measurements were ≤4.7%. These results may suggest that measurement of LAAWV using transthoracic TDE may allow noninvasive favorable analysis of LAA function.

Moreover, we aimed at studying the changes in LAA contraction and relaxation properties with aging in the physiological state. We were able to record both LAAWVc and LAAWVr in 95% of the healthy individuals. The positive results of this study in the measurement of LAAWV were superior to results of previous flow velocity studies using TTE, despite normal cardiac size in healthy subjects. The superiority of LAAWV measured by TDE to LAA Doppler flow measured by TTE may be attributable to the difference in the amplitude of ultrasound reflection power between the myocardium and blood cells. The myocardium is a much stronger ultrasound reflector than blood cells. TDE can detect low-velocity signals with high amplitude (flow is a high-velocity signal with relatively low amplitude) and provides better measurements than the Doppler flow method even in healthy subjects. Accordingly, even if the LAA wall is thin, this high-amplitude ultrasonic signal from the LAA wall may allow us to measure the wall velocity. The LAA wall motion Doppler signal may also include the pectinate muscle motion, but its effect may be considered small.

Changes with Aging in Contractility and Relaxation of LAA in Healthy Subjects:

There have been several studies on changes in LA body function with aging.[17–20] Many previous studies have indicated that the mitral flow velocity A and mitral annular velocity A′ increase with aging.[21,22] These results were confirmed in the present study. Thomas et al. indicated that the enhanced contractility of LA may contribute to augmentation of active atrial emptying with aging.[19,20]

However, there have been few studies on changes in LAA function with aging. Tabata et al. and Agmon et al. studied peak systolic LAA flow velocities using TEE and reported that the flow velocities decreased with aging.[1,2] However, in the present noninvasive study involving TTE, LAAWVs did not significantly change with aging. One reason for this discrepancy may be the selection bias. Because TEE is an invasive technique, it is not usually easy to perform in healthy subjects. The insertion of a TEE probe may lead to elevated blood pressure in elderly individuals and result in the decrease of contractility of LAA. Another reason may be the inaccurate correction of the ultrasonic beam angle of transthoracic TDE, that three-dimensional angle corrections is impossible for us at the present apparatus. However, the present study on TDE validation showed very close correlation between TEE and TTE.

We were unable to find any articles in the literature concerning changes in the relaxation function of LAA with aging. The present results indicated that LAAWVr had a significant negative correlation with age, suggesting that relaxation of the LAA may be impaired with aging. This phenomenon is similar to reduction in left ventricle (LV) relaxation with aging.[21,23] The cause of the abnormality of LAA relaxation in the elderly is not so clear, but the following reasons will be supposed. We have already reported that LA size increases with aging.[3] In the present study, LAAWVr had a negative and significant correlation with LAD. Therefore, LAA relaxation impairment may be caused by LA stretch with aging. The LAA emptying and filling may be also influenced by LV systolic and diastolic function and LA loading condition.[24] In the present study, LAAWVr had a positive correlation with mitral flow velocity E and mitral annular velocity E′. LV in the elderly may be stiffer than that in the young and LV diastolic pressure may be modestly higher in the elderly than in the young. This higher LV diastolic pressure may enhance the afterload against LAA contraction and may cause decrease of LAA contraction velocity and relaxation velocity. There is the possibility that relaxation changes may be more sensitively detected by TDE as compared with the contraction changes. Moreover, the pathological myocardial changes that occur with aging, such as fibrosis and fat deposits, may be also related to the abnormalities of LAA relaxation.[25]

Limitations:

Uretsky et al. showed that there are no differences in the assessment of LAA wall motion between parasternal and apical views of TTE.[8] We chose the parasternal short-axis view to determine LAA wall velocity by TDE. In the present study, the sample volume was placed as close as possible to the tip of the LAA. It was possible that the entire LAA was not visualized by the transthoracic

approach. However, the TDE may have detected wall motion of a considerably wide area near the LAA apex because the ultrasonic amplitude of TDE for the LAA wall velocity is much greater than that of blood flow signals. Thus, the values of TDE for LAA may show the maximum wall velocity near the LAA apex. Moreover, signals from adjacent structures such as the aorta and mitral valve ring may be present, but these signals can be excluded from the LAA contraction and relaxation signals by time analysis of monitoring ECG.

In this study, we analyzed only a single LAA region. However, each region in the LAA wall may show different myocardial velocities. Further studies are required to elucidate the significance of regional wall motion analysis of LAA.

Conclusions:

TDE by TTE may be a feasible noninvasive method for assessing LAA function. Relaxation of LAA may decrease significantly with aging and may be accompanied by age-related impairment of LV relaxation.

