Journal of the American Heart Association

RESEARCH LETTER

Rivaroxaban Monotherapy in Patients With Atrial Fibrillation and Coronary Stenting at Multiple Vessels or the Left Main Trunk: The AFIRE Trial Subanalysis

Mitsuru Ishii, MD, PhD; Masaharu Akao, MD, PhD; Satoshi Yasuda, MD, PhD; Koichi Kaikita, MD, PhD; Junya Ako, MD, PhD; Tetsuya Matoba, MD, PhD; Masato Nakamura, MD, PhD; Katsumi Miyauchi, MD, PhD; Nobuhisa Hagiwara, MD, PhD; Kazuo Kimura, MD, PhD; Atsushi Hirayama, MD, PhD; Kunihiko Matsui, MD, MPH; Hisao Ogawa, MD, PhD; on behalf of the AFIRE Investigators*

The atrial fibrillation and ischemic events with rivaroxaban in patients with stable coronary artery disease (AFIRE) trial demonstrated that rivaroxaban monotherapy is noninferior to combination therapy with rivaroxaban plus a single antiplatelet agent for cardiovascular events and death, and superior for major bleeding in patients with atrial fibrillation and stable coronary artery disease (CAD).[1] However, the risk for ischemic events may vary depending on the severity of CAD in patients who received percutaneous coronary intervention. Coronary lesions in multiple vessels or the left main trunk (LMT) are considered a more severe type of CAD. It is unclear whether the results of the AFIRE trial are consistent in these patients at high-risk of ischemic events.

The AFIRE trial randomly assigned 2240 patients with atrial fibrillation and stable CAD to receive either monotherapy with rivaroxaban or combination therapy with rivaroxaban plus an antiplatelet agent.[1] This trial was approved by an institutional review committee and the subjects gave informed consent. A total of 1402 patients who underwent coronary stenting before enrollment were chosen for this AFIRE trial subanalysis and were divided into 2 subgroups: patients receiving stenting in 1 vessel (1V, n=1020) and in multiple vessels or LMT (MV/LMT, n=382). The primary efficacy end point was the composite of stroke, systemic embolism, myocardial infarction, unstable angina requiring revascularization or death from any cause. The primary safety end point was International Society on Thrombosis and Hemostasis major bleeding. Cumulative event rates were estimated using the Kaplan–Meier method and log-rank test was performed to assess differences among groups. We compared the outcomes between treatment groups, using Cox proportional hazard analysis. The treatment effect in each subgroup was examined in separate models. The *P* value for interaction was assessed to examine the heterogeneity in subgroups. Statistical analyses were conducted using JMP 16.0.0. Study data are available from the corresponding author upon reasonable request.

There were no significant differences in major backgrounds between the treatment arms in both 1V and MV/LMT subgroups. Relative risks according to each

Key Words: antithrombotic therapy ■ atrial fibrillation ■ coronary stenting

Correspondence to: Masaharu Akao, MD, PhD. Department of Cardiology, National Hospital Organization Kyoto Medical Center, 1-1, Mukaihata-cho, Fukakusa, Fushimi-ku, Kyoto, 612-8555, Japan. Email: akao@kuhp.kyoto-u.ac.jp

*A complete list of the AFIRE Investigators has been provided as a Supplemental Material file.

Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.122.027107

For Sources of Funding and Disclosures, see page 3.

