

Circulation Journal 無断転載事件の概要と経過

1. 事件の概要

Medical Tribune 3 月 26 日号に掲載された日本高血圧学会ガイドライン (JSH2009) に対する専門家のコメント記事 (武田薬品提供) の中で、CJ 5 月号 (4 月 25 日発刊予定、既にオンラインジャーナルで公開) に掲載予定の論文から、無断で図 (Figure 4) が改変転載される (添付資料 1 / 下段の中央の図。添付資料 2 / 上嶋論文)。

2. 事件の経過

3 月 6 日 (金) 武田薬品担当者が、上記記事の取材で京大上嶋准教授 (京大 EBM 研究センター) を訪問し、当初掲載予定になかった CJ 上嶋論文のことを紹介され、同論文の結果 (Figure 4) を加えて 3 月中に記事を掲載することを思いつく (後日、上嶋准教授は原稿の校正を行うが、発刊時期については聞かされていない)。この時点で、武田薬品側は二重掲載になることの認識なく、また、担当者の上司も記事掲載の許可を出す。

3 月 18 日 (水) 広告代理店インフロント社より日循事務局に二次使用許諾申請書が届くが、掲載予定日 (Release date) の記載が無かったために日循学会 (3 月 19 ~ 22 日) 後に再度連絡してもらうことにする (添付資料 3)。

3 月 27 日 (金) インフロント社から連絡がないため、日循事務局から問い合わせの電話をして、記事の掲載は、当該 CJ 論文の発刊 (4 月 25 日) 以後でなくてはならないことを伝える。

3 月 30 日 (月) インフロント社より電話連絡があり、Medical Tribune 3 月 26 日号 (3 月 24 日発刊) に既に記事として掲載・郵送したことが判明。このため、米国出張中の下川編集委員長に連絡。編集長として、以下の対応を指示。

- (1) 無断転載記事掲載号の回収
- (2) Medical Tribune 誌での謝罪文と再発防止の書面の掲載
- (3) 関係 3 社の日循事務局と編集長への顛末の説明と謝罪
- (4) 今後の学会としての対応 (総務委員会・理事会)

4 月 1 日 (水) 関係 3 社が日循事務局を訪問して顛末の説明と謝罪。

4 月 3 日 (金) 関係 3 社が下川編集委員長を訪問して顛末の説明と謝罪。事情聴取

を行う。

同行していなかった武田薬品担当者にも急遽来訪してもらい、2度目の事情聴取。この時点で、CJ 5月号（4月25日発刊）に掲載予定の上嶋論文とそれに対する Editorial comment の掲載を6月号以降に延期するように、日循事務局と河北印刷に、緊急の指示を出す。

4月6日（月）京大の上嶋准教授に電話し、本人に二重掲載になることへの認識がなかったこと、関係3社より記事の掲載時期については連絡がなかったことを確認。

4月7日（火）以降 Medical Tribune と下川編集委員長との間で、回収文の文面（添付資料4）や謝罪文の表記（添付資料5）について、双方の弁護士を交えて協議。

3. 事件の原因の総括

今回の原因については、下記のような事実が判明した。

- （1）武田薬品学術部の著作権に対する認識不足
- （2）広告代理店（インフロント社）の転載許可への認識不足
- （3）Medical Tribune 社の最終チェック体制の不備
- （4）上嶋准教授には直接の責任なし

4. 編集委員会としての対応

- （1）Medical Tribune 誌無断転載記事掲載号の回収（4月23日）（添付資料4）
- （2）Medical Tribune 誌での謝罪文と再発防止の書面の掲載（4月23日）（添付資料5）
- （3）上嶋論文の CJ 73-6 への掲載の決定（編集委員29名中20名が同意、3名が反対ではないが異なる意見、6名が回答なし）

5. 総務委員会としての対応

- （1）総務委員会での対応検討（6月19日）
 - ・許諾が出ていない段階で掲載したことへの学会としての厳重注意
 - ・今後の予防策として、学会ホームページに今回の事例を掲載

以上



**Circulation
Journal**

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Circulation Journal 論文データの無断転載事件に関する報告書

Circulation Journal に掲載予定である論文のデータが、無断で商業誌に改変転載される事件が起きたので、その経過および編集委員会としての対応について、ご報告申し上げます。

事件の概要は、Medical Tribune 3月26日号に掲載された日本高血圧学会ガイドライン (JSH2009) に対する専門家のコメント記事 (武田薬品提供) の中で、CJ 5月号 (4月25日発刊予定) に掲載予定の論文から、無断で図が改変転載されたものです (詳細は、添付の概要と経過の報告書をご覧ください)。

関係者に直接事情聴取をしました結果、(1) 広告記事を作成した製薬メーカー (武田薬品) の学術部の著作権に対する認識不足、(2) 広告代理店 (インフロント社) の転載許可への認識不足 (3) Medical Tribune 社の最終チェック体制の不備、の三重ミスにより起こった事件であり、当該論文の筆頭著者である上嶋健治准教授 (京大 EBM センター) には、直接の責任はないと判断いたしました。

これを受けまして、編集委員会として、(1) Medical Tribune 誌無断転載記事掲載号の回収 (4月23日)、(2) Medical Tribune 誌での謝罪文と再発防止の書面の掲載 (4月23日)、(3) 掲載をいったん延期した上嶋論文を1ヶ月遅れで CJ 73-6 へ掲載することを決定いたしました。

以上、ご報告申し上げますとともに、学会 (総務委員会、理事会) としての関係3社に対する対応につきまして、ご検討を宜しくお願い申し上げます。なお、無断転載が起きたこと自体は大変残念ですが、その後の3社の対応には一定の誠意が認められたことを申し添えます。

添付ファイル: CJ 無断転載事件の概要と経過

資料1: CJ 無断転載資料

資料2: CJ 上嶋論文

資料3: 広告代理店 (インフロント社) からの申請書

資料4: Medical Tribune 回収社告 (4月23日)

資料5: Medical Tribune 謝罪文 (4月23日)

