に際しては意見を反映させていくことが必要であると考えられた。

F.健康危険情報(分担研究報告書には記入せずに、総括研究報告書にまとめて記入)

G.研究発表

1.論文発表

特になし

2.学会発表(発表誌名巻号・頁・発行年等も記入)

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H.知的財産権の出願・登録状況(予定を含む。)

1.特許取得

2009 年度は特になし。

2.実用新案登録

2009 年度は特になし。

3.その他

2009 年度は特になし。

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IV.研究成果の刊行物・別刷

Circulation Journal
Official Journal of the Japanese Circulation Society
http://www.j-circ.or.jp

ORIGINAL ARTICLE
Ischemic Heart Disease

Beta-Blocker Prescription Among Japanese Cardiologists and Its Effect on Various Outcomes

Takahide Kohro, MD; Dobun Hayashi, MD**; Tsutomu Yamazaki, MD*;
Ryozo Nagai MD**; The JCAD Investigators

Background: Beta-blockers are underprescribed for coronary artery disease (CAD) patients in Japan. Considering the vast amount of evidence showing their benefits in this group of patients, the aim of the present study was to investigate the use of β-blockers in a large cohort of CAD patients.

Methods and Results: The 13,812 patients with angiographically confirmed CAD were followed up for 2.7 years. From this group, 4,160 (30.1%) patients were prescribed β-blockers at the time of discharge. These patients were significantly more likely to have hypertension, hyperlipidemia, obesity, a family history of ischemic diseases and a higher number of diseased arteries. The rate of continuation for β-blockers was 90.8%. A propensity score matching analysis showed no additional benefits of β-blockers in reducing all-cause mortality, cardiac events and cerebrovascular events. Lipophilic β-blockers were significantly more effective than hydrophilic ones in reducing all-cause mortality (hazard ratio 0.467, 95% confidence interval 0.247–0.880, P=0.019).

Conclusions: Despite the low prescription rate of β-blockers for CAD patients among Japanese physicians, the continuation rate was relatively high. Lipophilic β-blockers may be a better choice than hydrophilic β-blockers in terms of mortality risk, although a randomized control study would need to be conducted to verify this assertion. (*Circ J* 2010; **74:** 962–969)

Key Words: Beta-blocker; Coronary artery disease; Observational cohort; Propensity score matching analysis

Beta-blockers are underprescribed by Japanese physicians, possibly because of their deleterious effects on metabolic profiles,[1,2] and patients with bronchial insufficiency,[3] or physicians' high awareness of bradycardia and hypotension induced by the drugs. It has been reported that even for patients with myocardial ischemia, calcium antagonists are preferred over β-blockers for the treatment of angina,[4] maybe from fear of coronary spasm, the rate of which is reported to be higher in the Japanese population than in Westerners.[5] Although β-blockers were being used off-label for congestive heart failure (CHF) in clinical settings, it was only in 2002 that carvedilol was officially approved for the treatment of CHF in Japan. Today, carvedilol remains the only β-blocker approved for the treatment of CHF in Japan. On the other hand, there is ample evidence that β-blockers are beneficial in reducing cardiovascular risks in many conditions.[6–9]

Editorial p 848

We conducted a large observational study (the JCAD study) to investigate the background and treatment of Japanese patients with confirmed coronary artery disease (CAD), defined as ≥75% stenosis in at least 1 branch of the coronary arteries in accordance with the American Heart Association (AHA) classification. We concluded that β-blockers were less likely to be prescribed in Japan than in the West,[10] but considering the enormous evidence of the beneficial effects of β-blockers in patients with cardiovascular diseases, we felt that a more thorough investigation of β-blocker usage was necessary. It has also been reported that different β-blockers produce different outcomes in certain situations,[11] so in the present study we looked at how various classes of β-blockers are used and what effects they had on outcomes.

Methods

Patients

The protocol and major outcomes of this study have been published previously.[12,13] Briefly, patients who underwent coronary angiography (CAG) at each participating institute and who were diagnosed as having ≥75% stenosis according to the AHA classification in at least 1 branch of the coronary arteries were registered. All CAGs were performed with

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Table 1. Background Characteristics of Patients With or Without β-Blockers

	Without β-blockers (n=9,652)	With β-blockers (n=4,160)	P value
Age	65.53±9.90	65.32±9.63	0.110
Male	7,466 (77.4%)	3,160 (76.0%)	0.075
Hypertension	5,345 (55.4%)	2,606 (62.6%)	<0.001
Hyperlipidemia	5,122 (53.1%)	2,425 (58.3%)	<0.001
IFG	3,857 (40.0%)	1,713 (41.2%)	0.181
Obesity	3,035 (31.4%)	1,407 (33.8%)	0.006
Smoking	3,834 (39.7%)	1,603 (38.5%)	0.190
Drinking	3,625 (37.6%)	1,589 (38.2%)	0.476
Family history	1,533 (15.9%)	748 (18.0%)	0.002
CHF	1,005 (10.4%)	393 (9.4%)	0.128
LMT disease	415 (4.3%)	207 (5.0%)	0.079
No. of affected arteries	1.73±0.79	1.89±0.81	<0.001
Statins	3,207 (33.2%)	1,864 (44.8%)	<0.001
Fibrates	285 (3.0%)	163 (3.9%)	0.003
CCBs	4,913 (50.9%)	2,015 (48.4%)	0.008
ACEIs	2,823 (29.2%)	1,543 (37.1%)	<0.001
ARBs	1,176 (12.2%)	692 (16.6%)	<0.001
α-blockers	187 (1.9%)	131 (3.1%)	<0.001
ATs	8,088 (83.8%)	3,960 (95.2%)	<0.001
Nitrates	5,805 (60.1%)	2,514 (60.4%)	0.750

P values of age and number of affected arteries were calculated by Kruskal-Wallis test. All other P values were calculated by chi-square test.
IFG, impaired fasting glycemia; CHF, congestive heart failure; LMT, left main trunk; CCB, calcium-channel blocker; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; AT, antithrombotic.

