Experimental studies indicated that increased parasympathetic activity may reduce mortality [27] and sudden cardiac death, including death from ventricular fibrillation [28, 29]. Furthermore, Schwartz et al. [30] reported that vagal stimulation improved activities of daily living and several echocardiographic parameters of the left ventricle in humans. Accordingly, parasympathetic stimulation may play a critical role in the care of heart disease. In this study, we demonstrated that enhancement of parasympathetic nerve activity, assessed by the HF domain of heart rate variability, was induced by intermittent arm ischemia.

Limitations of this study

The study has several limitations. First, we did not directly elucidate heart protection by RIPC by intermittent arm ischemia. Second, we did not assess the relevance of the brachial artery's dilatation and the enhancement of parasympathetic nerve activity by intermittent arm ischemia. Third, we observed vasodilatation of the contralateral upper limb, but the duration of vasodilatation is not clear. Furthermore, we could not directly measure brachial artery flow. Therefore, further studies are needed to clarify these points.

Conclusions

Intermittent arm ischemia was accompanied by vasodilatation of another artery and enhancement of parasympathetic activity. It may be associated with the mechanism of RIPC.

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Conflict of interest We have no financial relationship with the organization that sponsored the research. We declare that they have no conflict of interest.

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ORIGINAL ARTICLE
Imaging

Gender Differences in Age-Related Changes in Left and Right Ventricular Geometries and Functions

– Echocardiography of a Healthy Subject Group –

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Background: The purpose of the present study was to investigate gender differences in age-related changes of left ventricular (LV) and right ventricular (RV) geometries and functions throughout the entire adult age range using the Japanese Normal Values for Echocardiographic Measurements Project (JAMP) study database.

Methods and Results: Seven hundred healthy volunteers (aged 20–79 years) underwent 2-dimensional and Doppler echocardiography. The subjects were stratified into 6 different age groups and then stratified by gender in each age group. LV diastolic function was assessed from pulsed wave Doppler measurements of mitral early (E) and late (A) inflow velocities and tissue Doppler measurements of mitral early (e') and late (a') annular velocities. LV volume decreased and LV mass increased with age to a similar extent in both men and women. Furthermore, for subjects <50 years, women had significantly greater E, E/A ratio and e' than men, but these parameters were similar between genders in subjects >50 years. In addition, there was a significant interaction between age and gender that affected the differences in E, e' and E/e' among the groups ($P<0.03$, $P<0.01$, and $P<0.03$, respectively; ANOVA). There were no gender differences in age-related changes in RV parameters.

Conclusions: Gender differences were found in age-related changes in LV diastolic function in a healthy population. Gender differences should be considered for optimal diagnosis and management of cardiovascular disease. (*Circ J* 2011; **75:** 2840–2846)

Key Words: Echocardiography; Gender; Ventricular function

Gender-based differences in the management and outcomes of cardiovascular disease have been studied extensively.[1–4] In women, heart failure (HF) is associated more with left ventricular (LV) diastolic dysfunction than in men, whereas LV systolic dysfunction is the predominant cause of HF in men.[5–8] In particular, elderly women frequently have HF associated with a normal LV ejection fraction.[2] Recent studies have also emphasized the importance of gender differences in the management of cardiovascular disease.[1,8,9] Thus, recognition of gender difference in LV geometry and function has important implications for the optimal diagnosis and management of cardiovascular disease.

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Echocardiography is now recognized as an integral diagnostic tool that provides non-invasive quantification of cardiac chamber size, ventricular mass and function in the clinical setting. Furthermore, technological advancements in Doppler echocardiography have permitted quantitative assessment of ventricular diastolic as well as systolic function. Thus, echocardiography has become an important cardiac imaging technique to evaluate the efficacy of drug treatments or new therapeutic strategies in many clinical trials. Previous investigations reported age-related changes in LV diastolic indices derived from Doppler echocardiography.[10–13] There is little information, however, on the effect of gender on age-related changes in LV geometry and function throughout the entire adult age range in healthy subjects. Furthermore, the age-related changes in right ventricular (RV) geometry and function have also not been well investigated previously.

Recently, we conducted a multicenter study, the Japanese Normal Values for Echocardiographic Measurements Project (JAMP),[14] to determine normal values for echocardiographic measurements throughout the entire adult age range in a large, healthy population. To our knowledge, the JAMP study is the only study in which echocardiographic parameters were measured in a large population of Asian healthy volunteers. Therefore, the purpose of the present study was to investigate gender differences in age-related changes in LV and RV geometries and functions throughout the entire adult age range using the JAMP study database.

Methods

Subjects

A total of 700 healthy volunteers, aged 20–79 years, were registered in the JAMP study at 17 collaborating institutions (Table). A standard protocol for echocardiographic measurements was established for the present study. Subjects were excluded based on the following criteria: any history of hyperlipidemia, hypertension, diabetes mellitus, renal failure, cardiovascular disease, abnormal electrocardiographic findings including cardiac arrhythmia and bundle branch block, or abnormal echocardiographic findings (LV wall motion abnormalities or significant valvular disease). Subjects were also excluded if they had poor echocardiographic images, significant fever, anemia or hypertension (systolic ≥135 mmHg and/or diastolic ≥85 mmHg) at the time of echocardiography or if they were under any influence that could affect the echocardiographic measurements. The study protocol was approved by the local hospital ethics committees, and informed consent was obtained from all subjects.

Echocardiographic Chamber Quantification and Doppler Echocardiography

The methods and results of chamber quantification and Doppler Echocardiography in the JAMP study have been described previously.[14] In brief, echocardiography was performed using commercially available equipment with tissue Doppler capabilities at each institution according to a standard protocol. Two-dimensional (2-D) and color Doppler imaging were performed to screen for significant valvular disease. In each subject, cardiac chamber quantification on 2-D echocardiography was performed according to guidelines provided by the American Society of Echocardiography.[15] LV end-diastolic volume (EDV) and end-systolic volume (ESV) were measured using the biplane Simpson disk method. LV mass was calculated based on the area–length formula as previously described.[15] Maximum left atrial (LA) and LV volumes were measured using the biplane Simpson disk method using 2-D images from the apical 4- and 2-chamber views. Assessment of RV size was done by measuring RV end-diastolic area and end-systolic area from the apical 4-chamber view. For assessing RV function, RV fractional area change[15] was calculated using the equation 100×(end-diastolic area−end-systolic area)/end-systolic area. Each parameter obtained from chamber quantification was indexed for body surface area when appropriate.

