ences in the prevalence of these diseases in the present study.

Study Limitations

First, enrollment of consecutive patients with stroke, MI, and AF was recommended, but may not necessarily have occurred at each participating site and this possible selection bias could have affected the present results. Second, data for subjects with AF were collected from 3 categories of J-TRACE,[17,18] possibly resulting in increased prevalences of ischemic stroke and MI. However, this might not necessarily have affected sex-related differences in the frequency of these diseases in the present study. Actually, when only patients of AF category were analyzed, the results did not differ in terms of sex-related differences in mean age, CHADS2 score, and prevalences of heart failure, hypertension, smoking, drinking habit and warfarin usage (data not shown). Third, the study design of the J-TRACE did not define the diagnostic criteria of comorbidities, including hypertension, hypercholesterolemia and others; however, data of comorbidities were collected from the medical record. If strict diagnostic criteria of comorbidities were used, the present results would not have changed greatly. Finally, the intensity of anticoagulation was not determined systematically, and follow-up data are not yet available.

Clinical Implications

Our findings indicate sex-related differences in the clinical risk factor profile of patients with AF, with the CHADS2 score slightly but significantly higher in women with AF than in men with AF in the clinical setting in Japan. Further follow-up studies are required to elucidate the effects of these sex-related differences on subsequent thromboembolic events.

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Disclosure

There is no conflict of interest to declare.

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Appendix 1

J-TRACE Steering Committee
Yasuo Ikeda, Keio University School of Medicine (Chair); Kazuyuki Shimada, Jichi Medical School; Shinichiro Uchiyama, Tokyo Women's Medical University; Shinya Goto, Tokai University School of Medicine; and Hideki Origasa, University of Toyama School of Medicine and Pharmaceutical Sciences
Secretariat
Hiroko Usami, BIOMEDIS INTERNATIONAL LTD
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Kansai Masatsugu Hori, Yukihiro Koretsune
Hokuriku Shunro Endo, Hiroshi Inoue, Kouji Kajinami
Chugoku/Shikoku Naohisa Hamashige, Shotai Kobayash, Masayasu Matsumoto, Masunori Matsuzaki
Kyushu Yoichiro Hashimoto, Hisao Ogawa, Yasushi Okada, Shuuichi Okamatsu
Participating Investigators
Hokkaido Takeo Abumiya, Minoru Ajiki, Takeo Baba, Tomoo Furumoto, Shuuzaburou Fukuyama, Masatada Fukuoka, Takayuki Hirabayashi, Tooru Hasegawa, Kiyohiro Houkin, Katsuhisa Ishii, Satoshi Koyama, Kenji Kamiyama, Tetsuro Kohya, Satoshi Kuroda, Tsukasa Kubota, Takaaki Kato, Michifumi Kyuma, Takeo Murahashi, Tomoaki Matsumoto, Jyoji Nakagawara, Daigo Nagahara, Hiroshi Oimatsu, Toshiaki Osato, Hitoshi Ooiwa, Kazuhiro Sako, Motoi Sasaki, Toshihiro Shimizu, Yoshinobu Seo, Tetsuro Shoji, Tsukasa Satoh, Yasukuni Shikano, Mitsunori Shimazaki, Makoto Senoo, Yoshitoki Takagawa, Akihito Tsuchida, Shiho Takagawa, Hideki Takizawa, Shigemichi Tanaka, Hidekazu Takada, Shuuji Yonekura
Tohoku Morio Aihara, Mituaki Hatanaka, Yasuhiro Ishibashi, Hiroyuki Kuki, Takahiko Kikuchi, Yuichi Nozaki, Ayumu Ohnuma, Yukio Onodera, Hiroyuki Oosawa, Satoko Obara, Akifumi Suzuki, Nobuyuki Shiba, Hiroaki Takahashi, Kenichi Tamura, Hajime Yasuda
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Chiba/Saitama Nobuo Araki, Toshio Fukutake, Kouichi Honma, Yoshihiro Iijima, Shoichi Ito, Masatoshi Kusuhara, Yoichi Kuwabara, Yoshio Kobayashi, Kazutaka Matsui, Shinji Matsuda, Takashi Nakazato, Kyoichi Nomura, Toshio Nagai, Fumitaka Ohsuzu, Hideki Shige, Shigeki Tanaka, Kazuo Yamakawa
Tokyo/Kanagawa Hisanao Akiyama, Kuniya Asai, Eiiti Akiyama, Toshiaki Ebina, Mitsuaki Endo, Tsutomu Endo, Eri Furukawa, Hirotaka Fujita, Kazuki Fukui, Shinya Fukazawa, Taiji Furukawa, Shinya Goto, Yoshinari Goseki, Haruhiko Hoshino, Kazuhiro Hara, Kei Hatori, Jynya Hosoda, Satoshi Hida, Masaharu Hirano, Kazunori Iwade, Noriaki Iwahashi, Aritomo Inoue, Shinobu Imai, Taizo Ishiyama, Kensuke Ishii, Sugao Ishiwata, Yuji Ikari, Kohei Iguchi, Yutaka Kitamura, Eitaro Kodani, Yasuhisa Kitagawa, Haruhisa Kato, Hirotaka Kato, Takashi Kiyanagi, Ikuyoshi Kusama, Kazuo Kimura, Noriyuki Kawaura, Tsukasa Koboyashi, Takahide Kohro, Kimio Kikushima, Atsumi Kume, Mitsuharu Kawamura, Kazuhiro Muramatsu, Kohei Matsushita, Yoko Morita, Yoshino Minoura, Jun Masuda, Yukiko Morita, Takayuki Mitsuhashi, Nobuhiko Maejima, Minako Murayama, Takamichi Miyamoto, Kagari Matsudaira, Manabu Miyagi, Hiroyoshi Morino, Riichiro Nakayama, Takehiko Nagao, Hiroshi Nishimura, Masashi Nakamaru, Tatsuya Nakachi, Tomoyori Nakatogawa, Takeshi Nakagawa, Masyayuki Nakao, Akihiro Niwa, Hirotoshi Ohmura, Hiroyuki Ozaki, Syuuji Ono, Jun Okuda, Yasuo Ohkusu, Yuji Otsuka, Hisako Omori, Miei Shimura, Tomoaki Shimizu, Takahiro Shibata, Ryouma Shibue, Fumio Saito, Shigeru Nogawa, Kenichiro Saka, Toshihiko Saito, Toshiak Sato, Yutaka Shiina, Naohisa Shindo, Shigeharu Takagi, Makoto Takagi, Kengo Tsukahara, Tatuya Takahashi, Itaru Takamisawa, Tetsu Takamizawa, Naoyuki Takahashi, Shigemasa Tani, Koichi Tamura, Shinichi Takahashi, Hidehito Takase, Takeshi Tadera, Hirokazu Tanaka, Teruhisa Tanabe, Nobuhiro Tanaka, Yasuyoshi Takei, Yoko Takiyama, Shinichiro Uchiyama, Jun Umemura, Hiromi Uno/Terashi, Mikio Usui, Ikuyoshi Watanabe, Masayuki Yotsukura, Hideto Yano, Takeshi Yamakawa, Minako Yoshida
Tokai Tetsuo Ando, Mikio Hirayama, Takashi Hara, Kazuhiro Hara, Nozomi Hishikawa, Mizuki Ito, Noboru Imai, Tetsuya Kitamura, Sukenari Koyabu, Noriko Kodama, Osamu Kawakami, Takashi Kameyama, Takahisa Kondo, Masaaki Kanashiro, Toyoaki Murohara, Mamoru Nanasato, Mikiya Nakayabu, Hisayoshi Niwa, Masahiro Oya, Osamu Ohno, Makoto Sugiura, Hidetaka Watanabe
Kansai Ken Araki, Hideki Etani, Ryuzo Fukunaga, Shigetaka Furukado, Hisakazu Fuji, Katsuji Hashimoto, Hiroyuki Hashimoto, Kinji Ishikawa, Kazuo Kitagawa, Yukihiro Koretsune, Akio Kohama, Yoshiyuki Kijima, Shinsuke Nanto, Katsunori Nao, Yoshiyuki Nagai, Keiko Nagano, Osaka Police Hospital's Cardiology, Yutaka Okazaki, Masafumi Tagaya, Tsutomu Takahashi
Hokuriku Hironobu Akao, Shunro Endo, Nakaba Fujioka, Akira Fujiki, Tadakazu Hirai, Jun Harada, Hisanari Ishise, Hiroshi Inoue, Bunji Kaku, Michiya Kubo, Masanori Kyoi, Kiyoo Mori, Koichi Mizumaki, Yutaka Nitta, Takashi Nozawa, Makoto Nonomura, Ryoko Sato, Shutaro Takashima, Yoshihiro Takeuchi, Yoshiharu Taguchi, Kortaro Tanaka, Tsukasa Takabatake, Tomio Taguchi
Chugoku/Shikoku Hitoshi Fukuda, Yuhji Furutani, Kaori Fujibe, Takashi Fujii, Naohisa Hamashige, Naohisa Hosomi, Masahiko Harada, Yuji Hisamatsu, Koji Hirashita, Hijiri Ito, Takahiro Iwami, Shoichi Kato, Juri Kitamura, Masateru Kohno, Mitsuhiro Kitani, Hiromi Koide, Masayasu Kimura, Satoshi Kataoka, Kyoko Kobayashi, Toshiro Miura, Shingo Mitaki, Yasuhiro Manabe, Eiichi Nomura, Koichi Noda, Atsushi Nagai, Kiyoshi Nishino, Manabu Nasu, Takanori Namba, Fumiaki Nakao, Shiro Ono, Eiichi Ohnuki, Kazunori Okada, Takayuki Okamura, Tomohiko Ohshita, Hiroaki Sugiura, Kozaburo Seki, Tsuyoshi Torii, Taketo Tanigawa, Hideo Terasawa, Tsuyoshi Ueyama, Masahiro Yamasaki, Kyounori Yasumoto, Toshihiko Yamagata
Kyushu Yutaka Akatsuka, Yoshihiro Fukumoto, Yasuo Fukuda, Takako Fujiki, Yuji Fukutome, Koji Hiyamuta, Rikuzo Hamada, Yasuo Hayashi, Youichi Hokezu, Yoichiro Hashimoto, Yoshifumi Hirata, Tadashi Hamada, Takeshi Ideguchi, Takuroh Imamura, Masatoshi Koga, Junji Kawagoe, Sunao Kojima, Shigehiko Kumate, Ikuo Misumi, Junnko Mashiba, Takashi Matsuura, Hiroshi Nakane, Toshiyasu Ogata, Hirokuni Ohba, Shuichi Okamatsu, Hideki Oka, Yoshisato Shibata, Satoko Saito, Ichiro Shimada, Kazuhito Tsuruta, Kazuhiro Tashima, Yoshihide Taniwaki, Satoshi Terai, Takeshi Yamada, Hitoshi Yasumoto, Akira Yamada, Tohru Yamawaki

