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Losartan Reduces the Onset of Type 2 Diabetes in Hypertensive Japanese Patients With Chronic Hepatitis C

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The aim of this retrospective cohort study is to assess the cumulative development incidence and predictive factors for type 2 diabetes (T2DM) in HCV positive and hypertensive patients treated with losartan. Eighty Japanese patients were given 50 mg of losartan per day after diagnosis of hypertension (losartan group). Another 160 treated with spironolactone were selected as control (spironolactone group). Patients in spironolactone group were matched 1:2 with losartan group for age and sex. The mean observation period was 5.2 years in losartan group and 5.4 years in spironolactone group. An overnight (12 hr) fasting blood sample or a casual blood sample was taken for routine analyses during follow-up. The primary goal is the onset of T2DM. Evaluation was performed by using the Kaplan–Meier method and the cox proportional hazards analysis. Three patients in losartan group and 20 in spironolactone group developed T2DM. The 5th year cumulative appearance rates of T2DM were 5.4% in losartan group and 14.4% in spironolactone group. Multivariate cox proportional hazards analysis showed that T2DM development after the initiation of anti-hypertensive drugs occurred when anti-hypertensive drug was spironolactone (hazard ratio: 6.10; 95% confidence interval = 1.78–20.84; $P = 0.004$), histological staging was advanced (hazard ratio: 4.31; 95% confidence interval = 1.94–9.60; $P < 0.001$), fatty liver was present (hazard ratio: 3.28; 95% confidence interval = 1.47–7.27; $P = 0.004$), and patient had pre-diabetes (hazard ratio: 2.47; 95% confidence interval = 1.08–5.63; $P = 0.032$). Our results indicate losartan causes about 60% reduction of the onset of T2DM compared to patients treated with spironolactone. ***J. Med. Virol. 81:1584–1590, 2009.***

KEY WORDS: hepatitis C virus; hypertension; losartan; type 2 diabetes mellitus; a retrospective cohort study

INTRODUCTION

Hepatitis C virus (HCV) is one of the more common causes of chronic liver disease in world. Chronic hepatitis C is an insidiously progressive form of liver disease that relentlessly but silently progresses to cirrhosis and/or hepatocellular carcinoma (HCC) over a period of 10–30 years [Kiyosawa and Furuta, 1991; Alter et al., 1992; Ikeda et al., 1993; Tsukuma et al., 1993]. Additionally, data supporting a link between Type 2 diabetes mellitus (T2DM) and chronic hepatitis C

Abbreviations used: ALT, alanine aminotransferase; normal range = 11–36; AST, aspartate aminotransferase; normal range = 6–34; CI, confidence interval; FPG, fasting plasma glucose; HCV, hepatitis C virus; HR, hazard ratio.

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infection have been reported [Arao et al., 2003; Mehta et al., 2003; Romero-Gómez et al., 2008; Imazeki et al., 2008; Arase et al., 2009]. Recently, hypertension increased in chronic liver disease with increase of elderly patients in Japan. Administration of losartan has been proven to be useful for the treatment of hypertension [Dahlöf et al., 2002; Lindholm et al., 2002]. Some previous studies have presented conflicting results with some suggesting that angiotensin receptor antagonist improves insulin sensitivity and exert beneficial effects on glucose and lipid metabolism [Iimura et al., 1995; Yusuf et al., 2000; Ando and Fujita, 2006]. Whereas others found that losartan did not influence insulin sensitivity [Fogari et al., 1998]. These discrepancies might depend on factors such as race, age, stage of hypertension, structural vascular changes in precapillary arteries. However, in any case, there is little information on the yearly cumulative incidence and risk factors on the development rate of T2DM in hypertensive patients with type C chronic liver disease during the prolonged follow-up.

In Toranomon Hospital (Tokyo, Japan), the authors evaluate a large number of patients with HCV-related hepatitis, and often find hypertension and T2DM. With this background in mind, the cohort study was initiated to investigate the cumulative incidence and risk factors of T2DM after prolonged follow up in HCV-infected and hypertensive patients treated with antihypertensive drugs. The strength of the current study is the long-term follow-up of patients.