JAHA is available at: www.ahajournals.org/journal/jaha

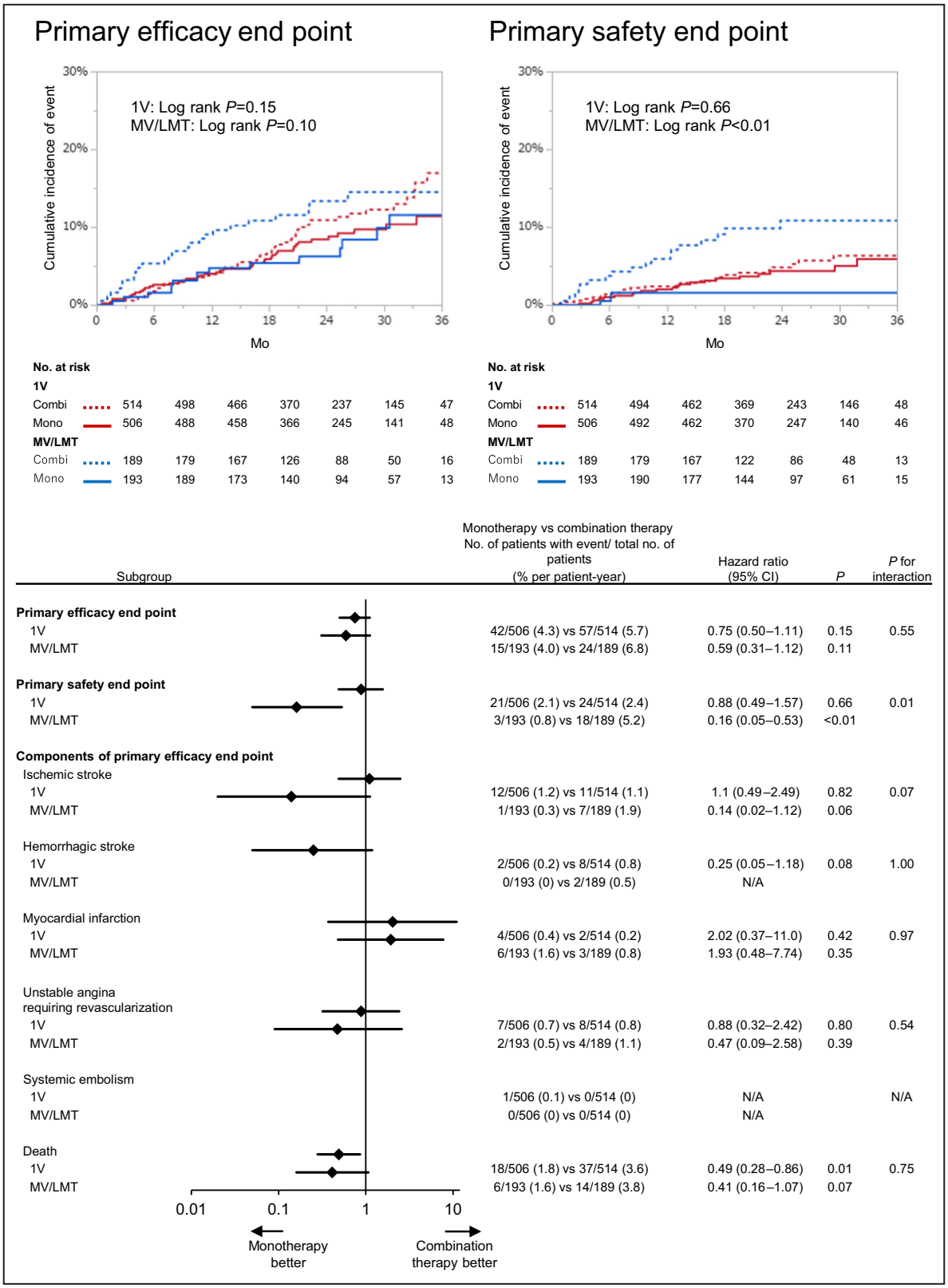

Figure. **Relative risk of the primary efficacy end point, the primary safety end point, and the components of the efficacy end point according to each subgroup.**

The primary efficacy end point was composite of stroke, systemic embolism, myocardial infarction, unstable angina requiring revascularization, or death from any cause. The primary safety end point was major bleeding. Data are presented as incidence rate (total events) per 100 person-years. 1V indicates 1 vessel; Combi, combination therapy; LMT, left main trunk; Mono, rivaroxaban monotherapy; and MV, multiple vessels.

subgroup are shown in the Figure. There were no statistically significant differences in the primary efficacy end point between the treatment arms in both 1V (hazard ratio [HR] 0.75 [95% CI, 0.50–1.11; *P*=0.15]) and MV/LMT (HR, 0.59 [95% CI, 0.31–1.12; *P*=0.11]) subgroups and there was no significant interaction (*P* for interaction 0.55). In contrast, there was a statistically significant difference in the primary safety end point in MV/LMT (HR, 0.16 [95% CI, 0.05–0.53; *P*<0.01]) subgroup, while not in 1V (HR, 0.88 [95% CI, 0.49–1.57; *P*=0.66]) subgroup. There was a significant interaction between 1V and MV/LMT subgroups in terms of safety (*P* for interaction 0.01). This was also the case with other bleeding end points, including any bleeding, nonmajor bleeding, and gastrointestinal bleeding (data not shown). In addition, in patients with coronary stenting in the LMT (n=46; 24 with monotherapy and 22 with combination therapy), neither primary efficacy nor safety end points occurred in the monotherapy group (efficacy/safety end points: monotherapy 0/0, combination therapy 1/3).