Pulsed wave Doppler imaging of mitral inflow and tissue Doppler imaging (TDI) of mitral annular motion at the septum were also performed to assess LV diastolic function as previously described.[16] Peak velocities of early (E) and late (A) diastolic flow, E/A ratio, and early flow deceleration time (Dct) were measured from pulsed wave Doppler imaging of mitral inflow. Early (e') and late (a') diastolic annular velocities were measured from TDI. The ratio of mitral E to TDI e' was also calculated using these measurements.

Table. Subject Characteristics

	Total	
	Male (n=383)	Female (n=317)
Age (years)	44±14	44±14
Height (cm)	170±6	157±6
Weight (kg)	65±9	51±7
Body surface area (m^2)	1.7±0.1	1.5±0.1
SBP (mmHg)	119±11	114±12
DBP (mmHg)	73±8	70±9
Heart rate (beats/min)	64±9	64±9
Age group (n)		
20–29 years	84	63
30–39 years	79	79
40–49 years	88	66
50–59 years	72	60
60–69 years	40	35
70–79 years	20	14

SBP, systolic blood pressure; DBP, diastolic blood pressure.

Statistical Analysis

Data analysis was performed using SPSS 17.0 (SPSS, Chicago, IL, USA). Subjects were stratified into 6 different age groups and then further stratified by gender. All results are expressed as mean±SD. Univariate regression analysis was used to assess liner correlations between age and the echocardiographic parameters. Unpaired t-test was used to compare the echocardiographic parameters between men and women in the same age group. Two-way analysis of variance (ANOVA) was used to determine if there was an interaction effect between gender and age that influenced any observed differences in the echocardiographic parameters among the groups. If there was a significant interaction effect between them, we considered that gender difference was significant in the age-related change in the echocardiographic parameter. $P<0.05$ was considered statistically significant.

Results

LV Volumes, Ejection Fraction and Mass

Both LV EDV and ESV indexes decreased with age to a similar extent in men and women, but these indices were significantly greater in men than in women in 3 age groups (20–29 years, 30–39 years and 50–59 years; Figures 1A,B). In

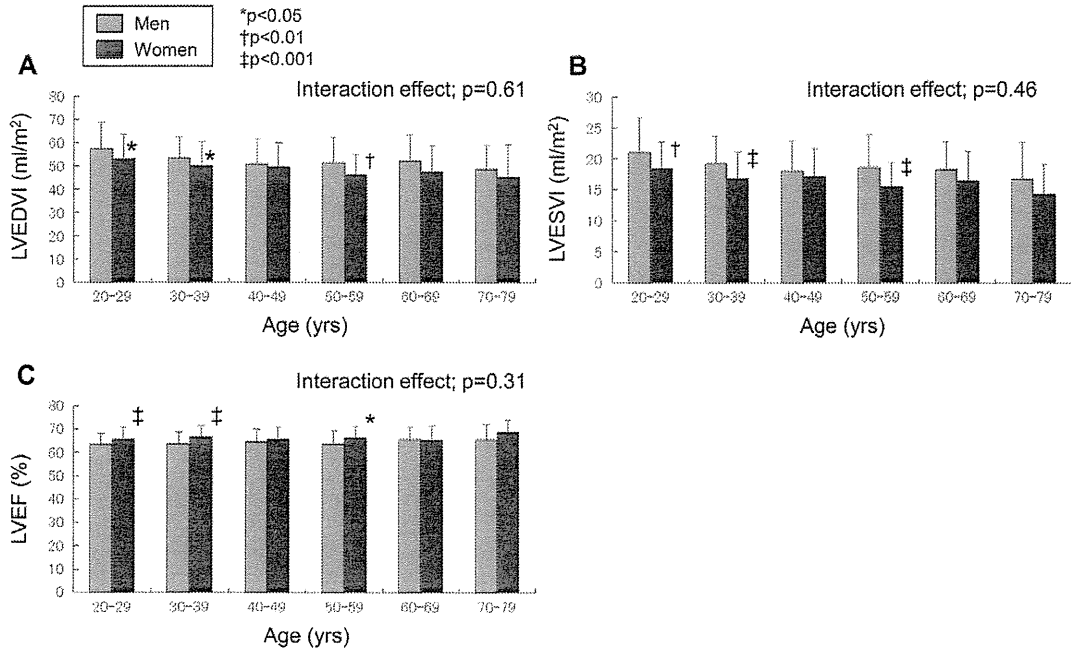

Figure 1. Effects of age and gender on left ventricular (LV) volumes and ejection fraction. Among subjects aged 20–29 years, 30–39 years and 50–59 years, (**A**) LV end-diastolic volume index (LVEDVI) and (**B**) LV end-systolic volume index (LVESVI) were greater, and (**C**) LV ejection fraction (LVEF) was lower in men than in women. There were no significant interaction effects, however, between age and gender that affected the differences in these parameters among the groups. *P<0.05, †P<0.01, ‡P<0.001.

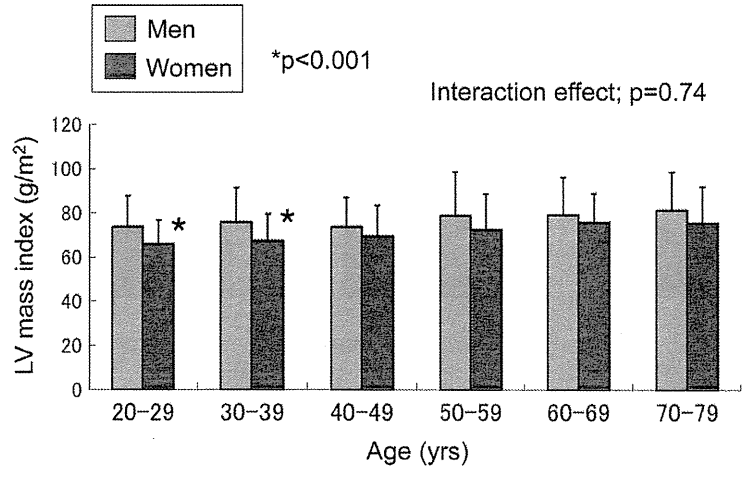

Figure 2. Effects of age and gender on left ventricular (LV) mass index. Among young subjects aged 20–29 years and 30–39 years, LV mass index was significantly greater in men than in women. There was no significant interaction effect, however, between age and gender that affected the differences in LV mass index among the groups. *P<0.001.

addition, LV ejection fraction was lower in men than in women in the same 3 age groups (Figure 1C). There were no significant interaction effects, however, between gender and age that influenced the observed differences in the LV volume indices and ejection fraction. LV mass index increased with age to a similar extent in both men and women (Figure 2). LV mass index was significantly lower in women than in men in the 2 youngest age groups (20–29 years and 30–39 years), and the increase in LV mass index with age seemed more pronounced in women than men. There was no significant interaction effect, however, between age and gender that affected the differences in LV mass index among the groups.