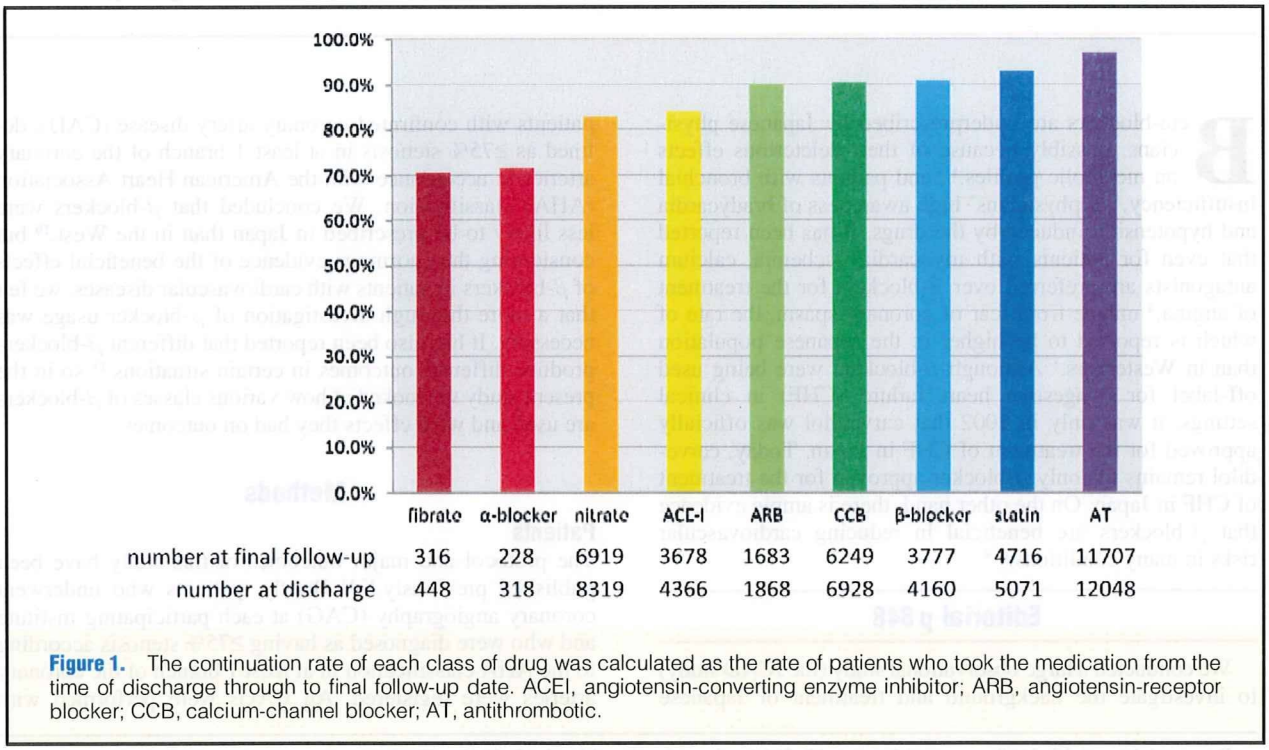

Figure 1. The continuation rate of each class of drug was calculated as the rate of patients who took the medication from the time of discharge through to final follow-up date. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; CCB, calcium-channel blocker; AT, antithrombotic.

written informed consent. Of the 15,628 patients who were initially registered in the study, 13,812 were followed up and included in the present analysis. Among these, 10,626 of the patients were male and 3,186 were female. Diagnoses at the time of registration included the following: acute myocardial infarction (2,955 patients), history of myocardial infarction (OMI: 3,913 patients), and unstable angina pectoris (UAP: 2,049). Patients were followed up for an average of 2.7 years.

Table 2. Classification of β-Blockers According to Solubility or Receptor Selectivity

Solubility classification			Receptor selectivity classification
Lipophilic β-blockers (n=3,257)	**No. and dosage (mg)***		**β1 selective (n=2,493)**
Amosulalol hydrochloride	2	20.0±14.1	Acebutolol hydrochloride
Arotinolol hydrochloride	53	14.9±6.2	Atenolol
Betaxolol hydrochloride	128	7.5±4.1	Betaxolol hydrochloride
Bevantolol hydrochloride	12	79.2±25.7	Bisoprolol fumarate
Bisoprolol fumarate	574	4.1±2.5	Celiprolol hydrochloride
Bopindolol malonate	5	0.9±0.2	Metoprolol tartrate
Carvedilol	1,421	10.3±5.5	
Metoprolol tartrate	913	49.0±28.6	**α β-blockers (n=1,491)**
Nipradilol	47	6.2±2.2	Amosulalol hydrochloride
Oxprenolol hydrochloride	1	40	Arotinolol hydrochloride
Pindolol	5	11.0±5.5	Bevantolol hydrochloride
Propranolol hydrochloride	96	32.6±20.5	Carvedilol
			Labetalol hydrochloride
Hydrophilic β-blockers (n=903)			**Non-selective β-blockers (n=176)**
Acebutolol hydrochloride	9	144.4±52.7	Bopindolol malonate
Atenolol	774	34.4±17.0	Bufetolol hydrochloride
Bufetolol hydrochloride	1	10	Bunitrolol hydrochloride
Bunitrolol hydrochloride	1	20	Carteolol hydrochloride
Carteolol hydrochloride	19	12.5±3.7	Nadolol
Celiprolol hydrochloride	95	243.3±403.2	Nipradilol
Labetalol hydrochloride	3	133.3±28.9	Oxprenolol hydrochloride
Nadolol	1	30	Pindolol
			Propranolol hydrochloride
		Total 4,160 (30.1% of all patients included in the analysis)	

*Dosage is represented as mean±1SD.

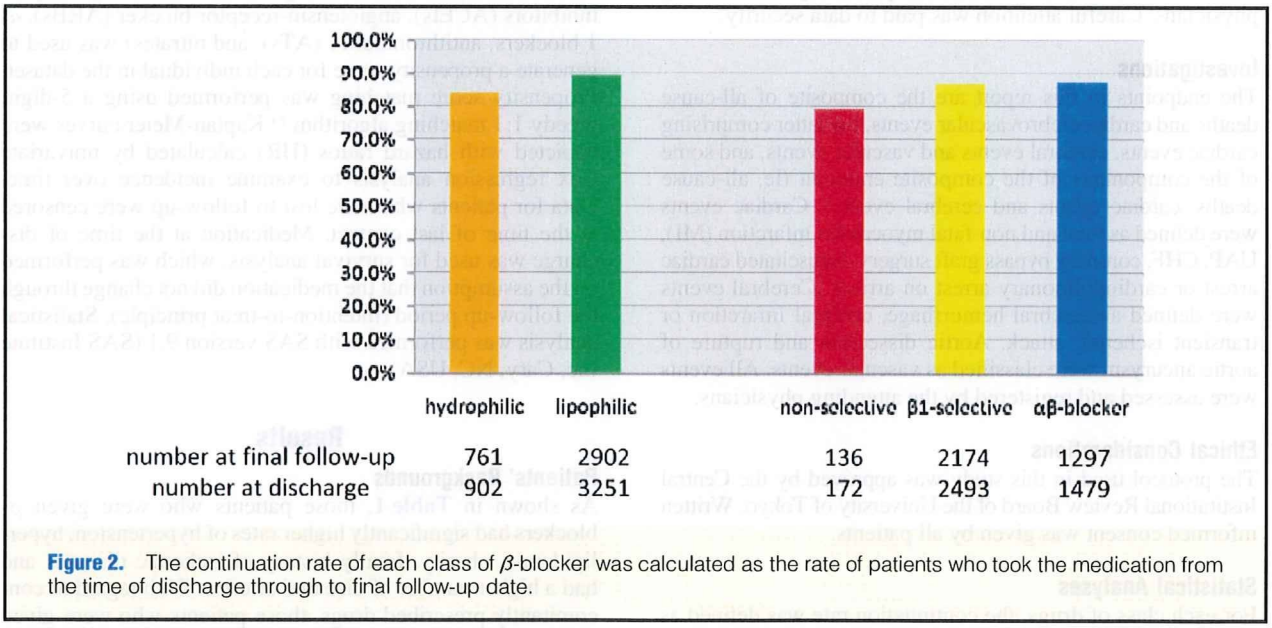

Figure 2. The continuation rate of each class of β-blocker was calculated as the rate of patients who took the medication from the time of discharge through to final follow-up date.