References

1. Tabata T, Oki T, Fukuda N, et al: Influence of aging on left atrial appendage flow velocity patterns in normal subjects. *J Am Soc Echocardiogr* 1996;9:274–280.
2. Agmon Y, Khandheria BK, Meissner I, et al: Left atrial appendage flow velocities in subjects with normal left ventricular function. *Am J Cardiol* 2000;86:769–773.
3. Yoshida N, Okamoto M, Makita Y, et al: Determinants of enhanced left atrial active emptying with aging: Left atrial preload, contractility or both? *Int Med* 2009;48:987–992.
4. Hoit BD, Walsh RA: Regional atrial distensibility. *Am J Physiol* 1992;262;1356–1360.
5. Tabata T, Oki T, Yamada H, et al: Role of left atrial appendage in left atrial reservoir function as evaluated by left atrial appendage clamping during cardiac surgery. *Am J Cardiol* 1998;81:327–332.
6. Fukuda N, Shinohara H, Sakabe K, et al: Transthoracic Doppler echocardiographic measurement of left atrial appendage blood flow velocity: Comparison with transesophageal measurement. *Eur J Echocardiogr* 2003;4:191–195.
7. Coletta C, Infusino T, Sciarretta S, et al: Transthoracic Doppler echocardiography for the assessment of left atrial appendage size and blood flow velocity: A multicentre study. *J Cardiovasc Med* 2008;9:147–152.
8. Uretsky S, Shah A, Bangalore S, et al: Assessment of left atrial appendage function with transthoracic tissue Doppler echocardiography. *Eur J Echocardiogr* 2009;10:363–371.
9. Carranza C, Abufhele A, Cartes F, et al: Transthoracic versus transesophageal two-dimensional echo Doppler determination of flow velocity in the left atrial appendage. *Echocardiography* 1997;14:357–362.
10. Pozzoli M, Selva A, Skouse D, et al: Visualization of left atrial appendage and assessment of its function by transthoracic second harmonic imaging and contrast-enhanced pulsed Doppler. *Eur J Echocardiogr* 2002:3:13–23.
11. Parvathaneni L, Mahenthiran J, Jacob S, et al: Comparison of tissue Doppler dynamics to Doppler flow in evaluating left atrial appendage function by transesophageal echocardiography. *Am J Cardiol* 2005;95:1011–1014.
12. Gurlertop Y, Yilmaz M, Acikel M, et al: Tissue Doppler properties of the left atrial appendage in patients with mitral valve disease. *Echocardiography* 2004;21:319–324.
13. Topsakal R, Eryol NK, Ozdoğru I, et al: Color Doppler tissue imaging to evaluate left atrial appendage function in patients with mitral stenosis in sinus rhythm. *Echocardiography* 2004;21:235–240.
14. Sahin T, Ural D, Kilic T, et al: Evaluation of left atrial appendage functions according to different etiologies of atrial fibrillation with a tissue Doppler imaging technique by using transesophageal echocardiography. *Echocardiography* 2009;26:171–181.
15. Sevimli S, Gundogdu F, Arslan S, et al: Strain and strain rate imaging in evaluating left atrial appendage function by transesophageal echocardiography. *Echocardiography* 2007;24:823–829.
16. Cayli M, Acartürk E, Demir M, et al: Systolic tissue velocity is a useful echocardiographic parameter in assessment of left atrial appendage function in patients with mitral stenosis. *Echocardiography* 2007;24:816–822.
17. Triposkiadis F, Tentolouris K, Androulakis A, et al: Left atrial mechanical function in the healthy elderly: New insights from a combined assessment of changes in atrial volume and transmitral flow velocity. *J Am Soc Echocardiogr* 1995;8:801–809.
18. Gardin JM, Henry WL, Savage DD, et al: Echocardiographic measurements in normal subjects: Evaluation of an adult population without clinically apparent heart disease. *J Clin Ultrasound* 1979;7:439–447.
19. Thomas L, Levett K, Boyd A, et al: Changes in regional left atrial function with aging: Evaluation by Doppler tissue imaging. *Eur J Echocardiogr* 2003;4:92–100.
20. Thomas L, Levett K, Boyd A, et al: Compensatory changes in atrial volumes with healthy aging: Is atrial enlargement inevitable? *J Am Coll Cardiol* 2002;40:1630–1635.
21. Miyatake K, Okamoto M, Kinoshita N, et al: Augmentation of atrial contribution to left ventricular inflow with aging as assessed by intracardiac Doppler flowmetry. *Am J Cardiol* 1984;53:586–589.
22. Yamada H, Oki T, Mishiro Y, et al: Effect of aging on diastolic left ventricular myocardial velocities measured by pulsed tissue Doppler imaging in healthy subjects. *J Am Soc Echocardiogr* 1999;12:574–581.
23. Kitabatake A, Inoue M, Asao M, et al: Transmitral blood flow reflecting diastolic behavior of the left ventricle in health and disease—a study by pulsed Doppler technique. *Jpn Circ J* 1982;46:92–102.
24. Hoit BD, Shao Y, Gabel M: Influence of acutely altered loading conditions on left atrial appendage flow velocities. *J Am Coll Cardiol* 1994;24:1117–1123.
25. Falk RH: Etiology and complications of atrial fibrillation: Insights from pathology studies. *Am J Cardiol* 1998;16:10N–17N.

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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.