The rates of repeat revascularization, stent thrombosis, and death were reported to be higher in patients with complex CAD lesions than simpler lesions.[2] Thus, in more severe types of CAD, more potent anti-thrombotic therapy, including combinations of anti-thrombotic drugs, has been recommended. However, this subanalysis did not support the advantage of combination therapy, even for patients with a high-risk of ischemic events. Another subanalysis of the AFIRE trial also demonstrated that the advantage of rivaroxaban monotherapy was consistent even in a high-risk subgroup of patients with prior atherothrombotic disease (myocardial infarction, stroke, and/or peripheral artery disease).[3] Patients with complex CAD concomitantly have features that significantly increase their bleeding risk such as multiple comorbidities, renal dysfunction, or previous bleeding.[4] With respect to bleeding, the benefit of rivaroxaban monotherapy was considered to be greater in patients with MV/LMT because such patients were considered to have multiple morbidities and poorer clinical backgrounds. In a subanalysis of the management of high bleeding risk patients post bioresorbable polymer coated stent implantation with an abbreviated versus standard DAPT regimen (MASTER DAPT) trial, abbreviated antiplatelet regimen after percutaneous coronary intervention did not result in the increase in net adverse events in patients with indication for oral anticoagulants, as compared with nonabbreviated regimen.[5] Therefore, rivaroxaban monotherapy may be not only sufficient to prevent thromboembolic events even in patients with a high-risk for ischemic events, but also superior to combination therapy through fewer bleeding events.

Our study had several limitations, in addition to those described in the main article.[1] We did not collect information on the disease severity scale such as SYNTAX score; a patient who had severe and diffuse coronary disease but received stenting only in 1 vessel may have been included in 1V subgroup. Patients with advanced CAD may have been excluded from the trial. Lastly, the number of events was relatively low, limiting statistical power.

Among patients with atrial fibrillation after percutaneous coronary intervention, the effects of rivaroxaban monotherapy for the efficacy and safety end points were consistent irrespective of coronary complexity, and the benefit was even greater in patients receiving stenting in MV/LMT than 1V regarding the safety end point.

ARTICLE INFORMATION

Received June 12, 2022; accepted September 19, 2022.
Registration: URL: https://www.clinicaltrials.gov; Unique identifier: NCT0264 2419.

Affiliations

Department of Cardiology, National Hospital Organization Kyoto Medical Center, Kyoto, Japan (M.I., M.A.); Department of Cardiovascular Medicine, Tohoku University Graduate School of Medicine, Sendai, Japan (S.Y.); National Cerebral and Cardiovascular Center, Osaka, Japan (S.Y.); Division of Cardiovascular Medicine and Nephrology, Department of Internal Medicine, Faculty of Medicine, University of Miyazaki, Miyazaki, Japan (K.K.); Department of Cardiovascular Medicine, Kitasato University School of Medicine, Sagamihara, Japan (J.A.); Department of Cardiovascular Medicine, Faculty of Medical Sciences, Kyushu University, Fukuoka, Japan (T.M.); Division of Cardiovascular Medicine, Toho University Ohashi Medical Center, Tokyo, Japan (M.N.); Department of Cardiovascular Medicine, Juntendo Tokyo Koto Geriatric Medical Center, Tokyo, Japan (K.M.); Department of Cardiology, Tokyo Women's Medical University, Tokyo, Japan (N.H.); Cardiovascular Center, Yokohama City University Medical Center, Yokohama, Japan (K.K.); Department of Cardiology, Osaka Police Hospital, Osaka, Japan (A.H.); Department of General Medicine and Primary Care, Kumamoto University Hospital, Kumamoto, Japan (K.M.); and Kumamoto University, Kumamoto, Japan (H.O.).

Sources of Funding

The Japan Cardiovascular Research Foundation conducted the trial using funds provided by Bayer Yakuhin, Ltd. These funds were provided without restrictions or requirements. Mebix, Inc, for their contribution in the selection of the participating centers; in the supervision or monitoring of the centers; in collecting trial data; in storing trial data; in data analysis of the trial results, and in the provision of editorial assistance with the preparation of the manuscript under the guidance of authors, were financed by the Japan Cardiovascular Research Foundation based on funds received from Bayer Yakuhin, Ltd. This work was supported by the Japan Cardiovascular Research Foundation based on a contract with Bayer Yakuhin, Ltd., who had no role in the design of the trial, collection or analysis of the data, interpretation of the trial results, or writing of the manuscript.