Data Registration and Gathering

All follow-up data were gathered electronically over the internet. At the time of registration, a diagnosis of CAD had been given by the attending physician. The brand names and dosages of all the drugs that the patients were taking were registered by the attending physicians. The definition of each risk factor was as follows: smoking, at least 1 incidence of smoking in the 2 years prior to registration; hyperlipidemia, serum total cholesterol ≥220 mg/dl and/or low-density-lipoprotein cholesterol ≥140 mg/dl and/or triglycerides ≥150 mg/dl; impaired fasting glycemia (IFG), defined as fasting blood glucose ≥110 mg/dl (diabetes mellitus was included in this study); hypertension, systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg; obesity, body

Table 3. Background Characteristics of Matched Patients With or Without β-Blockers

	Without β-blockers (n=3,892)	With β-blockers (n=3,892)	P value
Age	65.34±9.84	65.34±9.65	0.553
Male	2,965 (76.2%)	2,954 (75.9%)	0.770
Hypertension	2,448 (62.9%)	2,417 (62.1%)	0.468
Hyperlipidemia	2,221 (57.1%)	2,265 (58.2%)	0.313
IFG	1,591 (40.9%)	1,617 (41.5%)	0.549
Obesity	1,306 (33.6%)	1,321 (33.9%)	0.719
Smoking	1,459 (37.5%)	1,488 (38.2%)	0.498
Drinking	1,522 (39.1%)	1,491 (38.3%)	0.471
Family history	671 (17.2%)	683 (17.5%)	0.720
CHF	393 (10.1%)	391 (10.0%)	0.940
LMT disease	200 (5.1%)	191 (4.9%)	0.640
No. of affected arteries	1.88±0.81	1.88±0.81	0.946
Statins	1,703 (43.8%)	1,734 (44.6%)	0.479
Fibrates	159 (4.1%)	151 (3.9%)	0.643
CCBs	1,933 (49.7%)	1,900 (48.8%)	0.454
ACEIs	1,448 (37.2%)	1,444 (37.1%)	0.925
ARBs	657 (16.9%)	641 (16.5%)	0.627
α-blockers	122 (3.1%)	116 (3.0%)	0.693
ATs	3,697 (95.0%)	3,697 (95.0%)	1.000
Nitrates	2,409 (61.9%)	2,390 (61.4%)	0.658

P values of age and number of affected arteries were calculated by Kruskal-Wallis test. All other P values were calculated by chi-square test.
Abbreviations see in Table 1.

mass index ≥25; familial history, first-degree relative with CAD; and drinking, having a habit of alcohol consumption. These data were obtained from each patient by the attending physicians. Careful attention was paid to data security.

Investigations

The endpoints in this report are the composite of all-cause deaths and cardiocerebrovascular events, the latter comprising cardiac events, cerebral events and vascular events, and some of the components of the composite endpoint (ie, all-cause deaths, cardiac events and cerebral events). Cardiac events were defined as fatal and non-fatal myocardial infarction (MI), UAP, CHF, coronary bypass graft surgery, resuscitated cardiac arrest or cardiopulmonary arrest on arrival. Cerebral events were defined as cerebral hemorrhage, cerebral infarction or transient ischemic attack. Aortic dissection and rupture of aortic aneurysm were classified as vascular events. All events were assessed and registered by the attending physicians.

Ethical Considerations

The protocol used in this study was approved by the Central Institutional Review Board of the University of Tokyo. Written informed consent was given by all patients.

Statistical Analyses

For each class of drugs, the continuation rate was defined as the rate of patients who took the medication from the time of discharge through to follow-up date. Because the data for each patient, including prescriptions, were registered by the attending physicians every 6 months, we assumed that a drug was discontinued if a patient continued to be followed up, but the drug that the patient had been prescribed was not registered. The logistic model, which included both patient background characteristics (age, sex, hypertension, hyperlipidemia, IFG, obesity, smoking, drinking of alcohol, family history of CAD, CHF, left main trunk disease, and number of affected arteries) and drug classes (statins, fibrates, calcium-channel blockers (CCBs), angiotensin-converting enzyme inhibitors (ACEIs), angiotensin-receptor blocker (ARBs), α-1 blockers, antithrombotics (ATs), and nitrates) was used to generate a propensity score for each individual in the dataset. Propensity score matching was performed using a 5-digit, greedy 1:1 matching algorithm.[14] Kaplan-Meier curves were depicted with hazard ratios (HR) calculated by univariate Cox regression analysis to examine incidence over time. Data for patients who were lost to follow-up were censored at the time of last contact. Medication at the time of discharge was used for survival analysis, which was performed on the assumption that the medication did not change through the follow-up period (intention-to-treat principle). Statistical analysis was performed with SAS version 9.1 (SAS Institute Inc, Cary, NC, USA).

Results

Patients' Backgrounds

As shown in Table 1, those patients who were given β-blockers had significantly higher rates of hypertension, hyperlipidemia, obesity, family history of ischemic diseases and had a higher number of diseased arteries. With regard to concomitantly prescribed drugs, those patients who were given β-blockers were also significantly more likely to be prescribed statins, fibrates, α-1 blockers, ACEIs, ARBs, and ATs, and were significantly less likely to be prescribed CCBs.

Continuation Rate of Each Class of Drug

Figure 1 shows the continuation rate of several classes of drugs that were prescribed for the patients in this cohort. Fibrates continued to be administered to 70.5% of the patients who were prescribed the medicine at the time of

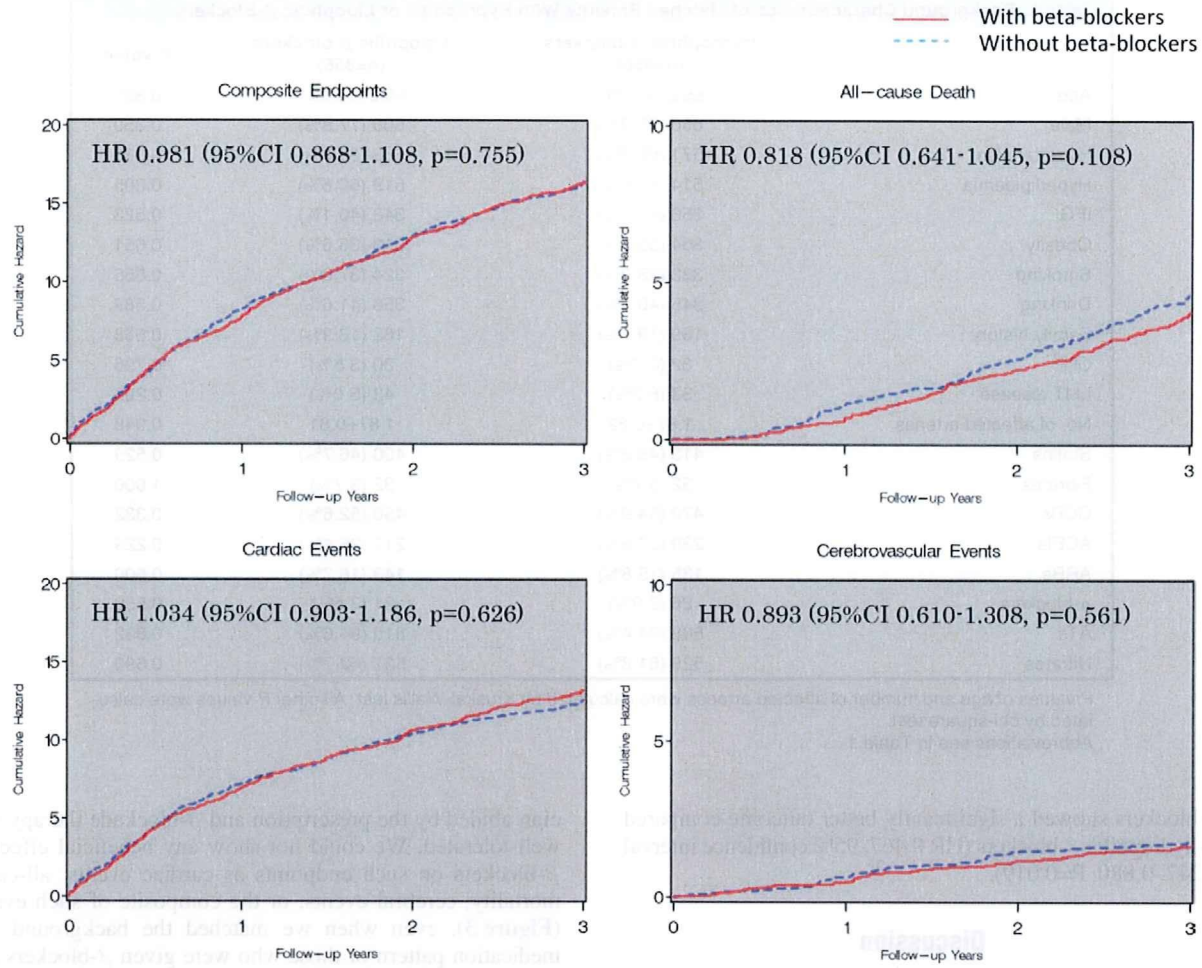

Figure 3. Patients who were taking β-blockers were matched with those who were not taking β-blockers based on propensity scores calculated by logistic regression. Kaplan-Meier analysis was performed on the 2 groups with various endpoints. HR, hazard ratio; CI, confidence interval.