Effects of Edaravone, a Free Radical Scavenger, on Serum Levels of Inflammatory Biomarkers in Acute Brain Infarction

Kenji Isahaya, MD, Koji Yamada, MD, PhD, Masato Yamatoku, MD, Kenzo Sakurai, MD, Satoshi Takaishi, MD, PhD, Bunta Kato, MD, PhD, Toshikazu Hirayama, MD, PhD, and Yasuhiro Hasegawa, MD, PhD

The potent free radical scavenger edavarone is widely used in Japan to treat acute ischemic stroke within 24 hours after onset. Recent experimental studies have shown that edavarone alleviates blood-brain barrier disruption in conjunction with suppression of the inflammatory reaction in acute brain ischemia. We investigated the effects of edaravone on circulating inflammatory biomarkers in patients with ischemic stroke. Patients with acute ischemic stroke admitted 12-36 hours after onset of symptoms were prospectively enrolled. Intravenous edaravone at 60 mg/day for 14 days was administered to patients admitted 12-24 hours after symptom onset (edaravone group; n = 29). Patients admitted 24-36 hours after onset served as controls (control group; n = 34). Venous blood samples were obtained on admission and at 48 hours, 7 days, and 14 days after symptom onset. Serum concentrations of high-sensitivity C-reactive protein, interleukin (IL)-6, IL-10, IL-18, tumor necrosis factor α, matrix metalloproteinase (MMP)-2, and MMP-9 were measured. General linear models were used to compare changes in concentrations of these biomarkers over time between the groups. In the control group, the mean MMP-9 concentration increased gradually from 3.857 ± 1.880 ng/mL to 4.538 ± 1.966 ng/mL over the 14-day period ($P = .027$, one-way repeated-measures analysis of variance [ANOVA]), but the edavarone group demonstrated no such increase ($P = .564$). A significant group–time interaction was demonstrated only for MMP-9 ($P = .029$, two-way repeated-measures ANOVA), and no significant differences in other biomarkers were seen between groups. Our data indicate that edaravone suppresses serum MMP-9 level in patients with acute ischemic stroke. Further studies with a larger sample size are needed to explore the relationship between circulating MMP-9 level and the protective effect of edaravone. **Key Words:** Brain infarction—biomarker—inflammation—tumor necrosis factor α—interleukin—metalloproteinase.

Free radicals are important mediators of tissue injury in cerebral ischemia.[1] These substances not only directly damage cells, but also trigger other pathways involved in the development of brain edema. Lipoperoxidation-induced increases in inflammatory cells, inflammatory mediators, and matrix metalloproteinases (MMPs) are involved in the pathogenesis of vasogenic brain edema through increased vascular endothelial permeability and disruption of the blood-brain barrier (BBB) caused by degradation of the extracellular matrix in blood vessels.[2,3] The free radical scavenger edavarone eliminates free radicals produced during ischemic reperfusion in various experimental models[4-7] and has inhibitory effects on MMP-9 expression in the ischemic brain.[8] Since its approval as a cerebroprotective agent in 2001, edaravone has been widely used in Japan and appears to affect

From the Department of Neurology, St. Marianna University School of Medicine.
Received February 19, 2010; accepted May 5, 2010.
Address correspondence to Yasuhiro Hasegawa, MD, PhD, 2-16-1 Sugao, Miyamae-ku, Kawasaki city, Kamagawa-Pref, 216-8511, Japan. E-mail: shinnai@marianna-u.ac.jp.
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inflammatory reactions along with free radical scavenging.[9-11] However, given the limited number of clinical studies in patients with acute cerebral infarction, the effects of edaravone on blood biomarkers have not yet been sufficiently investigated. The aim of the present study was to investigate the effects of edaravone on circulating inflammatory biomarkers, including MMP-9, in patients with acute cerebral infarction.

Patients and Methods

Patients

We prospectively enrolled 63 patients (39 men, 24 women; mean age, 70.5 ± 11.2 years) with acute brain infarction who were admitted to our hospital at 12-36 hours after onset between April 2007 and September 2008. Because systemic treatment with edaravone within a 24-hour window is an approved brain protective therapy for acute stroke in Japan, a placebo-controlled randomized study is not ethically feasible in candidates for edaravone treatment. Thus, we adopted a prospective observational design and studied patients admitted at 24 ± 12 hours after onset.

Edaravone was administered in patients admitted at 12-24 hours after onset (edaravone group; n = 29). Patients admitted at 24-36 hours after onset served as controls (control group; n = 34). In the edaravone group, 30 mg of edaravone diluted with 100 mL of saline was drip-infused intravenously over a 30-minute period, and this process was repeated every 12 hours for 14 days.

Acute cerebral infarction was diagnosed by neurologic examination and head computed tomography and/or magnetic resonance imaging (MRI) on admission to the hospital. In both groups, treatments for cerebral infarction other than edaravone were provided in accordance with established guidelines, with no other restrictions imposed. Patients were excluded from the study population for the following reasons: age <18 years; contraindications for edaravone treatment, including serious kidney dysfunction (blood urea nitrogen level ≥25 mg/dL or serum creatinine level ≥1.5 mg/dL); previous history of hypersensitivity to the ingredients in edaravone; serious liver disorder (aspartate aminotransferase or alanine aminotransferase ≥100 U, or presence of liver cirrhosis); previous history of heart failure, acute ischemic heart disease, infection, inflammatory disease, hematologic disorder, or malignancy requiring treatment; any of the aforementioned diseases/disorders as a concomitant disease; pregnancy or possibility of pregnancy; recurrent cerebral infarction occurring ≤6 months after the previous episode; disability with a modified Rankin scale (mRS) score ≥2 before onset; and the need for surgical or endovascular treatment during hospitalization. All study protocols were approved by the St Marianna University School of Medicine's Bioethics Committee. Informed consent to participate in the investigation was obtained from each patient before study initiation, after the purpose of the study was explained to the patient or a legal proxy.

