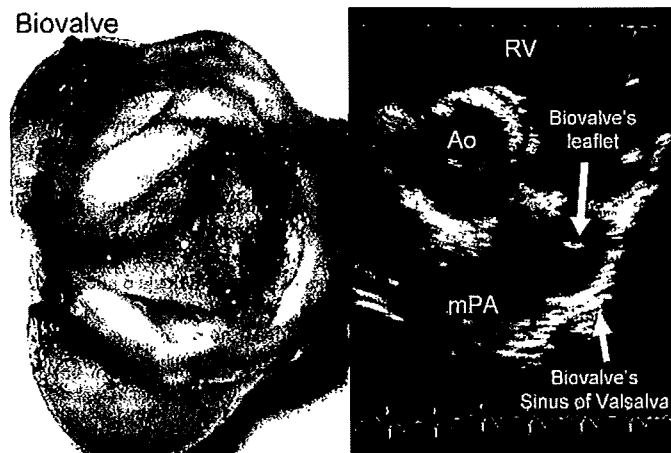


Autologous valved conduits with the sinus of valsalva were firstly developed by utilizing the living body as a reactor for tissue organization.

Biovalve



Symposium 14 (SY-14) (H)

Lifestyle Change Strategies for Primary and Secondary Prevention of Cardiovascular Disease

March 6 (Sat)

Room19 (Grand Prince Hotel Kyoto B2F Prince Hall 2)

11:10–12:40

Chairpersons:

Hirotsugu Ueshima
Department of Health Science, Shiga University of Medical Science, Otsu
Hiroyasu Iso
Public Health, Osaka University, Osaka

1

Methods and Effects of Population Approaches for Cardiovascular Disease Prevention: The HIPOP-OHP Study

¹Katsuyuki Miura

²Tomonori Okamura, ³Hirotsugu Ueshima

¹Department of Health Science, Shiga University of Medical Science, Otsu,

²Division of Cardiovascular Prevention, National Cardiovascular Center, Suita,

³Lifestyle-Related Disease Prevention Center, Shiga University of Medical Science, Otsu

Although the importance of population approach has been established for cardiovascular disease (CVD) prevention, its effective methods have not been well developed for Japanese people living in Japanese lifestyles. The High-Risk and Population Strategy for Occupational Health Promotion (HIPOP-PHP) Study is a large-scale controlled trial to develop the methods of population approaches and to evaluate their effectiveness on CVD risk factors. Six worksites (2,919 participants) participated for the intervention group and other 6 worksites (3,670 participants) participated for the control group; they were followed for 4 years. Intervention includes population approaches to improve dietary habits (reduction of salt and fat intake; increase in vegetable and fruit intake; adequate energy intake; adequate alcohol drinking), to increase physical activity, and to improve environment for smoking cessation. During the follow-up period, the absolute/proportional changes in serum HDL-cholesterol were 2.7 mg/dL (4.8%) in the intervention group and -0.6 mg/dL (-1.0%) in the control group; the differences were significant ($P < 0.001$). This difference was likely to be due to the significant increase in daily walking time in the intervention group ($P < 0.001$). A low-intensity multi-component intervention program for smoking cessation targeting the worksite environment was effective; smoking cessation rate during the follow-up was significantly higher in the intervention group than the control group (12.1% vs. 9.4%, $P = 0.021$). Several population approach methods to improve dietary habits were developed especially using worksite canteens, and we observed some evidences on salt reduction. Consequently, the estimated CVD risk was substantially reduced in the intervention group. These methods are now utilized for CVD prevention in many worksites and communities in Japan.

2

Total Smoking Ban in Public and Workplaces but not Specific Health Checkup and Intervention is Effective for Smoking Cessation

Chinori Kurata

Akihiko Uehara, Keiichi Odagiri

YAMAHA Health Care Center, Hamamatsu

The Japanese national screening and intervention program for metabolic syndrome (specific health checkup and intervention) are launched last year. In our institution, the results of specific health checkup and intervention including

OJ-153

The Heterogeneity of Proliferation and the Color of Neointima after Drug-eluting Stent Implantation -Observation by Angioscopy and OCT-

¹Tadateru Takayama
¹Takafumi Hiro, ¹Masafumi Akabane, ¹Yasuo Watanabe,
¹Hironori Haruta, ¹Daisuke Fukamachi, ¹Nobuaki Ishii,
¹Taro Kawano, ¹Makoto Ichikawa, ¹Daisuke Kitano, ¹Takashi Kanai,
¹Kanae Ikegami, ³Masaaki Chiku, ²Junko Hone, ³Satoshi Saitoh,
¹Atsushi Hirayama
¹Division of Cardiology, Department of Medicine, Nihon University School of Medicine, Tokyo, ²Shonan Kamakura General Hospital, Kanagawa, ³Keiai Hospital, Tokyo

Background: Drug-eluting stents (DES) are susceptible to late thrombosis due to delayed re-endothelialization, which may result in the fatal situation. Therefore, we performed a comparative serial investigation of Sirolimus-eluting stent(SES) and Paclitaxel-eluting stent (PES) using these imaging modalities Method: For 8 to 12 month (10.3 month average) follow up, 52 lesions (SES 24, PES 28) in 52 DES patients were imaged with angioscopy and OCT simultaneously. Heterogeneity index (HI) of neointima was calculated by OCT as: SD / average thickness of neointima. Results: Angioscopy showed that the grade of neointimal coverage in PES was significantly greater than that in SES (SES: 1.59, SES: 1.0, P<0.05). In-stent yellow grade of neointima in SES was significantly greater than in PES (SES: 1.16, PES: 0.66, p<0.05). OCT revealed the thickness of neointima in PES was much greater than in SES, however, HI was not different in both groups. (SES: 121.3±7.1µm, HI:0.89, PES: 219.9±10.4µm, 121.3±7.1µm, HI: 0.56, p=0.23). Conclusion: The neointima thickness was thinner in SES compared to PES. However, HI was comparable between SES and PES, by OCT. Furthermore, higher yellow grade of neointima were identified in SES by angioscopy, which was a possible cause for stent thrombosis. These data suggested that SES had a neointima with different tissue characteristics, which might provide different, rate of late thrombosis, rather than the heterogeneity of neointima proliferation.

spite of no differences of Rutherford class. Conclusions: Patency of AA might promise the good prognosis of CL after successful EVT.

Patency of Arcuate arteries	(A)	(B)	P value
No. of limbs (%)	106 (59.2%)	73 (40.8%)	
Rutherford 5-6 (%)	51 (51.9%)	40 (54.8%)	p= NS
pre SPP (mmHg)	32.9	27.9	p<0.05
post SPP (mmHg)	51.0	44.6	p<0.05
#MAE (%)	12 (11.3%)	18 (24.7%)	p<0.05

#MAE:Mortality and Major Amputation Rate

OJ-155

The Endovascular Stent Graft Raises Vascular Stiffness and Changes Cardiac Structure within a Very Short Term

¹Yasuharu Takeda
¹Yasushi Sakata, ¹Toshiaki Mano, ¹Daisuke Kamimura,
¹Shunsuke Tamaki, ¹Yosuke Ohmori, ¹Yasumasa Tsukamoto,
¹Yoshihiro Aizawa, ²Yukitoshi Shirakawa, ²Kazuo Shimamura,
²Toru Kuratani, ²Yoshiki Sawa, ³Kazuhiro Yamamoto, ¹Issei Komuro
¹Department of Cardiovascular Medicine, Osaka University Graduate School of Medicine, Suita, ²Department of Cardiovascular Surgery, Osaka University Graduate School of Medicine, Suita, ³The Center for Advanced Medical Engineering and Informatics, Osaka University, Suita

Background: The endovascular stent graft is used in the growing number of patients with thoracic or abdominal aortic aneurysm (TAA, AAA). However, its effects on vascular and cardiac function remain unclear. Methods: Echocardiographic study and the evaluation of the brachial-ankle pulse wave velocity (baPWV) were conducted before (pre-op) and after the endovascular stent grafting (post-op) in 36 consecutive patients with AAA or TAA. Patients were excluded if they had LV ejection fraction (EF) ≤40%, moderate-to-severe valvular diseases, aortic dissection and renal failure. Result: Post-op data were collected around 7 days after the operation. Blood pressure was decreased (pre-op:130±2, post-op:125±2mmHg, p<0.05), and baPWV (pre-op:1937±60, post-op:2104±84cm/s, p<0.05) and heart rate (pre-op:65±2, post-op:70±2bpm, p<0.05) were elevated after the grafting. There was no difference in LV end-diastolic volume, indices of transmitral flow velocity curves, a ratio of transmitral E velocity to early diastolic mitral annular velocity, and inferior vena cava dimension between pre-op and post-op status. LV mass (pre-op:157±6, post-op:164±7g, p<0.05) and left atrial volume (pre-op:48±2, post-op:53±2ml, p<0.05) significantly increased at post-op status. The changes in LV mass were positively correlated with those in baPWV (p<0.05, R=0.44). Furthermore, EF significantly decreased at post-op status (pre-op:67±1, post-op:65±1%, p<0.05). Conclusion: The endovascular stent graft raised vascular stiffness, induced LV hypertrophy, left atrial enlargement, and decreased EF within the very short term.