discharge, while ARBs, CCBs, β-blockers, statins, and ATs continued to be administered to over 90% of the patients who were prescribed the drugs at the time of discharge.

Continuation Rate of β-Blockers When Classified According to Lipophilicity/Receptor Binding Specificity

Beta-blockers can be classified according to their solubility or ability to specifically bind to β-1 receptors. Table 2 shows the classification, number of patients taking the drug, and mean dosage of all the β-blockers that physicians prescribed in this study. Figure 2 shows the continuation rate for β-blockers of each class. The continuation rate of hydrophilic β-blockers (84.4%) was significantly lower than that of lipophilic β-blockers (89.3%, P<0.001). The continuation rate of non-selective β-blockers (79.1%) was significantly lower than that of β-1-selective β-blockers (87.2%, P=0.003) or α-β-selective β-blockers (87.7%, P=0.002).

Effect of β-Blockers on Endpoints

In order to investigate the effect of β-blockers, we performed a propensity score matching analysis. Those who were given β-blockers at discharge were matched with those who were not given β-blockers at discharge. As shown in Table 3, all background characteristics and medication were well matched. Figure 3 shows the Kaplan-Meier plot for endpoint accumulation and HRs. There were no significant differences between those who were given β-blockers and those were not given β-blockers for any of the endpoints.

Differences in Effect of β-Blockers on Endpoints According to Lipophilicity

We sought to investigate if there were any differences in effectiveness between lipophilic and hydrophilic β-blockers on the endpoints. We performed propensity score matching between those who were given lipophilic β-blockers and those who were given hydrophilic β-blockers. As shown in Table 4, all background characteristics and medication were well matched. Figure 4 shows the Kaplan-Meier plot for endpoint accumulation and HRs. For the composite endpoints, cardiac endpoints and cerebral endpoints, there were no significant differences between lipophilic and hydrophilic β-blockers for outcome. For all-cause mortality, lipophilic

Table 4. Background Characteristics of Matched Patients With Hydrophilic or Lipophilic β-Blockers

	Hydrophilic β-blockers (n=856)	Lipophilic β-blockers (n=856)	P value
Age	65.27±9.09	65.24±9.98	0.825
Male	650 (75.9%)	666 (77.8%)	0.359
Hypertension	571 (66.7%)	563 (65.8%)	0.683
Hyperlipidemia	514 (60.0%)	519 (60.6%)	0.805
IFG	356 (41.6%)	343 (40.1%)	0.523
Obesity	304 (35.5%)	313 (36.6%)	0.651
Smoking	333 (38.9%)	324 (37.9%)	0.655
Drinking	345 (40.3%)	356 (41.6%)	0.589
Family history	169 (19.7%)	162 (18.9%)	0.668
CHF	32 (3.7%)	30 (3.5%)	0.796
LMT disease	53 (6.2%)	43 (5.0%)	0.293
No. of affected arteries	1.87±0.82	1.87±0.81	0.948
Statins	413 (48.2%)	400 (46.7%)	0.529
Fibrates	32 (3.7%)	32 (3.7%)	1.000
CCBs	470 (54.9%)	450 (52.6%)	0.332
ACEIs	239 (27.9%)	217 (25.4%)	0.229
ARBs	135 (15.8%)	143 (16.7%)	0.600
α-blockers	25 (2.9%)	21 (2.5%)	0.550
ATs	808 (94.4%)	810 (94.6%)	0.832
Nitrates	529 (61.8%)	537 (62.7%)	0.690

P values of age and number of affected arteries were calculated by Kruskal-Wallis test. All other P values were calculated by chi-square test.
Abbreviations see in Table 1.

β-blockers showed a significantly better outcome compared to hydrophilic β-blockers (HR 0.467, 95% confidence interval 0.247–0.880, P=0.019).

Discussion

In this study of a large cohort of Japanese patients with angiographically determined CAD, we showed that despite the low prescription rate of β-blockers among Japanese physicians, the continuation rate was relatively high and that lipophilic β-blockers may be a better choice than hydrophilic ones if mortality risks are considered.

As mentioned earlier, Japanese physicians have been reluctant to adopt β-blockers as a treatment for hypertension. Although the guidelines for the management of hypertension published by the Japanese Society of Hypertension in 2009 include β-blockers as a first-line therapy for hypertension,[15] among Japanese physicians it is generally perceived that compared to CCBs, ACEIs and ARBs, β-blockers are more difficult to use because of their unfavorable effects on glucose metabolism[1,2] and pulmonary diseases.[16] Cardiologists are also highly aware of the bradycardia and hypotension induced by β-blockers. Previous reports have shown that even for patients with CAD, the prescription rate of β-blockers is significantly lower in Japan (≈30%[4,17]) than in the West (≈85%[18]).

That trend was also observed in this study, in which only 30.1% of CAD patients were prescribed β-blockers. Despite the fact that in this study we combined α-β-blockers and pure β-blockers under the same classification of β-blockers, unlike in our previous report,[10] the overall prescription rate was still lower than that reported in Western studies.

However, this study showed that the adherence rate of β-blockers was over 90%, suggesting that for those patients in whom β-blockers were indicated, the attending physician abided by the prescription and β-blockade therapy was well tolerated. We could not show any beneficial effect of β-blockers on such endpoints as cardiac events, all-cause mortality, cerebral events, or the composite of such events (Figure 3), even when we matched the background and medication pattern of those who were given β-blockers and those who were not (Table 3). Before matching, patients who were prescribed β-blockers had a significantly higher rate of hypertension, hyperlipidemia, obesity, family history of CAD and a higher number of diseased arteries (Table 1). It is possible that other factors that were not measured in this study were unbalanced between the groups and affected the results so that beneficial effects were not observed for β-blockers. This problem in evaluating the efficacy of drugs in observational studies is known as "confounding by indication".[19]

Beta-blockers can be classified according to such properties as lipophilicity, β-receptor-blockade specificity and intrinsic sympathomimetic activity, which, aside from the class effect of β-blockers, reportedly cause differences in various outcomes,[20] with several clinical studies supporting this claim.[7,8,21] In the present study, lipophilic β-blockers reduced the risk of all-cause mortality significantly more than hydrophilic β-blockers, which is in contrast to a recent observational study that showed that the survival rate among 3 β-blockers, 2 of which were lipophilic and 1 of which was hydrophilic, did not differ after acute MI when adjusted for several factors.[22] However, the results of several randomized, controlled clinical trials using a hydrophilic β-blocker have failed to show any benefit in reducing cardiovascular or all-cause mortality against placebo in hypertensive patients.[21,23] Although the findings in our study cannot be directly extrapolated to daily practice, careful consideration may be needed when selecting a medication.