METHODS

Patients

The number of patients who were diagnosed with chronic HCV infection between April 1998 and March 2007 in the Department of Hepatology, Toranomon Hospital, Tokyo, Japan was 5,400. Out of these, 890 were given antihypertensive therapy after confirmation of blood pressure $\geq$140 mm Hg systolic and/or $\geq$90 mm Hg diastolic on at least 3 visits and absence of secondary causes of hypertension, previous cardiovascular disease and stroke, and life threatening conditions. Blood pressure was measured by a physician with a mercury sphygmomanometer, with subjects sitting and relaxed for at least 10 min. Inclusion criteria were as follows: (1) antihypertensive therapy by losartan; (2) 45–75 years old; (3) no evidence of diabetes mellitus for 3 months before the initiation of anti-hypertensive therapy: a plasma glucose concentration of $<$126 mg per deciliter (6.9 mmol/L) in the fasting state, $<$200 mg per deciliter (11.0 mmol/L) in casual state and/or 2 hr after a 75-g oral glucose load; (4) features of chronic hepatitis or cirrhosis diagnosed by clinical features, laboratory tests, ultrasonographic findings, or histological findings; (5) positive for anti-HCV and HCV-RNA; (6) negative for hepatitis B surface antigens (HBsAg), antinuclear antibodies, or antimitochondrial antibodies in serum, as determined by radioimmunoassay or spot hybridization; (7) no evidence of HCC nodules as shown by ultrasonography and/or computed tomography; (8) no underlying systemic disease, such as systemic lupus erythmatosus, rheumatic arthritis. Patients with either of the following criteria were excluded from the study: (1) they were taking medicines known to alter glucose tolerance, (2) decompensated stage of cirrhosis with encephalopathy, icterus, or refractory ascites (3) they had illnesses that could seriously reduce their life expectancy or their ability to participate in the trial. Eighty patients were selected as losartan group. Patients were classified as having normal glucose group or pre-diabetes group base to the fasting plasma glucose (FPG), casual plasma glucose, or 2-hr plasma glucose: (1) normal glucose group was regarded as having FPG of $<$100 mg/dl, casual plasma glucose of $<$140 mg/dl, and/or 2-hr plasma glucose of $<$140 mg/dl, (2) pre-diabetes group was regarded as having FPG of 100–125 mg/dl, casual plasma glucose of 140–200 mg/dl, and/or 2-hr plasma glucose of 140–200 mg/dl [Genuth et al., 2003] The patients in the losartan-group received 50 mg of losartan orally once a day.

In the same period, 382 hypertensive patients with HCV positive chronic liver disease were treated with spironolactone. The 321 patients were applied with seven inclusion criteria and three exclusion criteria described in losartan group. One hundred sixty subjects in spironolactone group were selected from these 321 patients by matching 1:2 with losartan group for age and sex. Thus, differences of the cumulative appearance rate of T2DM in the losartan group and spironolactone group were compared. The patients in spironolactone group were treated with spironolactone at a dose of 25 or 50 mg once daily. Next, predictive factors for T2DM in both groups were assessed. The physicians in charge explained the purpose and method of antihypertensive treatment to each patient and/or patients' family, who gave their informed consent for the treatment. All of the studies were performed retrospectively by collecting and analyzing data from the patient records. This study had been approved by Institutional Review Board of Toranomon hospital.

Outcome Measures

The primary outcome was T2DM, diagnosed by the use of the 2003 criteria of the American Diabetes Association [Genuth et al., 2003]. That is, the criteria for the diagnosis of diabetes mellitus include: (a) casual plasma glucose $\geq$200 mg/dl; (b) FPG $\geq$126 mg/dl; (c) 2 hr post-glucose (oral glucose tolerance test) $\geq$200 mg/dl. At the same time, clinical records of cardiovascular events (angina pectoris, heart infarction) and stroke (cerebral infarction, cerebral bleeding) were examined.