Measurement of Biomarkers and Clinical Data Collection

In both groups, serial blood samples (20 mL at each point) were obtained on admission and at 48 hours, 7 days, and 14 days after onset of symptoms. All blood samples were centrifuged at 3000 rpm for 10 minutes at 4°C. Serum was separated and stored at −80°C until analysis was performed. Serum concentrations of high-sensitivity C-reactive protein (hs-CRP), interleukin (IL)-6, IL-10, IL-18, tumor necrosis factor (TNF)-α, MMP-2, and MMP-9 were measured by enzyme-linked immunosorbent assay (ELISA) using commercially available ELISA kits (hsCRP: N-Latex CRP II; Siemens Healthcare Diagnostics, Tokyo, Japan; IL-6: Biotrak high-sensitivity human IL-6 ELISA system; GE Healthcare, Bucks, UK; IL-10: Biotrak high-sensitivity human IL-10 ELISA system, GE Healthcare; IL-18: Human IL-18 ELISA Kit; Medical & Biological Laboratories, Nagoya, Japan; MMP-2: MMP-2 Kit, Daiich Fine Chemical, Toyama, Japan; MMP-9: MMP-9 Activity Assay; GE Healthcare; TNF-α: Human TNF-α ELISA ultrasensitive kit; Biosource International, CA, USA). Detectable ranges in healthy controls were referred to data from the manufacturers.

Background factors, laboratory test values, National Institutes of Health Stroke Scale (NIHSS) scores on admission to and discharge from the hospital, mRS score at 3 months after onset, and levels of biomarkers were evaluated in the two groups. Definitions of risk factors were as follows. Hypertension was defined as two of more measurements of ≥140/90 mm Hg, a previous diagnosis of hypertension, or use of an antihypertensive agent. Diabetes was defined as a fasting blood glucose level ≥126 mg/dL and a hemoglobin A1c level ≥6.5% or receiving treatment for diabetes. Abnormal lipid metabolism was defined as total cholesterol concentration ≥220 mg/dL, neutral fat level ≥150 mg/dL, or use of an oral lipid-lowering agent. Smoking status was defined as a current or previous history of an addictive smoking habit.

Neurologic deficit was evaluated by NIHSS score on admission, at 14 days after onset, and at discharge. The duration of hospitalization was recorded. Functional outcome was evaluated by mRS score at 3 months after onset.

Statistical Analyses

Data on patient characteristics are reported as mean and standard deviation (SD) unless indicated otherwise. The unpaired Student *t* test was used to compare continuous variables, and the χ^2 test was used for nominal parameters. The Mann-Whitney *U* test was used for non-normally distributed data. A *P* value <.05 was considered significant. Two-way repeated-measures analysis of

Table 1. *Patient characteristics and drugs used within 14 days*

	Control group (n = 29)	Edaravone group (n = 34)	*P*
Male, n (%)	14 (48.3)	25 (73.5)	.070
Age, years, mean ± SD	72.4 ± 10.6	69.0 ± 11.6	.232
Body mass index, mean ± SD	21.7 ± 3.6	27.8 ± 2.9	.545
Time from onset to admission, hours, mean ± SD	17.9 ± 3.2	27.8 ± 3.6	.000
Comorbidity, n (%)			
Hypertension	24 (82.8)	27 (79.4)	1.000
Dyslipidemia	17 (58.6)	11 (32.3)	.045
Diabetes mellitus	8 (27.6)	6 (17.6)	.378
Smoking	6 (20.7)	17 (50.0)	.020
Stroke subtype, n (%)			
Lacunar	10 (34.5)	5 (14.7)	.081
Atherothrombotic	9 (31.0)	11 (32.4)	1.000
Cardioembolic	8 (27.6)	14 (41.2)	.299
Other	2 (6.9)	4 (11.8)	.678
NIHSS score at entry, mean ± SD*	4.8 ± 5.0	5.8 ± 4.8	.137
Systolic blood pressure, mm Hg, mean ± SD	164.9 ± 27.7	165.6 ± 25.9	.893
Diastolic blood pressure, mm Hg, mean ± SD	85.3 ± 19.9	92.0 ± 24.0	.237
Total cholesterol, mg/dL, mean ± SD	204.3 ± 50.3	178.1 ± 38.2	.028
Triglyceride, mg/dL, mean ± SD	97.4 ± 44.2	78.8 ± 50.8	.131
HDL cholesterol, mg/dL, mean ± SD	54.0 ±14.2	55.4 ± 15.2	.131
Glucose, mg/dL, mean ± SD	116.4 ± 28.9	119.1 ± 27.3	.702
HbA1c, %, mean ± SD	5.52 ± 0.66	5.45 ± 0.89	.754
D-dimer, mg/mL, mean ± SD	2.39 ± 3.93	2.56 ± 4.45	.874
Drugs used within 14 days after onset, n (%)			
Heparin	12 (41.3)	19 (55.9)	.258
Argatroban	3 (10.3)	8 (23.5)	.164
Warfarin	12 (41.3)	18 (53.0)	.357
Aspirin	15 (51.8)	14 (41.2)	.339
Clopidogrel	5 (17.2)	10 (29.4)	.133
Cilostazol	3 (10.3)	3 (12.5)	.841

*Mann-Whitney *U* test.

variance (ANOVA) was used to compare changes in concentrations of biomarkers over time between the groups. Noncorrelation was evaluated using the Mauchly sphericity test. If this assumption was not satisfied, then the Greenhouse-Geisser correction was used at a significance level of $P < .05$.[12] All statistical analyses were performed using PASW for Windows version 17.0 (SPSS Japan, Tokyo).

Results

No significant intragroup differences in male/female ratio, mean age, or body mass index were detected (Table 1). Because of the study design, the time between onset and admission differed significantly (17.9 ± 3.2 hours in the edaravone group vs 27.8 ± 3.6 hours in the control group; $P = .00$). In terms of risk factors, the control group had a slightly higher percentage of patients with dyslipidemia compared with the edaravone group ($P = .045$), and more patients in the edaravone group had a history of smoking ($P = .02$). No intragroup differences in subtypes of brain infarction were found. The mean NIHSS score tended to be higher in the edaravone group than in the control group, although the difference was not significant. No intragroup differences in laboratory test values on admission were noted, except for a higher total cholesterol level in the control group. The two groups used similar drugs within 14 days after admission. No patients ineither group used steroids or nonsteroidal anti-inflammatory drugs.

Concentrations of each biomarker at each time point are given in Table 2. Unpaired *t* tests at each time point for each biomarker demonstrated no significant intragroup differences except in mean MMP-9 concentration. In the control group, the mean MMP-9 level increased gradually from 3.857 ± 1.880 ng/mL to 4.538 ± 1.966 ng/mL ($P = .027$, one-way repeated-measures ANOVA). In contrast, the edavarone group demonstrated no significant difference in mean MMP-9 level during the observation period ($P = .564$). An unpaired *t* test revealed significantly lower mean MMP-9 levels at 7 and 14 days after onset in the edaravone group compared with the control group. To-way repeated-measures ANOVA