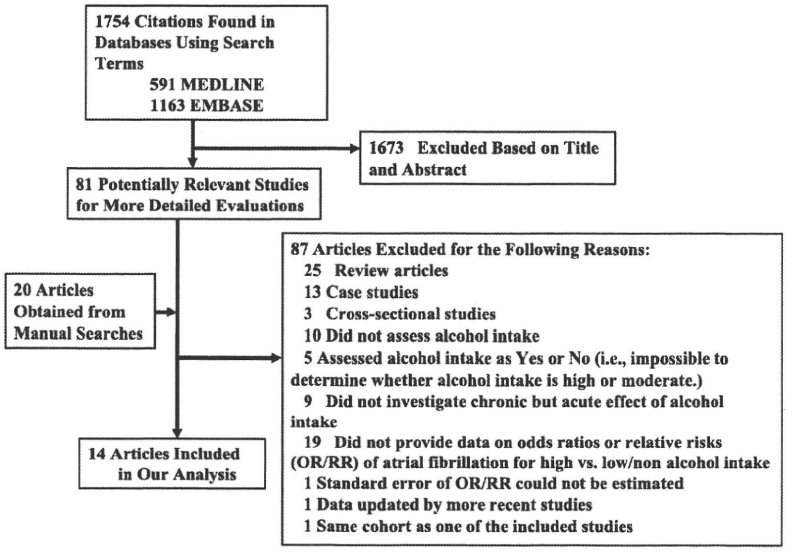

Figure 1 Study Flow Chart of Meta-Analysis

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

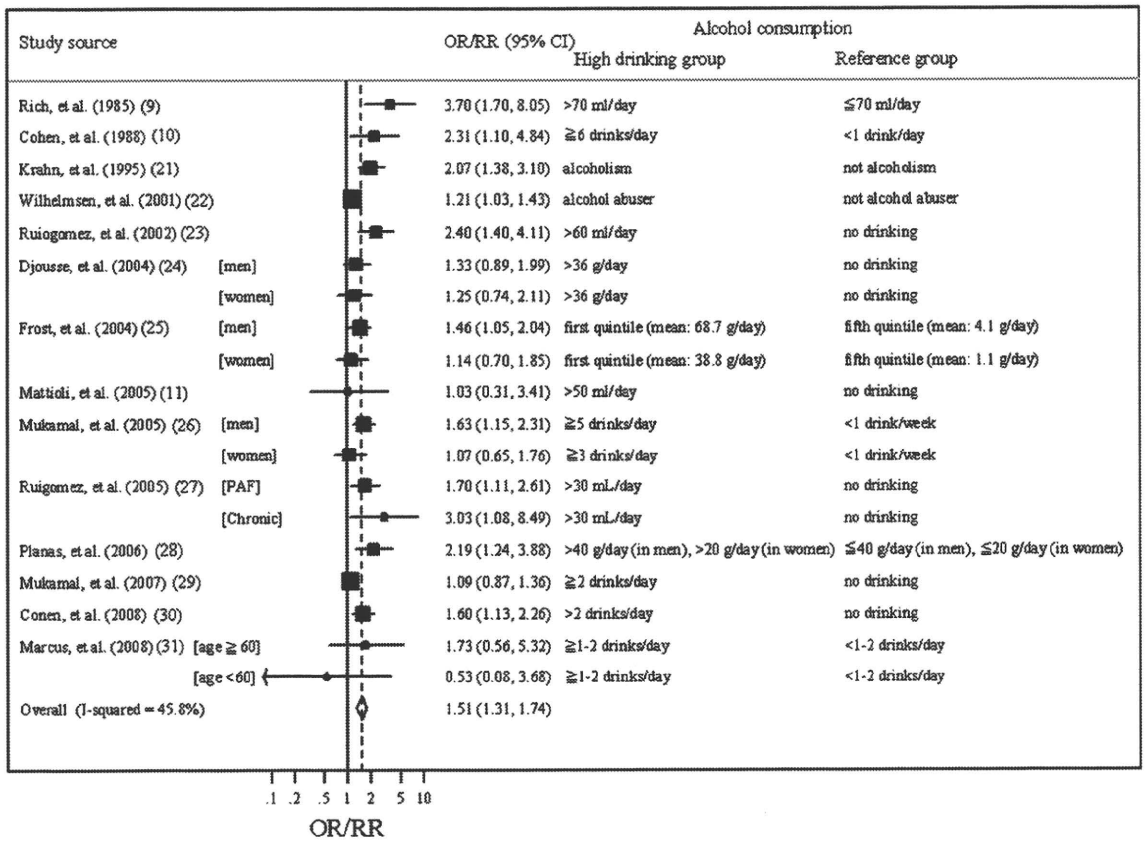

Figure 2 **OR/RR and 95% CI of AF by Alcohol Intake Group**

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.

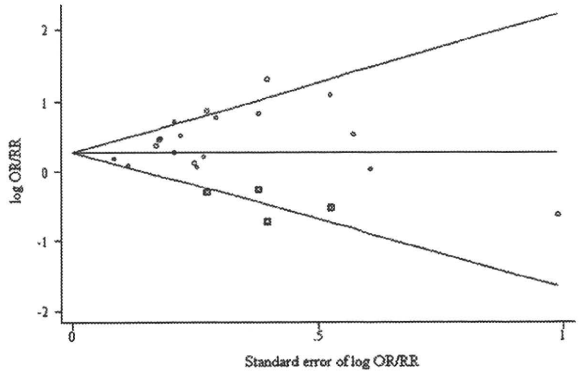

Figure 3 **Funnel Plot of High Alcohol Consumption and AF**

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

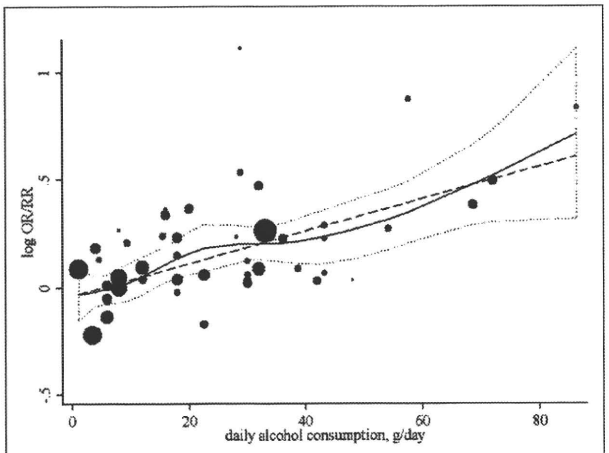

Figure 4 **Regression of Natural Log OR/RR for Atrial Fibrillation on Daily Alcohol Consumption**

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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REFERENCES