LV Diastolic Parameters and LA Volume

The results of mitral inflow and TDI are shown in Figures 3,4, respectively. A decline in mitral peak E velocity, an increase in mitral peak A velocity, a decline in mitral E/A ratio and an increase in mitral Dct were observed with age in both men and women. Of note, mitral peak E velocity and E/A ratio were significantly greater in women than men in subjects <50 years but were similar between men and women in subjects ≥50 years. In addition, there was a significant interaction effect

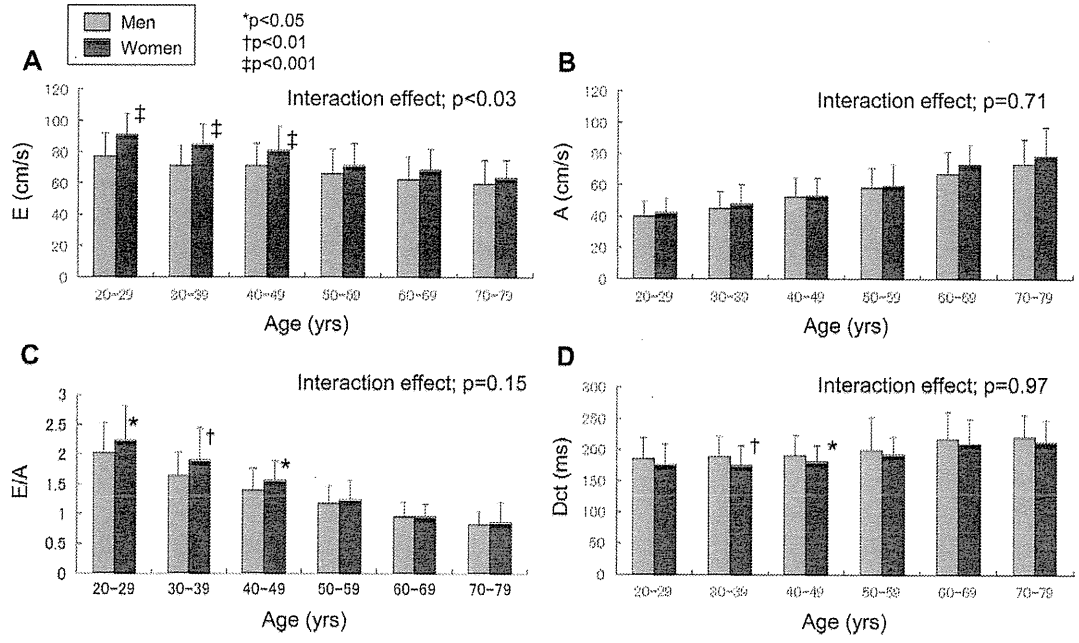

Figure 3. Effects of age and gender on mitral inflow parameters. Among subjects aged 20–29 years, 30–39 years and 40–49 years, (A) mitral peak E velocity and (C) mitral E/A ratio were greater in women than in men, and (D) among subjects aged 30–39 years and 40–49 years, mitral early flow deceleration time (Dct) was shorter in women than in men. There was a significant interaction effect between gender and age that affected the differences in peak E wave velocity among the groups. *P<0.05, †P<0.01, ‡P<0.001 (ANOVA).

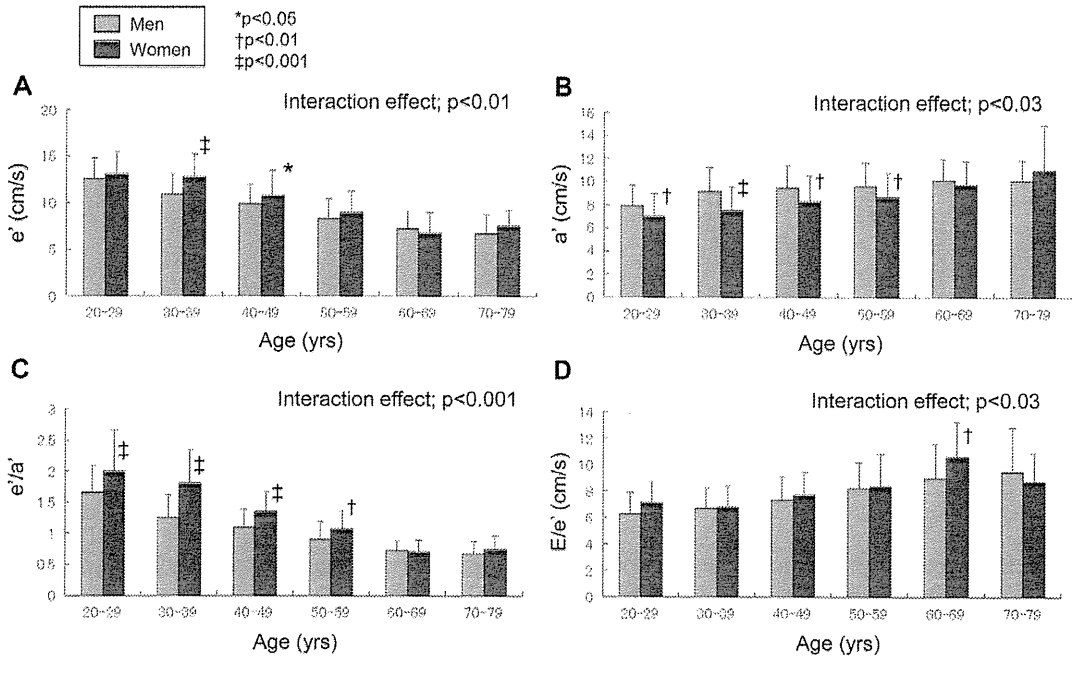

Figure 4. Effects of age and gender on tissue Doppler imaging (TDI) parameters. Among subjects aged 30–39 years and 40–49 years, (A) TDI e' velocity was greater in women than in men. Among subjects aged 20–29 years, 30–39 years, 40–49 years and 50–59 years, (B) TDI a' velocity was lower in women than in men, and (C) TDI e'/a' ratio was greater in women than in men. Among subjects aged 60–69 years, (D) E/e' ratio was greater in women than in men. There were significant interaction effects between gender and age that affected the differences in all of these parameters among the groups. *P<0.05, †P<0.01, ‡P<0.001 (ANOVA).