Table 2. *Biomarkers*

	Control group (n = 29)	Edaravone group (n = 34)	P*	Group × time interaction†
hsCRP, mg/L (normal, <2.0 mg/L)				
On admission	2.24 ± 2.23	3.70 ± 7.11	.072	
48 hours after onset	1.21 ± 2.20	6.84 ± 10.32	.419	P = .183
Day 7	8.73 ± 19.57	15.35 ± 26.84	.282	
Day 14	8.05 ± 22.00	5.70 ± 12.08	.660	
IL-6, pg/mL (normal, 0–14.9 pg/mL)				
On admission	6.171 ± 7.455	5.346 ± 7.308	.675	
48 hours after onset	6.125 ± 7.308	6.674 ± 9.155	.537	P = .403
Day 7	4.789 ± 8.354	15.259 ± 50.285	.227	
Day 14	6.314 ± 9.284	4.233 ± 6.073	.353	
IL-10, pg/mL (normal, 0–6.8 pg/mL)				
On admission	7.307 ± 9.284	20.938 ± 53.822	.162	
48 hours after onset	7.243 ± 9.302	20.694 ± 46.939	.188	P = .167
Day 7	8.931 ± 11.790	25.381 ± 58.787	.126	
Day 14	10.225 ± 12.399	33.9.8 ± 68.714	.074	
IL-18, pg/mL (normal, 81.5–170.5 pg/mL)				
On admission	240.507 ± 251.655	175.654 ± 146.357	.230	
48 hours after onset	206.925 ± 165.442	176.212 ± 182.832	.533	P = .357
Day 7	176.388 ± 118.778	162.914 ± 147.220	.701	
Day 14	157.543 ± 71.740	176.286 ± 144.520	.554	
TNF-α, pg/mL (normal, 0.55–2.81 pg/mL)				
On admission	1.850 ± 0.960	1.904 ± 0.975	.827	
48 hours after onset	1.858 ± 0.944	1.774 ± 0.944	.261	P = .509
Day 7	2.300 ± 1.180	1.837 ± 0.736	.459	
Day 14	2.281 ± 1.139	1.694 ± 0.665	.244	
MMP-2, ng/mL (normal, 452–688 ng/mL)				
On admission	824.44 ± 313.85	834.91 ± 363.90	.908	
48 hours after onset	774.79 ± 222.96	704.52 ± 208.48	.261	P = .280
Day 7	767.56 ± 220.00	725.28 ± 204.62	.459	
Day 14	758.51 ± 158.62	700.43 ± 191.50	.241	
MMP-9, ng/mL (normal, 0.5–16 ng/mL)				
On admission	3.857 ± 1.880	3.807 ± 1.897	.827	
48 hours after onset	4.029 ± 2.093	3.530 ± 1.869	.157	P = .029
Day 7	4.499 ± 1.800	3.449 ± 2.022	.042	
Day 14	4.538 ± 1.966	3.420 ± 1.971	.037	

*Student *t* test.
†Two-way repeated-measures analysis of variance.

demonstrated a significant group–time interaction factor for MMP-9 ($F_{[2,108]} = 3.645$; $P = .029$). No significant differences in NIHSS score at 14 days after onset, mRS score at 3 months after onset, or duration of hospitalization were seen between the two groups (Table 3).

Discussion

Our study demonstrates that edaravone treatment significantly suppressed circulating MMP-9 levels in patients with acute ischemic stroke. MMP-9 is rapidly upregulated in the ischemic brain in animal models and

Table 3. *Outcomes*

	Control group (n = 29)	Edaravone group (n = 34)	P
NIHSS score at 14 days after onset, median (range)*	1 (0–14)	2 (0–13)	.682
mRS score at 3 months, median (range)*	1 (0–5)	2 (0–4)	.266
Duration of hospitalization, days (SD)	23.3 ± 12.7	27.4 ± 12.5	.203

*Mann-Whitney *U* test.

stroke patients.[13-16] Although elevated plasma MMP-9 level is correlated with brain level within 24 hours after acute brain ischemia in rats,[17] in humans the contribution of brain tissue as a source of circulating MMP-9 within 14 days after ischemic stroke onset is unknown. A wide range of cell types, including fibroblasts, neurons, macrophages, and T cells, secrete MMPs as inactive proforms.[18] Gummesson et al[19] reported considerably higher MMP-9 mRNA levels in bone marrow, atherosclerotic plaques, and macrophages compared with subcutaneous adipose tissue and isolated adipocytes, suggesting that adipose tissue is not an important source of circulating MMP-9 in humans. The MMP-9 assay used in this study is designed to measure total MMP-9 without differentiating between the inactive proform and active form of MMP-9. Because in situ activation of MMP-9 is tightly regulated and localized, resulting in a short half-life of this enzyme,[20] the active-form MMP-9 from ischemic brain tissue might be expected to make only a small contribution to changes in total serum MMP level in the present study. Thus, our observations should not be considered to reflect the effects of edaravone in ischemic brain tissue per se. In fact, in the acute stage of neuroinflammatory disorders, such as multiple sclerosis and Guillain-Barre syndrome, increased serum and plasma MMP-9 levels have been associated with the entry of inflammatory cells (T cells and macrophages) into the nervous system and the breakdown of the blood-nerve barrier and BBB, respectively.[21-23]

Yagi et al[8] recently demonstrated that edaravone inhibits MMP-9 expression in the ischemic brain of rats and nuclear factor (NF)-κB activation in cultured human brain microvascular endothelial cells. Similar effects of edaravone on NF-kB have been demonstrated in collagen-induced arthritis mice and in human synovial cells stimulated by IL-1β.[24] The exact origin of MMP-9 in serum remains to be elucidated, but our study clearly demonstrates that edaravone inhibits circulating MMP-9 level.

We found no significant effect of edaravone on patients' functional outcomes. This study was not designed to demonstrate a neuroprotective effect of edaravone, however. A previous phase III double-blind study reported a significant benefit of edaravone in terms of functional outcome compared with placebo when administered within 24 hours after onset of ischemic stroke.[25] The discrepancy with our findings is likely related to that study's small sample size and insufficient statistical power.

Tissue plasminogen activator (tPA) is known to be neurotoxic, through activation of MMP-9 and aggravation of glutamate-induced neuronal damage, as well as increases in leukocytic infiltration and free radical reactions in infarcted areas.[26] MMP-9 expression has been correlated with increased oxidative stress in a clinical study,[27] and also has been related to the size and severity of acute cerebral infarction, development of concomitant hemorrhagic infarction, and aggravation of symptoms.[28-31] Edaravone is expected to alleviate neurotoxicity during IV thrombolysis using tPA.[32]

Modern MRI can reveal local disruption of the blood–cerebrospinal fluid barrier (BCSFB) and/or the BBB, and experimental models have demonstrated a pathological relationship with abnormal MMP regulation.[33,34] MRI evaluation of BCSFB and BBB status can provide indirect imaging markers of MMP regulation in blood and brain tissue.[35] The present study does not answer the question of whether suppression of circulating MMP-9 levels by edaravone can serve as a marker that truly correlates with stroke pathophysiology. However, our results offer a guide for future randomized controlled studies of edaravone and evaluation of the effects of edaravone coadministered with tPA-based revascularization therapy.

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ORIGINAL ARTICLE

Efficacy and safety of diuretics in combination with perindopril in hypertensive stroke patients: Results of the Japan Perindopril and Diuretics on Cerebrovascular Disease Study (J-PADOC)

YASUHIRO HASEGAWA[1], KAZUYUKI SHIMADA[2] & TAKENORI YAMAGUCHI[3]
FOR THE J-PADOC STUDY INVESTIGATORS

[1]*Department of Neurology, St. Marianna University School of Medicine, Kawasaki, Japan,* [2]*Division of Cardiovasucular Medicine, Jichi Medical School, Shimotsuke, Japan,* [3]*National Cardiovascular Center, Suita, Japan*

Abstract

Aims. An international randomized controlled trial has shown that anti-hypertensive therapy using perindopril and indapamide significantly reduces the recurrence of stroke. To evaluate the efficacy and safety of diuretics given as add-on therapy to stroke patients, as needed, to perindopril, we conducted a prospective multicenter observational study. *Methods.* A total of 3825 hypertensive patients with a history of stroke were enrolled. The patients received a two-step therapy, starting with perindopril alone, and those who failed to achieve the blood pressure target were subsequently given a diuretic. Each group was followed for 6 months. *Results.* 62.8% of the patients achieved the blood pressure goal. The incidence of adverse events was significantly higher in the perindopril plus diuretic combination therapy group than in the perindopril monotherapy group. Although these results may reflect that severely hypertensive patients were selectively assigned to combination therapy, the observed differences were essentially elevated serum creatinine, triglycerides, blood urea nitrogen and uric acid, whereas no significant inter-group difference was noted in total cholesterol and blood glucose. *Conclusions.* If adequate care of compromised renal function is taken, perindopril plus diuretic combination therapy exerts potent hypotensive effects without posing significant safety problems in patients with a history of stroke.

Key Words: *Cerebrovascular disease, diuretics, hypertension, perindopril*

Introduction

The large-scale Perindopril pROtection aGainst REcurrent Stroke Study (PROGRESS) demonstrated that angiotensin-converting enzyme inhibitor (ACE-I) perindopril-based antihypertensive therapy reduced the recurrence of stroke by 28% compared with placebo (1). In that study, 58% of patients in the active drug treatment group received combination therapy with perindopril plus indapamide. The degree of their blood pressure reduction was greater than that in patients on perindopril monotherapy, and their reduction in the risk for stroke was also greater. Based on these findings, the PROGRESS Collaborative Group concluded that concomitant treatment with these two agents should be considered routinely for patients with a history of stroke or transient ischemic attack (TIA) irrespective of their blood pressure levels.