Laboratory Inveastigation

Anti-HCV was detected using a second-generation enzyme-linked immunosorbent assay (ELISA II) (Abbott Laboratories, North Chicago, IL). HCV-RNA was determined by the Amplicor method (Cobas Amplicor HCV Monitor Test, v2.0, Roche, Tokyo, Japan). HBsAg was

tested by radioimmunoassay (Abbott Laboratories, Detroit, MI). The used serum samples were stored −80°C at the first consultation. Diagnosis of HCV infection was based on detection of serum HCV antibody and positive RNA. Height and weight were recorded at baseline and the body mass index (BMI) was calculated as weight (in kg)/height (in m^2)

Evaluation of Liver Cirrhosis and Fatty Liver

Status of liver cirrhosis was mainly determined on the basis of peritoneoscopy and/or liver biopsy. The 183 out of 260 were diagnosed by peritoneoscopy and/or liver biopsy. Liver biopsy specimens were obtained using a modified Vim Silverman needle with an internal diameter of 2 mm (Tohoku University style, Kakinuma Factory, Tokyo, Japan), fixed in 10% formalin, and stained with hematoxylin-eosin, Masson's trichrome, silver impregnation, and periodic acid-Schiff after diastase digestion. The size of specimens for examination was more than six portal areas. Baseline liver histology of chronic hepatitis was classified according to the extent of fibrosis, into four stages in progression order: stage 1, periportal expansion; stage 2, portoportal septa; stage 3, portocentral linkage or bridging fibrosis; stage 4, liver cirrhosis [Desmet et al., 1994]. Remaining patients were diagnosed by clinical features, laboratory tests, and ultrasonographic findings.

Diagnosis of fatty liver was based on the presence of an ultrasonographic pattern consistent with bright liver (brightness and posterior attenuation) with stronger echoes in the hepatic parenchyma than in the renal or spleen parenchyma, vessel blurring, and narrowing of the lumen of the hepatic veins. US was performed with a high-resolution, real-time scanner (model SSD-2000; Aloka Co., Ltd, Tokyo Japan. Mode Logic-700 MR; GE-Yokokawa Medical Systems, Tokyo, Japan).

Follow-Up

The starting time of follow-up was the initiation of antihypertensive therapy. After that, patients were followed up monthly to tri-monthly in our hospital. Physical examination and biochemical tests were conducted at each examination together with regular check up. An overnight (12 hr) fasting blood sample or a casual blood sample was taken for routine analyses. These included transaminase activities, total cholesterol, platelet counts, and serum HCV RNA level. Twenty-one patients were lost to follow-up. Because the appearance of T2DM and death was not identified in these 21 patients, they considered as censored data in statistical analysis [Fleming et al., 1984]. Patients treated with antiviral agents were regarded as withdrawals at the time of starting the treatment of antiviral agents. Moreover, patients with change or addition of hypertensive drugs were regarded as withdrawals at the time of change or addition of hypertensive drugs. Finally, patients with decompensated stage of cirrhosis with encephalopathy, icterus, or refractory ascites were regarded as withdrawals.

Statistical Analysis

The cumulative appearance rate of T2DM was calculated from the initiation of hypertensive drugs using the Kaplan–Meier method. Differences in the development of T2DM were tested using the log rank test. Independent factors associated with the incidence rate of T2DM were analyzed by the Cox proportional hazard model. The following eleven variables were analyzed for potential covariates for incidence of T2DM after the time of initiation of hypertensive drugs at our hospital: age, sex, hepatic staging (chronic hepatitis or liver cirrhosis), BMI, glucose level, aspartate aminotransferase (AST), alanine aminotransferase (ALT) level, triglyceride level, total cholesterol level, and treatment. A P-value of <0.05 was considered significant. Data analysis was performed using the computer program SPSS package (SPSS 11.5 for Windows, SPSS, Chicago, IL).

RESULTS

Patients' Characteristics

Table I shows the characteristics of the 240 HCV positive and hypertensive patients enrolled in the present study. There were no significant differences in clinical profiles between the losartan and spironolactone group. The mean observation period was 5.2 years in losartan group and 5.4 years in spironolactone group. On side effects, two patients treated with losartan had episodes of dizziness. In spironolactone group, four patients had gynecomastia and two patients had dizziness. However, they could continue without stopping the antihypertensive therapy using losartan or spironolactone.