Peripheral Circulation / Vascular Disease (Therapy) 4 (H)

OJ27

March 6 (Sat)

Room14(Kyoto International Conference Center 5F Room 501)

14:50—16:20

OJ-154

Patency of Arcuate Arteries (AA) Influences the Prognosis of Critical Ischemic Limbs (CL) after Successful Endovascular Therapy (EVT)

Yasutaka Yamauchi
 Akira Miyamoto, Masahiro Fukuda, Naohiro Hakamata,
 Takako Akita, Ryouji Kuhara, Shingo Tezuka
 Cardiovascular Center, Kikuna Memorial Hospital, Kanagawa

Objective: We investigated the relationship between the patency of AA and the prognosis of CL after successful EVT. Methods: The 179 CL with the establishment of one straight line to pedal arteries by EVT were assigned to Group A(106 CL with patency of AA) and Group B(73 CL without patency of AA). The patency of AA was defined as both dorsal and planter arteries angiographically visualized after EVT. We compared Rutherford class, SPP before and after EVT, 1 year MAE(Mortality and Major amputation) rate between Group A and B. Results: The table showed the relationship between Group A and B. Group A had significantly lower MAE rate and higher SPP than Group B de-

OJ-156

ADP Induced Platelet Aggregation after Superficial Femoral Artery Recanalization is a Predictor of Stent Restenosis

Michitaka Uesugi
 Takahito Sone, Hideyuki Tsuboi, Hiroaki Mukawa,
 Itsuro Morishima, Hiromi Sasaki, Ryota Morimoto, Yusuke Izumi,
 Toru Niwa, Toshihiko Yamamoto
 Department of Cardiology, Ogaki Municipal Hospital, Ogaki

Background; Thienopyridine resistance is known as predictor of restenosis after coronary intervention. However, it has not been investigated in lower extremity. Method; To evaluate platelet aggregation after superficial femoral ar-

Oral Presentation (Japanese)



昭和30年4月23日第三種郵便物認可 平成21年3月1日発行(毎月一回20日発行)増刊

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Vol.73 Supplement I

Mikamo Lecture
Mashimo Memorial Lecture
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Japan Heart Foundation Satoh Memorial Award Lecture
Young Investigator's Award Finalists Lectures
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Late Breaking Clinical Trials
The 8th Anti-Smoking Promotion Seminar

***The 73rd Annual Scientific Meeting
of the Japanese Circulation Society***

March 20-22, 2009, OSAKA

ABSTRACTS

Circ J

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Valvular Heart Disease / Pericarditis / Cardiac Tumor (M)

DPJ06

March 21 (Sat)

Digital Poster Presentation Room (Osaka International
Convention Center 12F Grande Toque)

10:10-10:55

DPJ-031

Different Contributions of Diabetes Mellitus to the Progressions of Aortic Valve Calcification and Valvular Stenosis

¹Tomohito Ohtani
²Yasushi Sakata, ²Yasuharu Takeda, ²Daisuke Kamimura,
²Shunsuke Tamaki, ²Yosuke Omori, ²Toshiaki Mano,
¹Kazuhiro Yamamoto

¹The Center for Advanced Medical Engineering and Informatics, Osaka University, Suita, ²Department of Cardiovascular Medicine, Osaka University Graduate School of Medicine, Suita

Background: Although the associations with some atherosclerotic risk factors and the progression of aortic valvular stenosis were reported, the contribution of diabetes mellitus is controversial. Moreover, factors for the progression of aortic valve calcification (AVC), main cause of valvular stenosis, are not still clarified. **Methods and Results:** We performed a retrospective analysis of 270 consecutive patients with AVC detected by echocardiography, who had also undergone echocardiographic examination 2-5 years before. Calcification grade was determined by echocardiography; Grade 0: non-calcification, 1: marked calcification of one leaflet, 2: calcification of two leaflets 3: calcification of all leaflets. Among 110 patients with Grade 0-1 at previous echo study, significant progressions of calcification (transition to Grade3) were observed in 51 patients. The presence of diabetes was at low risk for significant progression (odds risk: 0.31, CI: 0.12-0.86, $p < 0.05$). On the contrary, among the other 160 patients with Grade 2-3 at previous echo study, transvalvular velocity increased more in patients with diabetes than in those without diabetes (0.17 ± 0.15 vs. 0.08 ± 0.19 m/s/year, $p < 0.05$). **Conclusions:** Diabetes or medication for it is unlikely to promote AVC if it is mild. Once severe calcification occurs in aortic valves, valve stenosis is exaggerated by diabetes. These results suggest that the mechanisms underlying the progression of aortic valve disease may be different between early and advanced stages.

DPJ-032

Improvement of Severe Anemia in Patients with Aortic Stenosis Complicated with Gastrointestinal Angiodysplasia (Heyde's Syndrome) after Aortic Valve Repair

¹Tomohisa Tada
¹Toshihiro Tamura, ¹Kou Ono, ¹Masaharu Akao, ²ryuzo Sakata,
¹Toru Kita

¹Cardiovascular medicine, Kyoto University Hospital, Kyoto, ²Department of Cardiovascular Surgery, Kyoto University Hospital, Kyoto

[Background] Aortic stenosis (AS) complicated with gastrointestinal angiodysplasia (Heyde's syndrome) is associated with acquired type 2A von Willebrand syndrome (VWS-2A) which is characterized by the loss of the high-molecular-weight multimers of von Willebrand factor (HMW-VWF) by the shear stress of aortic valve stenosis. This hemorrhagic syndrome is rare but sometimes life-threatening anemia due to gastrointestinal bleeding from angiodysplasia for severe AS. **[Methods]** We experienced 5 cases of Heyde's syndrome received aortic valve repair (AVR) between 2005 and 2008. We analyzed significance of AS, anemia and HMW-VWF before and after AVR and investigated prognosis. **[Results]** The median age was 77 ± 3.5 years old and average mean pressure gradient, and aortic valve area (AVA) was 72.2 ± 22.2 mmHg, and 0.57 ± 0.19 cm² before AVR. All patients had gastrointestinal hemorrhage. 2 of them presented a shock state with bleeding. Angiodysplasia and deficiency of HMW-VWF were found in 4 patients before AVR. However improvement of severe anemia (Hb 7.1 ± 0.84 mg/dl vs. 12.3 ± 0.86 mg/dl, $p < 0.0001$) and nor-

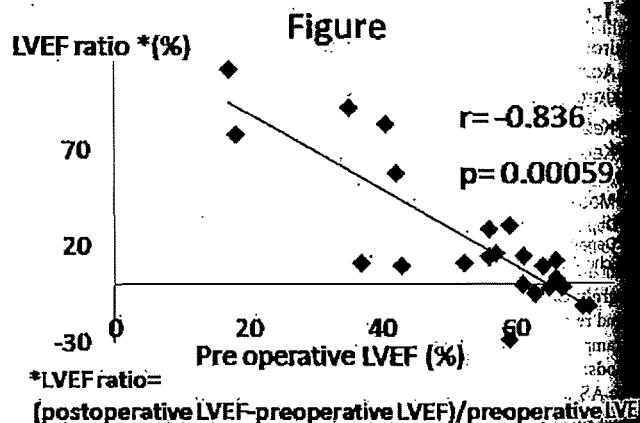
malization of HMW-VWF were observed in all patients after AVR. All patients survived and have no major bleeding episodes until now. **[Conclusion]** Even if there was severe anemia due to loss of HMW-VWF and gastrointestinal bleeding, it was dramatically improved by AVR.

DPJ-033

Preoperative Impaired Left Ventricular Function does not Predict an Insufficient Recovery Following Aortic Valve Replacement for Aortic Regurgitation

¹Emi Maekawa
¹Takayuki Inomata, ¹Tomoyoshi Yanagisawa, ¹Tomohiro Mizutani,
¹Takashi Naruke, ¹Toshimi Koitabashi, ¹Mototugu Nishii,
¹Ichirou Takeuchi, ¹Hitoshi Takehana, ²Shinzo Torii,
²Kuniyoshi Obara, ¹Toru Izumi
¹Department of Cardio-angiology, Kitasato University, School of Medicine, Kanagawa, ²Department of Cardiovascular Surgery, Kitasato University, School of Medicine, Kanagawa

Background: It is unclear in modern practice including beta-blocker therapy whether the left ventricle (LV) can functionally recover sufficiently after aortic valve replacement (AVR) in aortic regurgitation (AR) patients with preoperative severe LV dysfunction. **Methods & Results:** Forty-five consecutive AR patients who underwent AVR in 2001-7 were enrolled. Among clinical variables there was a significant negative correlation between the preoperative LVEF (left ventricular ejection fraction) and the altered LVEF 1 year thereafter (Figure; $R = -0.836$, $P = 0.00059$). The patients with preoperative lower LVEF stratified by the median value did not encounter higher perioperative and subsequent cardiovascular events for 1 year, compared with those with higher LVEF. **Conclusion:** In patients with lower preoperative LVEF, there was more improvement than those with a higher LVEF, without increased risks in AR patients following AVR.