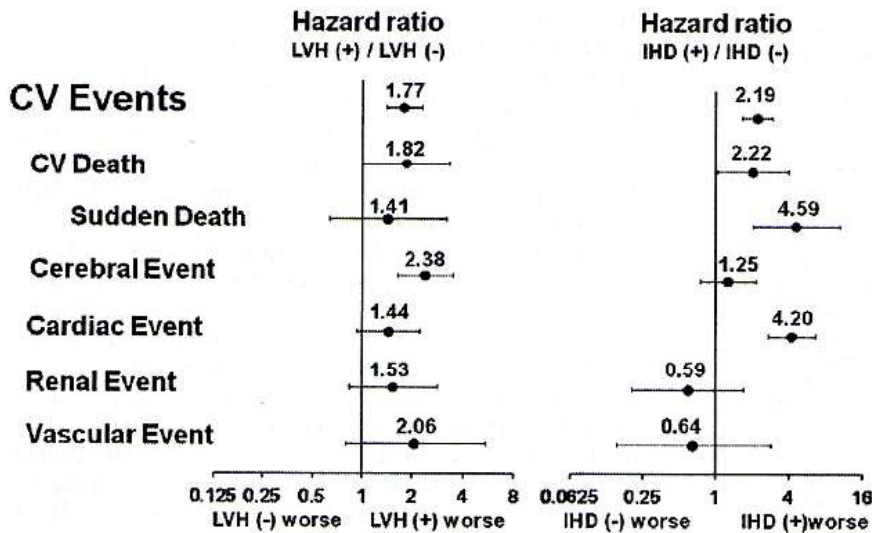


Figure 4. Comparison of each primary endpoint category in patients with or without left ventricular hypertrophy and in patients with or without ischemic heart disease. LVH, left ventricular hypertrophy; IHD, ischemic heart disease; CV events, cardiovascular events; CV death, cardiovascular death.

Ueshima K et al. Circ J (in press) / Advance Publication by J-STAGE

09を活かす 高血圧治療ガイドライン2009

心肥大を伴う高血圧症に対する降圧療法



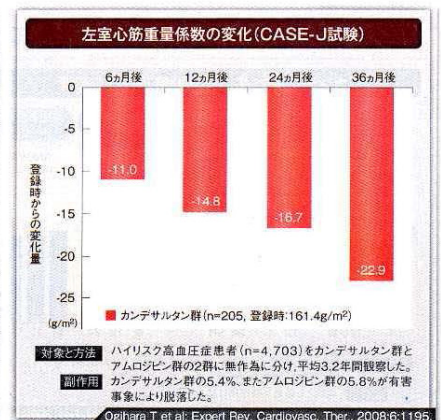
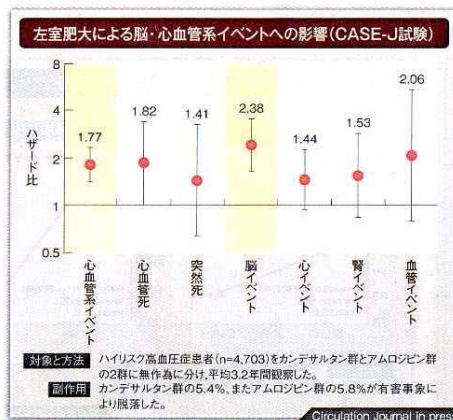
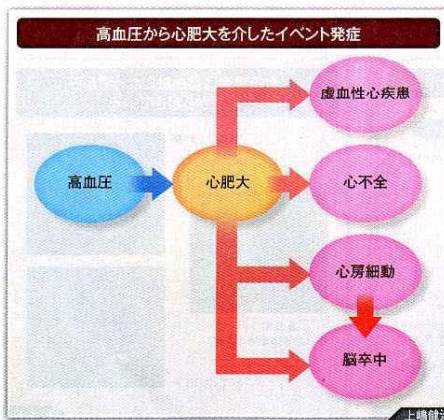
京都大学大学院 准教授 上嶋健治

心疾患合併高血圧症に対する降圧療法(JSH2009)		
心疾患	第一選択薬	留意点
心肥大	RA系阻害薬 長時間作用型Ca拮抗薬	持続的に十分な降圧をはかる
心筋梗塞後	RA系阻害薬 β遮断薬	血圧に130/80mmHg未満に降圧する 降圧が不十分な場合に長時間作用型Ca拮抗薬、 利尿薬の追加 低心機能症例にはアルドステロン拮抗薬の追加
狭心症	β遮断薬、長時間作用型Ca拮抗薬 (器質的心動脈硬化) 長時間作用型Ca拮抗薬 (冠狭窄) RA系阻害薬の追加 (降圧が不十分な時)	
心不全	RA系阻害薬+β遮断薬+利尿薬 (標準的治療) アルドステロン拮抗薬の追加 (重症例) 長時間作用型Ca拮抗薬の追加 (降圧が不十分な時)	
心房細動 (予防)	RA系阻害薬	十分な降圧が認められる 慢性心房細動患者では、心拍数コントロールのために β遮断薬や非ジヒドロピリジン系Ca拮抗薬を考慮する

日本高血圧学会 高血圧治療ガイドライン2009

心肥大は、虚血性心疾患や心不全の原因となるだけでなく、CASE-J試験のサブ解析からは脳卒中のリスク因子としても注意しなければならない。したがって、脳・心血管系イベントを抑制する観点からも、心肥大を退縮させることは、極めて重要である。JSH2009では、厳格かつ持続的な降圧が必要とした上で、カン

デサルタン等のRA系抑制薬を第一選択薬として推奨している。実際、CASE-J試験でカンデサルタンは、Ca拮抗薬と同様に血圧を厳格にコントロールした上で、優れた心肥大の退縮効果を認めている。カンデサルタンの特性でもある、強く、持続した降圧効果とRA系の抑制による結果であると言えるであろう。



カンデサルタンの効能・効果、用法・用量、禁忌を含む使用上の注意等については20～21頁D.I.をご参照ください。【資料請求先】 武田薬品工業株式会社 〒540-8645 大阪市中央区道修町四丁目1番1号 <http://www.takeda.co.jp/>

Medical Tribune 2009年3月26日

Effects of Cardiac Complications on Cardiovascular Events in Japanese High-Risk Hypertensive Patients

— Subanalysis of the CASE-J Trial —

Kenji Ueshima, MD*; Shinji Yasuno, MD*; Koji Oba, MS*; Akira Fujimoto, MS*;
Toshio Ogiwara, MD**; Takao Saruta, MD†; Kazuwa Nakao, MD*,††

Background: The Candesartan Antihypertensive Survival Evaluation in Japan (CASE-J) trial compared the effects of candesartan and amlodipine on cardiovascular events in Japanese high-risk hypertensive patients. The present study aimed to clarify the effect of cardiac complications on cardiovascular events in patients enrolled in CASE-J.