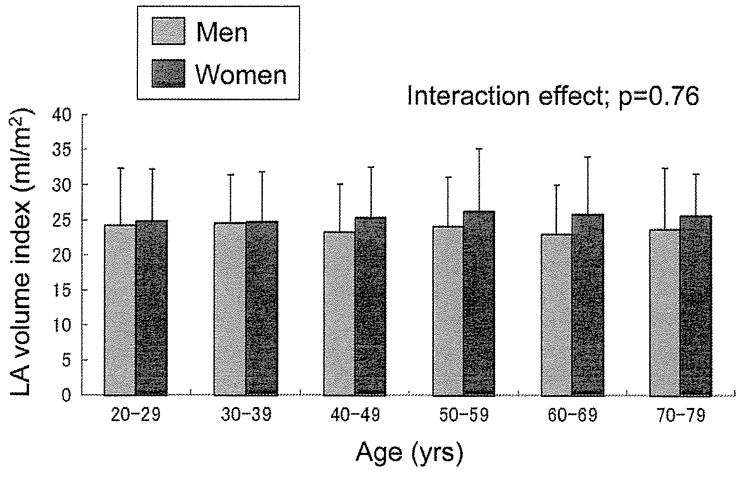

Figure 5. Effects of age and gender on left atrial (LA) volume index: LA volume index was similar between men and women across all age groups.

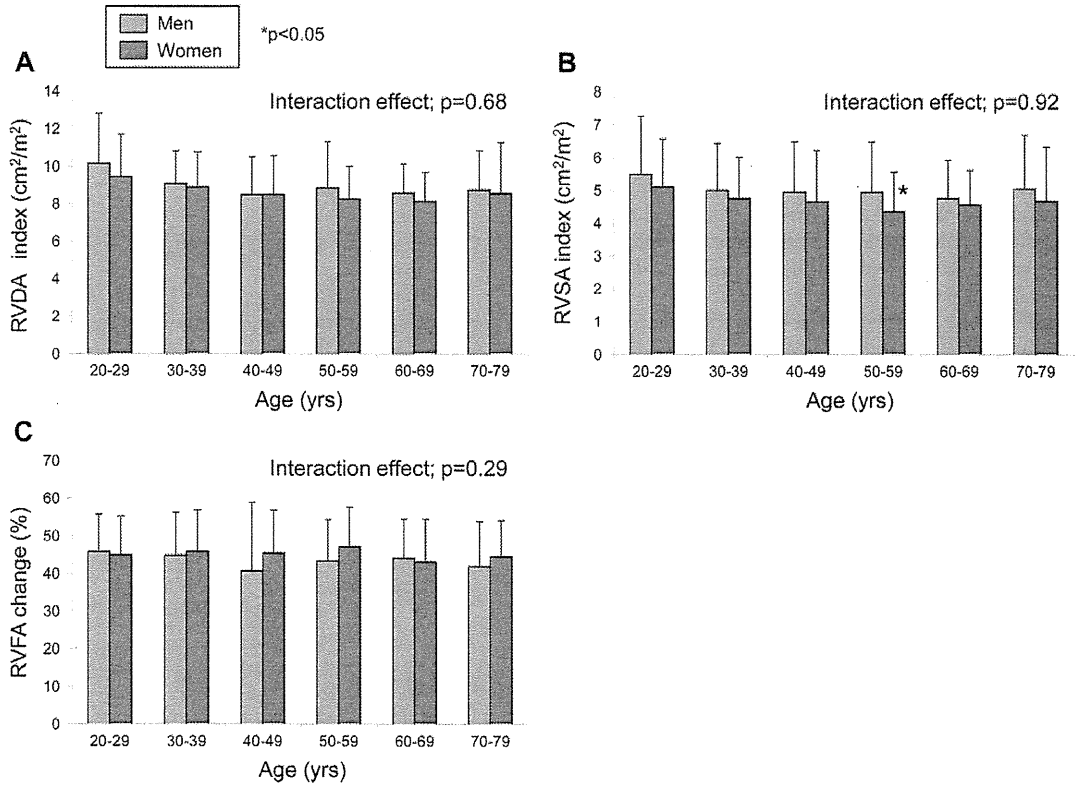

Figure 6. Effects of age and gender on right ventricular (RV) area and fractional area change. Both diastolic and systolic RV area indices slightly decreased with age similarly in both men and women. RV fractional area change was similar in both men and women across all age groups. RVDA, RV diastolic area; RVFA, RV fractional area; RVSA, RV systolic area. *P<0.05.

(P<0.03; ANOVA) between gender and age that affected the differences in peak E wave velocity among the groups. As shown in Figure 4, younger women had higher TDI, e' velocity and e'/a' ratio but lower a' than younger men; but there were no differences in these parameters between older men and women. Moreover, ANOVA indicated a significant interaction effect between gender and age that influenced the differences in all of the TDI-derived parameters among the groups.

For age-related changes in LA volume, women tended to have a larger age-related increase in LA volume than men (Figure 5). There was no significant interaction effect, however, between gender and age that influenced the differences in LA volume.

RV Size and Systolic Function

The results of RV area and fractional change are given in Figure 6. There were no significant differences in RV diastolic and systolic area indices, or in RV area fractional change between men and women, except for RV systolic area index among subjects aged 50–59 years. Accordingly, there were no gender differences in age-related changes in these RV parameters.

Discussion

In the present study we found significant gender differences in the age-related changes in LV diastolic parameters assessed on mitral inflow and TDI. Overall, younger women had better LV diastolic parameters and lower LV mass index compared with younger men, whereas these parameters were similar in older (>50 years) men and women. In contrast, there were no gender differences in age-related changes in RV size and systolic function. The present results indicate that gender differences should be considered in association with age in the management of cardiovascular disease. In addition, recognition of these differences is critical not only in routine clinical practice, but also in interpreting the results of clinical trials that use echocardiography to measure cardiac geometry and function.