Although β-blockers have recently been called into ques-

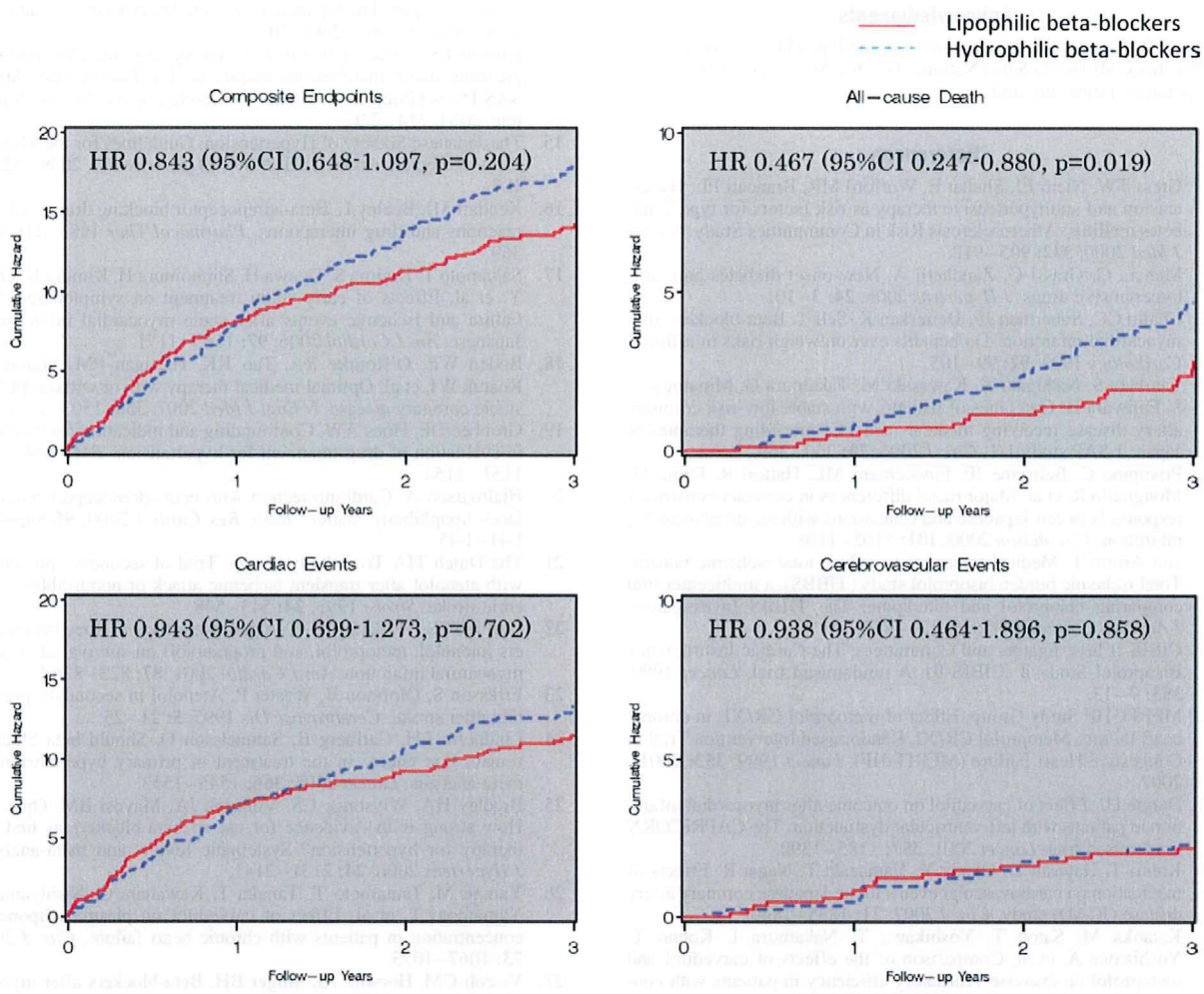

Figure 4. Patients who were taking lipophilic β-blockers were matched with those who were taking hydrophilic β-blockers based on propensity scores calculated by logistic regression. Kaplan-Meier analysis was performed on the 2 groups with various endpoints. HR, hazard ratio; CI, confidence interval.

tion as a first-line therapy for hypertension,[24,25] certain types have been shown to be effective in reducing cardiovascular risks for patients with comorbidities, such as CHF[7,8,26] or OMI.[9,27,28] We could not show that β-blockers as a class confer beneficial effects in reducing cardiovascular, cerebrovascular or all-cause mortality endpoints nor the composite of such endpoints in this study, which may be attributed to "confounding by indication". Within the β-blocker drug class, it appears that lipophilic β-blockers may be superior to hydrophilic β-blockers in reducing all-cause mortality, although a randomized controlled study is needed to confirm that result.

In conclusion, this study showed that despite the low prescription rate of β-blockers for CAD patients among Japanese physicians, the continuation rate was relatively high, which suggests that they are well tolerated. We could not show a clear benefit of β-blockers for various outcomes, which might be attributed to "confounding by indication". Better outcomes with lipophilic β-blockers compared with hydrophilic β-blockers were observed for all-cause mortality, although further investigation is needed to confirm this finding.

Adherence to guidelines that are based on rigid scientific evidence is necessary for the improvement of care, and observational studies similar to the JCAD study are warranted in the future to monitor and improve cardiovascular care.

Study Limitations

This study was an observational study and not a randomized controlled study. Although survival analysis was performed with propensity score matching, it is possible that factors that were not measured in this study were skewed between groups and affected the results. One major factor could be chronic kidney disease. No data regarding renal function was obtained in this study because, unlike the way it is viewed today, it was not regarded as a strong component of cardiovascular risk at the time the study was planned. It should also be noted that while analysis was performed on the assumption that patients were continually taking the medicines, it is possible that the prescription at the time of discharge was changed later in the follow-up period, which is suggested in the results of the continuation rate of drugs we have shown.

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Original Article

Association between Gamma-Glutamyltransferase Levels and Insulin Resistance According to Alcohol Consumption and Number of Cigarettes Smoked

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Aim: Alcohol intake may increase serum gamma-glutamyltransferase (GGT) but reduce insulin resistance. We analyzed the association between GGT and a marker of insulin resistance, homeostasis model assessment for insulin resistance (HOMA-IR), according to the drinking and smoking status.
Methods: After excluding former smokers and/or former drinkers, the data of 10,482 men who underwent general health screening were analyzed.
Results: Alcohol consumption showed a graded association with GGT. In men with current alcohol consumption of ≥40 g per day, ≥20 cigarettes per day further increased GGT levels. Alcohol consumption showed a U-shaped association with HOMA-IR. In contrast, smoking 20–39 and ≥40 cigarettes per day increased HOMA-IR as compared with never smokers. An interaction between alcohol consumption and smoking was present for GGT ($p<0.001$) and HOMA-IR ($p=0.059$). GGT was not a significant negative predictive value for HOMA-IR regardless of the drinking or smoking status.
Conclusions: Although alcohol intake showed a graded association with GGT and a U-shaped association with HOMA-IR, serum GGT can be utilized as a predictor of insulin resistance in current drinkers.