Methods and Results: Cardiac complications were defined as left ventricular hypertrophy (LVH) and ischemic heart disease (IHD). The primary endpoint was a composite of sudden death, cerebrovascular, cardiac, renal and vascular events. The study group was divided into 2,030 and 2,673 patients with and without cardiac complications. During 3.2 follow-up years, cardiovascular events occurred for a rate of 13.6 per 1000 patient-years in patients without cardiac complications, and 23.1 per 1000 patient-years in patients with cardiac complications (adjusted hazard ratio (HR): 2.22; $P < 0.001$). Furthermore, LVH was associated with the onset of cerebrovascular events (adjusted HR: 2.38; $P < 0.001$), whereas IHD was associated with the onset of cardiovascular death (adjusted HR: 2.22; $P < 0.05$), especially sudden death and other cardiac events.

Conclusions: Cardiac complications are independent predictors for cardiovascular events in Japanese high-risk hypertensive patients. In particular, LVH is related to cerebrovascular events and IHD is related to cardiac death and other cardiac events.

Key Words: Coronary heart disease; Hypertension; Hypertrophy; Japanese

Hypertension is one of the major risk factors for cardiovascular (CV) events. Recent advantages of drug treatment are well recognized and lead to better blood pressure (BP) control and prognosis in hypertensive patients. However, the CV events rate is still high in hypertensive patients with other cardiac risks and, moreover, CV risks are known to cluster in hypertensive patients!¹⁻⁴ The importance of identifying complicated CV risk factors has been repeatedly emphasized in national and international guidelines⁵⁻⁷. These guidelines suggest that initiation of anti-hypertensive treatment, as well as the choice of therapeutic drugs, should be based on a total risk factor evaluation.

channel blocker (CCB), amlodipine, on the incidence of CV events, represented as a composite of sudden death, cerebrovascular, cardiac, renal and vascular events in Japanese high-risk hypertensive patients^{8,9}. The CASE-J trial disclosed that candesartan and amlodipine equally suppressed total CV mortality and morbidity in high-risk hypertensive patients under strict BP control. Furthermore, primary CV events occurred in 134 patients in each of 2 treatment-based regimens and they were much lower than expected.

In this study, we consider the trial as an observational study irrespective of allocated drugs, and clarify the effect of cardiac complications, such as left ventricular hypertrophy (LVH) and ischemic heart disease (IHD), on CV events in Japanese high-risk hypertensive patients.

Editorial p ???

The Candesartan Antihypertensive Survival Evaluation in Japan (CASE-J) trial compared the effects of the angiotensin II receptor blocker (ARB), candesartan, and the calcium-

Methods

Study Design

The CASE-J trial was a prospective, multicenter, randomized, open-label, active-controlled, 2-arm parallel-group comparison study evaluating the efficacy of the ARB, candesartan, and the CCB, amlodipine, for reducing the incidence of CV events in high-risk hypertensive patients^{8,9}. The rationale and complete design of the CASE-J trial have been previously reported⁸. Briefly, 4,728 patients with high-risk hypertension were randomly assigned to either a candesartan- or amlodipine-based treatment regimen. High-risk was defined as the presence of any one of the following factors: (a) severe hypertension: systolic BP (SBP)/diastolic BP (DBP) $\geq 180/110$ mmHg; (b) type 2 diabetes mellitus; (c) history of stroke or transient ischemic attack (TIA) more

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Table. Baseline Characteristics of the Study Patients

	Cardiac complication (–)	Cardiac complication (+)
n	2,673	2,030
Candesartan (%)	1,347 (50.4)	1,007 (49.6)
Age (years)	63.7±10.5	64.0±10.6
Men (%) [*]	1,296 (48.5)	1,301 (64.1)
Body mass index (kg/m ²) [*]	24.7±3.8	24.4±3.4
SBP (mmHg) [*]	164.5±14.3	160.7±13.7
DBP (mmHg) [*]	92.5±11.5	90.6±10.7
Heart rate (beats/min) [*]	73.3±11.0	71.2±11.3
Severe HT (SBP ≥180 and/or DBP ≥110 mmHg) [*]	716 (26.8)	231 (11.4)
Type 2 diabetes ^{†,*}	1,414 (52.9)	604 (29.8)
Cerebrovascular disease		
Cerebral hemorrhage [*]	64 (2.4)	22 (1.1)
Cerebral infarction [*]	225 (8.4)	99 (4.9)
TIA [*]	62 (2.3)	12 (0.6)
Renal dysfunction		
Proteinuria [*]	606 (22.7)	299 (14.7)
sCr ≥1.3 mg/dl [*]	232 (8.7)	135 (6.7)
Vascular disease		
ASO [*]	38 (1.4)	15 (0.7)

Data are number of patients (%) or mean ± SD.

^{*}P<0.05; cardiac complication (–) vs cardiac complication (+).