Gender-based differences in the management and outcomes of patients with cardiovascular disease have been widely recognized and extensively investigated.[1–4] Recently, Okura et al reported gender-specific changes in LV relaxation with age in healthy individuals without arrhythmias, abnormal echocardiographic findings, a history of heart disease or hypertension.[17] In that study, subclinical conditions such as diabetes mellitus or renal failure that might have affected LV diastolic parameters could not be completely excluded. In contrast, we enrolled healthy volunteers without any systemic conditions including diabetes or renal failure that might have altered LV diastolic parameters in an attempt to assess only normal echocardiographic parameters. In fact, LV diastolic parameters in the Okura et al study appear to be attenuated compared with the same parameters measured in the same age group in the present subjects. Munagala et al and Redfield et al similarly reported age-related changes in LV diastolic parameters,[10,11] but because their subjects consisted of people aged >45 years, they were not able to identify gender-specific differences in echocardiographic LV parameters over the entire adult age range.

The effect of estrogen and postmenopausal status on smooth muscle proliferation[18] and vascular function[19,20] may play a role in gender-based differences in echocardiographic LV parameters. In the present study LV diastolic parameters were relatively worse in women than in men over 50, whereas younger women had better diastolic parameters than men in the same age range. Menopause usually occurs at the age of approximately 50, and rapid changes in LV diastolic parameters in women over 50 seem to be consistent with postmenopausal status.

Although we found gender differences in the changes in LV diastolic parameters with age, the present data did not suggest deteriorated LV diastolic function in elderly women compared with elderly men. At least, no significant differences in LV diastolic parameters were found between elderly men and women. The majority of diastolic HF occurs in association with hypertension[21,22] or diabetes mellitus.[23,24] Thus, future studies need to explore the mechanisms responsible for hypertension- or diabetes-induced diastolic dysfunction in elderly women. Moreover, the present study suggests that gender differences in age-related changes in LV geometry and function should be considered in the investigation of the pathophysiology of both diastolic and systolic HF.

Study Limitations

We investigated LV geometry and function in totally healthy volunteers in the present study. Therefore, the number of subjects aged 70–79 years was small, because of the difficulty in finding healthy volunteers in that age range without any conditions that affect echocardiographic parameters. Furthermore, the medical histories of participants were reviewed at each institution, therefore, the presence of unrecognized cardiovascular disease cannot be ruled out. In addition, echocardiographic measurements were performed at each institution according to a standard protocol. Thus, inter-observer variability might have affected the echocardiographic measurements. The standard deviations of the measurements, however, were small and similar to those reported in previous studies,[9,11] and the influence of inter-observer variability was considered to be negligible.

We excluded subjects with a history of hypertension and those with high blood pressure at the time of echocardiography, therefore we did not take into consideration the influence of blood pressure on LV geometry in the current study. There was, however, a slight age-related increase in blood pressure both in men and women, as presented in our previous study.[14] This age-related change of blood pressure might have influenced the present results.

Conclusions

We identified gender differences in age-related changes in LV geometry and function in a healthy population. The present results indicate the need for consideration of these gender differences in the optimal diagnosis and management of cardiovascular disease.

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Disclosure

None of the authors have relationships to disclose.

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Four-year clinical outcomes of the OLIVUS-Ex (impact of Olmesartan on progression of coronary atherosclerosis: Evaluation by intravascular ultrasound) extension trial

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ABSTRACT

Background: The previous OLIVUS trial reported a positive role in achieving a lower rate of coronary atheroma progression through the administration of Olmesartan, an angiotension-II receptor blocking agent (ARB), for stable angina pectoris (SAP) patients requiring percutaneous coronary intervention (PCI). However, the benefits between ARB administration on long-term clinical outcomes and serial atheroma changes by IVUS remain unclear. Thus, we examined the 4-year clinical outcomes from OLIVUS according to treatment strategy with Olmesartan.
Methods: Serial volumetric IVUS examinations (baseline and 14 months) were performed in 247 patients with hypertension and SAP. When these patients underwent PCI for culprit lesions, IVUS was performed in their non-culprit vessels. Patients were randomly assigned to receive 20–40 mg of Olmesartan or control, and treated with a combination of β-blockers, calcium channel blockers, glycemic control agents and/or statins per physician's guidance. Four-year clinical outcomes and annual progression rate of atherosclerosis, assessed by serial IVUS, were compared with major adverse cardio- and cerebrovascular events (MACCE).
Results: Cumulative event-free survival was significantly higher in the Olmesartan group than in the control group ($p = 0.04$; log-rank test). By adjusting for validated prognosticators, Olmesartan administration was identified as a good predictor of MACCE ($p = 0.041$). On the other hand, patients with adverse events ($n = 31$) had larger annual atheroma progression than the rest of the population (23.8% vs. 2.1%, $p < 0.001$).
Conclusions: Olmesartan therapy appears to confer improved long-term clinical outcomes. Atheroma volume changes, assessed by IVUS, seem to be a reliable surrogate for future major adverse cardio- and cerebrovascular events in this study cohort.

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1. Background

Despite the widespread application of established medical therapies, extensive cardiovascular disease remains the most important cause of morbidity and mortality in patients with ischemic coronary disease [1–11]. Although angina pectoris is characterized by a clustering of cardiovascular disease risk factors, such as dyslipidemia, diabetes, and hypertension, optimal atheroma management is a key strategy for preventing subsequent cardiovascular events [1,4–10,12–16]. Prior intravascular ultrasound (IVUS) trials reported a slowing of coronary atheroma progression or regression with some medicines, however, the direct benefits between drug administration on long-term clinical outcomes and atheroma volume changes, assessed by IVUS, have not been well clarified [1,4–10,12–16].

The OLIVUS trial, using serial volumetric IVUS, reported a positive role in achieving a lower rate of coronary atheroma progression through the administration of Olmesartan, an angiotension-II

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receptor blocking agent (ARB), for stable angina pectoris (SAP) patients requiring percutaneous coronary intervention (PCI) [17]. According to treatment strategy with Olmesartan, we investigated the 4-year OLIVUS follow up data to evaluate the relation between atheroma volume change and clinical outcomes.