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Key words; Drinking, Cigarette smoking, Epidemiology, Insulin resistance, Liver function

Introduction

Recent epidemiological studies have shown that, besides being a biomarker of alcohol intake[1-4], elevated gamma-glutamyltransferase (GGT) may be a predictor of cardiovascular events[5], stroke[6], liver cancer[7], metabolic syndrome and type 2 diabetes[8], associations that may also be present in nondrinkers[9]. Several factors other than alcohol are known to affect serum GGT levels, including coffee consumption[10, 11] and obesity[12]. In addition, a recent study has demonstrated that cigarette smoking may also increase serum GGT levels, especially in men with moderate to heavy alcohol consumption[13]. Furthermore, alcohol consumption may improve insulin sensitivity and lower the incidence of metabolic syndrome[14-19]; therefore, drinking may increase GGT and decrease insulin resistance. On the other hand, it has been reported that serum GGT has a positive association with insulin resistance[20, 21]. To this end, we investigated the effect of drinking and smoking on GGT and HOMA-IR values, and whether the mode of association between GGT and insulin resistance was affected by drinking and smoking in Japanese men who underwent general health screening.

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Methods

Study Population

The study was approved by the Ethics Commit-

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tee of Mitsui Memorial Hospital and the Faculty of Medicine, University of Tokyo. Between January 2004 and April 2007, 33914 individuals underwent general health screening, among which information on alcohol consumption was available in 26952. Of these 26952 individuals, information on smoking behavior was further available in 24811, of which 15183 were male individuals and were enrolled in the current study. We were unable to identify any specific reasons to explain why some subjects failed to complete the questionnaire about their smoking and drinking status. Among 15183 individuals enrolled in the current study, data on hepatitis C core antigen (HCcAg) and hepatitis B surface antigen (HBsAg) were available in 14829 individuals (98%), of which 71 were positive for HCcAg and 175 were positive for HBsAg. Individuals who were positive for either type of chronic hepatitis virus infection were significantly older (56±10 years) than hepatitis-negative subjects (53±10 years), although GGT levels were not different between hepatitis-positive (52±52 IU/L) and -negative (58±84 IU/L) individuals. We did not exclude individuals who were taking antihypertensive, antidiabetic, or antidyslipidemic drugs, which might have affected insulin resistance and serum GGT levels, from the current study population.

In Japan, regular health check-ups for employees are a legal requirement; all or most of the costs of the screening are paid for either by the employee's company (about two thirds of individuals attending our institute) or by the subject themselves (about one third of individuals attending our institute). Blood pressure was measured after about 10 min of rest by an automated sphygmomanometer. Individuals were judged to be former smokers and/or former drinkers, if they had stopped cigarette smoking and/or alcohol drinking, respectively, more than one month before their attendance.

Laboratory Analysis

Blood samples were taken from the subjects after an overnight fast. Serum levels of total cholesterol (TC), HDL-cholesterol (HDL-C), and triglycerides (TG) were determined enzymatically. Serum GGT levels were measured enzymatically. Hemoglobin A1c was determined by latex agglutination immunoassay. Plasma glucose was measured by the hexokinase method and serum insulin by enzyme immunoassay. Homeostasis model assessment for insulin resistance (HOMA-IR) was calculated according to the following formula: HOMA-IR=[fasting immunoreactive insulin (μU/mL)×fasting plasma glucose (FPG; mg/dL)]/405.

Statistical Analysis

Data are expressed as the mean±SD unless stated otherwise. Analyses of variance with trend analysis, Dunnett's post-hoc analysis and multiple linear regression analysis were appropriate to assess the statistical significance of differences between groups using computer software, StatView ver. 5.0 (SAS Institute, NC) and Dr. SPSS II (SPSS Inc., Chicago, IL). A value of $p<0.05$ was significant.

Results

Baseline Characteristics

The baseline characteristics of the study subjects are described in **Table 1**. Among 15183 men, 4534 were former smokers and 416 were former drinkers. Individuals who were former smokers and/or drinkers ($n=4701$) were significantly older than the remaining 10482 individuals.

GGT and HOMA-IR According to Smoking and Drinking Status

Current smokers who smoked 1–9, 10–19, and 20–39 cigarettes per day were significantly younger than never smokers (**Fig. 1A**). The daily amount of alcohol consumption showed a negative graded association with age. The number of cigarettes smoked showed a positive graded association with GGT (**Fig. 1B**) and, as compared with never smokers, individuals who currently smoked 1–9, 10–19, 20–39, and ≥40 cigarettes per day had significantly higher GGT levels (by Dunnett's post-hoc analysis). Similarly, the daily amount of alcohol consumption showed a graded association with GGT, and individuals who drank 1–19, 20–39, 40–59, and ≥60 g per day had significantly higher GGT levels than never drinkers (by Dunnett's post-hoc analysis). Individuals who smoked 20–39 and ≥40 cigarettes per day had significantly higher HOMA-IR than never-smokers (**Fig. 1C**). On the other hand, as compared with never drinkers, individuals who drank 1–19, 20–39, and 40–59 g alcohol per day had significantly lower HOMA-IR levels (by Dunnett's post-hoc analysis), demonstrating a U-shaped association.

GGT and HOMA-IR According to Cross Strata of Number of Cigarettes Smoked and Alcohol Consumption

In the following analysis, we analyzed the data from 10482 individuals after excluding former smokers and/or former drinkers. The mean GGT levels and HOMA-IR values according to the smoking and drinking category are shown in **Table 2**. Current

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Table 1. Baseline characteristics

Variables	Whole	Former smokers and/or drinkers [A]	Except former smokers and drinkers [B]	*p* value ([A] vs. [B])
N	15,183	4,701	10,482	
Age, years	52.9 ± 10.4	55.6 ± 9.9	51.7 ± 10.4	<0.001
Height, cm	169.6 ± 6.0	169.1 ± 5.9	169.7 ± 6.0	<0.001
Weight, kg	68.3 ± 9.5	68.5 ± 8.9	68.2 ± 9.7	0.117
Body mass index, kg/m^2	23.7 ± 2.8	23.9 ± 2.7	23.6 ± 2.9	<0.001
Systolic blood pressure, mmHg	124.7 ± 18.6	127.6 ± 18.5	123.3 ± 18.4	<0.001
Diastolic blood pressure, mmHg	79.0 ± 11.3	81.0 ± 11.0	78.2 ± 11.3	<0.001
Heart rate, bpm	63.3 ± 9.5	63.4 ± 9.6	63.2 ± 9.5	0.373
LDL-cholesterol, mg/dL	126.7 ± 30.5	127.3 ± 30.0	126.5 ± 30.8	0.112
HDL-cholesterol, mg/dL	55.3 ± 13.4	56.9 ± 13.4	54.6 ± 13.3	<0.001
Triglycerides, mg/dL	133.7 ± 94.2	129.8 ± 83.9	135.5 ± 98.4	0.001
AST, IU/L	23.8 ± 12.1	24.0 ± 10.5	23.7 ± 12.7	0.208
ALT, IU/L	27.3 ± 19.4	26.5 ± 18.8	27.6 ± 19.6	0.001
GGT, IU/L	58.2 ± 82.9	58.3 ± 67.0	58.1 ± 89.1	0.926
Fasting glucose, mg/dL	100.3 ± 20.5	101.7 ± 20.8	99.7 ± 20.4	<0.001
Hemoglobin A1c, %	5.38 ± 0.74	5.41 ± 0.72	5.36 ± 0.75	<0.001
HOMA-IR	1.69 ± 1.52	1.74 ± 1.31	1.67 ± 1.60	0.007
Antihypertensive medication, N (%)	1,909 (12.6)	831 (17.7)	1,078 (10.3)	<0.001
Antidiabetic medication, N (%)	474 (3.1)	169 (3.6)	305 (2.9)	0.026
Antidyslipidemic medication, N (%)	674 (4.4)	276 (5.9)	398 (3.8)	<0.001
Smoking and drinking status				
Never smoker				
Never drinker, N (%)	791 (14.1)	0 (0)	791 (14.3)	
Former drinker, N (%)	90 (1.6)	90 (100)	0 (0)	
Current drinker, N (%)	4,744 (84.3)	0 (0)	4,744 (85.7)	
Former smoker				
Never drinker, N (%)	263 (1.7)	263 (1.7)	0 (0)	
Former drinker, N (%)	249 (1.6)	249 (1.6)	0 (0)	
Current drinker, N (%)	4,022 (26.5)	4,022 (26.5)	0 (0)	
Current smoker				
Never drinker, N (%)	416 (8.3)	0 (0)	416 (8.4)	
Former drinker, N (%)	77 (1.5)	77 (100)	0 (0)	
Current drinker, N (%)	4,531 (90.2)	0 (0)	4,531 (91.6)	