[†]Type 2 diabetes mellitus was defined by fasting blood glucose ≥126 mg/dl, casual blood glucose ≥200 mg/dl, hemoglobin A_{1c} ≥6.5%, 2 h blood glucose on 75-g oral glucose tolerance test ≥200 mg/dl, or current treatment with hypoglycemic agents at baseline. SBP, systolic blood pressure; DBP, diastolic blood pressure; HT, hypertension; TIA, transient ischemic attack; sCr, serum creatinine; ASO, atherosclerosis obliterans.

than 6 months prior to the screening; (d) LVH (SV1+RV5 ≥3.5 mV on ECG and/or left ventricular (LV) wall thickness ≥12 mm on echocardiography), angina pectoris (AP) or history of myocardial infarction (MI) more than 6 months prior to the screening; (e) proteinuria or serum creatinine concentration ≥1.3 mg/dl; (f) arteriosclerotic peripheral artery obstruction. The exclusion criteria are also reported elsewhere.⁸ After randomization the enrolled patients were given candesartan administered orally at a dose of 4–12 mg/day or amlodipine administered orally at a dose of 2.5–10 mg/day. The target BPs were determined according to the guideline of the Japanese Society of Hypertension.⁷ Finally, 4,703 randomly assigned patients were included in the analysis.

Outcome Measurements

The primary endpoint was the first fatal/non-fatal CV event (a composite of sudden death, which is unexpected death within 24 h without external cause; cerebrovascular events including stroke or TIA; cardiac events including heart failure (HF), AP or acute MI; renal events, including serum creatinine concentration ≥4.0 mg/dl, doubling of the serum creatinine concentration (however, creatinine ≤2.0 mg/dl was not regarded as an event), or end-stage renal disease; and vascular events including dissecting aortic aneurysm or arteriosclerotic occlusion of a peripheral artery).⁸ The event evaluation was performed independently by the Event Evaluation Committee, which was blinded to the assigned treatment groups and adjudicated according to the protocol criteria.

Baseline Characteristics

In the present study, we focused on the cardiac complications of the inclusion criteria in the CASE-J trial as LVH and IHD, including AP or a history of MI. Enrolled patients were divided into 2,030 patients with cardiac complications (LVH alone, IHD alone, and both LVH and IHD: 1,434, 418, and 178 patients, respectively) and 2,673 patients without cardiac complications. **Table** shows their baseline

characteristics. Of the 1,612 patients with LVH, 927 met the ECG criteria, 463 met the echocardiographic criteria, and 222 met both the ECG and echocardiographic criteria for LVH. When we analyzed the data of patients with or without cardiac complications as an observational study, irrespective of allocated drugs, there were statistical differences between the dichotomized groups in the sex ratio, body mass index (BMI), SBP, DBP, heart rate and complicated risk factors. Next, the analyses were adjusted by baseline characteristics as described below.

Statistical Analysis

Data are expressed as mean ± SD or proportions. We compared continuous variables using Student's *t*-test. Frequency analysis was performed by χ^2 test. The cumulative CV events rate was calculated by the Kaplan-Meier method, and the groups were compared with the log-rank test. The hazard ratio (HR) and 95% confidence intervals (CIs) were estimated using Cox regression analysis. We also used the multiple Cox regression analysis to examine the association between the CV events rate and the effects of cardiac complications adjusted by baseline characteristics (allocated drugs, age, sex, BMI, and complicated risk factors). All statistical tests were 2-sided with an alpha level of 0.05, and were performed using SAS version 9.1 (SAS Institute Inc, Cary, NC, USA).

Results

Changes in BP

BP was strictly controlled to <140/80 mmHg in both groups. However, the mean SBP/DBP was 160.7/90.6 mmHg at baseline and 134.6/76.8 mmHg after 3 years in patients with cardiac complications compared with 164.5/92.5 mmHg at baseline and 135.9/77.2 mmHg after 3 years in patients without cardiac complications. Both SBP and DBP in the patients with cardiac complications were slightly but significantly lower than those without cardiac complications

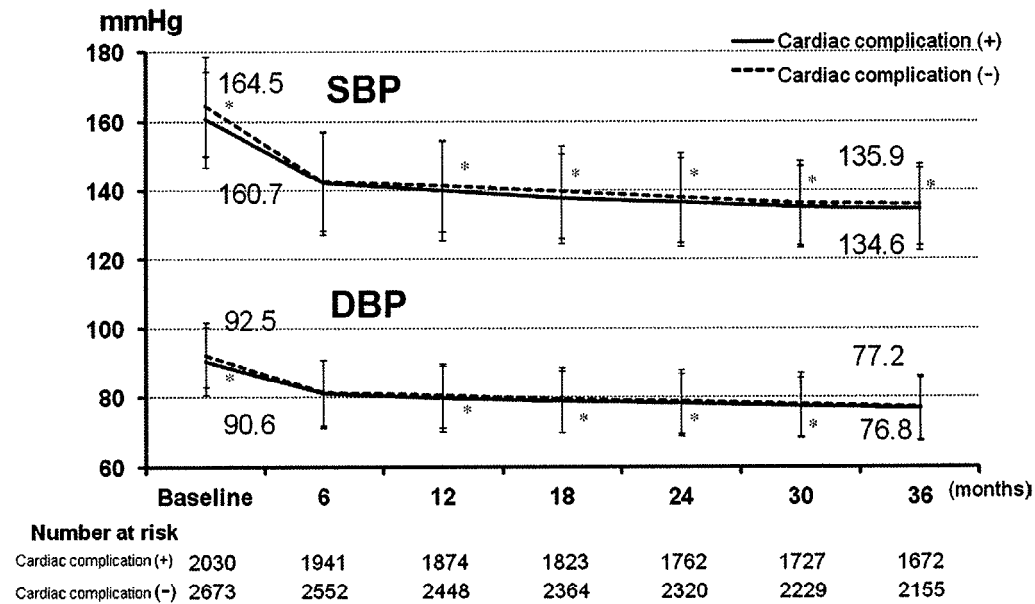


Figure 1. Changes in SBP and DBP during follow-up. Mean SBP and mean DBP measured in the treatment groups and differences between the means. SBP, systolic blood pressure; DBP, diastolic blood pressure. * $P<0.05$; cardiac complication (-) vs cardiac complication (+).