2. Methods

2.1. Patients and study design

The OLIVUS trial is a prospective, randomized, multicenter trial which examined the impact of Olmesartan on the progression of coronary atherosclerosis; evaluation by intravascular ultrasound (OLIVUS) [17]. Patients with hypertension and clinically stable angina pectoris scheduled for percutaneous coronary intervention (PCI) were enrolled. After PCI for their culprit lesions, IVUS was performed over 40 mm in their non-culprit vessels, defined as without angiographically documented coronary stenosis <50%, to determine plaque volume at baseline. Hemodynamically unstable patients, recent myocardial infarction within 4 weeks, ejection fraction <25%, and patients already on ACE inhibitors or ARBs were excluded from the trial. Patients were randomized to control or Olmesartan 10–40 mg titrated to maximally tolerated dose by 8 weeks. In addition, patients were treated with a combination of β-blockers, calcium channel blockers, diuretics, nitrates, glycemic control agents and/or statins per physician's guidance. After 12–16 months, IVUS of the originally examined coronary artery was performed during the routine follow-up angiogram. The extended-OLIVUS trial increased the follow-up period of the OLIVUS trial to evaluate associations between clinical prognosis, coronary atheroma changes and Olmesartan treatment. The study protocol was approved by all participating institutional review boards and all patients provided written informed consent. The primary endpoint was the incidence of major adverse cardio- and cerebrovascular events (MACCE), including the composite of death from cardiac or cerebral causes, myocardial infarction, stroke, rehospitalization due to unstable or progressive angina according to the Braunwald unstable angina classification and the Canadian Cardiovascular Society angina classification, deterioration of heart function or renal failure. Stroke was diagnosed based on the presence of a neurologic deficit confirmed by computed tomography or magnetic resonance imaging. Outcome data were collected by serial contact with the patients or their families until July 31, 2011. Medical records of patients who died or who were treated at participating hospitals were analyzed.

2.2. Intravascular ultrasound

IVUS studies were performed using a commercially available imaging system with a 40-MHz mechanical transducer ultrasound catheter (Boston Scientific Corporation, Natick, MA). Using automated pullback (0.5 mm/s), ultrasound images were obtained and recorded for off-line quantitative analysis. The images were digitized and three-dimensional volumetric analysis was performed using Simpson's method (EchoPlaque, Indec Systems, Mountain View, CA). Measurements included vessel, lumen and atheroma volumes (ATV) over the 40 mm segment in the non-PCI-culprit vessels. To standardize for vessel size, percent atheroma volume (%ATV), defined as plaque volume divided by vessel volume, was also calculated. The serial progression rate of atherosclerosis was compared with change in absolute atheroma volume and change in percent atheroma volume, measured by (follow-up ATV − baseline ATV)/baseline ATV, and (follow-up %ATV − baseline %ATV)/baseline %ATV, respectively. All analytic methods were previously reported [17,18].

Table 1
Baseline patient characteristics and medications.

	Control ($n=121$)	Olmesartan ($n=126$)	p
Gender (male, %)	68	76	ns
Age (years)	68.4 ± 8.8	67.8 ± 8.7	ns
Smoking (%)	31	34	ns
Diabetes (%)	35	31	ns
Previous MI (%)	13	15	ns
Aspirin (%)	100	100	ns
β-Blocker (%)	13.2	12.7	ns
Calcium channel blockers (%)	49.6	41.3	ns
Statins (%)	74.0	71.4	ns
Oral diabetic agents (%)	17.3	19.8	ns
Insulin (%)	7.1	5.6	ns

2.3. Statistical methods

Analyses were performed using SPSS 11 software (SPSS Inc., Chicago, IL). Laboratory and ultrasound parameters were reported as the mean value ± SD. Continuous variables are expressed as means ± SD. Data from two independent groups were compared using a t-test or Wilcoxon rank-sum test. Intra-group data were analyzed using a paired t-test or the Wilcoxon signed-rank test. Categorical data were tabulated as frequencies and percentages and compared using the χ^2 test or Fisher's exact test. Event-free survival probabilities for MACCE were estimated using the Kaplan–Meier method and group differences were assessed using a log-rank test. Unadjusted hazard ratios for variables, namely administration of Olmesartan, statin, age, gender, atheroma volume changes, baseline percent atheroma volume, hypertension, diabetes, smoking, prior history of coronary artery disease and baseline LDL-C values, were calculated using the Cox proportional hazards model. A two-sided p-value of <0.05 was considered significant.

3. Results

Between February 2006 and August 2007, 247 patients with stable angina pectoris patients undergoing PCI were enrolled in this trial. Prognostic data were fully documented during the entire follow-up period (mean duration, 4.1 ± 1.3 years). During follow up, 15 patients in the control group and 17 patients in the Olmesartan group dropped out of the trial because of MACCE, laboratory abnormality or having withdrawn consent. Even though serial volumetric IVUS analyses were completed in 205 patients, vital status was ascertained in 233 (93.3%) patients at the end of the study. Of the 118 (93.6%) patients taking Olmesartan at the end of the study, 107 (84.9%) were on the full dose (20–40 mg), with only 4 (3.2%) on a reduced dose.

3.1. Patient characteristics and blood pressure changes

Patient characteristics and medications are summarized in Tables 1 and 2. All data are identical between the control and Olmesartan groups. Serial changes in blood pressure are presented in Fig. 1. In this trial, blood pressure control was at the physician's discretion except for administration of Olmesartan. While significant improvement in blood pressure, LDL/HDL cholesterol and glycemic control were observed in both groups, there was no significant difference between the control and Olmesartan group.

3.2. Volumetric IVUS analysis

Significant development of atheroma volume (ATV) and percent atheroma volume (%ATV) was found in the control group between baseline and 14-months follow-up (from 208.8 ± 151.5 to 215.9 ± 156.8 (mm^3), $p<0.01$ for ATV, from 40.6 ± 10.8 to

Table 2
Blood parameters of patients at baseline and 4-years follow-up.

	Baseline			Follow-up		
	Control	Olmesartan	*p*-Value	Control	Olmesartan	*p*-Value
Total cholesterol (mg/dl)	185.9 ± 34.3	183.3 ± 29.6	0.554	183.8 ± 37.0	181.4 ± 30.4	0.941
HDL-C (mg/dl)	50.4 ± 12.6*	47.1 ± 12.7*	0.073	56.1 ± 15.2*	52.6 ± 13.3*	0.084
Triglyceride (mg/dl)	142.4 ± 64.6	163.9 ± 126.4	0.131	140.4 ± 73.9	158.7 ± 81.0	0.093
LDL-C (mg/dl)	108.0 ± 30.2†	106.8 ± 24.8†	0.405	101.7 ± 30.8†	101.2 ± 26.2†	0.915
Body Mass Index (kg/m^2)	23.9 ± 3.5	24.7 ± 3.2	0.091	23.7 ± 3.0	24.3 ± 4.3	0.270
Creatinine (mg/dl)	1.00 ± 0.41	0.99 ± 0.25†	0.844	0.92 ± 0.44	0.97 ± 0.29†	0.153
e-GFR (ml/min/1.73 m^2)	57.9 ± 19.2	59.6 ± 17.5	0.517			
HbA1c (%)	5.9 ± 1.2†	6.1 ± 1.1†	0.358	5.7 ± 0.9†	5.9 ± 0.9†	0.242
BNP (pg/dl)	49.8 ± 47.2	45.1 ± 29.7	0.482	46.9 ± 67.9	37.4 ± 32.3	0.211

* $p < 0.01$.
† $p < 0.05$ between baseline to follow-up.