DPJ-034

The Important Factors of Left Ventricular Function after Mitral Valve Repair for Mitral Regurgitation

¹Kazuto Yamaguchi
²Tomoko Tani, ²Minako Katayama, ¹Toshikazu Yagi,
²Natsuhiko Ehara, ²Makoto Kinoshita, ²Koichi Tamita,
²Shuichiro Kaji, ²Atsushi Yamamuro, ²Shigefumi Morioka,
²Yutaka Furukawa, ²Yukikatsu Okada, ⁴Kazuaki Tanabe
¹Clinical Laboratory, Kobe City Medical Center General Hospital, Kobe, ²Department of Cardiology, Kobe City Medical Center General Hospital, Kobe, ³Department of Cardiovascular Surgery, Kobe City Medical Center General Hospital, Kobe, ⁴Division of Cardiology, Shimane University Faculty of Medicine, Izumo

Objective: The operative timing of mitral valve (MV) repair for mitral regurgitation (MR) had been showed in AHA/ACC guidelines. The purpose of this study was to evaluate postoperative LV function and to investigate important factors for postoperative LV function in patients with MR. **Methods:** We enrolled 160 patients (mean 58 ± 14 years) with MR due to degenerative MV regurgitation who underwent MV repair. Echocardiographic studies were performed before and late after MV repair (mean follow-up 4.9 ± 3.9 years). We also examined clinical factors as follows; hypertension (HT), hyperlipidemia (HL), diabetes mellitus (DM) and renal dysfunction (CRF). **Results:** 26 patients (16%) revealed reduced LVEF ($< 50\%$, mean $46 \pm 6\%$) after operation. HT was observed in 35 patients, HL in 15 patients, DM in 10 patients and CRF in 5 patients. There were no significant relationships between the clinical factors and preoperative LVEF (HT: $p = 0.89$, HL: $p = 0.75$, DM: $p = 0.74$, CRF: $p = 0.82$). In

Valvular Heart Disease / Pericarditis / Cardiac Tumor 2 (M)

OJ39

March 22 (Sun)

Room 19 (Hotel NCB 2F YODO)

13:50-15:20

OJ-229

Twelve Months Following Percutaneous Mitral Valve Repair Using the Edge-to-Edge Repair with the MitraClip™ Device

Norio Tada
Saibal Kar

Department of Cardiology, Cedars-Sinai Medical Center, Los Angeles, U.S.A

Background/Method: Mitral valve repair, as compared to replacement, is associated with a good long-term outcome and lower mortality rate for the treatment of mitral regurgitation (MR). A percutaneous edge-to-edge repair approach with the MitraClip system (Evalve, Inc., Menlo Park, CA), inspired by Alfieri edge-to-edge repair characterized by suturing together the leading edges of central scallops of the two mitral leaflets, was studied in EVEREST I and II in north America. **Results:** 104 patients with moderate-to-severe or severe MR (degenerative-81, functional-23) were enrolled. One or More clips (one - 62, two - 31) were deployed in 93 of 104 patients. Acute procedural success was achieved in 79 of 93 patients (85%). 20 patients underwent surgery within 1 year, and there were 1 death unrelated to the clip, and 1 stroke with complete recovery. Of the 79 patients with acute procedural success 85% had freedom from death, surgery or MR > 2+ at 1 year. There was favorable reverse ventricular remodeling demonstrated at 12 months compared to baseline. **Conclusion:** Percutaneous mitral valve repair resulted in sustained MR reduction in the majority of patients. There was favorable left ventricular remodeling as well as corresponding clinical improvement in majority of the patients. The percutaneous edge to edge mitral valve repair provides safer and less traumatic options for patients with degenerative and functional MR.

OJ-230

Comparison of Regional LV Function after MVR with or without Chordal Preservation or Mitral Valve Repair: 2D-Speckle Tracking Strain Analysis

¹Makoto Miyake

¹Chisato Izumi, ²Shuichi Takahashi, ²Sumiyo Hashiwada,

¹Kazuya Yamao, ¹Kouji Hanazawa, ¹Jiyou Sakamoto,

¹Kazuyasu Yoshitani, ¹Makoto Motoooka, ¹Kazuaki Kaitani,

¹Toshiaki Izumi, ¹Yoshihisa Nakagawa

¹Department of Cardiology, Tenri Hospital, Tenri, ²Department of Clinicopathology, Tenri Hospital, Tenri

Background: Chordal preservation during mitral valve replacement (MVR) has been demonstrated to preserve global left ventricular (LV) function. However, its effect on regional LV function is little known. **Methods:** We studied 27 patients who underwent mitral valve surgery and whose postoperative LV size and function were normal by conventional echocardiography. Chordae tendineae were preserved in 8 patients and resected in 10 patients during MVR. Mitral valve repair was performed in 9 patients. Radial strain and circumferential strain measured by novel 2D speckle tracking strain analysis were compared among the three groups. **Results:** There was no significant difference in LV end-diastolic dimension and LV ejection fraction. However, significantly decreased radial strain was observed in inferior wall in the group without chordal preservation compared to the group with chordal preservation ($29.2 \pm 10.4\%$ vs. $57.6 \pm 30.7\%$; $p < 0.05$) and the mitral valve repair group ($29.2 \pm 10.4\%$ vs. $62.6 \pm 22.6\%$; $p < 0.005$). There was no significant difference in radial strain between the group with chordal preservation and the mitral valve repair group. Circumferential strain showed no difference among the three groups. **Conclusion:** Regional LV dysfunction is present after MVR without chordal preservation even when global LV function seems normal by conven-

tional echocardiography. Chordae tendineae deserve to be preserved during MVR to maintain regional LV function as well as mitral valve repair.

OJ-231

Strict Blood Pressure Control is Useful for Preventing the Progression of Mild Aortic Stenosis in Hypertensive Patients

¹Hirokuni Akahori

¹Takeshi Tsujino, ¹Akira Ezumi, ¹Kana Wakabayashi,

¹Yoshiro Naitoh, ¹Masaaki Kawabata, ¹Shinji Nakao, ¹Akiko Goda,

¹Misato Kawaguchi, ¹Chikako Yoshida, ¹Mika Matsumoto,

²Yasushi Sakata, ²Kazuhiro Yamamoto, ¹Tohru Masuyama

¹Cardiovascular Division, Department of Internal Medicine, Hyogo College of Medicine, Hyogo, ²Department of Cardiovascular Medicine, Osaka University, Osaka

Objectives: The aim of the study is to examine the effect of blood pressure control on the progression of mild AS in treated Japanese hypertensive patients. **Methods:** We retrospectively studied 206 consecutive treated hypertensive patients with native valves and with peak aortic flow velocity (PV) ≥ 2.0 m/sec (2.4 ± 0.8 m/s, mean \pm SD) in whom 2 or more echocardiograms were done with an interval of at least 6 months in our echo lab (aged 72 ± 10 years, 106 female). The yearly changes in PV (Δ PV/y) were compared among 3 groups divided according to the JSH 2004 guideline; namely the normal BP group (SBP < 130 mmHg), the high normal group (SBP \geq 130 and < 140 mmHg), and the hypertension group (SBP \geq 140 mmHg). **Results:** There was no difference in age, gender, LDL-cholesterol, HDL-cholesterol, triglyceride, and the presence of diabetes mellitus and hemodialysis among the 3 groups. The Δ PV/y was higher in the hypertension group than in the normal BP group (the normal BP group vs. the high normal group vs. the hypertension group: 0.113 ± 0.300 m/s/y vs. 0.155 ± 0.259 vs. $*0.230 \pm 0.344$, $*p < 0.05$ vs. normal group). **Conclusions:** The SBP < 130 mmHg was associated with slow progression of mild AS in treated hypertensive patients. Strict blood pressure control may retard the progression of mild AS.

OJ-232

Geometric Morphology of Mitral Valve Apparatus and Severity of Mitral Regurgitation in Functional Mitral Regurgitation

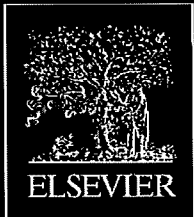
¹Hidetoshi Yoshitani

¹Masaaki Takeuchi, ¹Kyoko Okamoto, ¹Hiroshi Nakai, ¹Kyoko Kaku,

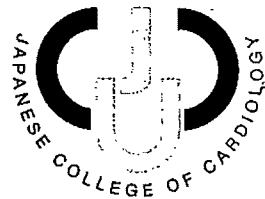
¹Nobuhiko Haruki, ²Toshiyuki Oota, ¹Yutaka Otsuji

¹Second Department of Internal Medicine, University of Occupational and Environmental Health, Kitakyushu, ²University of Occupational and Environmental Health, Kitakyushu

Background: Mitral tenting area is known to be a major determinant for severity of mitral regurgitation (MR) in patients with functional MR. Real-time 3D transesophageal echocardiography (3DTEE) allows comparison between tenting volume and indices for MR severity. **Methods:** 3DTEE was performed in 22 patients with functional MR. From 3D full volume datasets, mitral tenting volume at mid-systole was measured using quantitative software (MVQ, QLAB, Phillips). Vena contracta (VC) area, VC width at anterior-posterior (AP) and commissure-commissure (CC) plane, and the radius of proximal isovelocity surface area (PISA) were measured from full-volume 3D color Doppler datasets at mid-systole. **Results:** Average tenting volume and VC area was 5.3 ± 2.5 ml (range: 2 to 11.6 ml) and 0.65 ± 0.49 cm² (range: 0.18 to 2.07 cm²); respectively. A significant correlation between tenting volume and VC area was noted ($r = 0.60$, $p < 0.01$). VC width at AP and CC plane, and PISA radius were also correlated with tenting volume ($r = 0.63$, 0.44 , 0.47 , $p < 0.05$). **Conclusions:** Mitral tenting volume could be measured by 3DTEE. Moderate correlation between tenting volume and MR severity suggests other coexisting factors also affect severity of functional MR.