Disclosures

Dr. Akao reports grants from the Japan Agency for Medical Research and Development (AMED), personal fees from Bristol Myers Squibb and Nippon Boehringer Ingelheim, and grants and personal fees from Bayer Yakuhin and Daiichi-Sankyo. Dr. Yasuda reports grants from Takeda Pharmaceutical, Abbott, and Boston Scientific, and personal fees from Daiichi-Sankyo and Bristol Myers Squibb. Dr. Kaikita reports grants and personal fees from Bayer Yakuhin and Daiichi-Sankyo. Dr. Ako reports personal fees from Bayer Yakuhin and Sanofi, and grants and personal fees from Daiichi-Sankyo. Dr. Matoba reports grants from the Japan Cardiovascular Research Foundation and personal fees from Nippon Boehringer Ingelheim, Daiichi-Sankyo, AstraZeneca, and Bayer Yakuhin. Dr. Nakamura reports grants and personal fees from Bayer Yakuhin, Daiichi-Sankyo, and Sanofi, and personal fees from Bristol Myers Squibb and Nippon Boehringer Ingelheim. Dr. Miyauchi reports personal fees from Amgen Astellas BioPharma, Astellas Pharma, MSD, Bayer Yakuhin, Sanofi, Takeda Pharmaceutical, Daiichi-Sankyo, Nippon Boehringer Ingelheim, and Bristol Myers Squibb. Dr. Hagiwara reports grants and personal fees from Bayer Yakuhin, grants from Nippon Boehringer Ingelheim, and personal fees from Bristol Myers Squibb. Dr. Kimura reports grants from the Japan Cardiovascular Research Foundation,

grants and personal fees from Bayer Yakuhin, Daiichi-Sankyo, Sanofi, MSD, and AstraZeneca, and personal fees from Bristol Myers Squibb and Nippon Boehringer Ingelheim. Dr. Hirayama reports grants and personal fees from Boston Scientific Japan, Otsuka Pharmaceutical, Sanofi, Astellas Pharma, Bristol Myers Squibb, Daiichi-Sankyo, and Bayer Yakuhin, grants from Fukuda Denshi, Abbott Japan, Japan Lifeline, Takeda Pharmaceutical, and Sumitomo Dainippon Pharma, and personal fees from Toa Eiyo, Nippon Boehringer Ingelheim, Amgen Astellas BioPharma, and AstraZeneca. Dr. Ogawa reports personal fees from Bayer Yakuhin, Novartis Pharma, Bristol-Meyers Squibb, Daiichi-Sankyo, Pfizer, Eisai, Behringer Ingelheim, Takeda Pharmaceutical, Towa Yakuhin, Toa Eiyo, Teijin, and Abbott Medical Japan LLC. The remaining authors have no disclosures to report.

Supplemental Material

Appendix S1. AFIRE Study Committees and Investigators

REFERENCES

1. Yasuda S, Kaikita K, Akao M, Ako J, Matoba T, Nakamura M, Miyauchi K, Hagiwara N, Kimura K, Hirayama A, et al. Antithrombotic therapy for atrial fibrillation with stable coronary disease. *N Engl J Med*. 2019;381:1103–1113. doi: 10.1056/NEJMoa1904143
2. Kereiakes DJ, Yeh RW, Massaro JM, Cutlip DE, Steg PG, Wiviott SD, Mauri L. DAPT score utility for risk prediction in patients with or without previous myocardial infarction. *J Am Coll Cardiol*. 2016;67:2492–2502. doi: 10.1016/j.jacc.2016.03.485
3. Matsuzawa Y, Kimura K, Yasuda S, Kaikita K, Akao M, Ako J, Matoba T, Nakamura M, Miyauchi K, Hagiwara N, et al. Antithrombotic therapy for atrial fibrillation and coronary artery disease in patients with prior atherothrombotic disease: a post hoc analysis of the AFIRE trial. *J Am Heart Assoc*. 2021;10:e020907. doi: 10.1161/JAHA.121.020907
4. Gallego P, Roldán V, Torregrosa JM, Gálvez J, Valdés M, Vicente V, Marín F, Lip GY. Relation of the HAS-BLED bleeding risk score to major bleeding, cardiovascular events, and mortality in anticoagulated patients with atrial fibrillation. *Circ Arrhythm Electrophysiol*. 2012;5:312–318. doi: 10.1161/CIRCEP.111.967000
5. Smits PC, Frigoli E, Tijssen J, Jüni P, Vranckx P, Ozaki Y, Morice MC, Chevalier B, Onuma Y, Windecker S, et al. Abbreviated antiplatelet therapy in patients at high bleeding risk with or without oral anticoagulant therapy after coronary stenting: an open-label, randomized, controlled trial. *Circulation*. 2021;144:1196–1211. doi: 10.1161/CIRCULATIONAHA.121.056680

SUPPLEMENTAL MATERIAL

AFIRE Study Committees and Investigators

Principal Investigator: Satoshi Yasuda, National Cerebral and Cardiovascular Center

Steering Committee: Hisao Ogawa, National Cerebral and Cardiovascular Center (Deputy Principal Investigator), Kazuo Kimura, Cardiovascular Center, Yokohama City University Medical Center, Nobuhisa Hagiwara, Department of Cardiology, Tokyo Women's Medical University, Atsushi Hirayama, Department of Cardiology Osaka Police Hospital, Masato Nakamura, Division of Cardiovascular Medicine, Toho University Ohashi Medical Center, Katsumi Miyauchi, Department of Cardiology, Juntendo University School of Medicine