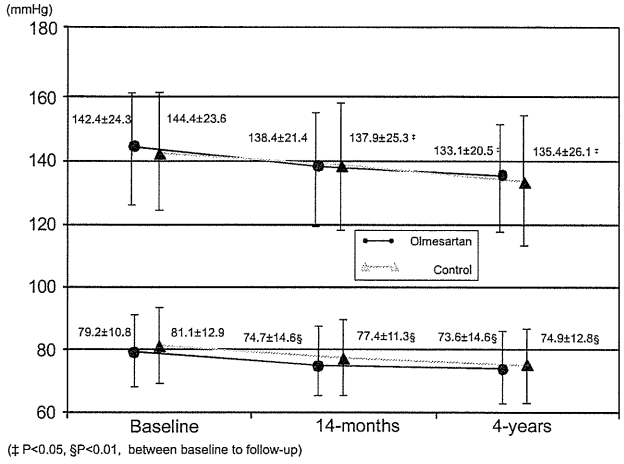

Fig. 1. Serial changes of blood pressure in the study period.

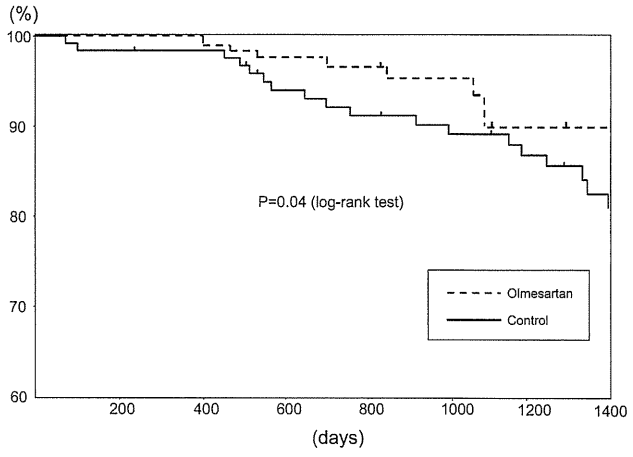

Fig. 2. Cumulative event-free from cardio or cerebrovascular death, myocardial infarction, stroke, angina, or heart/renal failure.

41.7 ± 11.5 (%), $p < 0.05$ for %ATV). However, there was no difference between ATV and %ATV in the Olmesartan group (230.2 ± 151.7 to 227.6 ± 145.8 (mm^3) for ATV, 43.8 ± 10.2 to 43.7 ± 10.4 (%) for %ATV, p = ns for all). Furthermore, serial change in ATV and %ATV were significantly lower in the Olmesartan group than in the control group (0.6 ± 12.9 vs. 5.4 ± 15.5 (%) $p = 0.016$ for ATV, −0.7 ± 13.6 vs. 3.1 ± 12.5%, $p = 0.038$ for %ATV, respectively). However, in this trial, there was no statistically significant correlation between blood pressure reduction and plaque progression rate.

3.3. *Major adverse cardio- and cerebrovascular events (MACCE)*

Adjudicated major adverse cardio- and cerebrovascular events are summarized in Table 3. While there was no difference in terms of individual cardio- and cerebrovascular event between the two groups, the composite event rate of cardio- and cerebrovascular death, MI, stroke, angina, or heart/renal failure was significantly lower in the Olmesartan group ($p = 0.041$). Cumulative event-free from MACCE was significantly higher in the Olmesartan group than in the control group ($p = 0.04$, log-rank test; Fig. 2, Hazard ratio 0.41 (95% CI: 0.18–0.91, Relative risk reduction = 0.54)). Estimates of hazard ratios for MACCE are presented in Fig. 3. Advanced age, prior history of coronary artery disease, 3-vessel disease, poorly controlled diabetes, higher %ATV increase and higher original %ATV were identified as poor predictors of MACCE. However, administration of Olmesartan and statins were selected as predictors for reduced MACCE. Comparison of serial atheroma progression rate for patients with adverse events ($n = 31$) and the rest of the population is presented in Fig. 4. Patients with adverse events had larger annual atheroma progression than the rest of the population ($p < 0.001$). During the follow-up period, there were no adverse events attributed to Olmesartan.

Table 3
Four-years adjudicated major cardiovascular events.

	Control ($n = 121$)	Olmesartan ($n = 126$)	*p*
Composite of cardio or cerebrovascular death, MI, stroke, angina, or heart/renal failure	17.4	8.0	0.04
Death (all cause)	3.3	3.2	0.95
Death (cardio or cerebrovascular)	1.7	0.8	0.51
Nonfatal myocardial infarction	0.8	1.6	0.59
Nonfatal stroke	1.7	0	0.15
Unstable angina/increasing angina	10.7	4.8	0.10
(Culprit related/new de novo coronary lesions)	(5.0/5.7)	(3..2/1.4)	
Deterioration of heart/renal failure	2.5	0.8	0.30

MI indicates myocardial infarction.

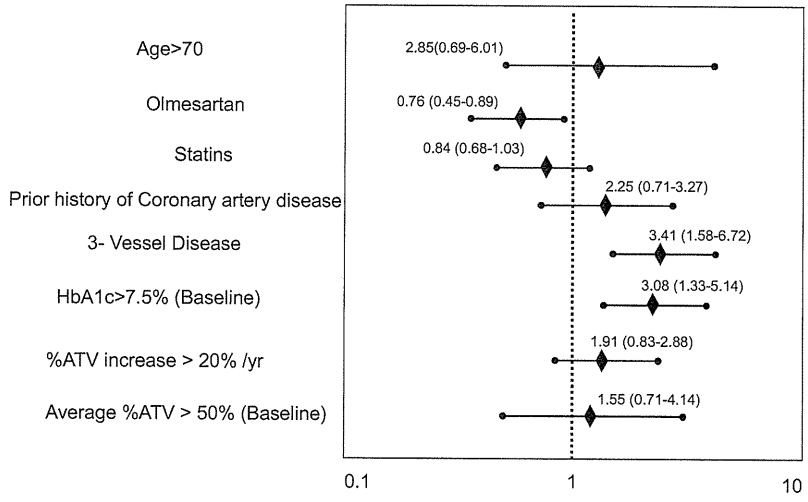

Fig. 3. Hazard ratio for major adverse cardio- and cerebrovascular events (MACCE) are presented. Hazard ratio and 95% CI value are listed.