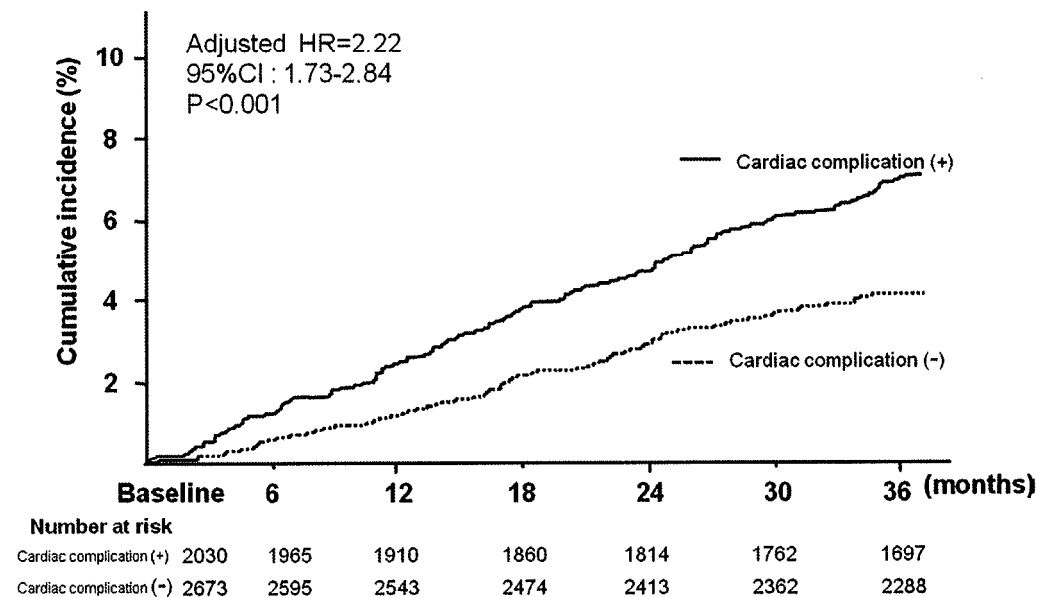


Figure 2. Kaplan-Meier curves for the primary composite endpoint in patients with or without cardiac complications. The primary endpoint was the time to the first cardiovascular event. HR, hazard ratio; CI, confidence interval.

at several points during the follow-up period (**Figure 1**).

Prognostic Value of Cardiac Complications for CV Events Rate

During 3.2 ± 0.9 years of follow-up, CV events occurred in 118 (4.4%) patients without cardiac complications at baseline for a rate of 13.6 per 1,000 patient-years and in 150 (7.4%) patients with cardiac complications at baseline for a rate of 23.1 per 1,000 patient-years (adjusted HR: 2.22; 95%CI: 1.73–2.84; $P<0.001$; **Figure 2**). In addition, we evaluated the prognostic value of the cardiac complications

for each event category. As shown in **Figure 3**, cardiac complications were associated with the onset of CV death (adjusted HR: 2.14; 95%CI: 1.14–4.02; $P=0.018$), including sudden death (adjusted HR: 2.79; 95%CI: 1.16–6.70; $P=0.022$), cerebrovascular events (adjusted HR: 2.27; 95%CI: 1.54–3.35; $P<0.001$) and other cardiac events (adjusted HR: 2.63; 95%CI: 1.71–4.05; $P<0.001$), including MI, AP or congestive HF. However, the incidences of renal and vascular events were unaffected by cardiac complications.

Although both complicated LVH and IHD were associated with the CV events rate, there were different effects on

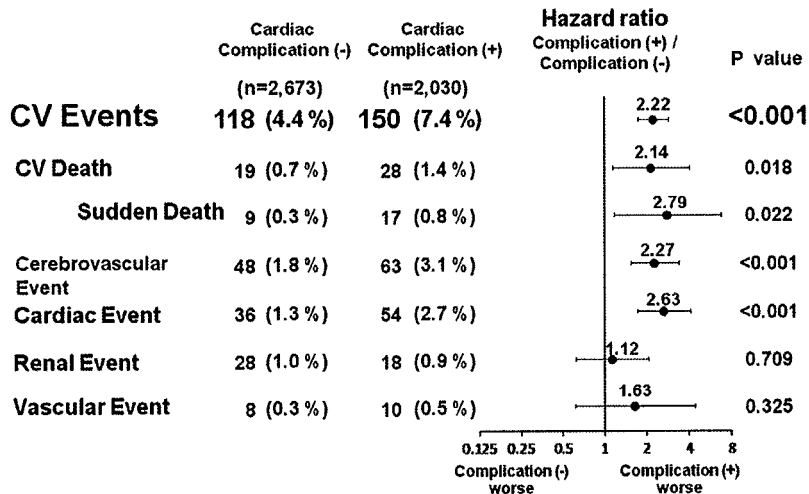


Figure 3. Comparison of each primary end-point category in patients with or without cardiac complications. CV events, cardiovascular events; CV death, cardiovascular death.

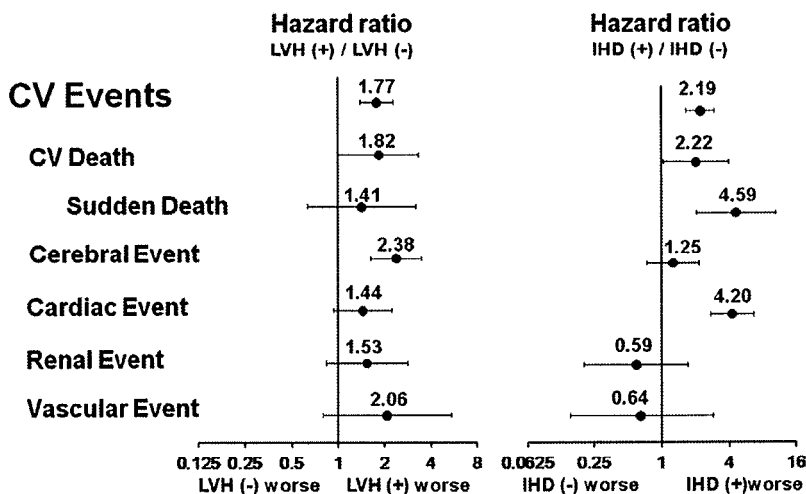


Figure 4. Comparison of each primary end-point category in patients with or without left ventricular hypertrophy and in patients with or without ischemic heart disease. LVH, left ventricular hypertrophy; IHD, ischemic heart disease; CV events, cardiovascular events; CV death, cardiovascular death.