The percentage of patients in whom indapamide was used in combination with perindopril was >40% in all countries participating in PROGRESS with the exception of Japan, where the percentage was markedly lower (7%) (2). Furthermore, in a survey conducted in Japan in 2002, only about 6% of the respondent physicians answered that they used a diuretic in combination with other antihypertensives, and another survey performed the same year also revealed a low percentage of patients receiving diuretics (about 10–20%) in combination with any other antihypertensive drug (3,4). Furthermore, among Japanese physicians who participated in PROGRESS, 69% reported that their prescription of diuretics in combination with ACE-I did not increase (data not shown), although the PROGRESS sub-study demonstrated that combination therapy including diuretics resulted in no increase of silent

Correspondence: Yasuhiro Hasegawa, Department of Neurology, St. Marianna University School of Medicine, Miyamae-ku, Kawasaki-city, Kanagawa 216-8511, Japan. Tel: +81 (44)977-8111. Fax: +81 (44)976-8516. E-mail: Shinnai@marianna-u.ac.jp

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brain infarct and suppressed the progression of white matter lesions (5,6). In short, the frequency of diuretics prescription does not seem to have increased in Japan, even after publication of the PROGRESS results.

One possible reason for such a low prescription of diuretics in Japan might be the concern of unfavorable influence of diuretics on the general metabolism. Although a subanalysis of the ALLHAT Study concluded that the use of diuretics did not affect the onset of events, it has also been reported that diuretics cause elevation of fasting blood glucose more markedly than calcium-channel blockers (CCB) and ACE-I, and may induce new onset of diabetes mellitus (7). Furthermore, diuretics are considered to affect other aspects of metabolism, causing gout, hypocalcemia, and so on. Another possible reason is that many Japanese physicians consider that diuretics are inappropriate antihypertensive drugs for patients with history of stroke. Indeed, there is a shortage of data on the hypotensive efficacy and safety of perindopril plus diuretic combination therapy in patients with a history of stroke in Japan.

Under such circumstances, and following the usefulness of this intervention as demonstrated in the PROGRESS Study, the Japan Perindopril and Diuretics on Cerebrovascular Disease Study (J-PADOC) was conducted to assess the hypotensive effects and safety of perindopril plus diuretics combination therapy in Japanese patients, by collecting data on routine clinical use of diuretics given as add-on therapy, as needed, to perindopril.

Methods

Patient registration and data collection

This study was a prospective multicenter observational study conducted by the J-PADOC Study Group at 800 collaborating hospitals in Japan. Patients eligible for inclusion in the study were those with a history of mild-to-moderate stroke, TIA or amaurosis fugax complicated by essential hypertension with systolic blood pressure (SBP) ≥140 mmHg and/or diastolic blood pressure (DBP) ≥90 mmHg irrespective of taking antihypertensive medications. Patients were considered candidates for antihypertensive therapy with perindopril according to the indications of this medication and those who could additionally receive diuretics to achieve blood pressure targets. Patients with severe hypertension (DBP>115 mmHg) or in the acute stage of stroke (within 1 month after onset); those treated with diuretics within 2 weeks before the run-in period; those with a history of resistance to or contraindication for ACE-I or diuretics or severely compromised hepatic or renal function; pregnant or possibly pregnant women; and other patients rated by the investigators as inappropriate for the study were excluded.

As patient background variables, data before starting the run-in period were collected including history and type of stroke and onset of TIA. During the run-in period, each candidate continued to receive his or her previous therapy in addition to perindopril and was followed for ≥2 weeks. At the end of the run-in period, patients who adequately tolerated the drug were enrolled in the study; those with SBP<140 mmHg and DBP<90 mmHg were assigned to receive antihypertensive therapy using perindopril 4 mg/day alone, whereas patients with SBP≥140 mmHg and/or DBP≥90 mmHg were assigned to receive combination therapy using perindopril 4 mg/day plus diuretic. The standard follow-up period was 6 months after inclusion. Concomitant use of any diuretic was prohibited in the perindopril monotherapy group, whereas in the perindopril plus diuretic combination therapy group, the type of diuretic used was selected at the discretion of each attending physician. The dose level of diuretic was classified into standard dose or low dose (half the standard dose or less; Table I). In both treatment groups, concomitant use of any additional antihypertensives was prohibited. In addition, concomitant use of ACE-I other than perindopril was strictly prohibited in this study.

Based on reports from participating physicians, all adverse events occurring during the run-in period and 6-month follow-up period were processed by coding system using the Medical Dictionary for Regulatory Activities (MedDRA) (8). Blood pressure measurements (SBP, DBP) and hematological and biochemical tests including transamylase, serum lipid, fasting blood glucose, hemoglobin A_{1c} (HbA_{1c}), creatine phosphokinase (CPK), blood urea nitrogen (BUN), serum creatinine, uric acid and electrolytes were performed at the start and end of the run-in period as well as 1, 3 and 6 months thereafter and, if possible, upon discontinuation of medication.

Data analysis

Analysis was conducted of the time-course of blood pressure, data on adverse events (type and frequency) and time-course of laboratory parameters.

Repeated-measurement analysis of variance (ANOVA) with Dunnett adjustment was used for

Table I. Dose of diuretic agents in the combination group.

	Low dose	Standard dose
Thiazide diuretic, mg		
Trichlormethiazide	≤1	2–4
Hydrochlorothiazide	12.5	25
Benzylhydrochlorothiazide	≤4	8
Non-thiazide diuretic, mg		
Indapamide	≤1	2
Chlortalidone	25	50
Tripamide	7.5	15
Meticrane	75	150
Mefruside	12.5	25

analysis of the time-course of blood pressure and laboratory parameters. Data on triglycerides were tested after logarithmic conversion. The incidence of adverse events was compared between the two groups by Fisher's exact test. All p-values <0.05 (two-sided) were considered statistically significant.

Ethics

This study was carried out as a special survey on Coversyl® tablet (perindopril) in accordance with the standards of post-marketing studies of medicines (Good Post Marketing Surveillance Practices; GPMSP) prepared by the Ministry of Health, Labour and Welfare of Japan.

Results

Study population

During the period from June 2003 to September 2005, a total of 3825 patients from 800 facilities were enrolled in this study. At end of the study, 81 patients with insufficient data were excluded; 3744 patients were subjected to safety evaluation (perindopril monotherapy group, $n=2479$; combination therapy group, $n=1265$). The main reasons of insufficient data were case report forms not collected (72 patients) and incomplete follow-up (nine patients). In these 3744 cases, adverse events and the time-course of laboratory parameters were analyzed. After additional exclusion of 203 patients for protocol violations, the time-course of blood pressure was evaluated in 3541 cases (monotherapy group, $n=2358$; combination therapy group, $n=1183$) as shown in Figure 1 (efficacy evaluation). The violations of inclusion/exclusion criteria were composed of severe hypertension with DBP>115 mmHg, without a history of stroke, and so on. The violations of protocol medications were composed of those treated with diuretics within 2 weeks before the run-in period, and so on.

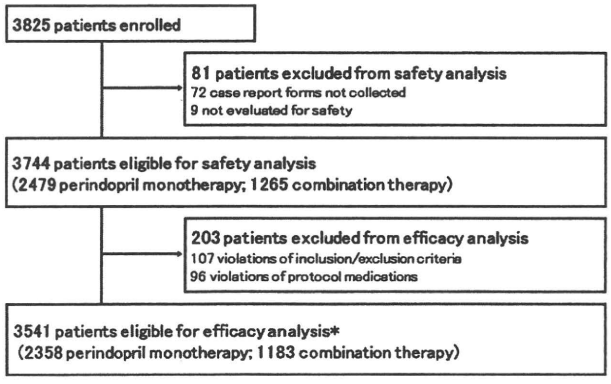

Figure 1. Disposition of the subjects. *Patients received two-step therapy starting with perindopril alone, and those who failed to achieve the blood pressure target of systolic blood pressure (SBP) <140 mmHg and/or diastolic blood pressure (DBP) <90 mmHg were subsequently given a diuretic as add-on therapy.