1. Gajewski J, Singer RB. Mortality in an insured population with atrial fibrillation. JAMA 1981;245:1540–4.
2. Benjamin EJ, Levy D, Vaziri SM, D'Agostino RB, Belanger AJ, Wolf PA. Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham Heart Study. JAMA 1994;271:840–4.
3. Schoonderwoerd BA, Smit MD, Pen L, Van Gelder IC. New risk factors for atrial fibrillation: causes of "not-so-lone atrial fibrillation." Europace 2008;10:668–73.
4. Ettinger PO, Wu CF, De La Cruz C Jr., Weisse AB, Ahmed SS, Regan TJ. Arrhythmias and the "holiday heart": alcohol-associated cardiac rhythm disorders. Am Heart J 1978;95:555–62.
5. Balbao CE, de Paola AA, Fenelon G. Effects of alcohol on atrial fibrillation: myths and truths. Ther Adv Cardiovasc Dis 2009;3:53–63.
6. Corrao G, Bagnardi V, Zambon A, La Vecchia C. A meta-analysis of alcohol consumption and the risk of 15 diseases. Prev Med 2004;38:613–9.
7. Costanzo S, Di Castelnuovo A, Donati MB, Iacoviello L, de Gaetano G. Alcohol consumption and mortality in patients with cardiovascular disease: a meta-analysis. J Am Coll Cardiol 2010;55:1339–47.
8. Di Castelnuovo A, Costanzo S, Bagnardi V, Donati MB, Iacoviello L, de Gaetano G. Alcohol dosing and total mortality in men and women: an updated meta-analysis of 34 prospective studies. Arch Intern Med 2006;166:2437–45.
9. Rich EC, Siebold C, Campion B. Alcohol-related acute atrial fibrillation. A case-control study and review of 40 patients. Arch Intern Med 1985;145:830–3.
10. Cohen EJ, Klatsky AL, Armstrong MA. Alcohol use and supraventricular arrhythmia. Am J Cardiol 1988;62:971–3.
11. Mattioli AV, Bonatti S, Zennaro M, Mattioli G. The relationship between personality, socio-economic factors, acute life stress and the development, spontaneous conversion and recurrences of acute lone atrial fibrillation. Europace 2005;7:211–20.
12. National Institute of Alcohol Abuse and Alcoholism. The Physicians' Guide to Helping Patients with Alcohol Problems. Washington, DC: U.S. Department of Health and Human Services, National Institutes of Health, 1995.
13. Berlin JA, Longnecker MP, Greenland S. Meta-analysis of epidemiologic dose-response data. Epidemiology 1993;4:218–28.
14. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002;21:1539–58.
15. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177–88.
16. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994;50:1088–101.

17. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. Br Med J 1997;315:629–34.
18. Duval S, Tweedie R. Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. Biometrics 2000;56:455–63.
19. Di Castelnuovo A, Rotondo S, Iacoviello L, Donati MB, De Gaetano G. Meta-analysis of wine and beer consumption in relation to vascular risk. Circulation 2002;105:2836–44.
20. Sterne JA, Gavaghan D, Egger M. Publication and related bias in meta-analysis: power of statistical tests and prevalence in the literature. J Clin Epidemiol 2000;53:1119–29.
21. Krahn AD, Manfreda J, Tate RB, Mathewson FA, Cuddy TE. The natural history of atrial fibrillation: incidence, risk factors, and prognosis in the Manitoba Follow-Up Study. Am J Med 1995;98:476–84.
22. Wilhelmsen L, Rosengren A, Lappas G. Hospitalizations for atrial fibrillation in the general male population: morbidity and risk factors. J Intern Med 2001;250:382–9.
23. Ruigomez A, Johansson S, Wallander MA, Rodriguez LA. Incidence of chronic atrial fibrillation in general practice and its treatment pattern. J Clin Epidemiol 2002;55:358–63.
24. Djousse L, Levy D, Benjamin EJ, et al. Long-term alcohol consumption and the risk of atrial fibrillation in the Framingham study. Am J Cardiol 2004;93:710–3.
25. Frost L, Vestergaard P. Alcohol and risk of atrial fibrillation or flutter: a cohort study. Arch Intern Med 2004;164:1993–8.
26. Mukamal KJ, Tolstrup JS, Friberg J, Jensen G, Gronbaek M. Alcohol consumption and risk of atrial fibrillation in men and women: the Copenhagen City Heart Study. Circulation 2005;112:1736–42.
27. Ruigomez A, Johansson S, Wallander MA, Garcia Rodriguez LA. Predictors and prognosis of paroxysmal atrial fibrillation in general practice in the UK. BMC Cardiovasc Disord 2005;5:20.
28. Planas F, Romero-Menor C, Vazquez-Oliva G, Poblet T, Navarro-Lopez F. [Natural history of and risk factors for idiopathic atrial fibrillation recurrence (FAP Registry)]. Rev Esp Cardiol 2006;59:1106–12.
29. Mukamal KJ, Psaty BM, Rautaharju PM, et al. Alcohol consumption and risk and prognosis of atrial fibrillation among older adults: the Cardiovascular Health Study. Am Heart J 2007;153:260–6.
30. Conen D, Tedrow UB, Cook NR, Moorthy MV, Buring JE, Albert CM. Alcohol consumption and risk of incident atrial fibrillation in women. JAMA 2008;300:2489–96.
31. Marcus GM, Smith LM, Whiteman D, et al. Alcohol intake is significantly associated with atrial flutter in patients under 60 years of age and a shorter right atrial effective refractory period. Pacing Clin Electrophysiol 2008;31:266–72.
32. Denison H, Jern S, Jagenburg R, Wendestam C, Wallerstedt S. Influence of increased adrenergic activity and magnesium depletion on cardiac rhythm in alcohol withdrawal. Br Heart J 1994;72:554–60.
33. Maki T, Toivonen L, Koskinen P, Naveri H, Harkonen M, Leinonen H. Effect of ethanol drinking, hangover, and exercise on adrenergic activity and heart rate variability in patients with a history of alcohol-induced atrial fibrillation. Am J Cardiol 1998;82:317–22.
34. Preedy VR, Siddiq T, Why H, Richardson PJ. The deleterious effects of alcohol on the heart: involvement of protein turnover. Alcohol Alcoholism 1994;29:141–7.
35. Steinbigler P, Haberl R, Konig B, Steinbeck G. P-wave signal averaging identifies patients prone to alcohol-induced paroxysmal atrial fibrillation. Am J Cardiol 2003;91:491–4.
36. Habuchi Y, Furukawa T, Tanaka H, Lu LL, Morikawa J, Yoshimura M. Ethanol inhibition of Ca2+ and Na+ currents in the guinea-pig heart. Eur J Pharmacol 1995;292:143–9.
37. McKenna CJ, Codd MB, McCann HA, Sugrue DD. Alcohol consumption and idiopathic dilated cardiomyopathy: a case control study. Am Heart J 1998;135:833–7.
38. Lazarevic AM, Nakatani S, Neskovic AN, et al. Early changes in left ventricular function in chronic asymptomatic alcoholics: relation to the duration of heavy drinking. J Am Coll Cardiol 2000;35:1599–606.
39. Athyros VG, Liberopoulos EN, Mikhailidis DP, et al. Association of drinking pattern and alcohol beverage type with the prevalence of metabolic syndrome, diabetes, coronary heart disease, stroke, and peripheral arterial disease in a Mediterranean cohort. Angiology 2007;58:689–97.
40. Taylor B, Irving HM, Baliunas D, et al. Alcohol and hypertension: gender differences in dose-response relationships determined through systematic review and meta-analysis. Addiction 2009;104:1981–90.
41. Sharma SK, Kumpawat S, Banga A, Goel A. Prevalence and risk factors of obstructive sleep apnea syndrome in a population of Delhi, India. Chest 2006;130:149–56.
42. Howard AA, Arnsten JH, Gourevitch MN. Effect of alcohol consumption on diabetes mellitus: a systematic review. Ann Intern Med 2004;140:211–9.