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抄録集

Abstracts of 56th Annual Scientific Session of
the Japanese College of Cardiology
Tokyo, Sep. 8-10, 2008

Volume 2
Supplement I, 2008

日本心臓病学会

195 高血圧症例における大動脈弁狭窄進行の規定因子

兵庫医科大学 循環器内科、兵庫医科大学 冠疾患科¹
 大阪大学大学院 循環器内科²
 江角 肇、辻野 健、若林 加奈、合田 亜紀子、中尾 伸二
 松本 美佳、吉田 千佳子、内藤 由朗、大塚 美里
 川端 孝正明、佐古田 剛¹、坂田 泰史²、山本 一博²
 大柳 光正¹、増山 理

【目的】変性性大動脈弁狭窄症(AS)の機序には動脈硬化との類似点が多く、高血圧などが増悪因子と考えられている。我々は心エコー法にてASの年次変化を評価し、高血圧症におけるASの増悪因子を検討した。【方法】対象は兵庫医科大学病院において2005年2月より2007年3月までの間に心エコー検査を施行した高血圧症例のうち、自然弁での大動脈弁通過最大血流速度(PV)2m/s以上であり、6ヵ月以上の間隔でPVを2回以上計測し得た206例(平均年齢71.5±9.5歳、男性100例、女性106例)。2回以上のPVの測定からこの年次変化(ΔPV, m/s/yr)を求めた。ΔPVの増加に影響を及ぼす因子として性別、脂質異常症の有無、高血圧のコントロールの状態、糖尿病の有無、Body Mass Index (BMI) ≥25の肥満の関与を後ろ向きに検討した。【結果】全体ではΔPV 0.18±0.32m/s/yrであり、性差を認めなかった。脂質異常症に関しては、低HDLコレステロール血症(<40mg/dl)、高LDLコレステロール血症(≥140mg/dl)、高中性脂肪血症(≥150mg/dl)の存在は何れも増悪因子では無かった。高血圧のコントロールの状態は収縮期血圧140mmHg以上の不良群でΔPV 0.23±0.34m/s/yr (n=95)、良好群でΔPV 0.13±0.28m/s/yr (n=111)と、高血圧のコントロール不良は増悪因子(P<0.05)であった。またΔPVは、糖尿病合併例(n=91)で非合併例に比し有意に大であった(0.23±0.33m/s/yr vs 0.13±0.28m/s/yr P<0.05)。肥満の有無は増悪因子で無かった。【結語】高血圧症例において大動脈弁通過最大血流速度の年次変化からみた大動脈弁狭窄症の増悪因子は高血圧のコントロールの不良と糖尿病の合併であった。

196 INOUE Balloonによる重症大動脈弁狭窄症(AS)に対する経中隔的大動脈弁形成術(BAV)の成績

池上総合病院 ハートセンター循環器内科
 北海道大学病院 循環器外科¹、東海大学 循環器内科²
 葉山 泰史、田代 晃子、笠井 智司、白井 和胤、坂田 芳人
 渡辺 淳、榊原 守、松居 喜郎¹、田辺 晃久²、長岡 優多
 円谷 斉子

【目的】重症大動脈弁狭窄症(AS)の治療としては外科的大動脈弁置換術が適応であるが、高齢や全身状態から手術の適応外となることがある。今回我々は手術適応外の重症AS症例にINOUE Balloonを用いた経中隔的大動脈弁形成術(BAV)を80歳以上の高齢者(最高95歳)に実施しその効果と安全性を検討した。今回の症例の中には、2度目のBAV施行が3症例含まれる。【方法】右大腿静脈から心房中隔を経て順行性に左房-僧帽弁-左室-大動脈弁-大動脈に0.032inch stiff wireを左室内にループを作って通過させ、INOUE Balloon (22-26mm)を用いて大動脈弁を拡張した。【結果】2005.10月から2008.2月までの重症AS:16症例(男3,NYHA4:14)、年齢80-95 (mean 86)。BAV施行により拡張前AVP:61.37 mmHg-拡張後AVP:30.55 mmHgに改善した(p<0.05)。NYHAscoreも改善した(p<0.05)。平均術時間は127 min (180-90)。今回は術後誤嚥性肺炎を起こし10日目に死亡した症例を1名経験した。死亡例を除いた症例の検討では心不全の増悪や呼吸器を含む合併症の悪化した症例はなく、術関連の合併症はなく、BAV後退院までの平均日数は10日であった。【考察】経中隔的BAVは高齢等の理由で手術できない重症AS症例の症状改善に有用であると考えられた。2度目のBAV施行患者3例の2nd BAVまでの期間は22-9ヶ月で、2nd BAVも合併症なく症状の改善をみた。



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Mikamo Lecture
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Symposia
Joint Symposia
Controversies
Topics
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Oral Presentations
Poster Presentations
Japan Heart Foundation Satoh Memorial Award Lecture
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ABSTRACTS

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OE-198

Increased Interleulin-18 Expression in Non-Rheumatic Aortic Valve Stenosis

¹Yoshiro Naito

¹Takeshi Tsujino, ¹Kana Wakabayashi, ¹Mika Matsumoto, ¹Chikako Yoshida, ¹Masaaki Lee-Kawabata, ²Hiroyuki Hao, ²Seichi Hirota, ³Masataka Mitsuno, ³Yuji Miyamoto, ¹Tohru Masuyama

¹Cardiovascular Division, Department of Internal Medicine, Hyogo College of Medicine, Nishinomiya, ²Department of Surgical Pathology, Hyogo College of Medicine, Nishinomiya, ³Department of Cardiovascular Surgery, Hyogo College of Medicine, Nishinomiya

Background: Non-rheumatic aortic stenosis (NR-AS) gradually but consistently progresses with aging, and the number of patients with NR-AS has rapidly increased recently. Several studies have demonstrated that some features of pathogenesis of atherosclerosis and NR-AS are shared. Interleulin-18 (IL-18) has been reported to play an important role for pathogenesis of atherosclerosis, and thus, it may be involved in the progression of NR-AS. **Methods:** We evaluated 15 NR-AS valves, obtained by aortic valve replacement surgery and 4 control valves, obtained from patients without aortic stenosis at autopsy. IL-18 expression was detected in the aortic valves by immunohistochemistry. We also detected endothelial cells by von Willebrand factor (vWF) staining, myofibroblasts by alpha-smooth muscle actin (alpha-SMA) staining, and macrophage by CD68 staining in the aortic valves. **Results:** Hematoxylin-eosin staining and immunohistochemistry of cell type markers revealed that massive calcified lesion was surrounded by inflammatory cells and neovascularization in NR-AS. Immunohistochemistry revealed that IL-18 was very weakly expressed in some interstitial cells in control valves. In NR-AS tissues, the expression of IL-18 was dramatically increased compared with control valves. Strong IL-18 immunoreactivity was found in macrophages and alpha-SMA-positive myofibroblasts in NR-AS valves. **Conclusions:** IL-18 is expressed by interstitial cells in the aortic valves and is upregulated in NR-AS valves. These findings suggest that IL-18 may participate in pathophysiology of NR-AS valves.

OE-199

Diabetes Mellitus is an Accelerator of Aortic Stenosis

¹Kana Wakabayashi

¹Takeshi Tsujino, ¹Akiko Goda, ¹Shinji Nakao, ¹Yoshiro Naito, ¹Misato Ohtsuka, ¹Mika Matsumoto, ¹Chikako Yoshida, ¹Masaaki Lee-Kawabata, ¹Akira Ezumi, ³Yasushi Sakata, ³Kazuhiro Yamamoto, ²Mitsumasa Ohyanagi, ¹Tohru Masuyama
¹Cardiovascular Division, Department of Internal Medicine, Hyogo College of Medicine, Hyogo, ²Department of Internal Medicine, Division of Coronary Heart Disease, Hyogo College of Medicine, Hyogo, ³Department of Cardiovascular Medicine, Osaka University Graduate School, Hyogo

Objective: To define what factors accelerate the progression of aortic stenosis (AS) in Japanese population. **Methods:** Study population consisted of 293 consecutive patients with native aortic valve in whom peak flow velocity (PV) was ≥ 2.0 m/sec and who had been studied at least twice at an interval of ≥ 6 months. The data were retrospectively reviewed to determine yearly changes of PV (Δ PV/yr). Information of risk factors such as age, gender, HDL, LDL, triglyceride, presence of hypertension (BP $\geq 140/90$ mmHg or taking antihypertensive agents) and diabetes mellitus (DM: fasting plasma glucose ≥ 126 mg/dl or HbA1C $\geq 6.5\%$ or receiving antidiabetic medications), and use of statins were obtained from charts. The impacts of risk factors on Δ PV/yr were analyzed by t-test and stepwise multiple linear regression analysis. **Results:** Δ PV/yr was significantly larger in patients with DM than those without DM (0.14 ± 0.03 vs. 0.24 ± 0.03 m/sec, mean \pm SEM, $p < 0.05$), and DM was the only independent predictors. In treated DM, Δ PV/yr in patients under excellent control (HbA1C $< 6.5\%$) was smaller than in patients not under excellent control (HbA1C $\geq 6.5\%$) (0.18 ± 0.04 vs. 0.27 ± 0.02 m/sec, $p < 0.05$). Such a difference was not observed in untreated DM (HbA1C $< 6.5\%$ vs. HbA1C $\geq 6.5\%$: 0.23 ± 0.04 vs. 0.27 ± 0.04 m/sec, n.s.). **Conclusions:** DM is an accelerator of AS, but progression of AS can be slowed if blood glucose was strictly controlled.