each event category of CV events between LVH and IHD. As shown in **Figure 4**, LVH was strongly associated with the onset of cerebrovascular events (adjusted HR: 2.38; 95%CI: 1.62–3.48; $P<0.001$ in LVH, and adjusted HR: 1.25; 95%CI: 0.74–2.12; $P=0.401$ in IHD), whereas IHD was strongly associated with the onset of CV death (adjusted HR: 1.82; 95%CI: 0.99–3.28; $P=0.053$ in LVH, and adjusted HR: 2.22; 95%CI: 1.02–3.96; $P=0.043$ in IHD), especially sudden death (adjusted HR: 1.41; 95%CI: 0.63–3.17; $P=0.408$ in LVH, and adjusted HR: 4.59; 95%CI: 2.02–10.41; $P<0.001$ in IHD), and other cardiac events (adjusted HR: 1.44; 95%CI: 0.93–2.21; $P=0.100$ in LVH, and adjusted HR: 4.20; 95%CI: 2.69–6.55; $P<0.001$ in IHD). Neither LVH nor IHD was related to the onset of renal or vascular events.

Discussion

The present study extends the clinical implication of cardiac complications such as LVH and IHD in high-risk hypertensive patients. Because the baseline clinical characteristics were different in patients with or without cardiac complications, the HRs for CV events were adjusted by the baseline characteristics. We demonstrated that cardiac com-

plications are an independent predictor for CV events. Moreover, LVH and IHD were independent predictors for CV events. To our knowledge, this is the first report of the separate effect of LVH and IHD on the incidence of CV events, including renal events, analyzed in high-risk hypertensive patients. Although BP lowering was substantial in both groups of patients, the achieved BP was slightly different between them. Because the BP level achieved in patients with cardiac complications was lower than that in the patients without cardiac complications, this result was not caused by inadequacy of BP lowering in patients with cardiac complications.

LVH is an adaptive response that reduces LV wall stress against volume and pressure overload^{10,11}. Although this was originally thought to be a compensatory and beneficial response to normal wall stress, large population studies have provided evidence that LVH confers increased risk for CV events.^{12–15} The reasons why LVH is a powerful predictor for CV events are not yet clear, and there are various mechanisms to explain the relationship between LVH and CV events.^{16,17} Two important concepts have been proposed for the clinical implication of LVH. First, LVH has been predominantly considered a valuable surrogate index for CV events, reflecting longstanding exposure to high BP. There-

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Cardiac Complications in Hypertensive Patients

fore, the complication of LVH indicates advanced arteriosclerosis in various organs including the brain and kidneys.¹⁸⁻²⁰ The present study results indicated a strong relationship between LVH and the onset of cerebrovascular events. Elevated SBP, which sets up LVH, is associated with a profound increase in the risk of cerebrovascular events. The ARIC study demonstrated that incident stroke was predicted by the echocardiographic LV mass index (LVMI).²¹ Another study also revealed that LVH was associated closely with stroke, and that the risk ratio of the LVMI was 1.020 for each 1 g/m² increase.²² Second, LVH may contribute directly to CV events through pathological changes, including fibrosis and relative ischemia caused by hypertrophy.^{17,23} LVH is related to adverse LV remodeling as a result. We believed that the reason why LVH failed to predict the onset of CV events other than cerebrovascular events is mainly for statistical reasons based on the small numbers in this study. The total number of cerebrovascular events was 111, whereas cardiac events occurred in only 90 cases.

This study indicated that a history of prior IHD is closely connected with CV events. In particular, the adjusted HRs of sudden death and cardiac events, including MI, AP and congestive HF, in patients with IHD was almost 3-fold or more than those in patients with LVH. Because these events are closely related to coronary lesions, the effect of a history of IHD was strong. Conversely, hypertension increases the risk of CV events including stroke, HF and death after MI.²⁴ Ravipati et al reported that the risk ratio of prior MI was 3.29 for either new stroke or new MI or death in 306 patients with hypertension or diabetes mellitus.²²

Study Limitations

First, because this analysis was post-hoc, the numbers in each category of CV events, particularly renal and vascular events, may not be enough to analyze the effect of cardiac complications on these events. Recently, higher urinary albumin excretion has been observed in patients with LVH,²⁵⁻²⁷ suggesting that cardiac and glomerular vascular damage may occur in parallel. Systemic inflammation and endothelial damage are possible mechanisms of the relationship between them.²⁸ In the present study, however, cardiac complications, both LVH and IHD, failed to predict the onset of renal events. Therefore, we should focus on the time-course of renal function as well as the onset of renal events. Accordingly, the effects of cardiac complications on the kidney remain unknown. Second, in this study, hypertensive patients with any one of the high-risk factors, including LVH and IHD, were enrolled, so when we evaluated the data of patients with or without cardiac complications, the analyses had to be adjusted by the baseline characteristics because of their statistical differences. Third, the definition of LVH consisted of ECG criteria (SV1+RV5 ≥ 3.5 mV) and echocardiographic criteria (LV wall thickness ≥ 12 mm). Because echocardiography is only performed when feasible, there were small numbers of patients who underwent echocardiography. Accordingly, we had to combine different criteria of either ECG or echocardiography. Fourth, 3.2 years of mean follow-up may not be long enough to evaluate the relationship between underlying risks and the incidence of CV events. The CASE-J trial was extended for 3 years from 2006 as an observational study named CASE-J Ex²⁹ and it may resolve this issue in the near future.

In conclusion, cardiac complications are independent predictors for CV events in Japanese high-risk hypertensive patients, but the clinical implication differs between LVH

and IHD. LVH is related to cerebrovascular events and IHD is related to cardiac death, including sudden death and other cardiac events.