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

information

News & Trend

国立国際医療研究センターによる「糖尿病情報サービス」の展開

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はじめに

糖尿病情報センターは，国立国際医療センター（現 独立行政法人国立国際医療研究センター）内に，わが国の糖尿病情報の発信センターとして平成20年10月1日付けで設置された．

糖尿病は適切な生活習慣や治療により合併症の重症化を防止することが可能な疾患であるが，放置されたり適切な治療が行われなかったりした場合には，網膜症・腎症・神経障害・脳卒中や急性心筋梗塞などの合併症が進行し，しばしば失明・透析・足の切断などの高度な合併症や死亡にもつながり得る．糖尿病は食生活や運動習慣などの生活習慣の変化や高齢化の進行に伴って増加の一途を辿っており，厚生労働省の「国民健康・栄養調査」（平成19年度）によれば，「糖尿病が強く疑われる人」は約890万と，過去5年間で約150万人増加しているとともに，「糖尿病の可能性が否定できない人」も約1,320万人と，同じく約440万人増加している．世界各国でも糖尿病は著増しており，地球規模での糖尿病対策が求められている．

このような状況に鑑み，厚生労働省は，（独）国立国際医療研究センターなどに，糖尿病などの生活習慣病対策の国としての中核的な役割を負託し，また，各都道府県に対しては，その作成する医療計画のなかで糖尿病の予防・治療についての地域における医療連携体制を整えることを求めている．

本稿では，当センターの糖尿病情報センターにおける「糖尿病情報サービス」が提供を開始した医療機関検索機能や地域連携パス情報，患者データベース，糖尿病診療マニュアルなどについて解説する．

糖尿病情報サービスにおける論文情報と糖尿病診療マニュアル

EBM論文情報（http://www.ncgm-dmic.jp/public/articleKeyWordSearch.do）

このページでは，糖尿病に関する知識を深めることに役立つよう，医療従事者向けに論文の読み方についての解説や診療に活用できる診療マニュアル，論文の批評を掲載している．

EBM（evidence-based medicine）とは，個々の臨床判断に際して理論や経験則だけに頼るのではなく，エビデンス（臨床研究による実証）も判断の基盤として重視し，安全性・確実性を備えた患者中心の医療とその質の向上を目指すアクションである．ここで気をつけるべき点は，エビデンスは従来の医療に取って代わるものではなく，相互に補足的なものであることである．エビデンスを金科玉条のガイドラインとして盲信することがEBMではなく，個々の症例でエビデンスを取捨選択して患者と協働判断を行うことがEBMの真髄である．

＜論文の読み方＞

近年，糖尿病治療に関するエビデンスが急増してきているが，解釈が誤っているためにエビデンスが正しく理解・活用されていないことが多い．EBMを実践するには，臨床経験・コミュニケーション技能に加え，統計学的基本知識も必要である．自分の目でエビデンスの質を批評できないと統計学の罠にはまり，エビデンスに振り回されてしまう．このコーナーではEBMについての総論

表1　治療に関する論文の読み方(チェックリスト)の例

治療・予防に関する論文の読み方(チェックリスト)

治療の対象は患者であり検査値ではありません．予後や診療内容を変えないような治療は無用です．リスク差や副作用を秤にかけて患者と協働判断をします．

臨床問題

P(患者)
I(治療・予防)
C(比較対照)
O(アウトカム)

妥当性の評価

①研究デザイン：無作為化比較試験か？　比較対照はあるか？
②患者：明確な基準で選考・除外されているか？
③研究実施場所・施設：一般性はあるか？
④背景因子の等：治験開始時に2群間で違いがなかったか？
⑤治療の方法：治療方法に違いがなかったか？
⑥アウトカムの内容と基準：臨床的転帰で客観的な基準か？
⑦盲検：介入者と被験者は治療の内容を知らなかったか？
⑧フォローアップ：追跡期間は十分長く追跡率は高いか？
⑨Intention-to-treat解析：脱落者やプロトコール逸脱者を割り付け時のグループに含めて解析しているか？