Incidence of T2DM in Hypertensive Patients With HCV

A total of 25 subjects (15 men and 10 women) developed T2DM during the observation period. Three patients in losartan group and 22 in spironolactone group developed T2DM. The 5th year cumulative appearance rates of T2DM were 5.9% in losartan group and 14.0% in spironolactone group (Fig. 1). Multivariate cox proportional hazards analysis showed that development of T2DM when anti-hypertensive drug was spironolactone (hazard ratio: 6.10; 95% confidence interval = 1.78–20.84; $P = 0.004$), histological staging was advanced (hazard ratio: 4.31; 95% confidence interval = 1.94–9.60; $P < 0.001$), fatty liver was present (hazard ratio: 3.28; 95% confidence interval = 1.47–7.27; $P = 0.004$), and patient had pre-diabetes (hazard ratio: 2.47; 95% confidence interval = 1.08–5.63; $P = 0.032$) (Table II). Our results indicate losartan causes about 60% reduction of the risk of T2DM development compared to spironolactone.

Figure 2 shows the impact of reduction due to administration of losartan on the incidence of T2DM in patients with liver cirrhosis, or pre-diabetes, or fatty liver. When patients with liver cirrhosis are treated with

TABLE I. Clinical Characteristics at the Time of Initiation of Anti-Hypertensive Drug

	Total	Losartan group	Spironolactone group	*P*-value
N	240	80	160	
Age (years)	65.2 ± 8.2	65.2 ± 8.0	65.2 ± 8.2	1.0
Sex (male/female)	120/120	40/40	80/80	1.0
Blood pressure				
Systolic (mm Hg)	161.8 ± 13.0	163.0 ± 14.1	160.9 ± 12.3	0.366
Diastolic (mm Hg)	94.3 ± 7.4	95.1 ± 8.2	93.9 ± 6.9	0.596
Staging (chronic hepatitis/liver cirrhosis)	194/46	64/16	130/30	0.863
F1/F2/F3/F4[a]	51/79/22/40	14/31/7/14	37/48/15/24	0.251
Fatty liver (+/−)[b]	48/192	14/66	34/126	0.608
BMI	23.7 ± 4.5	23.2 ± 3.5	23.9 ± 5.2	0.250
AST (IU/L)	77.5 ± 60.3	73.7 ± 49.2	78.8 ± 63.2	0.297
ALT (IU/L)	108.6 ± 99.8	108.8 ± 101.0	106.7 ± 94.2	0.604
Albumin (g/dl)	4.2 ± 0.4	4.2 ± 0.4	4.2 ± 0.5	0.717
γ-GTP (IU/L)	59.3 ± 58.5	58.2 ± 59.3	59.6 ± 60.8	0.862
Platelet count ($\times 10^4/mm^3$)	16.9 ± 5.6	15.8 ± 6.3	17.2 ± 5.4	0.089
Glucose level (prediabetes/normal)	42/198	15/65	27/133	0.722
T cholesterol (mg/dl)	172.8 ± 33.4	176.2 ± 53.5	172.5 ± 32.5	0.965
Triglyceride (mg/dl)	104.5 ± 47.1	97.0 ± 28.9	105.2 ± 48.9	0.063

Data are number of patients or mean ± standard deviation, ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; γ-GTP, γ-glutamyl transpeptidase.
[a]Histological diagnosis of the liver.
[b]Diagnosis of fatty liver by the ultrasonography.