Coronary circulation, basic / clinical(01)
(IHD)

OE34

March 28 (Fri)

Room 17 (Fukuoka Sun Palace Hotel & Hall 2F Heian)

16 : 30 - 18 : 00

OE-200

Coronary Microvascular Resistance Index Immediately after Primary Percutaneous Coronary Intervention Predicts the Transmural Extent of Infarction in Acute Myocardial Infarction

Hironori Kitabata

Manabu Kashiwagi, Hiroki Matsumoto, Yuu Arita, Hideyuki Ikejima, Keishi Ohkouchi, Hiroto Tsujioka, Akio Kuroi, Satoshi Ueno, Hideaki Kataiwa, Takashi Tanimoto, Takashi Yamano, Shigeo Takarada, Takashi Kubo, Nobuo Nakamura, Kumiko Hirata, Atsushi Tanaka, Masato Mizukoshi, Toshio Imanishi, Takashi Akasaka

Department of Cardiovascular Medicine, Wakayama Medical University, Wakayama

[Background] The state of coronary microcirculation is an important determinant of myocardial viability and clinical outcomes in acute myocardial infarction (AMI). The aim of this study was to assess the relationship between coronary microvascular resistance index (MVRI) and myocardial viability after primary percutaneous coronary intervention (PCI) in AMI. **[Methods and Results]** We enrolled 24 patients (20 men, mean age 65 ± 11 years) who underwent primary PCI for a first anterior AMI. Immediately after primary PCI, a novel 0.014-inch dual-sensor guidewire was placed distal to the culprit lesion to take per-beat averages of pressure and flow velocity simultaneously. MVRI was determined as the ratio of mean distal pressure to average peak flow velocity during maximal hyperemia. Delayed contrast-enhanced MRI (De-MRI) was also performed in all patients 2 weeks after the onset of AMI. Transmural extent of infarction (TEI) by De-MRI was graded from 1 to 4 based on the extent of hyperenhanced tissue. A significant positive correlation was observed between MVRI and the TEI ($p < 0.0002$). Furthermore, MVRI was strongly correlated with peak CK-MB value ($r = 0.85$, $p < 0.0001$). The cut-off value of 1.1 mmHg/cm/s in the MVRI can discriminate between transmural (grade 4) and non-transmural MI (grade 1-3) with the sensitivity of 100%, the specificity of 88.9%. **[Conclusion]** MVRI immediately after primary PCI is a useful predictor for the TEI in AMI.

OE-201

Significant Collateral Circulation and Death after Discharge in Patients with Acute Myocardial Infarction

¹Yasuhiko Sakata

¹Hiroshi Sato, ¹Masahiko Shimizu, ¹Shinichiro Suna, ¹Masaya Usami, ²Young-Jae Lim, ³Tatsuya Sasaki, ¹Masatsugu Hori
¹Department of Cardiovascular Medicine, Osaka University Graduate School of Medicine, Suita, ²Cardiology Division, Kawachi General Hospital, Higashi-Osaka, ³Cardiology Division, National Hospital Organization Osaka Minami Medical Center, Osaka

Background: It is still controversial whether collateral flow is associated with an improved mortality after acute myocardial infarction (AMI) in the real world. **Methods:** We investigated 2,114 consecutive AMI patients (76% men, mean 64 years) with an occluded infarct related artery (IRA), registered to the Osaka Acute Coronary Insufficiency Study (OACIS) between 1999 and 2001. Angiographic collateral flow was evaluated with Rentrop's (R) score: R-0 = no collaterals, to R-3 = collaterals completely filling the IRA. **Results:** Patients with R-0, R-1, R-2, and R-3 collaterals had significant difference in peak CK levels ($3,626 \pm 2,759$, $3,352 \pm 2,460$, $2,825 \pm 2,290$ and $2,637 \pm 2,217$ U/L, respectively, $p < 0.001$), and 30-day mortality (5.9%, 1.4%, 1.5% and 1.6%, respectively, $p < 0.001$). Interestingly, however, R-3 collaterals was associated with the worst 1-year mortality (7.6%, 2.5%, 3.2% and 8.8%, for patients with

Oral Presentation
(English)

Hypertension, clinical(04) (H)

PE035

March 28 (Fri)

Presentation Room 1 (Marine Messe Fukuoka 1F Arena)

15 : 30 - 16 : 20

PE-203

Angiotensin Converting Enzyme Inhibitor Slows the Progression of Aortic Stenosis in Hypertensive Patients

Kana Wakabayashi, Takeshi Tsujino, Akiko Goda, Shinji Nakao, Yoshiro Naitoh, Misato Otsuka, Mika Matsumoto, Chikako Yoshida, Masaaki LeeKawabata, Akira Ezumi, Yasushi Sakata, Kazuhiro Yamamoto, Mitsumasa Ohyanagi, Toru Masuyama
 Cardiovascular Division, Department of Internal Medicine, Hyogo College of Medicine, Hyogo, Department of Internal Medicine, Division of Coronary Heart Disease, Hyogo College of Medicine, Hyogo, Department of Cardiovascular Medicine, Osaka University Graduate School, Osaka

Methods: We studied 212 consecutive treated hypertensive patients with native valves with peak aortic flow velocity (PV) ≥ 2.0 m/sec in whom 2 or more echocardiograms were done with an interval of at least 6 months. We reviewed antihypertensive agents that had been administered more than 6 months during the follow-up period. Yearly changes of PV (Δ PV/yr) were determined, and impacts of antihypertensive agents atherosclerotic risk factors on Δ PV/yr were examined by using t-test and stepwise multiple regression analysis. **Results:** Δ PV/yr was smaller in patients taking ACE inhibitors (ACE-Is) than in those not taking ACE-Is (0.04 ± 0.22 vs. 0.20 ± 0.33 m/s/y, $p < 0.05$). Such protective associations were not observed for beta blockers, calcium antagonists, and diuretics. Δ PV/yr was larger in patients taking angiotensin type 1 receptor blockers (ARBs) than in those not taking ARBs (0.26 ± 0.38 vs. 0.13 ± 0.28 m/s/y, $p < 0.05$). Multiple linear regression analysis revealed that use of ACE-Is slowed the progression of AS. Administration of ARBs was not associated with accelerated progression of AS after the effects of other risk factors were adjusted with multiple linear regression analysis. **Conclusions:** ACEI is the only drug that slows the progression of AS among first-line antihypertensive agents.

PE-204

Telmisartan Improves Endothelial Function and Arterial Stiffness in Hypertensive Patients

An Duk Jeong, Wan Kim, Sang-Chol Cho, Won-Yu Kang, Sun-Ho Hwang, Weon Kim
 Cardiovascular Center, Gwangju Veterans Hospital, Republic of Korea

BACKGROUND: Telmisartan is selective angiotensin II-type 1 receptor blocker with PAR gamma activation increases insulin sensitivity. The effectiveness of telmisartan to improve human endothelial function and arterial stiffness in hypertensive patients is unclear. **METHODS:** The influence of telmisartan 40mg daily for 8 weeks on endothelium-dependent vasodilator function and arterial stiffness were determined in 25 moderate hypertensive patients (60.5 years, 20 male). Endothelial function was assessed using the flow-mediated dilation (FMD) and arterial stiffness [brachial-ankle pulse wave velocity (PWV-b), carotid-femoral pulse wave velocity (PWVcf)] were measured using CompliorX (Colins, Japan). **RESULTS:** Routine laboratory exam has not shown abnormal finding after treatment. HDL, hsCRP, HbA1C, and NT-proBNP were improved after treatment but, not statistically significant. And, telmisartan therapy improves HOMA index ($p < 0.05$). Systolic BP (151 ± 15 vs 132 ± 18 mmHg, $p < 0.01$) and diastolic BP (90 ± 14 vs 82 ± 10 mmHg, $p = 0.025$) were significantly decreased. FMD after 8 weeks significantly increased from 7.4 ± 0.6 to $8.9 \pm 2.5\%$ ($P = 0.01$). There was no effect of telmisartan on the endothelium-independent responses to nitrate. All arterial function indices were improved after telmisartan therapy (PWVba: from 1647 ± 197 to 1506 ± 177

cm/sec, $p < 0.01$, PWVhf: from 1091 ± 172 to 1007 ± 156 cm/sec, $p < 0.01$ and PWVhe: from 998 ± 203 to 923 ± 206 cm/sec, $p < 0.01$). Multivariate regression analysis revealed that PWVba change was independent of systolic BP change ($p < 0.05$). **CONCLUSION:** Telmisartan was associated with significant improvement of FMD and PWV in hypertensive patients.

PE-205

Effects of Calcium Channel Blockers in Combination with an Angiotensin II Receptor Blocker on Urine Excretion of Albumin

¹Tomonori Sugiura, ²Ai Nakazawa, ²Koichi Miyagawa, ¹Sumiyo Yamashita, ¹Yasuaki Dohi, ¹Genjiro Kimura

¹Department of Cardio-Renal Medicine and Hypertension, Nagoya City University Graduate School of Medical Sciences, Nagoya, ²Department of Internal Medicine, Nagoya Kosein Geriatric Hospital, Nagoya

Objective: This crossover trial was designed to investigate whether different calcium channel blockers (CCBs) in combination with an angiotensin receptor blocker exert different renoprotective effects in elderly hypertensive patients with albuminuria. **Methods:** Elderly hypertensive patients with albuminuria ($170 \pm 23/87 \pm 10$ mmHg, 71 ± 6 years old, $n=17$) were randomly assigned to receive either benidipine (4mg/day) or amlodipine (5mg/day) combined with olmesartan (10mg/day). The dose of CCBs was increased if depressor effects were not enough. After 3 months, CCBs were switched in each patient and the same protocol was applied for 3 months. Urinary excretion of albumin and self-measured blood pressure in consecutive 6 days before and after each treatment were analyzed. **Results:** Both regimens, including benidipine and amlodipine, reduced self-measured blood pressure to a similar extent ($139 \pm 22/75 \pm 11$ and $133 \pm 17/72 \pm 10$ mmHg, respectively; both $p < 0.001$), while urine albumin decreased only after benidipine-based regimen (11.7 ± 6.1 mg/g creatinine, $p < 0.05$). Although reduction in urine albumin was correlated with that of blood pressure during both benidipine- ($r=0.59$, $p < 0.01$) and amlodipine-based regimens ($r=0.52$, $p < 0.05$), the correlation coefficient was greater during benidipine- than amlodipine-based regimen ($p < 0.05$). **Conclusions:** Benidipine, but not amlodipine, combined with olmesartan, reduced urinary albumin excretion in elderly hypertensive patients. These results suggest the importance of selecting medications used in combination with angiotensin II receptor blockers in hypertensive patients with albuminuria.