Changes in SBP and DBP

Table II summarizes the background variables for the 3541 patients included in the efficacy evaluation. Because patients who failed to respond well to perindopril monotherapy during the run-in period were assigned to the combination therapy group, blood pressure at baseline in these individuals was significantly higher than in the perindopril monotherapy group. However, there was no marked inter-group difference in terms of age, sex, complications, stroke type and frequency of concomitant use of other drugs.

Figure 2 shows the time-course of SBP and DBP in the two groups. Patients assigned to the monotherapy group continued to show a favorable course of blood pressure during the treatment period. In the combination therapy group, on the other hand, whereas mean SBP/DBP during the run-in period was high at 165/91 mmHg, the level fell to 143/82 mmHg at 1 month and to 139/79 mmHg at 6 months after the start of combination therapy, a statistically significant difference ($p<0.0001$). Thus the two-step regimen, administering a diuretic in combination with perindopril in patients who failed to achieve SBP/DBP<140/<90 mmHg on perindopril alone, achieved the blood pressure target in 62.8% of patients overall within 6 months after the start of treatment.

Adverse events and laboratory data

Laboratory parameters and adverse events were analyzed in 3744 patients in whom safety data were available (Table III). Adverse events were observed in 688 (18%) of all patients. By therapy, adverse events were observed in 15.5% (384 of 2479 patients) whereas in those receiving combination therapy the rate was 24.0% (304 of 1265 patients). The overall incidence of adverse events was significantly ($p<0.0001$) higher in the combination therapy group than in the monotherapy group. When individual types of adverse events were analyzed, there was no significant inter-group difference in terms of the incidence of anemia, cough, abnormal hepatic function, elevated total cholesterol, CPK, blood glucose, γ-glutamyltransferase and glycosylated hemoglobin, whereas the incidence of elevated serum creatinine, triglycerides, BUN and uric acid was significantly higher in the combination therapy group than in the monotherapy group. Recurrence of stroke was significantly higher in the combination therapy group (1.7%; 22/1265, including 19 cases of ischemic stroke and three cases of hemorrhagic stroke) than in the monotherapy group (0.6%; 14/2479, including 13 cases of ischemic stroke and one case of hemorrhagic stroke; $p=0.0011$).

Table II. Patient characteristics.

	Total (n=3541)	Perindopril monotherapy (n=2358)	Combination therapy (n=1183)	p-value[a]
Male, n (%)	1955 (55)	1286 (55)	669 (57)	0.2668
Age, years[b]	69±11	69±11	69±11	0.6976
Complication, n (%)	1947 (55)	1305 (55)	642 (54)	0.5667
Diabetes mellitus	763 (22)	513 (22)	250 (21)	0.6966
Gout	229 (7)	163 (7)	66 (6)	0.1472
Hyperlipidemia	778 (22)	534 (23)	244 (21)	0.1823
SBP, mmHg[bd]	159±14	156±12	165±15	<0.0001
DBP, mmHg[bd]	89±11	88±10	91±11	<0.0001
Type of cerebrovascular disease, n (%)				
Cerebral infarction	2704 (76)	1793 (76)	911 (77)	0.5297
Lacunar	1708 (48)	1134 (48)	574 (49)	
Atherothrombotic	621 (18)	394 (17)	227 (19)	
Cardioembolic	82 (2)	60 (3)	22 (2)	
Unknown	313 (9)	221 (9)	92 (8)	
Intracerebral hemorrhage, n (%)	396 (11)	267 (11)	129 (11)	0.7268
TIA, n (%)	370 (11)	250 (11)	120 (10)	0.7268
Amaurosis fugax	6 (0)	4 (0)	2 (0)	1.0000
Unknown	122 (4)	77 (3)	45 (4)	0.4347
Medication, n (%)				
Other antihypertensives	1674 (47)	1118 (47)	556 (47)	0.8305
Calcium channel blockers	1361 (38)	923 (39)	438 (37)	0.2270
ARBs	574 (16)	373 (16)	201 (17)	0.3843
Beta-blockers	185 (5)	119 (5)	66 (6)	0.5221
Alpha-blockers	120 (3)	75 (3)	45 (4)	0.3269
Antiplatelet agents	1564 (44)	996 (42)	568 (48)	0.0012
Lipid-lowering agents	743 (21)	517 (22)	226 (19)	0.0542
Hypoglycemic agents	279 (8)	194 (8)	85 (7)	0.2906
Antigout agents	183 (5)	123 (5)	60 (5)	0.9359
Laboratory data[b] (Start of run-in period)				
ALT (GPT), IU/l	23.7±18.6	23.5±16.5	24.1±22.1	0.4159
Glucose, mmol/l	6.3±2.1	6.2±2.1	6.3±2.1	0.5414
Creatinine, μmol/l	72.76±25.55	72.60±25.97	73.06±24.74	0.6309
Uric acid, mmol/l	0.32±0.09	0.32±0.09	0.32±0.09	0.0555
BUN, mmol/l	5.7±1.8	5.7±1.8	5.7±1.8	0.5892
Triglycerides, mmol/l[c]	1.3±0.02	1.3±0.02	1.4±0.02	0.0001

[a]Based on Fisher's exact test for categorical valuables, and unpaired t-test for continuous valuables. [b]Mean ± SD. [c]Geometric mean (approximate SD). [d]At start of the run-in period. SBP, systolic blood pressure; DBP, diastolic blood pressure; TIA, transient ischemic attack; ARB, angiotensin receptor blocker.

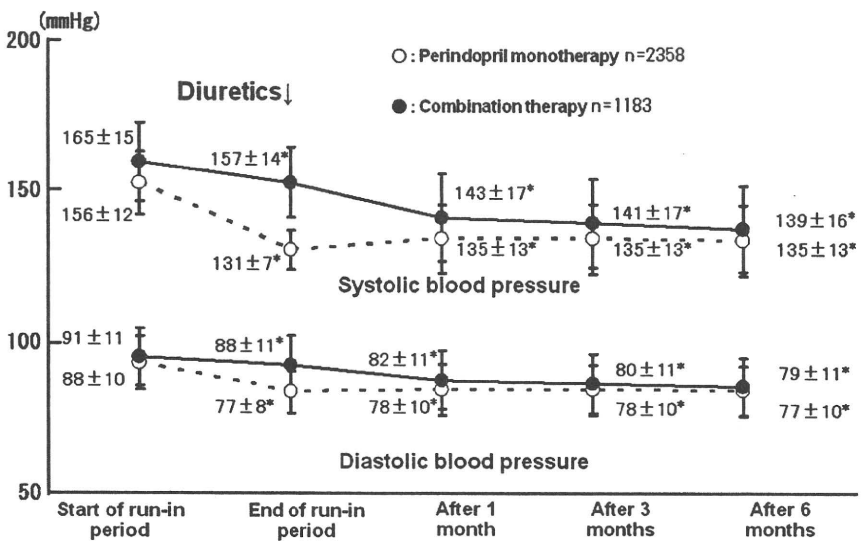

Figure 2. Changes in systolic and diastolic blood pressure among participants assigned perindopril monotherapy and combination therapy. Values are mean±SD. *p<0.01 (vs start of the run-in period; analysis of variance, ANOVA, with Dunnett adjustment). ○ Perindopril monotherapy (n=2358); • combination therapy (n=1183).

Table III. Adverse events (AEs).[a]

	Total (n=3744)	Perindopril monotherapy (n=2479)	Combination therapy (n=1265)	p-value
Total AEs, n (%)	688 (18)	384 (15.5)	304 (24.0)	<0.0001
Anemia	17 (0.5)	10 (0.4)	7 (0.6)	0.6083
Cough	245 (6.5)	156 (6.3)	89 (7.0)	0.4020
Abnormal hepatic function	28 (0.7)	16 (0.6)	12 (0.9)	0.3201
High blood cholesterol	29 (0.8)	18 (0.7)	11 (0.9)	0.6943
High blood CPK	18 (0.5)	10 (0.4)	8 (0.6)	0.3298
High blood creatinine	30 (0.8)	8 (0.3)	22 (1.7)	<0.0001
High blood glucose	19 (0.5)	10 (0.4)	9 (0.7)	0.2281
High blood triglycerides	42 (1.1)	18 (0.7)	24 (1.9)	0.0026
High blood urea	38 (1.0)	10 (0.4)	28 (2.2)	<0.0001
High blood uric acid	62 (1.7)	18 (0.7)	44 (3.5)	<0.0001
High γ-glutamyltransferase	25 (0.7)	16 (0.6)	9 (0.7)	0.8335
High HbA_{1c}	17 (0.5)	9 (0.4)	8 (0.6)	0.3039
Kidney dysfunction	8 (0.2)	2 (0.1)	6 (0.5)	0.0210
Ischemic heart disease	4 (0.1)	2 (0.1)	2 (0.2)	0.6075
Stroke	36 (1.0)	14 (0.6)	22 (1.7)	0.0011
Discontinued because of AEs, n (%)	302 (8.1)	185 (7.5)	117 (9.2)	0.0656

[a]Incidence rates of AEs occurring in ≥0.5% in the perindopril monotherapy and combination therapy groups are shown except for Ischemic heart disease. CPK, creatine phosphokinase.