Protocol Committee: Junya Ako, Department of Cardiovascular Medicine, Kitasato University School of Medicine (Chair), Masaharu Akao, Department of Cardiology, National Hospital Organization Kyoto Medical Center, Koichi Kaikita, Department of Cardiovascular Medicine, Graduate School of Medical Sciences, Kumamoto University, Tetsuya Matoba, Department of Cardiovascular Medicine, Kyushu University Hospital

Clinical Events Committee

(1) Cardiac Region: Yukihiro Koretsune, Clinical Research Center, National Hospital Organization Osaka Medical Center, Takafumi Hiro, Department of Cardiovascular Medicine, Nihon University Graduate School of Medicine, Tetsuya Sumiyoshi, Sakakibara Heart Institute

(2) Brain Region: Kazumi Kimura, Department of Neurology, Graduate School of Medicine, Nippon Medical School, Yoichiro Hashimoto, Regional Alliances Room, Department of Neurology, Kumamoto City Hospital, Teruyuki Hirano, Stroke Medicine, Kyorin University School of Medicine

Data Safety Monitoring Committee: Hiroyuki Daida, Department of Cardiovascular Medicine, Juntendo University Graduate School of Medicine (Chair), Yasushi Okada, Clinical Research Center, National Hospital Organization Kyushu Medical Center, Tsutomu Yamazaki, International University of Health and Welfare, Innovation and Research Support Center

Principal Statistician: Kunihiko Matsui, Department of General Medicine, Kumamoto University Hospital

Publication Committee: Hisao Ogawa, National Cerebral and Cardiovascular Center (Deputy Principal Investigator), Kazuo Kimura, Cardiovascular Center, Yokohama City University Medical Center, Nobuhisa Hagiwara, Department of Cardiology, Tokyo Women's Medical University, Atsushi Hirayama, Department of Cardiology Osaka Police Hospital, Masato Nakamura, Division of Cardiovascular Medicine, Toho University Ohashi Medical Center, Katsumi Miyauchi, Department of Cardiology, Juntendo University School of Medicine, Junya Ako, Department of Cardiovascular Medicine, Kitasato University School of Medicine, Masaharu Akao, Department of Cardiology, National Hospital Organization Kyoto Medical Center, Koichi Kaikita, Department of Cardiovascular Medicine, Graduate School of Medical Sciences, Kumamoto University, Tetsuya Matoba, Department of Cardiovascular Medicine, Kyushu University Hospital, Kunihiko Matsui, Department of General Medicine, Kumamoto University Hospital

Clinical Research Organization: Mebix, Inc

List of Investigators

A. Nakamura (Iwate Prefectural Central Hospital), E. Tamiya (Koto Hospital), T. Yamamoto (Hokkaido Cardiovascular Hospital), S. Suetake (Kaetsu Hospital), T. Noguchi (National

Cerebral and Cardiovascular Center Hospital), S. Nakamura (JCHO Hitoyoshi Medical Center), A. Matsumura (Kameda Medical Center), J. Kojima (Kojima Clinic), S. Suwa (Juntendo University Shizuoka Hospital), H. Yamaguchi (YamaguchI Hiroshi Clinic), K. Kaikita (Kumamoto University Hospital), T. Yasu (Dokkyo Medical University Nikko Medical Center), A. Nakajima (New Tokyo Hospital), T. Yamada (Osaka General Medical Center), H. Arai (Kanoya Heart Center), Y. Hata (Minamino Cardiovascular Hospital), T. Sakanashi (Sakanashi Heart Clinic), H. Tateishi (Koyo New Town Hospital), T. Nakayama (Nakayama Clinic), Y. Nozaki (Hokkokinen Hospital), M. Akao (National Hospital Organization Kyoto Medical Center), Y. Okumura (Nihon University Itabashi Hospital), M. Tokue (Toho University Ohashi Medical Center), N. Kuroki (Tokyo Metropolitan Bokutoh Hospital), Y. Maruyama (Iwatsuki-minami Hospital), T. Matoba (Kyushu University Hospital), N. Hagiwara (Tokyo Women's Medical University Hospital), H. Suzuki (Showa University Fujigaoka Hospital), Y. Nishida (Kouseikai Takai Hospital), M. Ajioka (Tosei General Hospital), K. Yumoto (Yokohama Rosai Hospital), S. Shimizu (Mashiko Hospital), T. Aoyama (Fukui Prefectural Hospital), H. Shimomura (Fukuoka Tokushukai Hospital), T. Takeda (Koto Memorial Hospital), K. Oshiro (Ohama Dai-ichi Hospital), N. Sugishita (Sugishita Clinic), Y. Shibata (Miyazaki Medical Association Hospital), T. Otonari (Otonari Clinic), H. Kihara (Kihara Cardiovascular Clinic), H. Ogawa (Kita Akita Municipal Hospital), A. Ohno (Medical Corporation Shoikai Kasai Shoikai Hospital), M. Hazama (Nijigaoka Hospital), M. Shimizu (Social welfare corporation Goodwill welfare association International Goodwill Hospital), K. Tsukahara (Fujisawa City Hospital), S. Haruta (Fukuyama Cardiovascular Hospital), T. Wakeyama (JCHO Tokuyama Central Hospital), T. Haruna (Kitano Hospital, Tazuke Kofukai Medical Research Institute), M. Ito (Mie University Hospital), K. Fujii (Sakurabashi Watanabe Hospital), N. Atsuchi (Tenyoukai Central Clinic), M. Sata (Tokushima University Hospital), K. Kimura (Yokohama City University Medical Center), N. Hasebe (Asahikawa Medical