結果の評価

①結　果

	治療群	対照群
アウトカム発生率	a%	b%

②治療効果・信頼性(統計学的有意性)
相対リスク(リスク比)＝a÷b＝　　p＝　，信頼区間(　)
またはハザード比＝　　p＝　，信頼区間(　)
絶対リスク低下(リスク差)＝b－a＝　　p＝　，信頼区間(　)

患者への適用性・臨床的意義

①リスク差は臨床的に意味があるか？
②実際の患者は論文の患者の臨床像に合致するか？
③実際の患者にこの治療は役立つか？(すべてのアウトカムを考慮した臨床判断)
④患者の意向・価値観は？

と診断・治療・ガイドラインに関するエビデンスの批評(批判的吟味)の仕方についての解説を掲載している(**表1**)．

＜論文の活用＞

このコーナーではエビデンスに立脚した糖尿病診療マニュアルを公開している．日本糖尿病学会による診療ガイドラインの内容は包括的であるが，以下の主要な問題点がある．

- 難解で具体性に乏しく実用性が低い．
- エビデンスの批評が甘く，誤用や寄せ集めに終わっていることが少なくない．
- EBMに則ったガイドラインを標榜しておきながら，血糖管理目標では「優・良・可・不可」という患者の人格を否定しかねない反EBM的評価呼称を採用していて矛盾している．さらに「優」カテゴリーでは死亡が増加する可能性もあり，不可解であるどころか混乱を招く．
- 理論と現実(エビデンス)の不一致が放置されている推奨内容もある．

当センターでは，ガイドラインを実用化し診療を最適化するために，妥当性の高いエビデンスを一義的に重視してそれに立脚した一般診療所・クリニック向けの糖尿病診療マニュアルを作成した(**図1**)．その特長は次のとおりである．

- 検査の頻度や選択薬剤の優先度を明記．
- 専門医・拠点病院への紹介の適応とタイミングを記載(循環型地域パス推進)．
- 診療効果の確実性と安全性を重視．
- 100件以上のエビデンスの批評・査定による推奨：インターネットで一般公開中．(http://www.ncgm-dmic.jp/doc/diabetes_treatment_manual.pdf)

ただし，本マニュアルは個々の臨床状況での理論・経験に基づく医師の判断を拘束したり，特定の方向づけを強制したりするものではなく，参考となる診療補助情報として活用されるべきものである．

論文の紹介(2010年8月頃公開予定)

このコーナーでは，日常診療の改善や糖尿病診療マニュアルのアップデートに役立つように，最近の主要なエビデンスを切り裁いて紹介する．単なる論文紹介とそれに対するコメントではなく，「論文の読み方」に則って研究の妥当性・信頼性についての鑑定を交えていることが特長である(**表2**)．