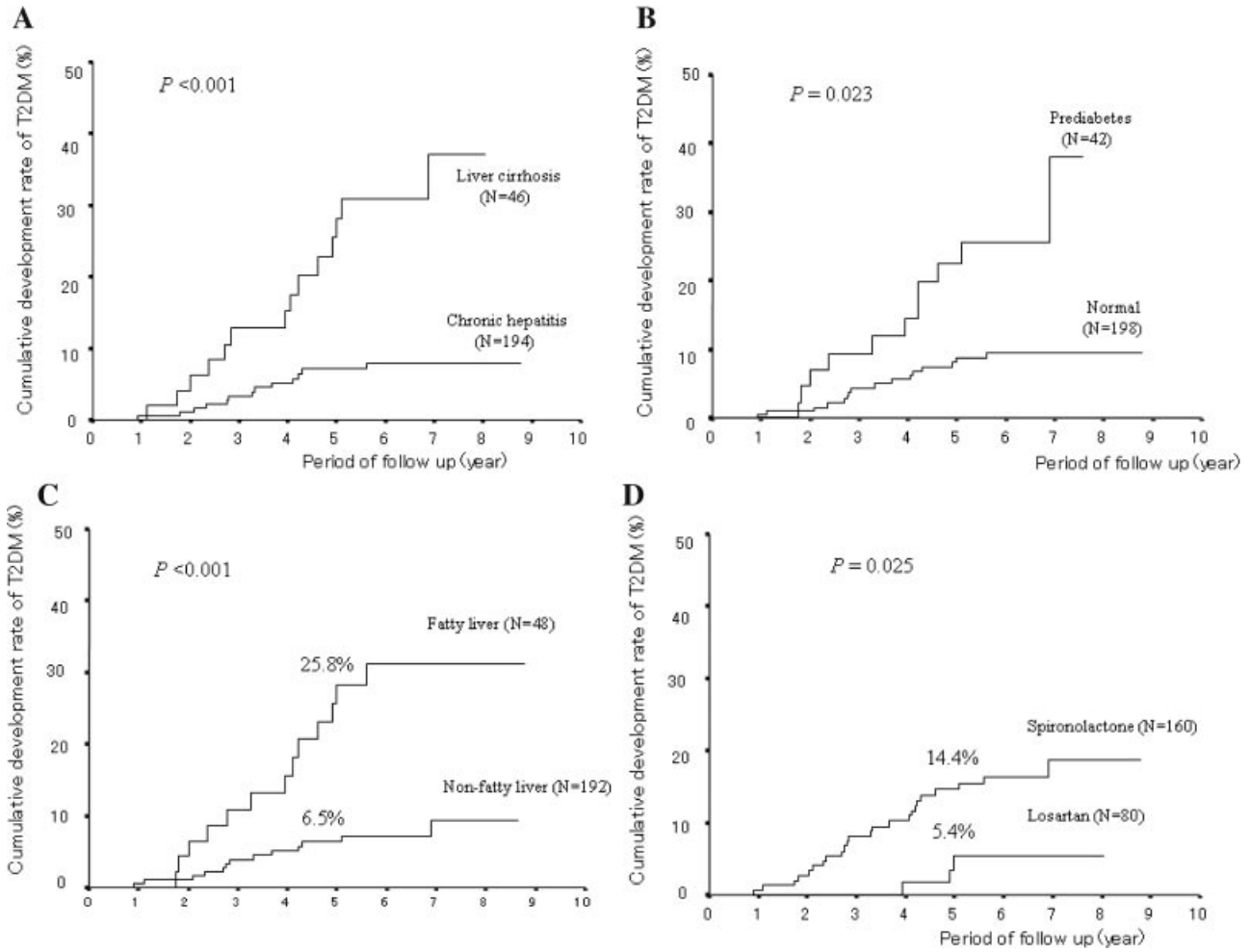

Fig. 1. Cumulative development rate of T2DM in patients treated with interferon. **Panel A**: Cumulative development rate of T2DM based on difference of hepatic fibrosis; (**Panel B**), cumulative development rate of T2DM based on the difference of glucose level; (**Panel C**), cumulative development rate of T2DM based on the difference of fatty liver; (**Panel D**), cumulative development rate of T2DM based on the difference of anti-hypertensive drugs.

TABLE II. Predictive Factors for T2DM Development

Variables	N	Univariate analysis		Cox-regression	
		HR (95% CI)	*P*	HR (95% CI)	*P*
Age (years, ≥65/<65)	121/119	2.28 (1.02–5.07)	0.044		
Sex (female/male)	120/120	0.60 (0.28–1.28)	0.184		
BMI (≥25/<25)	60/180	2.42 (1.091–5.33)	0.028		
Maximum BMI (≥25/<25)	55/141	1.76 (0.76–4.06)	0.190		
Fatty liver (+/−)	48/192	4.35 (2.01–5.07)	<0.001	3.28 (1.47–7.27)	0.004
Genotype (1/2)	162/45	0.91 (0.39–2.88)	0.905		
ALT (IU/L, ≥50/<50)	151/89	1.14 (0.38–3.42)	0.822		
Glucose level (prediabetes/normal)	42/198	2.93 (1.33–6.48)	0.022	2.47 (1.08–5.63)	0.032
Triglyceride (mg/dl, ≥150/<150)	34/135	1.85 (0.83–5.98)	0.095		
Cholesterol (mg/dl, <220/≥220)	172/40	0.54 (0.06–5.16)	0.590		
Staging (liver cirrhosis/chronic hepatitis)	46/194	4.25 (1.97–9.18)	0.023	4.31 (1.94–9.60)	<0.001
AST (IU/L, ≥38/<38)	168/72	0.96 (0.32–2.881)	0.942		
Treatment (spironolactone/losartan)	160/80	3.94 (1.19–13.15)	0.025	6.10 (1.78–20.84)	0.004