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Disclosures

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References

1. Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: Analysis of worldwide data. *Lancet* 2005; **365**: 217-223.
2. Lopez AD, Mathers CD, Ezzati M, Jamison DT, Murray CJ. Global and regional burden of disease and risk factors, 2001: Systematic analysis of population health data. *Lancet* 2006; **367**: 1747-1757.
3. Nakamura Y, Saitoh S, Takagi S, Ohnishi H, Chiba Y, Kato N, et al. Impact of abnormal glucose tolerance, hypertension, and other risk factors on coronary heart disease. *Circ J* 2007; **71**: 20-25.
4. Kohro T, Hayashi D, Okada Y, Yamazaki T, Nagai R; JCAD Investigators. Demographics and changes in medical/interventional treatment of coronary artery disease patients over a 3.5-year period in Japan: The Japanese Coronary Artery Disease Study: Trend examination. *Circ J* 2008; **72**: 1397-1402.
5. Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. The JNC 7 Report. *JAMA* 2003; **289**: 2560-2572.
6. Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, et al. 2007 guidelines for the management of arterial hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J* 2007; **28**: 1462-1536.
7. Japanese Society of Hypertension Guidelines Subcommittee for the Management of Hypertension. Guidelines for the management of hypertension for general practitioners. *Hypertens Res* 2001; **24**: 613-634.
8. Fukui T, Rahman M, Hayashi K, Takeda K, Higaki J, Sato T, et al. Candesartan Antihypertensive Survival Evaluation in JAPAN (CASE-J) trial of cardiovascular events in high-risk hypertensive patients: Rationale, design, and methods. *Hypertens Res* 2003; **26**: 979-990.
9. Ogiwara T, Nakao K, Fukui T, Fukiyama K, Ueshima K, Oba K, et al. Candesartan Antihypertensive Survival Evaluation in Japan trial Group. Effects of candesartan compared with amlodipine in hypertensive patients with high cardiovascular risks: Candesartan Antihypertensive Survival Evaluation in Japan trial. *Hypertension* 2008; **51**: 393-398.
10. Grossman W, Jones D, McLaurin P. Wall stress and patterns of hypertrophy in the human left ventricle. *J Clin Invest* 1975; **56**: 56-64.
11. Ganau A, Devereux RB, Pickering TG, Roman MJ, Schnall PL, Santucci S, et al. Relation of left ventricular hemodynamic load and contractile performance to left ventricular mass in hypertension. *Circulation* 1990; **81**: 25-36.
12. Meijis MF, De Windt LJ, De Jonge N, Cramer MJ, Bots ML, Mali WP, et al. Left ventricular hypertrophy: A shift in paradigm? *Curr Med Chem* 2007; **14**: 157-171.
13. Kannel WB, Levy D, Cupples LA. Left ventricular hypertrophy and risk of cardiac failure: Insights from the Framingham Study. *J Cardiovasc Pharmacol* 1987; **10**(Suppl 6): S135-S140.
14. Levy D, Garrison RJ, Savage DD, Kannel WB, Castelli WP. Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study. *N Engl J Med* 1990; **322**: 1561-1566.
15. Brown DW, Giles WH, Croft JB. Left ventricular hypertrophy as a predictor of coronary heart disease mortality and the effect of hyper-

- tension. *Am Heart J* 2000; **140**: 848–856.
16. Heckbert SR, Post W, Pearson GD, Arnett DK, Gomes AS, Jerosch-Herold M, et al. Traditional cardiovascular risk factors in relation to left ventricular mass, volume, and systolic function by cardiac magnetic resonance imaging: The Multiethnic Study of Atherosclerosis. *J Am Coll Cardiol* 2006; **48**: 2285–2292.
 17. Krauser DG, Devereux RB. Ventricular hypertrophy and hypertension: Prognostic elements and implications for management. *Herz* 2006; **31**: 305–316.
 18. Messerli FH, Williams B, Ritz E. Essential hypertension. *Lancet* 2007; **370**: 591–603.
 19. de Simone G. Left ventricular geometry and hypotension in end-stage renal disease: A mechanical perspective. *J Am Soc Nephrol* 2003; **14**: 2421–2427.
 20. Shigematsu Y, Hamada M, Ohtsuka T, Hashida H, Ikeda S, Kuwahara T, et al. Left ventricular geometry as an independent predictor for extracardiac target organ damage in essential hypertension. *Am J Hypertens* 1998 **11**: 1171–1177.
 21. Fox ER, Alnabhan N, Penman AD, Butler KR, Taylor HA Jr, Skelton TN, et al. Echocardiographic left ventricular mass index predicts incident stroke in African Americans: Atherosclerosis Risk in Communities (ARIC) Study. *Stroke* 2007; **38**: 2686–2691.
 22. Ravipati G, Aronow WS, Ahn C, Alappat RM, McClung JA, Weiss MB. Incidence of new stroke or new myocardial infarction or death at 39-month follow-up in patients with diabetes mellitus, hypertension or both with and without microalbuminuria. *Cardiology* 2008; **109**: 62–65.
 23. Gosse P. Left ventricular hypertrophy as a predictor of cardiovascular risk. *J Hypertens* 2005; **23**(Suppl 1): S27–S33.
 24. Thune JJ, Signorovitch J, Kober L, Velazquez EJ, McMurray JJ, Califf RM, et al. Effect of antecedent hypertension and follow-up blood pressure on outcomes after high-risk myocardial infarction. *Hypertension* 2008; **51**: 48–54.
 25. Kramer H, Jacobs DR Jr, Bild D, Post W, Saad MF, Detrano R, et al. Urine albumin excretion and subclinical cardiovascular disease: The Multi-Ethnic Study of Atherosclerosis. *Hypertension* 2005; **46**: 38–43.
 26. Wachtell K, Palmieri V, Olsen MH, Bella JN, Aalto T, Dahlöf B, et al. Urine albumin/creatinine ratio and echocardiographic left ventricular structure and function in hypertensive patients with electrocardiographic left ventricular hypertrophy: The LIFE study (Losartan Intervention for Endpoint Reduction). *Am Heart J* 2002; **143**: 319–326.
 27. Lieb W, Mayer B, Stritzke J, Doering A, Hense HW, Loewel H, et al. Association of low-grade urinary albumin excretion with left ventricular hypertrophy in the general population: The MONICA/KORA Augsburg Echocardiographic Substudy. *Nephrol Dial Transplant* 2006; **21**: 2780–2787.
 28. Salles GF, Fiszman R, Cardoso CR, Muxfeldt ES. Relation of left ventricular hypertrophy with systemic inflammation and endothelial damage in resistant hypertension. *Hypertension* 2007; **50**: 723–728.
 29. Ueshima K, Oba K, Yasuno S, Fujimoto A, Sato Y, Fukiyama K, et al. Long-term effects of candesartan and amlodipine on cardiovascular mortality and morbidity in Japanese high-risk hypertensive patients: Rationale, design, and characteristics of Candesartan Antihypertensive Survival Evaluation in Japan Extension (CASE-J Ex). *Contemp Clin Trials* 2009; **30**: 97–101.