PE-206

Seasonal Changes in Twenty-Four-Hour Blood Pressure Variation Profiles : Cold Pressor Stress Augment Morning Blood Pressure Surge in Winter

¹Shougo Murakami, ²Norihiro Hotta, ²Takashi Yamanaka, ²Yutaka Kubo, ¹Akiko Soyama, ¹Tatsuya Umeda, ¹Hideaki Morita, ¹Tatsuji Kohno, ²Kuniaki Ohtsuka, ¹Yasushi Kitaura

¹Third Department of Internal Medicine, Osaka Medical College, Takatsuki, ²Department of Medicine, Tokyo Women's Medical University, Medical Center East, Toyko

Background: The incidence of cardiovascular events has been observed in cold than in hot months. Abnormal diurnal blood pressure (BP) patterns, such as non-dipper, extreme dipper, and morning BP surge are closely associated to an increase in the target organ damage and cardiovascular morbidity. **Objectives:** We investigated seasonal variation of ambulatory BP (ABP) values and to clarify the association between the ambient temperature and ABP values. **Methods:** We performed twenty-four-hour ABP monitoring for 7 days in 253 community-dwelling subjects (mean age 58.1 ± 0.8 years, 109 males), total 1736 twenty-four-hour ABP profiles were analyzed. We calculated non-dipper ($< 10\%$ asleep systolic BP fall), extreme dipper ($\geq 20\%$ asleep systolic BP fall), and exaggerated morning BP surge (the average 3 hour morning systolic BP minus asleep systolic BP ≥ 40 mmHg). In addition, we compared ABP values in the coldest day with those in the warmest day among 7 days. **Results:** Although there were not found seasonal changes in non-dipper and extreme dipper status, the exaggerated morning BP surges were more frequent in winter than in other seasons (winter: 7.5% versus the other seasons: 4.2%, $P < 0.01$). Morning BP surges in the coldest day were higher than those in the warmest day in winter (20.6 ± 1.6 versus 16.1 ± 1.7 mmHg, $P = 0.03$). **Discussion:** For the adequate management of BP, we should take into consideration seasonal variations in BP and pressor effect by ambient temperature in winter.

Poster Session (English)

研究成果の刊行に関する一覧表

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ORIGINAL ARTICLE

Prognostic factors for progression of early- and late-stage calcific aortic valve disease in Japanese: The Japanese Aortic Stenosis Study (JASS) Retrospective Analysis

Kazuhiro Yamamoto^{1,2}, Hideya Yamamoto³, Kiyoshi Yoshida⁴, Akira Kisanuki⁵, Yutaka Hirano⁶, Nobuyuki Ohte⁷, Takashi Akasaka⁸, Masaaki Takeuchi⁹, Satoshi Nakatani¹⁰, Tomohito Ohtani², Takashi Sozu¹ and Tohru Masuyama¹¹

Calcific aortic valve disease (CAVD) is the most common etiology of acquired valvular heart disease, and hypertension is a principal underlying disease. The Japanese Aortic Stenosis Study (JASS) Retrospective Analysis is a retrospective observational study to clarify the prognostic factors for progression of CAVD in Japanese. Data from 556 subjects who met the following criteria were analyzed: (1) ≥ 50 years old; (2) calcification in any aortic valve leaflet or peak aortic jet velocity $\geq 2 \text{ m s}^{-1}$ on an echocardiographic study performed between July 2004 and June 2007; and (3) availability of earlier echocardiographic data from within the previous 2–5 years to assess the progression of CAVD. The subjects were divided into two groups according to CAVD severity on the preceding echocardiographic examination. In early-stage subjects with calcification in one or zero leaflets who were without aortic stenosis on the preceding echocardiographic study ($n=157$), the prognostic factors for progression were the following: (1) no use of angiotensin receptor blockers (ARB) and (2) use of warfarin. In late-stage subjects with calcification in two or three leaflets and/or aortic stenosis on the preceding echocardiographic study ($n=399$), progression was observed in females and in subjects with low hemoglobin and a concentric left ventricle. There was no relation between medications and changes in CAVD. Prognostic factors for the progression of CAVD were different between the early and late stages. Initiation of ARB treatment during the early stage may be effective, and we should be vigilant about progression of CAVD in patients treated with warfarin.

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Keywords: angiotensin receptor blocker; aortic valve; calcification

INTRODUCTION

The prevalence of calcific aortic valve disease (CAVD) increases with aging,¹ and CAVD is the most common etiology of acquired valvular heart disease in developed countries.² Hypertension is a principal underlying disease,^{3–6} and previous studies in Western countries have shown an association between several clinical factors and the presence and/or progression of CAVD.^{3,6,7} The Cardiovascular Health Study showed that African-American ethnicity was associated with lower risk of CAVD progression.⁶ Although several risk factors are shared between atherosclerotic diseases and CAVD, discrepancies in their

pathogenesis have also been identified.^{8–10} These results highlight the necessity of investigating prognostic factors for incidence and progression of CAVD in Asian populations.

The Japanese Aortic Stenosis Study (JASS) is a multicenter, hospital-based observational study that includes retrospective and prospective studies. The JASS Retrospective Analysis is a retrospective study to investigate the prognostic factors for progression of CAVD in Japanese subjects. As previous studies in Western countries suggest that prognostic factors differ according to CAVD severity,^{4,6,11} the study subjects were divided on the basis of the presence of early- vs. late-stage diseases.

¹The Center for Advanced Medical Engineering and Informatics, Osaka University, Suita, Japan; ²Department of Cardiovascular Medicine, Osaka University Graduate School of Medicine, Suita, Japan; ³Department of Cardiovascular Medicine, Hiroshima University, Graduate School of Biomedical Sciences, Hiroshima, Japan; ⁴Department of Cardiology, Kawasaki Medical School, Kurashiki, Japan; ⁵School of Health Sciences, Kagoshima University, Kagoshima, Japan; ⁶Division of Central Clinical Laboratory, Kinki University Hospital, Osakasayama, Japan; ⁷Department of Cardio-Renal Medicine and Hypertension, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan; ⁸Department of Cardiovascular Medicine, Wakayama Medical University, Wakayama, Japan; ⁹Second Department of Internal Medicine, University of Occupational and Environmental Health, School of Medicine, Kitakyushu, Japan; ¹⁰Department of Health Sciences, Division of Functional Diagnostics, Osaka University Graduate School of Medicine, Suita, Japan and ¹¹Cardiovascular Division, Department of Internal Medicine, Hyogo College of Medicine, Nishinomiya, Japan

Correspondence: Dr K Yamamoto, The Center for Advanced Medical Engineering and Informatics, Osaka University, 2-2 Yamadaoka, Suita 565-0871, Japan.

E-mail: kazuhiro@medone.med.osaka-u.ac.jp

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METHODS

Subjects

The JASS Retrospective Analysis enrolled 775 Japanese subjects who met the following criteria: (1) age ≥ 50 years old; (2) markedly increased reflectivity (calcification) of any aortic valve leaflet or peak aortic jet velocity of at least 2 m s^{-1} on an echocardiographic recording performed between July 2004 and June 2007; and (3) availability of a report or recording from an echocardiographic study performed 2–5 years back. Subjects with rheumatic valvular disease or who had undergone aortic valve replacement were excluded. In 556 of the 775 subjects, we were able to assess whether CAVD had progressed or not compared with the previous echocardiographic study. Mean follow-up duration was 2.8 years. In these 556 subjects, laboratory data from the time of the preceding echocardiographic examination were collected from the medical records. Phlebotomy was performed in the fasting or non-fasting state. The glomerular filtration rate (eGFR) was calculated using an equation modified for the Japanese: $\text{eGFR (ml min per } 1.73 \text{ m}^2) = 194 \times \text{age}^{-0.287} \times \text{serum creatinine}^{-1.094}$ (if female, $\times 0.739$).¹²

This retrospective study conforms to the guiding principles for epidemiologic studies of the Ministry of Health, Labour and Welfare, Japan, and was approved by all relevant institutional ethical committees.

Echocardiography and assessment of the progression of CAVD

Doppler echocardiography was conducted using commercially available echocardiographic machines as described previously.^{13,14} In the routine echocardiographic examination, measurements were conducted on-line. Ejection fraction was calculated using a modification of the method of Quinones *et al.*¹⁵ as described previously.^{13,14} In subjects with regional wall motion abnormalities, the biplane Simpsons' method was used.^{13,14} Left ventricular (LV) mass was calculated following a formula derived from data compiled by the American Society of Echocardiography¹⁶ as described previously.^{13,14} LV mass index was calculated as a ratio of LV mass to height^{2.7,14}. The number of aortic valve leaflets with calcification was evaluated by an experienced cardiologist and/or sonographer.

The 556 subjects were divided into two groups according to the degree of CAVD at the preceding echocardiography. The group with early-stage CAVD comprised subjects with calcification on one or no leaflet and peak aortic transvalvular flow velocity $< 2 \text{ m s}^{-1}$ ($n=157$).^{6,17–19} The late-stage CAVD group comprised subjects with two or three calcified aortic valves and/or with peak aortic transvalvular flow velocity of $\geq 2 \text{ m s}^{-1}$ ($n=399$). Eleven patients had bicuspid aortic valve, and all met the criteria for late-stage CAVD. As of their small number, their data were analyzed with other late-stage subjects.

Progression in the late-stage group was defined as a $\geq 0.3 \text{ m s}^{-1}$ per year rate of increase in peak aortic transvalvular flow velocity at follow-up, as described previously.^{17,20} In the early-stage group, progression was defined as the appearance of two or three newly calcified leaflets or the onset of aortic stenosis (peak aortic transvalvular flow velocity of $\geq 2 \text{ m s}^{-1}$) at follow-up.