University Hospital), Y. Kobayasi (Chiba University Hospital), K. Ohsato (Fukui Cardiovascular Center), K. Hironaga (Fukuoka City Hospital), Y. Naganuma (Hachinohe Red Cross Hospital), K. Anzaki (Izumi Regional Medical Center), K. Oiwa (JCHO Yokohama Chuo Hospital), S. Okazaki (Juntendo University Hospital), Y. Nakagawa (Kawanishi City Hospital), K. Tokuhiro (Misato Central General Hospital), K. Tanaka (Miyoshi Central Hospital), T. Momose (Nagano Matsushiro General Hospital), Y. Fukushima (Nagatsuta Kosei General Hospital), R. Kametani (Nagoya Tokushukai General Hospital), K. Kawamitsu (Nanbu Tokushukai Hospital), Y. Saito (Nara Medical University), S. Akashi (National Hospital Organization Hamada Medical Center), K. Kumagai (Odawara Cardiovascular Hospital), K. Eshima (Saga-Ken Medical Centre Koseikan), T. Tobaru (Sakakibara Heart Institute), T. Seo (Seo Heart Clinic), K. Okuhara (Shobara Red Cross Hospital), K. Kozuma (Teikyo University Hospital), Y. Ikari (Tokai University Hospital), T. Takahashi (Tokyo Saiseikai Central Hospital), I. Michishita (Yokohama Sakae Kyosai Hospital), H. Fujikura (Fujikura Clinic), S. Momomura (Jichi Medical University Saitama Medical Center), Y. Yamamoto (Kansai Medical University Medical Center), K. Otomo (Ome Municipal General Hospital), T. Matsubara (Shinrakuen Hospital), H. Tashiro (St. Mary's Hospital), T. Inoue (Dokkyo Medical University Hospital), M. Ishihara (Hyogo College Of Medicine College Hospital), I. Shiojima (Kansai Medical University Hospital), E. Tachibana (Kawaguchi Municipal Medical Center), J. Ako (Kitasato University Hospital), K. Sumii (Mazuda Hospital), N. Yamamoto (Miyazaki Prefectural Nobeoka Hospital), N. Ohmura (Nakata Clinic), T. Nakamura (National Hospital Organization Kyushu Medical Center), Y. Morita (National Hospital Organization Sagamihara National Hospital), N. Takahashi (Oita University Hospital), K. Watanabe (Saiseikai Matsuyama Hospital), H. Fujinaga (Tokushima Prefectural Central Hospital), M. Maruyama (Toyama Prefectural Central Hospital), T. Oka (Tsuyama Chuo Hospital), T. Shirayama (University Hospital, Kyoto Prefectural University of Medicine), T. Amano (Aichi Medical