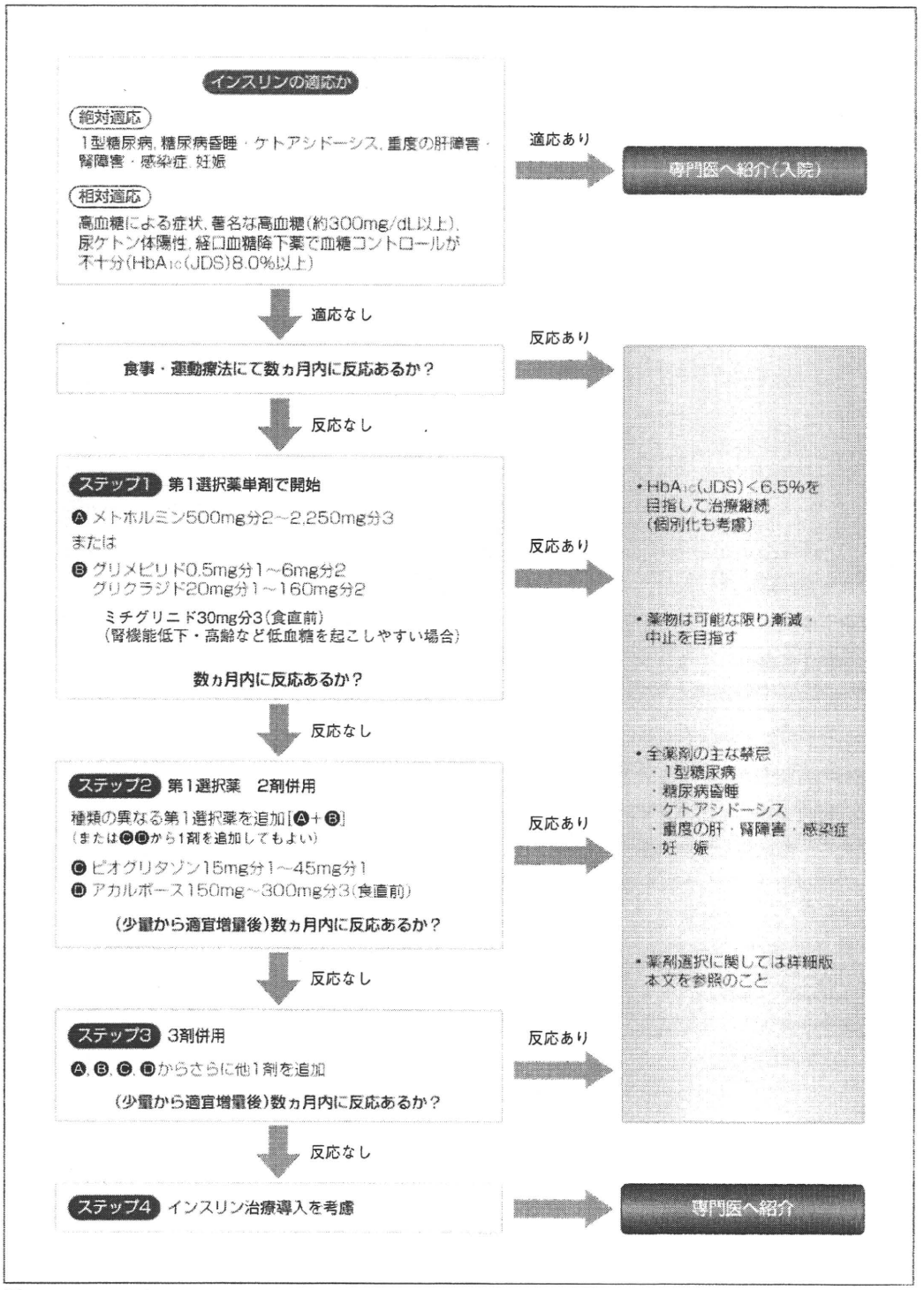

図1 国立国際医療研究センター病院 糖尿病標準診療マニュアルの一部
2型糖尿病患者の治療の流れを示す．薬剤選択は血管合併症に対するエビデンスの有無により判断した．

表2　論文の批判的紹介の例

結　論	メトホルミンはがん発生を抑制する可能性がある.
タイトル	New users of metformin are at low risk of incident cancer : a cohort study among people with type 2 diabetes.
著　者	Libby G, et al.
掲載誌	Diabetes Care. 2009, 32. 1620-5.
PMID	(PubMedリンク)
臨床問題	P(患者)　：スコットランドの2型糖尿病患者(年齢35歳以上・男性45.5%) I(治療)　：メトホルミン新規服用(4,085人) C(比較対照)　：メトホルミン非服用(4,085人) O(アウトカム)：がん発生率は低下するか?
研究方法	デザイン：コホート研究 盲検化　：なし 追跡期間：最長10年間・追跡率：100%
結　果	メトホルミン服用群では発がんリスクが有意に低下した.

アウトカム	メトホルミン服用	メトホルミン非服用	相対リスク	絶対リスク差
がん発生率	7.3%	11.6%	調整ハザード比0.63 (95%信頼区間0.53～0.75) (P<0.05)	4.3%
がん発生までの期間(中央値)	3.5年	2.6年	ログランク検定p<0.001	報告なし

コメント	2型糖尿病ではがんのリスクが増加することが報告されている*. とくに日本では, がんは糖尿病の有無にかかわらず主要な死因であるため, 糖尿病患者においても心血管疾患と同様に一層の重要性をもつ. 日本でのメトホルミンの処方数・投与量は欧米に比べ著明に少ないが, 今後メトホルミンの有用性が増加していく可能性が高い. この観察研究で提唱された仮説の無作為化比較試験などでの検証が待ち望まれる.
備考	*：Inoue M, et al. Diabetes mellitus and the risk of cancer : results from a large-scale population-based cohort study in Japan. Arch Intern Med. 2006, 166. 1871-7. 97,771人を対象としたコホート研究

糖尿病情報サービスにおける医療機関検索機能と地域連携パス情報

2007年に「良質な医療を提供する体制の確立を図るための医療法等の一部を改正する法律」が施行され, 医療連携の手法により糖尿病診療の質を均てん化し, 糖尿病合併症の進行阻止を目指すという方向性が示された. これを受けて国立国際医療センター(現 国立国際医療研究センター)内に新たに設置された糖尿病情報センター情報サービスは, 2010年4月より糖尿病関連医療機関情報の収集および公開を開始した.

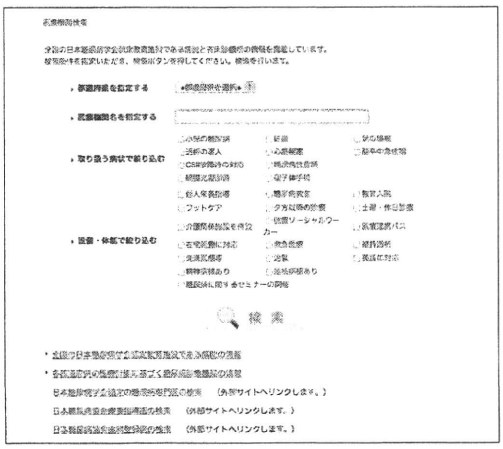

図2　糖尿病医療機関検索のページ

医療機関検索(http://www.ncgm-dmic.jp/public/hospitalInfoSearch.do)

図2に医療機関検索のページを示す. このページは,

- 糖尿病患者が糖尿病に関する知識を深める(糖尿病教室, 栄養指導, いわゆる教育入院などができる医療機関情報の提供)ための情報提供.
- 特殊な併発疾患や患者の状況(精神科疾患, 結核, 介護など)を有する糖尿病患者に対応できる施設の情報.
- 専門的治療(CSII：持続皮下インスリン注入など)や急性増悪期(ケトアシドーシスなど)の治療, 先進医療(膵臓移植, 膵臓島移植など)を担う医療機関情報の提供.
- 糖尿病の診療に対応できる逆紹介先の検索.