Among the 1265 patients who received a diuretic, 790 did so at low-dose and 440 at standard-dose level. No difference in the incidence of adverse events was detected between the low-dose group and the standard-dose group in terms of either overall adverse events or each type of adverse event (data not shown).

Medication planned during this study was discontinued because of adverse events in 185 patients (7.5%) in the monotherapy group and 117 patients (9.2%) in the combination therapy group. In most of these cases, cough was the cause of discontinuation of medication (137 cases or 5.5% in the monotherapy group and 74 cases or 5.8% in the combination therapy group). Other adverse events responsible for discontinuation of medication were recorded in a relatively small number of patients, including increases of blood uric acid and blood creatinine in <1% of both treatment groups.

Figure 3 shows the time-course of creatinine, BUN, uric acid and triglycerides levels. Their elevation (an adverse event) was significantly more frequently reported in the combination therapy group. The mean level of creatinine, BUN and uric acid at each time-point during the follow-up period was significantly higher than that at the start of the run-in period. Triglycerides levels were not very different from those at the start of the run-in period.

Discussion

It is often difficult to achieve blood pressure reduction goals specified in guidelines with single-drug regimens (9–11). In Japan, inhibitors/blockers of the renin–angiotensin–aldosterone system (RAAS), angiotensin receptor blockers and ACE-I, combined with CCB, are commonly used to achieve such goals, whereas diuretics are used much less frequently (3,4). Since ALLHAT demonstrated that diuretics reduce the incidence of cardiovascular events to a degree comparable with or higher than that achieved by CCB or ACE-I, and because diuretics are more economical, JNC-7 and WHO/ISH 2003 strongly recommend the use of thiazide-type diuretics as first-line drugs (9,12,13). Similarly in Japan, the Guidelines for the Management of Hypertension (2009) recommend the use of low-dose diuretics in combination with other antihypertensives (10). Among others, the combination of RAAS drugs with diuretics is considered favorable because of its dual pharmacological action and alleviation of hypokalemia by the diuretic (14,15).

The greatest benefit of diuretic plus ACE-I therapy probably lies in its potent blood pressure-lowering effect. The PROGRESS investigators pointed out the possibility that large reductions of blood pressure arising from perindopril plus diuretics combination therapy contributed greatly to preventing the onset of cardiovascular events. Similarly, in the present study, SBP decreased more markedly (by 26 mmHg on average) in subjects receiving combination therapy compared with baseline levels. This difference was much greater than that observed between the placebo group and active drug group in PROGRESS, suggesting that the combined use of diuretics can greatly contribute to improving the prognosis of patients who fail to show adequate blood pressure reduction with perindopril monotherapy.

The incidence of adverse events in the present study was 15.5% in the monotherapy group and 24.0% in the combination therapy group. Cough is generally the most frequently observed side-effect of ACE-I. In the present study, we found that cough accounted for about one-third of all adverse events (6.3% in the monotherapy group and 7.0% in the combination

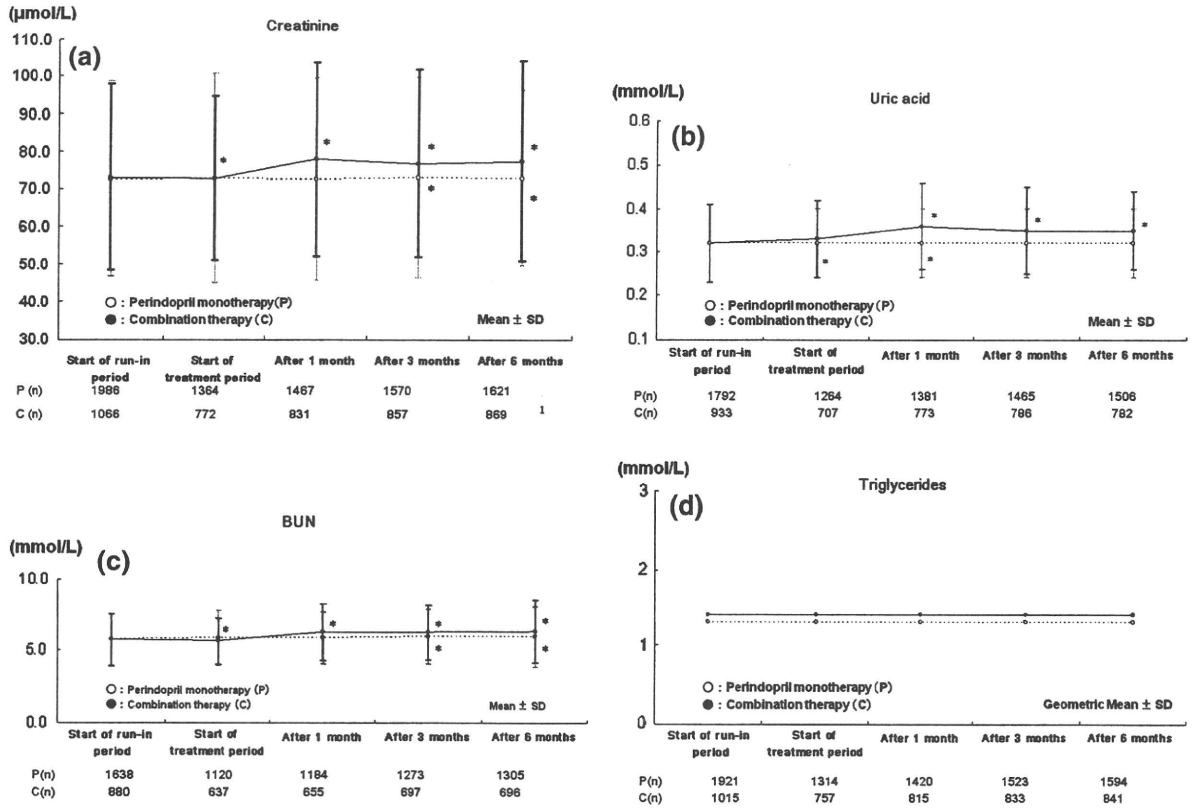

Figure 3. Changes in (a) creatinine, (b) uric acid, (c) blood urea nitrogen (BUN) and (d) triglycerides among participants assigned perindopril monotherapy and combination therapy. $*p<0.05$ (vs. run-in period; analysis of variance, ANOVA, with Dunnett adjustment).

therapy group). The recurrence of stroke was higher in the combination therapy group. This finding may reflect the result that because of the study design, patients assigned to the combination therapy group had markedly higher blood pressure at the time of inclusion. It seems unlikely that this finding is associated with any difference in the regimen of antihypertensive treatment between the two groups.

What needs special attention when using a diuretic in combination with other antihypertensive drugs is the possible effect on renal function (its site of action). Indeed, the incidence of elevated serum creatinine and BUN was higher in the combination therapy group in the present study. This result endorses the necessity of adequate care of patients' renal function when using diuretics. Strict attention should also be paid to the effects of diuretics on uric acid level and markers of insulin sensitivity and lipid metabolism (16). In this respect, the present study revealed a higher incidence of adverse events such as elevated blood uric acid and triglycerides levels in the combination therapy group than in the monotherapy group. However, in terms of the incidence of abnormally high blood glucose and HbA_{1c}, no significant difference was noted between the two groups. This may be interpreted by an offset of the known adverse effect of diuretics on glucose metabolism by the concomitant use of perindopril, which favorably affects glucose metabolism (13). In this regard, a recent clinical trial, ADVANCE, demonstrated that a fixed-dose combination of perindopril plus indapamide in patients with type 2 diabetes reduced the risk of major vascular events including death regardless of their blood pressure at baseline (17). These results support the Japanese guidelines' recommendations on the combination of diuretics with RAAS drugs from the aspect of safety.