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Medical Tribune 3 月 26 日号 73 ページ、PR 記事中の図「左室肥大による脳・心血管系イベントへの影響 (CASE-J 試験)」を社団法人日本循環器学会発行『Circulation Journal』への掲載前に掲載しました。つきましては、先生にご送付いたしました 3 月 26 日号を回収したく、お手数でも同封の封筒(切手不要)にてご返送いただきたくお願い申し上げます(73、74 ページの 2 ページ分を切り取ってご返送いただくだけでも結構です)。

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大腸がんスクリーニング受検率が向上 郵便と電子媒体による案内で

〔シカゴ〕Brigham and Women's病院(BWH)とハーバード大学(ともにボストン)のThomas D. Sequist博士らは、患者への郵送による案内で大腸がんスクリーニングの受検率が向上し、担当するプライマリケア医への電子媒体によるリマインダー機能で、頻繁に来診する患者の受検率が向上するようだとArchives of Internal Medicine(2009; 169: 364-371)に発表した。

簡単な方法で効果

米国では、大腸がんはがん死亡原因の第2位である。便潜血検査、S状結腸鏡検査、大腸内視鏡検査を含むスクリーニング・プログラムは、前がん腺腫の除去を通じて大腸がんの発生率を低下させ、治療が望める早期段階でがんを発見し、死亡率を低下させる。

米国のガイドラインでは、平均的リスクを有する50歳以上の成人は大腸がんスクリーニングを受けべきだとしているが、調査時点

で検査を受けていた人は60%にとどまっている。

Sequist博士らは、2006年4月~07年6月に、プライマリケア医110人の患者2万1,860例(50~80歳)を対象に大腸がんスクリーニングの受検率と大腸腺腫(腫瘍)検出率を追跡した。

患者の半数(1万930人)は、教育パンフレット、便潜血検査キット、S状結腸鏡検査または大腸内視鏡検査を直接予約する方法についての指示書を郵送で受け取る群(郵便群)にランダムに割り付けられ

た。プライマリケア医の半数(55人)は、診察する患者の大腸スクリーニング検査の期日が過ぎていることを知らせる案内を電子媒体で受け取る群(電子リマインダー群)にランダムに割り付けられた。

スクリーニング受検率と大腸腺腫(腫瘍)の検出率を、介入開始から15か月間追跡した。

その結果、郵便群のスクリーニング受検率は、受け取らなかった群より有意に高かった(44.0%対38.1%, $P<0.001$)。郵便は高齢者ほど有効で、50歳代では3.7%, 60歳代では7.3%, 70~80歳代では10.1%受検率が向上した。

電子リマインダー群の医師が担当した患者と、案内を受け取らなかった群の医師が担当した患者を比較するとスクリーニング受検率に差はなかった(41.9%対40.2%, $P=0.47$)。3回以上受診した患者については電子リマインダー群の医師が担当した患者でスクリーニング受検率の上昇傾向が見られた(59.5%対52.7%, $P=0.07$)。

腺腫の検出率は、郵便群(5.7%対5.2%, $P=0.10$)、電子リマインダー群の医師が担当した患者(6.0%対4.9%, $P=0.09$)でそれぞれ増加傾向が見られた。

同博士らは「患者への資料郵送は大腸がんスクリーニングの受検率を少し押し上げ、医師がリマインダーを活用することで頻繁に診察を受ける患者の受検が促進された。このような相補的なアプローチが、スクリーニングの普及に役立つかもしれない」と述べている。

がん生存者で高い失業率

〔米オハイオ州クリーブランド〕学術医療センター(AMC、アムステルダム)Coronel労働衛生研究所のAngela G.E.M. de Boer博士らが、雇用情勢は健康人にとっても厳しいが、がん生存者が就業機会を得るのはさらに厳しいとJAMA(2009; 301: 753-762)に発表した。

失業リスクは健康人の1.37倍

de Boer博士は、がん生存者の半数近くが65歳未満であるにもかかわらず、厳しい就業状況が存在する理由について「がん生存者の多くが再雇用を望んでいるが、①仕事上の差別②治療のためフルタイムの就業ができない③身体的あるいは精神的限界を有している④がん関連の症状がある—など不利な立場にある」と説明している。

同博士らは、計2万366人のがん生存者群と15万7,603人の健康対照群を対象とした36件の研究を解析した。その結果、全体的にがん生存者の失業リスクは健康対照群より1.37倍高いことが判明した。

がんの種類による失業率の差も認められた。両群の失業率をがんの種類別に検討したところ、乳がん生存者では35.6%対31.7%、消化器がんでは48.8%対33.4%、女性生殖器官がんでは49.1%対38.3%であった。しかし、前立腺がん、精巣がん、白血病の生存者に関しては、失業リスクの上昇は著明ではなかった。

同博士は「症状の管理、リハビリテーション、障害に対する便宜などの改善を目指した職場での介入が求められる」と指摘している。

お詫び

今般、下記三社は、社団法人日本循環器学会に帰属する著作物の図を同法人の事前許可を得ないまま、同法人発行の『Circulation Journal』への掲載前に本紙(3月26日号、73ページ、PR記事中の図「左室肥大による脳・心血管系イベントへの影響(CASE-J試験)」)に掲載してしまいました。

社団法人日本循環器学会および関係者の皆様、京都大学大学院・上嶋健治准教授および共同著者の先生方、そして読者の皆様には大変ご迷惑をおかけいたしましたことを深くお詫び申し上げます。

今後は、こうした事態を防止するために、著作権法遵守のための社内体制をより強化していく所存です。

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