Statistical analysis

Statistical analysis was performed using SAS 9.1 (SAS Institute, Cary, NC, USA). Continuous data are summarized as mean \pm s.d. Categorical data are presented as percentages. The Student's *t*-test was used for normally distributed data, especially demographic data, and the Wilcoxon rank sum test was used for non-normally distributed data (for example, laboratory data). The χ^2 test was used for binary data (for example, use of concomitant medication). The Mantel test was applied for ordered categorical data, that is, the degree of aortic and mitral regurgitation. The significance level was fixed at 5%.

RESULTS

Subject characteristics

Baseline characteristics are listed in Table 1. Age and prevalence of hypertension, diabetes mellitus, dyslipidemia and renal insufficiency were increased in subjects with late-stage CAVD. Systolic blood pressure was higher, but diastolic blood pressure was lower in late- vs. early-stage subjects. The prescription rate of angiotensin-converting

Table 1 Subject characteristics

	All	Early stage	Late stage
<i>n</i>	556	157	399
Age (years)	73.7 \pm 9.0	71.1 \pm 8.0	74.7 \pm 9.2*
Male (%)	52.3	55.4	51.1
Body mass index (kg m^{-2})	22.5 \pm 3.4	23.0 \pm 3.2	22.3 \pm 3.4
Systolic blood pressure (mm Hg)	135 \pm 18	133 \pm 16	137 \pm 19*
Diastolic blood pressure (mm Hg)	74 \pm 11	77 \pm 12	73 \pm 11*
<i>Comorbidity (%)</i>			
Hypertension	72.8	65.6	75.7*
Diabetes mellitus	29.0	22.9	31.3*
Dyslipidemia	49.1	40.1	52.6*
Renal insufficiency	23.4	12.1	27.8*
<i>Medications (%)</i>			
Angiotensin converting enzyme inhibitor	20.5	33.8	15.3*
Angiotensin receptor blocker	30.9	23.6	33.8*
β -blocker	21.8	28.0	19.3*
Calcium channel blocker	41.7	49.0	38.9*
Warfarin	18.9	17.2	19.6
Statins	27.5	24.8	28.6
Oral hypoglycemic medications	10.8	9.6	11.3
Insulin	4.5	6.4	3.8

* $P < 0.05$ vs. early stage.

Table 2 Preceding echocardiographic data

	All	Early stage	Late stage
Left atrial dimension (mm)	41 \pm 8	40 \pm 9	41 \pm 8*
Left ventricular end-diastolic dimension (mm)	48 \pm 7	49 \pm 7	48 \pm 7
Left ventricular end-systolic dimension (mm)	31 \pm 7	31 \pm 8	30 \pm 7
Ejection fraction (%)	66 \pm 11	65 \pm 12	66 \pm 10
Left ventricular mass index ($\text{g m}^{-2.7}$)	55.3 \pm 17.2	51.2 \pm 15.7	57.0 \pm 17.6*
<i>The degree of aortic regurgitation (%)</i>			
0	37.8	52.2	32.1
I	34.4	28.7	36.6
II	21.6	16.6	23.6
III	5.8	2.6	7.0
IV	0	0	0
		$P < 0.0001$ vs. early stage	
<i>The degree of mitral regurgitation (%)</i>			
0	28.2	31.9	26.8
I	50.4	47.8	51.4
II	17.3	15.9	17.8
III	3.6	3.8	3.5
IV	0.2	0.6	0
		$P = 0.5567$ vs. early stage	

* $P < 0.05$ vs. early stage.

enzyme (ACE) inhibitors, β -blockers and calcium channel blockers was lower, and angiotensin receptor blocker (ARB) use was higher in subjects with late- vs. early-stage CAVD.

Data from the previous echocardiographic studies are shown in Table 2. Average left atrial dimension and LV mass index were higher

Table 3 Laboratory data at the preceding echocardiography

	All	Early stage	Late stage
Hemoglobin (g per 100 ml)	12.5 ± 2.1	13.3 ± 1.8	12.2 ± 2.2*
White blood cell count (μl ⁻¹)	5885 ± 1943	5880 ± 1486	5887 ± 2102
Platelet (10 ⁴ per μl)	19.8 ± 7.6	20.8 ± 5.5	19.4 ± 8.3*
Serum glucose (mg per 100 ml)	114 ± 32	107 ± 26	117 ± 33*
Total cholesterol (mg per 100 ml)	193 ± 38	197 ± 35	192 ± 39
Triglyceride (mg per 100 ml)	123 ± 61	117 ± 49	126 ± 66
Creatinine (mg per 100 ml)	1.7 ± 2.4	1.3 ± 2.0	1.8 ± 2.6
eGFR (ml min ⁻¹ per 1.73 m ²)	56.9 ± 27.3	60.8 ± 22.4	55.3 ± 28.8*

Abbreviation: eGFR, glomerular filtration rate.
**P* < 0.05 vs. early stage.

in subjects with late- vs. early-stage disease. Aortic regurgitation was observed in more than half of subjects with late-stage CAVD, but in less than half of subjects with early-stage disease.

Laboratory data measured at the time of the preceding echocardiographic examination are shown in Table 3. Hemoglobin and platelet levels and eGFR were lower, whereas serum glucose level was higher in subjects with late- vs. early-stage CAVD.

Prognostic factors for progression of CAVD at the early and late stages

Of the 157 subjects with early-stage CAVD on the preceding echocardiographic study, progression during the follow-up period was observed in 75 subjects and was associated with the use of warfarin and nonuse of ARBs. About half of the subjects without progression were free of mitral regurgitation, but more than 80% of those with progression did have mitral regurgitation. There was no significant difference in the prevalence of atrial fibrillation between subjects with and without progression (17.8 and 22.0%, respectively). There was no association between progression and any other factors listed in Tables 1–3 (Tables 4 and 5).

Of 399 subjects with late-stage CAVD on the preceding echocardiographic study, progression during the follow-up period was observed in 73 subjects. Those with disease progression were more likely to be female, with smaller LV end-diastolic and end-systolic dimensions and lower hemoglobin levels than those without progression (Tables 4 and 6). There was no significant difference in the prescription rates of any medications listed in Table 4.

Hypertension, diabetes mellitus, dyslipidemia and renal insufficiency were not associated with progression in subjects in either early or late stages of CAVD.

DISCUSSION

Previous studies have shown that factors such as aging, male gender, high low-density lipoprotein (LDL) levels and a history of hypertension were related to the progression of CAVD.^{4,6,20} However, prognostic factors are likely to differ between the early and late stages, and moreover, the Cardiovascular Health Study has shown the effects of ethnicity on CAVD pathogenesis.⁶ This retrospective study analyzed data from Japanese patients and showed that early-stage subjects with mitral regurgitation, nonuse of ARBs or warfarin use tended to undergo progression of CAVD. In late-stage subjects, progression was associated with female gender, small LV cavity and low level of hemoglobin. Although the prevalence of hypertension, diabetes mellitus, dyslipidemia and renal insufficiency was higher in subjects with late- vs. early-stage disease, none of these comorbidities affected CAVD progression in early- or late-stage disease.

Table 4 Association of each factor with the progression of CAVD

	Early stage P-value	Late stage P-value
Age	0.8944	0.6187
Gender	0.1427	0.0311*
Body mass index	0.5917	0.4317
Systolic blood pressure	0.7145	0.5081
Diastolic blood pressure	0.8594	0.4913
<i>Comorbidity</i>		
Hypertension	0.3331	0.4744
Diabetes mellitus	0.2416	0.5502
Dyslipidemia	0.5380	0.8114
Renal insufficiency	0.6284	0.9579
<i>Medications</i>		
Angiotensin-converting enzyme inhibitor	0.5699	0.4971
Angiotensin receptor blocker	0.0326*	0.4604
β-Blocker	0.4810	0.0521
Calcium channel blocker	0.6974	0.6043
Warfarin	0.0308*	0.3148
Statins	0.8156	0.4776
Oral hypoglycemic medications	0.6502	0.9641
Insulin	0.0692	0.8388
Left atrial dimension	0.1437	0.7268
Left ventricular end-diastolic dimension	0.6562	0.0144*
Left ventricular end-systolic dimension	0.4471	0.0120*
Ejection fraction	0.3298	0.3087
Left ventricular mass index	0.1241	0.9572
The degree of aortic regurgitation	0.4532	0.1558
The degree of mitral regurgitation	0.0001*	0.8057
Hemoglobin	0.3684	0.0166*
White blood cell count	0.7898	0.6567
Platelet	0.3102	0.8894
Serum glucose	0.6124	0.9110
Total cholesterol	0.6096	0.3299
Triglyceride	0.1737	0.0630
Creatinine	0.6067	0.2260
eGFR	0.8014	0.3299

Abbreviations: CAVD, calcific aortic valve disease; eGFR, glomerular filtration rate.