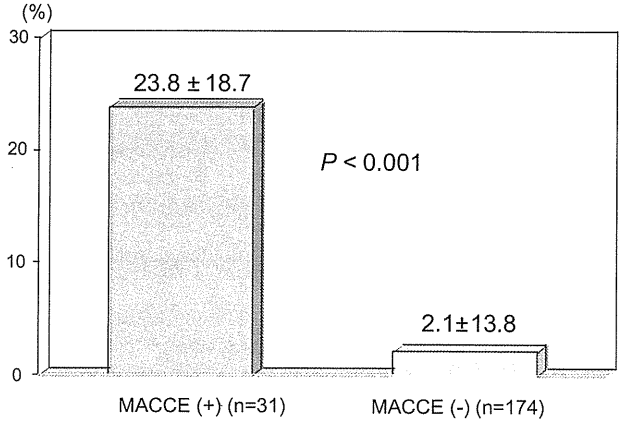

Fig. 4. Comparison of major adverse cardio- and cerebrovascular events (MACCE) and annual atheroma progression.

4. Discussion

The present study demonstrated that administration of Olmesartan was associated with reduced incidence of long-term cardio- and cerebrovascular events in patients with hypertension and stable angina pectoris after PCI. In addition, the 14-months IVUS follow-up showed that patients who had greater atheroma progression had an increase in subsequent cardio- and cerebrovascular events. In previous IVUS trials, interventions that targeted established risk factors demonstrated favorable effects on the rate of progression of coronary atherosclerosis. In the initial stage of the current trial, significant plaque regression was observed in patients receiving Olmasartan, an ARB, compared with the control group during the 14-months follow-up period. The extended-OLIVUS trial demonstrated sustained reduction in incidence of composite cardiovascular complications during the 4-years while receiving Olmesartan. Currently, ARBs are widely used for the treatment of hypertension. They also have beneficial effects on hypertension-related cardiovascular end organ damage, possibly due to reduction of oxidative stress and inflammation [19–21]. While there are several ARBs available in the clinical setting, Olmesartan is thought to have a significantly stronger antihypertensive effect than other ARBs with their respective starting doses [19–23]. In addition, previous studies as well as the OLIVUS trial have reported the potential decrease of atheromatous plaque burden in human coronary arteries after administration of Olmesartan, compared with the control group [17]. Furthermore, previous trials reported a significant reduction in the incidence of stroke and angina pectoris in patients receiving ARBs [20]. Our study data show the corroborating efficacy for these medicines in terms of preventing the progression of atherosclerosis, even though the number of enrolled patients was relatively small. However, the underlying mechanisms as well as the clinical impact of ARBs remain a matter of ongoing debate. There was no significant difference in terms of changes of blood pressure. In this trial, control of blood pressure was left to physician's discretion except for administration of ARBs and ACE inhibitors, therefore, an incremental dose of other antihypertensive agents, such as β-blockers, calcium channel blockers and/or diuretics, may have contributed to the similarities in blood pressure control between the 2 groups. In the present trial, there was no statistically significant correlation between the degree of blood pressure reduction and plaque progression rate or event rate. This may suggest the potential manifold action of Olmesartan apart from the antihypertensive effect that might be beneficial, such as activity leading to plaque stabilization and reduction. In the present trial, however, there was no significant effect on the hard events including cardiac and cerebral deaths and myocardial infarction during the 4-years follow-up period. Most events were re-hospitalizations for unstable or progressive angina, therefore, death from cardiac causes, cardiac arrest, and myocardial infarction were less common. The effects of increasing disease burden on death or myocardial infarction were not evident in this analysis, which likely reflects the finding that there were few mortal events under the current optimal medical therapy [16,24]. These results are consistent with previous trials suggesting that effects on hard endpoints using ARB showed close to the significance compared with the control group [20,23].

In the current trial, Olmesartan and statins were selected as predictors of MACCE reduction. However, a high proportion of patients in our study were showing relatively lower LDL cholesterol level at baseline, and already being treated with lipid-lowering agents (57.0% in the control and 52.3% in the Olmesartan group), which might have minimized the differences in MACCE events seen between the two randomized groups than in previous trials [1–3,5,6,9,10,12,25,26]. In the present study, it may be important to note that atheroma volume, reflecting the interaction between the artery wall and atheroma throughout the imaged segment, did associate with the likelihood of having a clinical event.

Volumetric IVUS analyses were completed exclusively in entire vessels (more than 40 mm); therefore, these IVUS parameters may represent atheroma progression of coronary as well as cerebral arteries, since atherosclerosis progresses systemically. The results suggest that atheroma volume changes, assessed by serial IVUS, seem to be a reliable surrogate for future major adverse cardio- and cerebrovascular events in this study cohort [4,12,16,17,24,27–29].

The present analysis demonstrates a relationship between the progression of coronary atherosclerosis, as determined by IVUS, and the prospective risk for cardio- and cerebrovascular events. To diminish subsequent cardiovascular risk, therapeutic strategies designed to prevent or delay the progression of coronary disease is of great clinical importance. We believe this is the first clinical trial that shows the direct potential benefits between long-term drug administration on long-term clinical outcomes and atheroma volume changes, assessed by IVUS, using an ARB. Our study data may add another striking benefit to the ever-growing list of positive outcomes associated with Olmesartan administration.

5. Limitations

There are several limitations in our study. First, a small number of patients with stable angina pectoris were enrolled; therefore, some selection bias may exist. Second, the IVUS results showed relatively larger standard deviations, however, these are not unusual for this kind of study. In addition, a high proportion of patients in our study were already being treated with optimal lipid-lowering therapy, therefore, it may be difficult to show an effect in addition to that treatment.

6. Conclusions

These observations suggest that administration of Olmesartan was associated with reduced incidence of long-term cardio- and cerebrovascular events in patients with hypertension and stable angina pectoris after PCI. Atheroma volume changes, assessed by serial IVUS, seem to be a reliable surrogate for future major adverse cardio- and cerebrovascular events in this study cohort.

Conflict of interest

None.

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