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; HCV, hepatitis C virus; HR, hazards ratio.

losartan, losartan could statistically reduce the onset of T2DM compared to those with spironolactone.

Incidence of Cardio Vascular Disease or Stroke in Patients With HCV

A total of eight subjects (five men and three women) developed vascular events during the observation period. In losartan group, two patients developed stroke. In spironolactone group, three patients developed cardiovascular disease and another three patients developed stroke.

Figure 3 shows the impact of reduction due to difference of antihypertensive drugs on the incidence of cardiovascular disease or stroke in two groups. There was little difference on losartan group and spironolactone group.

DISCUSSION

We have described the development incidence of T2DM after the initiation of antihypertensive therapy in HCV positive patients treated with antihypertensive drugs in the present study. The present study was limited by a retrospective cohort trial. About the sample size in losartan and spironolactone group, the number of the patients enrolled in the present study was sufficient to detect hazards ratios of about threefold with 80% power at the 5% level of significance. The strength of the present study is a long-term follow-up in the patients included.

The present study shows several findings with regard to development of T2DM after the initiation of losartan or spironolactone for HCV positive and hypertensive patients. First, the T2DM development rate in losartan group was lower than that in spironolactone group. The administration of losartan caused about 60% reduction in the onset of T2DM in the course of follow-up. What losartan enhances the insulin sensitivity has been reported by some authors [Iimura et al., 1995; Ando and Fujita, 2006; Alderman, 2008]. However, protection of T2DM development by losartan in the present study was effective compared to that based on Dahlöf's report [Dahlöf et al., 2002]. This discrepancy is thought to be due to difference of race and HCV infection. Our previous study shows that clearance of HCV causes a two-thirds reduction of the onset of T2DM in hepatitis C virus positive patients treated with interferon [Arase et al., 2009]. This means that patients with HCV have a high tendency of the onset of T2DM. Moreover, although the prevalence of T2DM is increasing dramatically in USA, increases in newly developed and developing countries in Asia have been ever greater [Yoon et al., 2007]. Thus, Asian patients with HCV are thought to have high risk of T2DM. Anti-diabetic effect of losartan may also enhance in patients with high risk of T2DM.

Though the role of losartan in preventing development of DM remains speculative, the following possible mechanism have been reported, (1) losartan elevates the serum level of adiponectin that improves insulin sensitivity [Clasen et al., 2005]; (2) losartan enhance the insulin-like growth factor (IGF)-1 that plays a protective role in the development of glucose intolerance [Zandbergen et al., 2006].

Second, in addition to administration of spironolactone, the present study suggests that aging, progression of hepatic staging, pre-diabetes enhanced the onset of T2DM in HCV patients treated with anthypertensive drugs.

The present study indicates that losartan reduce the onset of T2DM in Japanese patients with HCV. Our retrospective study suggests that the annual incidence of T2DM among patients with HCV was determined to be 1.0–1.1% in losartan group and 2.8–3.0% in spironolactone group. Moreover, several lines of evidence have shown that angiotensin receptor antagonist can have a beneficial role in the early stages of hepatic fibrosis of patients with hepatitis C [Terui et al., 2002]. Thus, when physicians regarding the daily management of patients with virus hepatitis give antihypertensive therapy for HCV patients, they should