Prognostic factors for progression of early-stage CAVD

We have shown that the prognostic factors for progression of CAVD in Japanese subjects differ between the early and late stages, a conclusion that is compatible with previous studies of Caucasian subjects.^{4,6,11,17}

In this study, nonuse of ARBs was associated with progression in early-stage subjects. Previous studies showed that ACE and angiotensin II type 1 receptor were upregulated when angiotensin II was expressed in the calcified human aortic valve compared with the normal valve.^{21,22} An experimental study showed that in hypercholesterolemic rabbits, ARBs prevented lesion formation in the aortic valve, specifically preventing the accumulation of macrophages, myofibroblasts and osteoblasts, upregulation of osteopontin and ACE, and disruption of endothelial integrity.²³ Findings from these earlier studies and this study suggest that ARBs prevent progression of CAVD during the early stage. However, use of ACE inhibitors did not affect CAVD progression in this study. This may be partly explained by upregulation of chymase and ACE in the calcified aortic valve²² and by

Table 5 Prognostic factors for the progression of CAVD in subjects at the early stage

	Progression	
	+	-
1. Angiotensin receptor blocker		
Use	16.0%	30.5%
No use	84.0%	69.5%
	Odds ratio 0.434 (95% CI; 0.200, 0.944), $P=0.0326$	
2. Warfarin		
Use	24.0%	11.0%
No use	76.0%	89.0%
	Odds ratio 2.561 (95% CI; 1.071, 6.126), $P=0.0308$	
3. Mitral regurgitation		
0	13.3%	48.8%
I	61.3%	35.4%
II	17.3%	14.6%
III	8.0%	0.0%
IV	0.0%	1.2%
	$P=0.0001$	

Abbreviations: CAVD, calcific aortic valve disease; CI, confidence interval.

Table 6 Prognostic factors for the progression of CAVD in subjects at the late stage

	Progression	
	+	-
1. Gender		
Male	39.7%	53.7%
Female	60.3%	46.3%
	Odds ratio 0.569 (95% CI; 0.339, 0.954), $P=0.0311$	
2. Left ventricular end-diastolic dimension (mm)		
	46 ± 6	48 ± 7
		$P=0.0144$
3. Left ventricular end-systolic dimension (mm)		
	28 ± 5	31 ± 9
		$P=0.0120$
4. Hemoglobin (g per 100 ml)		
	11.6 ± 2.1	12.3 ± 2.2
		$P=0.0166$

Abbreviations: CAVD, calcific aortic valve disease; CI, confidence interval.

the inadequate suppression of angiotensin II production in the aortic valve by ACE inhibitors.

Warfarin use was also associated with CAVD progression. Matrix γ -carboxyglutamic acid protein is a mineral-binding extracellular matrix protein and a potent inhibitor of tissue calcification. Vitamin K antagonists such as warfarin induce the incomplete γ -carboxylation of matrix γ -carboxyglutamic acid protein and attenuate the synthesis and function of matrix γ -carboxyglutamic acid protein.²⁴ Previous observational studies in Western countries showed that aortic valve

calcifications were significantly larger in patients treated with oral anticoagulants,^{25,26} a finding that is compatible with our current data from Japanese patients. In a society with many elderly, such as in Western countries and Japan, the use of oral anticoagulants to prevent thromboembolic events has increased correspondingly with the rising prevalence of atrial fibrillation, but the effects of warfarin on the progression of CAVD were independent of the presence of atrial fibrillation in this study. We should be aware of this potential adverse effect of warfarin.

Subjects with progression of CAVD had a higher prevalence of mitral regurgitation. Jassal *et al.*²⁷ reported the close relationship between mitral annular calcification and aortic valve calcification in patients with aortic stenosis. We did not assess the effects of mitral annular calcification, but the relationship between mitral regurgitation and progression of early-stage CAVD may be partly explained by the previous finding.

Prognostic factors for progression of late-stage CAVD

This study showed that more subjects with progression of late-stage CAVD were female. A valvular origin of heart failure, such as aortic stenosis, was more common in women than in men.^{28,29} However, some studies of Caucasian patients found that male gender was a prognostic factor for the development of aortic stenosis,^{6,7} whereas others found no influence of gender.^{11,20} The effects of gender on coronary artery calcification differed even between patient cohorts from the Western countries.³⁰ It is plausible that gender influence on the incidence and progression of CAVD differs among racial groups.

The subjects with CAVD progression had a smaller LV cavity than those without progression. There was no difference in LV mass index, and our results therefore indicate that the LV cavity was more concentric in subjects with progression. Aortic valve area is altered by transvalvular flow and increases during exercise. However, exercise-induced increases are small in subjects with stiff aortic valves leading to excessive pressure overload and concentric remodeling of the LV cavity. Thus, the aortic valve of subjects with concentric LV cavity might have already been more severely injured at the time of the preceding echocardiographic study. Subjects with CAVD progression also had lower hemoglobin levels than those without progression. The enhanced shear stress associated with stenosis of the native aortic valve can theoretically induce intravascular hemolysis.³¹⁻³³ Aortic stenosis is sometimes associated with loss of high molecular von Willebrand multimers and with a greater tendency to bleed.^{34,35} Although these issues are of clinical significance only in cases of severe anemia requiring transfusion, mild anemia in our subjects may exist in part because of these mechanisms. If so, the low hemoglobin level may also indicate that aortic valve injury was more severe at the earlier echocardiographic examination in subjects with progression. Although renal insufficiency is closely related to anemia in patients with cardiovascular diseases, there was no significant difference in serum creatinine or eGFR levels between subjects with vs. without progression. These results suggest that CAVD progression is closely related to its severity at baseline in the late-stage subjects, a conclusion that is compatible with findings from previous studies.^{4,11,20} However, the mechanisms of this relationship cannot be explained by this study, and future studies are required.

Differences in comorbidities between subjects with early- and late-stage CAVD. The prevalence of hypertension, diabetes mellitus, dyslipidemia and renal insufficiency was higher in subjects with late- vs. early-stage CAVD (Table 1). This suggests that the presence of these comorbidities is related to the progression of CAVD; however, none

were found to be prognostic factors for progression in subjects in either early- or late-stage disease. This discrepancy was also observed in the Cardiovascular Health Study.^{3,6} The follow-up duration was only 2.8 years in this study, and each comorbidity may require a much longer time to affect the aortic valve. Treatment for each comorbidity during the study follow-up period might have masked its effects. In addition, although the data concerning cholesterol fractions were available for less than 70% of our study subjects, high-density lipoprotein levels tended to be high in subjects without CAVD progression compared with those with progression in both the early- and late-stage groups. This study does not necessarily rule out the effects of comorbidities, particularly those that are untreated, on incidence and/or progression of CAVD.

Study limitations

There are several limitations of this study. First, this is a retrospective and hospital-based study, and thus, the selection of study subjects might be biased. The results presented here should be confirmed by prospective studies such as JASS Prospective Analysis (<https://center.umin.ac.jp/cgi-open-bin/ctr/ctr.cgi?function=brows&action=brows&recptno=R000000842&type=summary&language=E>). Second, it is well known that the prevalence of CAVD is high in patients with chronic kidney disease, particularly those requiring hemodialysis,³⁶ but renal insufficiency and eGFR were not identified as predictive factors for progression in this study. This may be because very few hemodialysis patients participated in this study, and the follow-up period was not long enough for the renal insufficiency to exacerbate CAVD. Third, the severity of CAVD at baseline was varied even within each group, and analysis of data from the late-stage subjects suggests that whether or not CAVD progresses is closely related to its severity at baseline. If subjects were divided into more groups, the effects of the baseline severity might have been omitted, and other prognostic factors might have been unmasked. However, the number of patients with severe CAVD (peak aortic transvalvular flow velocity $> 4 \text{ m s}^{-1}$) was too small in this study to identify prognostic factors. To exclude the effects of baseline disease severity and to unmask other prognostic factors, future studies with larger number of subjects are required. Fourth, the follow-up period was not the same between subjects with and without progression in either groups. In the late-stage group, the follow-up period in subjects with progression was shorter than in those without progression. CAVD gradually progresses in general, and thus, even if the follow-up period were lengthened for subjects with progression, the classification of each subject might not be affected. In the early-stage group, the difference in the follow-up period was only 0.39 year, and thus, the effects of a difference in follow-up period were probably small even if present. Fifth, phlebotomy was not necessarily performed in the fasting state, and data concerning cholesterol fractions were unavailable in more than 30% of our study subjects. Thus, this study might not be able to make conclusive statements about the relationship between CAVD progression and dyslipidemia.

Clinical implications

Moura *et al.*³⁷ reported the attenuated progression of aortic stenosis in patients who received rosuvastatin because their low-density lipoprotein levels were $> 130 \text{ mg per } 100 \text{ ml}$ at baseline, compared with those who did not receive rosuvastatin because their baseline low-density lipoprotein was $< 130 \text{ mg per } 100 \text{ ml}$; in addition, the greater decrease in low-density lipoprotein was associated with less progression of aortic stenosis in the rosuvastatin-treated patients. Recent clinical trials failed to find beneficial effects of pharmacological lipid-lowering therapy in preventing progression of aortic stenosis in patients for

whom lipid-lowering therapy is not indicated according to current guidelines.^{19,38,39} In this study, the subset of patients with aortic stenosis fell into the cohort of subjects with late-stage CAVD, and as in the previous studies, results from this group found that use of statins or other medications had no effect on the progression of disease in the late stage. Use of statins may attenuate the progression of late-stage CAVD in patients for whom lipid-lowering therapy is indicated according to the current guidelines; however, administering statins beyond these guidelines in an effort to prevent progression of late-stage CAVD through their non-lipid-lowering effects is likely to be unjustified. Currently, there is no pharmacological therapy that is specific for late-stage CAVD.

In contrast, use of ARBs during early-stage CAVD was associated with lack of progression in this study. The prevalence of aortic stenosis is because of high CAVD in developed countries, and the only established therapeutic strategy is aortic valve replacement. This finding suggests that initiation of ARBs during early-stage disease may prevent progression of CAVD and avoid aortic valve replacement. To clarify the effects of ARBs, randomized trials should be performed.

CONCLUSIONS

Prognostic factors for progression of CAVD differed between early- and late-stage disease in a Japanese patient cohort. This study suggests that initiation of ARB treatment during the early stage is effective in preventing disease progression, and that caution is indicated in patients treated with oral anticoagulants. Female gender is predictive for disease progression during the late stage, and progression may be more rapid in patients who have a more severe aortic valve injury.

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