BMI, body mass index; LDL, low density lipoprotein; HDL, high density lipoprotein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma-glutamyl transpeptidase; HOMA-IR, homeostasis model assessment for insulin resistance

drinking showed a graded association with GGT regardless of the smoking status. Cigarette smoking was also positively associated with GGT in some drinking categories: smoking 10–19 ($p<0.01$), 20–39 ($p<0.001$) and ≥40 ($p<0.001$) cigarettes per day was associated with greater GGT values than never smoking in individuals who drank 40–59 g/day, and smoking 20–39 ($p<0.001$) and ≥40 ($p<0.001$) cigarettes per day was associated with greater GGT values than never smoking in individuals who drank ≥60 g/day.

Individuals with alcohol consumption of 1–19, 20–39, or 40–59 g/day had lower HOMA-IR value than never drinkers, showing a U-shaped association between current drinking and HOMA-IR. This U-shaped relationship was absent or not significant in current smoking of 20–39 or ≥40 cigarettes per day (**Table 2**). Individuals who smoked 20–39 ($p<0.001$) and ≥40 ($p<0.001$) cigarettes per day had higher HOMA-IR than never smokers (**Table 2**).

Multiple Linear Regression Analysis

Next, multiple linear regression analysis using GGT and HOMA-IR as a dependent variable and age, BMI, amount of smoking, and alcohol consump-

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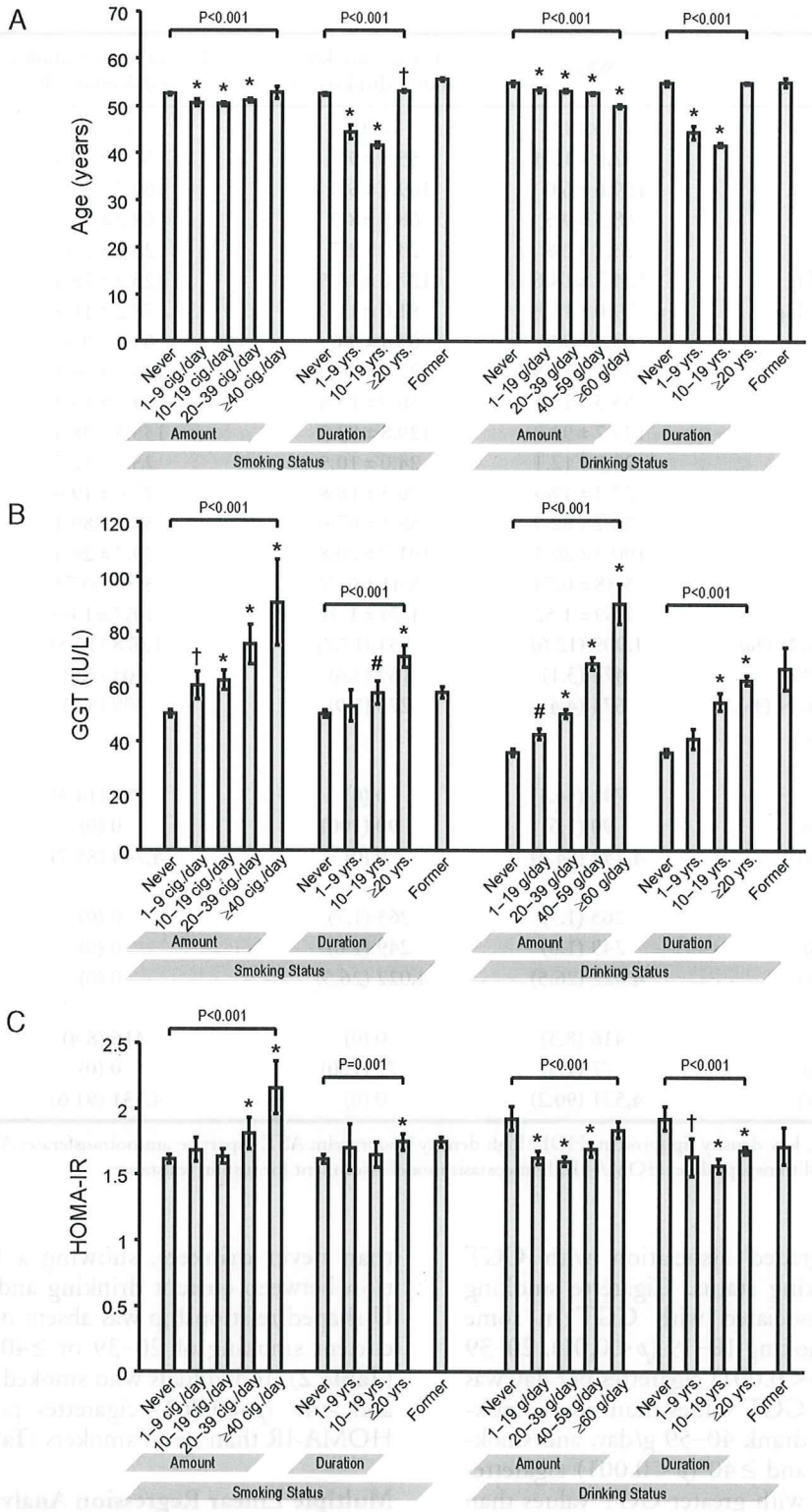

Fig. 1. Age, GGT, and HOMA-IR according to smoking and drinking status.

Bar graphs indicate the mean and 95% CI of age (A), GGT (B), and HOMA-IR. *P* values are for ANOVA trend tests. #, †, and * indicate $p<0.05$, $p<0.01$, and $p<0.001$, respectively, versus never smokers or never drinkers by Dunnett's post-hoc analysis.