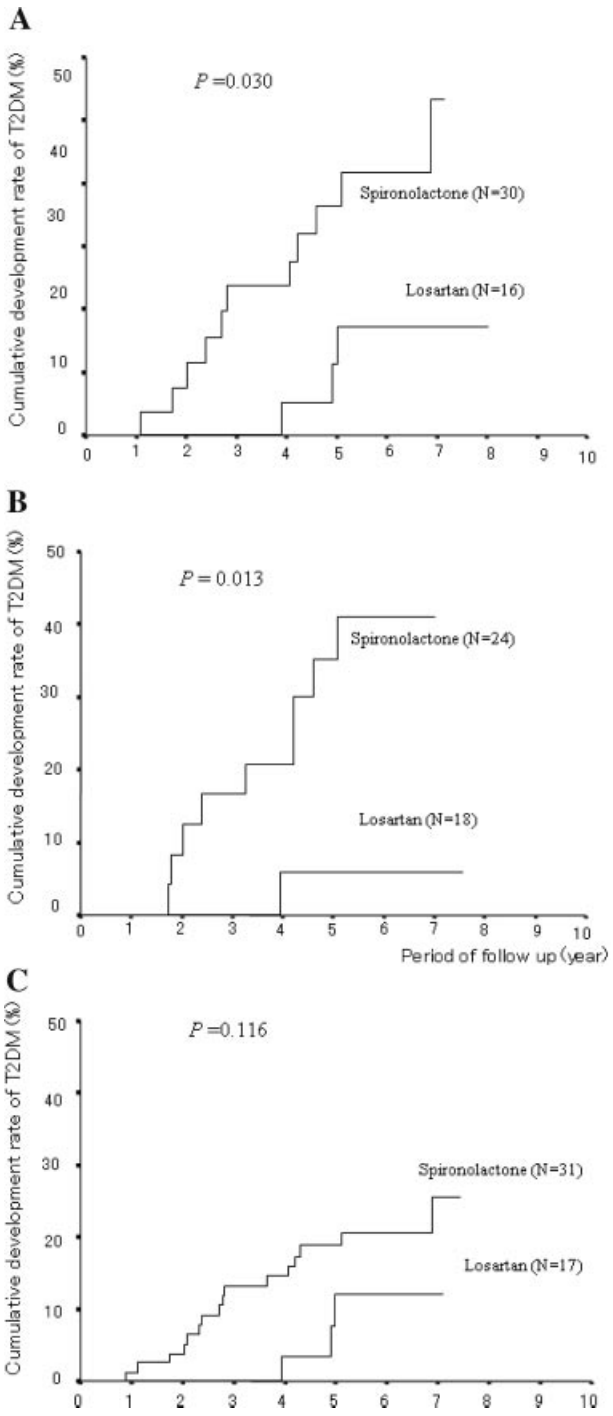

Fig. 2. Cumulative development rate of T2DM in patients with losartan or spironolactone. **Panel A**: Cumulative development rate of T2DM based on the difference of anti-hypertensive drugs in patients with liver cirrhosis; (**Panel B**), cumulative development rate of T2DM based on the difference of anti-hypertensive drugs in patients with pre-diabetes; (**Panel C**), cumulative development rate of T2DM based on the difference of anti-hypertensive drugs in patients with fatty liver.

consider the indication of losartan for protecting the onset of T2DM and progression of liver fibrosis.

In conclusion, our results indicate losartan causes about 60% reduction of the risk of T2DM development in HCV positive, hypertensive, Japanese patients.

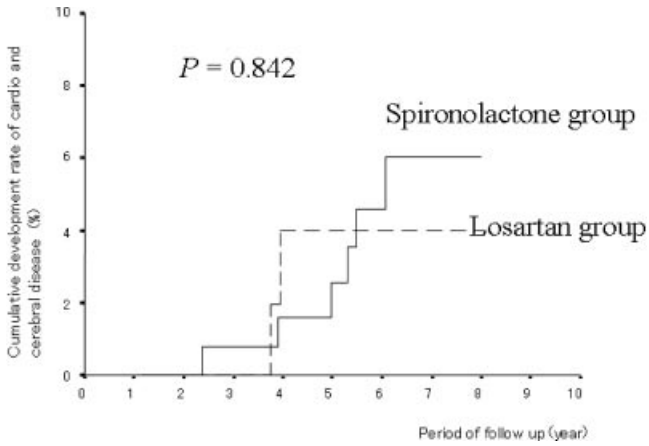

Fig. 3. Cumulative development rate of cardiovascular disease and stroke based on the difference of anti-hypertensive drug.

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