University Hospital), K. Fukui (Kanagawa Cardiovascular and Respiratory Center), K. Ando (Kokura Memorial Hospital), S. Oshima (Kumamoto Chuo Hospital), S. Kagiyama (Kyushu Central Hospital of the Mutual Aid Association of Public School Teachers), H. Teragawa (Medical Corporation JR Hiroshima Hospital), M. Yuge (Odawara Municipal Hospital), S. Ono (Saiseikai Yamaguchi General Hospital), T. Koga (Steel Memorial Yawata Hospital), K. Fujiu (The University of Tokyo Hospital), M. Kuwabara (Toranomon Hospital), Y. Ohya (University of the Ryukyus Hospital), Y. Yumoto (Fuji Hospital), N. Kuji (Good Heart Clinic), M. Ikemura (Ikemura Medical Clinic), K. Kario (Jichi Medical University Hospital), K. Chatani (Kawasaki Municipal Tama Hospital), K. Sato (Kumamoto City Hospital), H. Miyagi (Miyagi Clinic), M. Murakami (Murakami Clinic), K. Saito (Nishiarai Heart Center Hospital), M. Hoshiga (Osaka Medical College Hospital), S. Sato (Saiseikai Imabari Hospital), N. Kubo (Saitama Medical Center), Y. Sakamoto (Sakamoto Cardiovascular Clinic), K. Ashida (Seirei Yokohama Hospital), H. Sakamoto (Shizuoka General Hospital), S. Murasaki (Tama-Hokubu Medical Center), H. Uehara (Urasoe General Hospital), T. Akasaka (Wakayama Medical University Hospital), Y. Ooba (Chihaya Hospital), S. Nakahara (Dokkyo Medical University Saitama Medical Center), Y. Hanaoka (Hanaoka Cardiovascular Clinic), T. Nishimiya (Japanese Red Cross Asahikawa Hospital), R. Tsunoda (Japanese Red Cross Kumamoto Hospital), Y. Onuma (JR Sapporo Hospital), S. Higuchi (Kamiamakusa General Hospital), A. Tani (Kano General Hospital), A. Wada (Kusatsu General Hospital), M. Kato (Mie Heart Center), H. Obata (National Hospital Organization Obihiro National Hospital), Y. Higuchi (Osaka Police Hospital), T. Endo (Saiseikai Yokohamashi Nanbu Hospital), R. Katou (Saitama Medical University International Medical Center), T. Matsunaga (Seiwakai Suizenji-Tohya Hospital), T. Matsuoka (Uji Tokushukai Medical Center), H. Noguchi (Fukuoka Wajiro Hospital), M. Usui (Hamanomachi Hospital), T. Hayashi (Hayashi Medical Clinic), Y. Otsuji (Hospital of the University of Occupational and Environmental Health), T. Osaki (Iwate Prefectual Kuji

Hospital), H. Zaizen (JA Oita Koseiren TsurumiI Hospital), H. Yoshihara (JA Toride Medical Center), K. Kadota (Kurashiki Central Hospital), T. Hirose (Minamata City Hospital & Medical Center), T. Miyazawa (Miyazawa Heart Clinic), A. Mori (National Hospital Organization Iwakuni Clinical Center), M. Takano (Nippon Medical School Chiba Hokusoh Hospital), W. Shimizu (Nippon Medical School Hospital), M. Wake (Okinawa Prefectural Chubu Hospital), S. Oriso (Oriso Internal Medicine & Cardiology Clinic), M. Yoshiyama (Osaka City University Hospital), S. Kakinoki (Otaru Kyokai Hospital), T. Nishioka (Saitama Medical Center), T. Ozaki (Sapporo Orthopaedics and Cardiovascular Hospital), K. Nomoto (Tokyo Rinkai Hospital), K. Seki (Yamaguchi Rosai Hospital), K. Kawai (Chikamori Hospital), Y. Ozaki (Fujita Health University Hospital), S. Miura (Fukuoka University Hospital), M. Kawasaki (Gifu University Hospital), R. Funada (Gunma University Hospital), K. Dote (Hiroshima City Asa Citizens Hospital), T. Nagano (Iwasa Hospital Iwasa Maternity), S. Okamoto (Iwasaki Hospital), T. Kubo (Matsuyama Red Cross Hospital), Y. Murozono (Oita Red Cross Hospital), T. Owada (Fukushima Red Cross Hospital), T. Doke (Kohka Public Hospital), T. Matsumura (Kumamoto Rosai Hospital), M. Horiuchi (Medical Association Sugimura Hospital), A. Takaishi (Mitoyo General Hospital), M. Yamamoto (National Center for Global Health and Medicine), H. Nakashima (National Hospital Organization Kagoshima Medical Center), M. Munemasa (National Hospital Organization Okayama Medical Center), Y. Sakata (Osaka University Hospital), N. Inoue (Sendai Kousei Hospital), T. Ota (Takanohara Central Hospital), Y. Hamano (Tawaramachi Hamano Hospital), N. Abe (Tokyo Medical University Ibaraki Medical Center), T. Tsubokura (Tsubokura Cardiovascular Clinic), M. Goto (Watanabe Hospital), I. Kubota (Yamagata University Hospital), M. Yano (Yamaguchi University Hospital), K. Umetani (Yamanashi Prefectural Central Hospital), A. Matsumura (Awa Regional Medical Center), T. Date (Date Naika Clinic), H. Morimoto (Fukagawa Municipal Hospital), T. Noda (Gifu Prefectural General Medical Center), S. Goto (Goto Clinic), K. Hibi (Gumyoji