など，糖尿病診療医療機関に関するさまざまな情報を提供することを目的としている．

具体的には，医療機関検索のページでは，

- 糖尿病の専門的治療施設の情報として，日本糖尿病学会認定教育施設である病院・有床診療所の情報（当該施設へのアンケートの回答）が検索できるようになっている．今後，調査対象施設を順次拡大していく予定である．
- 各都道府県が医療計画のなかで公表している糖尿病診療機関情報へのリンク．
- 日本糖尿病協会へのリンク（日本糖尿病協会登録医・歯科医師登録医の情報）．
- 日本糖尿病学会の認定糖尿病専門医の情報．

をとりあつかっている．

地域連携パス情報（http://www.ncgm-dmic.jp/html/pass.html）

糖尿病診療にかかわる諸機関の連携には，

- 受診者の側からは，何のために，どのような診療・患者教育・検査・投薬などを，どこで受けるのかについてのロードマップ．
- 医療者の側からは，ほかの医療機関で行われた診療・患者教育・検査・投薬などに関する情報の共有のための連携パス．

があると大変便利である．

そこで現在，実際に糖尿病の地域連携を行っている施設・地域・医師会・自治体などのご好意を得て，現在実際に使われている糖尿病診療地域連携パスなど，地域連携関連資料をとりまとめたリンク集を公開した．これから糖尿病の地域連携を立ち上げる多くの地域が，これらの資料を参考にして，地域の実情に見合った連携体制を構築していくことを願っている．

糖尿病患者データベースの構築

当糖尿病情報センターでは，多数の病院やクリニックの糖尿病患者情報（診療に伴って得られる種々の検査結果，処方歴，病歴などの診療情報）をそれぞれの施設において匿名化して収集し，当糖尿病情報センターの患者登録システムに格納することにより，わが国の糖尿病診療の状況把握および今後の方向性の検討に資するべく，糖尿病患者データベースを構築している．

登録データは匿名化して個人情報を保護するとともに，国立国際医療研究センターの倫理委員会の承認を得て，昨年度（平成21年度）末の時点で4,300人以上の患者登録を行っている．登録された診療情報は統合し，これによって糖尿病の治療・合併症の実態把握や合併症の進行などに関する要因分析を行うものである．

おわりに－糖尿病情報センターに求められるもの

糖尿病診療の均てん化と糖尿病に関する全国の医療水準の向上を進めるためには，糖尿病に関する情報の提供および技術的支援を行う体制の整備が望まれる．そのような社会的要請のなかで当情報センターの果たすべき役割は，❶情報登録・発信機能と，❷研修支援機能に集約される．

❶情報登録・発信機能に関しては，ⓐ医療機関情報，地域連携パスに関する情報を収集しこれを発信する，ⓑ倫理面に最大限の配慮をしつつ，糖尿病情報についての登録を行い，登録データを集約・分析する，ⓒ医療者向け糖尿病論文情報などを収集・登録・公開することを，❷研修支援機能に関しては，糖尿病にかかわるメディカルスタッフに対する研修会を企画・開催することを主たる使命として活動している．

本稿では詳細に触れられなかったが，研修会を含めた当糖尿病情報センターの活動については，センター（および研究活動に関するものについては糖尿病・代謝症候群診療部）のホームページ（http://ncgm-dm.jp/naibunpitu/index.html）をぜひ参照されたい．

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COMMENTARY

Pathophysiology of cognitive dysfunction in older people with type 2 diabetes: vascular changes or neurodegeneration?

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Abstract

Recent studies have revealed that type 2 diabetes mellitus (T2DM) is a risk factor for cognitive dysfunction or dementia, especially those related to Alzheimer's disease (AD). Basic research suggests that insulin accelerates Alzheimer-related pathology through its effects on the amyloid beta (Aβ). Several pathological studies with autopsy samples have demonstrated, however, that dementia subjects with diabetes have less AD-related neuropathology than subjects without diabetes. We and others have reported that small vessel diseases affect cognitive function in older diabetics. Asymptomatic ischemic lesions in T2DM subjects may lower the threshold for the development of dementia and this may explain the inconsistency between the basic research and clinicopathological studies. Longitudinal follow-up of T2DM subjects without overt dementia using both amyloid imaging and magnetic resonance imaging may elucidate these issues. Following up until the development of overt dementia would make it possible to compare both amyloid load and ischemic lesions before and after the development of dementia. Moreover, amyloid imaging in non-demented older people with or without insulin resistance would verify the role of insulin in the processing and deposition of Aβ. Vascular risk factors may represent a therapeutic target, while neurodegenerative pathologies have not yet been amenable to treatment. It remains to be investigated whether medical interventions on vascular risk factors have protective effects against the development and progress of dementia.

Keywords: *Alzheimer's disease, ischemic lesions, dementia, insulin, Aβ*

The prevalence of type 2 diabetes mellitus (T2DM) increases with age, and dementia also increases its incidence in later life. Therefore, the coincidence of T2DM and dementia increases with ageing. Moreover, recent studies have indicated that older people with T2DM have a higher risk of cognitive dysfunction or dementia [1]. There is ample evidence that T2DM is related not only to vascular dementia but also to clinical diagnosis of Alzheimer's disease (AD)-type dementia [2]. The precise mechanisms underlying T2DM-related cognitive dysfunction or development of dementia, especially AD-type dementia, remain to be elucidated, although several hypothetical mechanisms have been proposed. High glucose concentration, a major pathological characteristic of diabetes, may have toxic effects on neurons in the brain through osmotic insults and oxidative stress, and the maintenance of chronic high glucose also leads to the enhanced formation of advanced glycation endoproducts, which have potentially toxic effects on neurons. Diabetes is associated with an increased release of inflammatory cytokines, and the excess inflammation may be neurotoxic.

T2DM, especially in conjunction with obesity, is characterised by insulin resistance and/or hyperinsulinaemia. Insulin resistance is defined as an inadequate response by insulin target tissues, such as skeletal muscle, liver and adipose tissue, to the physiological effects of circulating insulin, and often is accompanied by raised insulin levels. Basic research suggests that insulin accelerates AD-related pathology through its effects on the amyloid beta (Aβ) metabolism and tau phosphorylation [2]. Insulin reportedly raises Aβ concentrations in plasma in AD subjects, and these effects may contribute to the risk of AD in T2DM. The desensitization of insulin receptors, insulin resistance, reduces the synthesis of several proteins, including insulin-degrading enzyme (IDE). IDE degrades Aβ as well as insulin, and reduced amounts of IDE may result in greater