Table 2. GGT and HOMA-IR according to smoking and drinking status

Smoking category (cig./day)	Drinking category																				
	#Overall				0 g/day (never drinker)				1-19 g/day				20-39 g/day				40-59 g/day				≥60g/day				†p value
	N	GGT			N	GGT			N	GGT			N	GGT			N	GGT			N	GGT			
		Mean	95%CI			Mean	95%CI			Mean	95%CI			Mean	95%CI			Mean	95%CI			Mean	95%CI		
§Overall	10,482	58.1	56.4	59.8	1,207	35.5	33.9	37.2	1,872	41.7	39.8	43.6	3,062	50.1	48.0	52.1	2,957	68.7	65.9	71.6	1,384	95.2	85.4	104.9	<0.001
									*p=	0.156			*p<	0.001			*p<	0.001			*p<	0.001			
0 (never smoker)	5,535	49.5	48.2	50.9	791	35.6	33.4	37.8	1,222	43.2	40.6	45.8	1,812	47.2	45.3	49.1	1,258	60.7	57.3	64.2	452	69.3	62.0	76.6	<0.001
									*p=	0.004			*p<	0.001			*p<	0.001			*p<	0.001			
1-9	771	59.8	54.7	64.9	48	44.0	32.4	55.6	147	39.0	33.8	44.1	207	51.1	45.4	56.8	253	69.5	57.8	81.2	116	87.1	70.3	103.9	<0.001
									*p=	0.950			*p=	0.845			*p=	0.055			*p=	0.001			
10-19	2,201	61.9	58.3	65.5	196	32.9	30.0	35.7	322	39.0	35.3	42.7	616	55.4	47.7	63.2	758	72.9	66.3	79.6	309	89.9	79.9	100.0	<0.001
									*p=	0.764			*p=	0.003			*p<	0.001			*p<	0.001			
20-39	1,748	75.6	68.1	83.0	151	35.4	32.1	38.7	158	37.0	33.1	40.9	399	55.1	50.3	59.8	623	77.0	71.4	82.6	417	122.1	93.0	151.3	<0.001
									*p=	1.000			*p=	0.413			*p=	0.010			*p<	0.001			
≥40	227	91.1	75.3	107.0	21	39.0	27.0	51.0	23	47.4	36.5	58.4	28	40.9	32.1	49.8	65	93.4	62.1	124.7	90	128.5	97.3	159.6	<0.001
									*p=	0.996			*p=	1.000			*p=	0.171			*p=	0.006			

Smoking category (cig./day)	Drinking category																								†p value
	#Overall				0 g/day (never drinker)				1-19 g/day				20-39 g/day				40-59 g/day				≥60g/day				
	N	HOMA-IR			N	HOMA-IR			N	HOMA-IR			N	HOMA-IR			N	HOMA-IR			N	HOMA-IR			
		Mean	95%CI			Mean	95%CI			Mean	95%CI			Mean	95%CI			Mean	95%CI			Mean	95%CI		
§Overall	10,482	1.67	1.64	1.70	1,207	1.89	1.79	1.99	1,872	1.57	1.51	1.63	3,062	1.5	1.51	1.59	2,957	1.7	1.62	1.77	1,384	1.8	1.78	1.92	<0.001
									*p<	0.001			*p<	0.001			*p=	0.001			*p=	0.878			
0 (never smoker)	5,535	1.62	1.58	1.65	791	1.83	1.70	1.96	1,222	1.58	1.50	1.66	1,812	1.54	1.49	1.59	1,258	1.57	1.51	1.64	452	1.80	1.67	1.94	<0.001
									*p<	0.001			*p<	0.001			*p<	0.001			*p=	0.995			
1-9	771	1.67	1.58	1.77	48	2.20	1.52	2.89	147	1.50	1.31	1.69	207	1.54	1.41	1.67	253	1.68	1.53	1.84	116	1.90	1.64	2.15	0.002
									*p=	0.003			*p=	0.004			*p=	0.026			*p=	0.338			
10-19	2,201	1.64	1.58	1.69	196	1.96	1.77	2.16	322	1.52	1.38	1.66	616	1.43	1.34	1.51	758	1.70	1.60	1.80	309	1.80	1.65	1.96	<0.001
									*p<	0.001			*p<	0.001			*p=	0.030			*p=	0.385			
20-39	1,748	1.82	1.70	1.94	151	2.03	1.74	2.32	158	1.49	1.31	1.66	399	1.74	1.61	1.87	623	1.92	1.62	2.22	417	1.80	1.68	1.92	0.274
≥40	227	2.17	1.97	2.37	21	1.91	1.29	2.52	23	2.71	1.98	3.45	28	1.96	1.46	2.46	65	1.84	1.52	2.16	90	2.39	2.02	2.76	0.068

†*p* values were for ANOVA trend tests. **p* values are versus never drinkers by Dunnett's post-hoc analysis. #Overall indicates all never or current drinkers, and §Overall indicates all never or current smokers. GGT, gamma-glutamyl transpeptidase; HOMA-IR, homeostasis model assessment for insulin resistance.

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Table 3. Linear regression analysis using GGT and HOMA-IR as dependent variable

	β	95%CI		Standardized β	p value
Dependent variable: GGT					
Age	−0.57	−1.82	0.68	−0.01	0.372
BMI	2.25	1.79	2.71	0.08	<0.001
Smoking	3.18	2.17	4.19	0.05	<0.001
Alcohol consumption	12.34	11.19	13.49	0.17	<0.001
Dependent variable: HOMA-IR					
Age	0.04	0.01	0.06	0.02	0.001
BMI	0.23	0.22	0.24	0.43	<0.001
Smoking	0.04	0.03	0.06	0.04	<0.001
Alcohol consumption	−0.08	−0.10	−0.06	−0.06	<0.001

For the calculation of β values, age was subdivided into 10-year increments. Alcohol consumption (g/day) corresponding to 0 (never drinker), 1–19, 20–39, 40–59, and ≥60 was coded as 0, 1, 2, 3, and 4, respectively, and smoking (cigarettes/day) corresponding to 1–9, 10–19, 20–39, and ≥40 was coded as 0, 1, 2, 3, and 4, respectively. GGT, gamma-glutamyl transpeptidase; HOMA-IR, homeostasis model assessment for insulin resistance.

tion as independent variables was performed in 10482 individuals (**Table 3**). In this model, alcohol consumption (g/day) corresponding to 0 (never drinker); 1–19, 20–39, 40–59, and 60 or more was coded as 0, 1, 2, 3, and 4, respectively, and smoking (cigarettes/day) corresponding to 1–9, 10–19, 20–39, and 40 or more were defined as 0, 1, 2, 3, and 4, respectively. Alcohol consumption was associated positively with GGT, but negatively with HOMA-IR. On the other hand, smoking was found to be associated positively with both GGT and HOMA-IR. When an interaction term between alcohol consumption and smoking was used as additional independent variable, the interaction term was found to be significantly associated with GGT ($p<0.001$), and showed a borderline significant association with HOMA-IR ($p=0.059$). The variance inflation factor (VIF) scores of all independent variables tested were less than 10 (data not shown).

Association between GGT and HOMA-IR According to Alcohol Consumption

Next, we investigated whether the mode of association between GGT and HOMA-IR differs according to the amount of alcohol consumption. For this purpose, multiple regression analysis was performed in which age, BMI, and GGT were used as independent variables and HOMA-IR was used as a dependent variable after subdividing individuals according to alcohol consumption (**Table 4**). GGT was found be a positive predictive value for HOMA-IR in 19 out of the 25 drinking × smoking categories. In some combinations of drinking and smoking, such as drinking 0 g/day and smoking 1–9 cig./day, GGT was not a statistically significant predictor of HOMA-IR. This may be in part because the number of subjects with specific drinking and smoking conditions was relatively small.

Discussion

In the current study, by analyzing the data of men who underwent general health screening, except former smokers and/or former drinkers, we observed several points: (1) Alcohol consumption showed a graded association with GGT; (2) In individuals who drank 40 g or more per day, smoking 20 cigarettes or more per day further increased GGT levels (**Table 2**); (3) alcohol consumption showed a U-shaped association with HOMA-IR, when the daily number of cigarettes smoked was less than 20 per day; (4) Individuals who smoked 20–39 and ≥40 cigarette per day had higher HOMA-IR than never smokers (**Table 2**); (5) GGT was found be a positive predictive value of HOMA-IR in 19 out of the 25 drinking × smoking categories, and GGT was not a significant negative predictor of HOMA-IR regardless of the drinking or smoking status. These data collectively indicate that, although current drinking may increase GGT and reduce insulin resistance, GGT can be utilized as a marker of insulin resistance regardless of the drinking status.

Many studies have shown that serum GGT is a biomarker of increased alcohol consumption[1-4, 22]; however, GGT is known to be affected by other con-