Eye Heart Clinic), A. Nakano (Hikone Municipal Hospital), S. Hiramitsu (Hiramitsu Heart Clinic), Y. Kihara (Hiroshima University Hospital), M. Sugi (Imaki City Medical Center), N. Shiba (International University of Health and Welfare Hospital), D. Izumi (Japanese Red Cross Ise Hospital), T. Sato (Japanese Red Cross Okayama Hospital), S. Tayama (JCHO Kumamoto General Hospital), T. Matsui (JCHO Shiga Hospital), A. Suzuki (JCHO Tokyo Yamate Medical Center), K. Ajiki (JR Tokyo General Hospital), M. Oishi (Kagoshima University Hospital), M. Kiryu (Kanagawa Cardiovascular Medicine), T. Ko (Kashima Heart Clinic), H. Ando (Keiai Hospital), S. Miyazaki (Kindai University Hospital), T. Kinugawa (Kinugawa Cardiology Clinic), H. Otake (Kobe University Hospital), H. Kitaoka (Kochi Medical School Hospital), Y. Hirata (Kumamoto Regional Medical Center), S. Honda (Minami Municipal National Insurance Hospital), M. Manita (Naha City Hospital), Y. Ishii (Ogikubo Hospital), H. Oka (Oka Clinic), Y. Nanba (Okayama Rosai Hospital), M. Nishino (Osaka Rosai Hospital), T. Sakamoto (Saiseikai Kumamoto Hospital), T. Saito (Saito Clinic), H. Sakai (Sakai Clinic), M. Ichikawa (Sekishindo Hospital), S. Namiuchi (Sendai Open Hospital), K. Inoue (South Miyagi Medical Center), N. Komiyama (St. Luke's International Hospital), Y. Akashi (St. Marianna University School of Medicine Hospital), Y. Nakamura (Takeda General Hospital), T. Komaru (Tohoku Medical and Pharmaceutical University Hospital), T. Hosokawa (Tokyo Heart Center), T. Chikamori (Tokyo Medical University Hospital), H. Tanaka (Tokyo Metropolitan Tama Medical Center), O. Arasaki (Tomishiro Central Hospital), K. Aonuma (University of Tsukuba Hospital), Y. Wakasa (Wakasa Medical Clinic), T. Yoshizawa (Yamato Municipal Hospital), T. Sugano (Yokohama City University Hospital), N. Yokota (Yokota Naika), A. Kakutani (Yoshinoawa Medical Center), T. Suzuki (Aizawa Hospital), Y. Abe (Akeno Clinic), T. Kataoka (Bell-land General Hospital), H. Okayama (Ehime Prefectural Central Hospital), H. Yokoi (Fukuoka Sanno Hospital), K. Chin (Hakuai Clinic), K. Hasegawa (Hasegawa Outpatients Clinic for Cardiovascular Disease), H. Tomita (Hirosaki University Hospital), H.

Honzyo (Honzyo Medical Hospital), H. Kawai (Hyogo Brain And Heart Center At Himeji), K. Yamamoto (Iida Municipal Hospital), Y. Morino (Iwate Medical University Hospital), S. Tsujiyama (JA Hiroshima General Hospital), S. Hamasaki (Kagoshima City Hospital), Y. Niijima (Kan-etsu Chu-oh Hospital), T. Aoyama (Kizawa Memorial Hospital), Y. Mizuno (Kumamoto Kinoh Hospital), A. Maki (Maki Clinic), K. Tanabe (Mitsui Memorial Hospital), T. Murohara (Nagoya University Hospital), T. Nakamura (Nakamura Clinic), S. Naomi (Naomi Medicinal Clinic), M. Arikawa (National Hospital Organization Oita Medical Center), T. Kato (National Hospital Organization Tochigi Medical Center), N. Matsumoto (Nihon University Hospital), T. Minamino (Niigata University Medical & Dental Hospital), H. Sairenji (Nishiyama Ichou Jyunkanki Geka Clinic), N. Miyamoto (NTT-East Sapporo Hospital), H. Ito (Okayama University Hospital), Y. Matsuura (Sakaemachi Clinic), S. Hata (Sasebo City General Hospital), Y. Nakatsu (Shioda Memorial Hospital), T. Onodera (Shizuoka City Shizuoka Hospital), M. Yoshimura (The Jikei University Hospital), H. Amano (Toho University Omori Medical Center), E. Tokutake (Tokutake Clinic), M. Kasao (Tokyo Metropolitan Police Hospital), M. Moriguchi (Toshiba Rinkan Hospital), K. Yamamoto (Tottori University Hospital), M. Tsuji (Tsuji Internal Medicine and Cardiology and Dental Clinic), H. Yamamoto (Yamamoto Clinic), Y. Yanbe (Yokohama General Hospital), T. Iwasawa (Yokohama General Hospital Uwamachi), M. Suzuki (Yokohama Minami Kyousai Hospital), H. Mori (Yokohama Sotetsu Building Clinic)