Since in this study a slight but significant elevation of creatinine, BUN and uric acid was noted after co-therapy with a diuretic, it seems advisable to take adequate care of patients with or suspected of having compromised renal function or hyperuricemia. In most patients, however, the combined use of a diuretic reinforced the blood pressure-lowering effect with relatively high safety whenever adequate hypotensive action could not be achieved by perindopril alone.

Limitation

There are several limitations to our interpretation of the results from this study, which was designed as a prospective observational study (not a randomized comparative study) aimed at collecting data on efficacy and safety of combined antihypertensive therapy administered in common clinical practice (i.e. at the discretion of participating physicians). First, since patients having failed to achieve the goal of blood pressure reduction with perindopril monotherapy were assigned to the combination therapy group, hypertension was probably more severe in more cases

in that group than in the monotherapy group. This difference at baseline needs to be taken into account when the incidence of adverse events or stroke is interpreted. However, the results show that if adequate care is taken of changes in creatinine, BUN and uric acid (diuretics' known side-effects), the safety profile of perindopril plus diuretic combination therapy differs little from that of perindopril monotherapy. Second, since the follow-up period in this study was quite short at 6 months, we do not know the long-term prognosis of patients receiving this therapy, and we should refrain from making any conclusions about the influence of this regimen on new onset of diabetes mellitus and renal dysfunction. We adopted a 6-month study period because this perindopril-based blood pressure-lowering regimen was shown in the PROGRESS Study, in which Japan participated, as a valid means of preventing stroke.

Conclusions

Supporting the results of the multi-country PROGRESS Study, the present study conducted in Japanese patients with a history of stroke suggests that in individuals in whom perindopril monotherapy did not adequately lower blood pressure levels additional use of diuretics may achieve target. Furthermore, as long as adequate care is taken of individuals with compromised renal function, hyperuricemia, and the like, this combination therapy exerts potent blood pressure-lowering effects without posing significant safety problems. Considering as well the economic advantage of diuretics, we conclude that antihypertensive therapy with this regimen is highly useful for achieving blood pressure goals as specified in current guidelines.

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特集 脳静脈系の病態と脳血管障害

脳静脈・静脈洞血栓症における抗凝固療法の有効性と安全性

長谷川泰弘
HASEGAWA Yasuhiro
聖マリアンナ医科大学神経内科

脳静脈・静脈洞血栓症に対する抗凝固療法の有効性と安全性は，小児，新生児など一部を除けば，これまでおこなわれた多数の観察研究にもとづいて，ほぼコンセンサスが得られている．治療開始前における頭蓋内出血の存在は抗凝固療法の禁忌とはならず，早期からヘパリンによる抗凝固療法をおこなうことが転帰改善に役立つと考えられる．急性期治療後の経口抗凝固療法の目標 INR 値や期間は不明であり，個々の症例のリスクを考慮して決定すべきものと思われる．

Key Words
脳静脈，静脈洞，血栓症，抗凝固療法，脳出血

はじめに

脳静脈・静脈洞血栓症（cerebral vein and sinus thrombosis：CVST）に対して血栓の進展を阻止すべく抗凝固療法をおこなうことは，その病態からも理にかなったものである．頭蓋内出血や出血性梗塞を合併しやすいという本症の特徴から，その効果と安全性についてはながらく議論されてきたが，現在では抗凝固療法の有効性と安全性について，おおむね明確なコンセンサスが得られている．CVST に対する抗凝固療法は 1940 年ごろからはじまり，すでに 70 年の歴史があるが，脳血管障害の 1%未満という発生率の低さから，無作為化比較試験はわずかしかなく，治療の根拠となるエビデンスはおもに観察研究などの治療経験にもとづいている．本稿では，CVST に対する抗凝固療法の有効性と安全性の根拠についてまとめる．

1 観察研究による検証と治療実態

1941 年に Lyons[1]が 2 例の海綿静脈洞血栓症例に対しヘパリンの全身投与をおこなって以降，大小さまざまな観察研究が報告され，抗凝固療法の効果と安全性が検証されてきた．1985 年 Bousser ら[2]は，血管撮影により確定しえた CVST 38 例の治療に関する後ろ向き研究を報告している．彼らの経験によれば，ヘパリン治療をおこなった 23 例中 1 例も死亡はみられず，全例が良好な転帰をとり，19 例が完全回復を得たと報告し，頭蓋内出血を伴うものであってもヘパリンを用いるべきことを論じた．ポルトガルの登録調査[3]によれば，1980～1998 年までに抗凝固療法がおこなわれた 112 例中，治療後に新たな頭蓋内出血がみられたものは 4 例（3.6%）で，抗凝固療法をおこなわなかったものの頻度（30 例中 2 例，

6.7%）よりも少なく，多変量解析により抗凝固療法の施行は，完全回復の有意な予測因子（オッズ比 3.8）であることが明らかとなった．また，International Study on Cerebral Vein and Dural Sinus Thrombosis（ISCVT）による CVST 患者の大規模国際登録[4]によれば，1998～2001 年までに登録された症例の 83.3%がヘパリンによる抗凝固療法を受けており，抗凝固療法をほぼ必須の治療と考える CVST の治療実態を反映したものと考えられる．

画像診断の進歩によりこれまで診断が困難であった新生児の CVST の実態も明らかとなってきた．Berfelo ら[5]は，1999 年 1 月～2009 年 3 月までに 6 施設で経験された新生児 CVST 52 例（39 例男児）の後ろ向き調査の成績を報告している．症状としては，痙攣が多く（52 例中 29 例），検査をできた 18 例中 2 例でプロトロンビン G20210A 変異が確認された（11%）．抗凝固療法は 22 例でおこなわれ，出血合併症はなかったが，38%に中等～高度の神経症状が残り，死亡率は 19%であったとしている．新生児 CVST の抗血栓療法の効果と安全性，予測因子を明らかにする目的でおこなわれている大規模国際共同研究 International Pediatric Stroke Study（IPSS）[6]では，登録された 341 例の新生児のうち，84 例が脳静脈・静脈洞の単独血栓症を有していたが，抗凝固療法をおこなわれたものは 52%であった．カナダの登録調査（Canadian Pediatric Ischemic Stroke Registry）でも抗凝固療法を受けた新生児 CVST は 36%にとどまっており，抗凝固療法施行率は成人の CVST よりもきわめて低い[7]．これは，米国内でも American college of chest physician のガイドライン[8]が，著明な頭蓋内出血を伴わない新生児の抗凝固療法を推奨している一方，American heart association（AHA）のガイドライン[9]では，血栓の伸長，複数の脳塞栓，全身の塞栓あるいは高度の血栓準備状態の存在があるときのみ抗凝固療法を推奨するなど，治療のコンセンサスがいまだ得られていないことを反映している．欧州の共同研究[10]によれば，2 歳以上とそれ以下の小児の治療法に差はなかったとしており，新生児，小児の CVST についてはなお未解決の部分が多い．

2 無作為化比較試験とメタ解析

抗凝固療法の有効性を検証した無作為化比較試験は，わずか 2 つしかない．CVST のほとんどに対して抗凝固療法がおこなわれるという今日の治療実態やガイドラインの推奨などから，今後プラセボ対照試験がおこなわれることはないと思われるので，これら 2 つの研究のもつ歴史的な意味は大きい．

1．Einhäupl ら，1991 年[11]

目的：CVST 患者に対するヘパリン静注（用量調節）の転帰改善効果の検証

試験デザイン：無作為化群間比較試験（患者と評価者のみの盲検）

対象：非感染性 CVST 20 例（ヘパリン群 10 例，対照群 10 例）

方法：ヘパリンはまずボーラスで投与し，その後持続静注とし，活性化部分トロンボプラスチン時間（activated partial thromboplastin time：APTT）を 80～100 秒として治療した．対照群は生理食塩水の点滴のみおこなった．患者と評価者は盲検化されているが，治療医はヘパリン用量を調節するため盲検化されていない．研究者が新たに開発した重症度スケール（SVT 重症度スケール）を用いて無症候 0 点～死亡 9 点までの 10 段階で経時的に評価した．

結果：SVT 重症度スケールは，治療開始 3 日後よりヘパリン群で有意に良好となり，8 日後も有意のままであった．治療 3 週目には，ヘパリン群と対照群の SVT 重症度スケールスコアは 0.6 と 3.9 で有意にヘパリン群が勝った（$P<0.005$）．3 ヵ月後ヘパリン群 10 例中 8 例は完全回復し 2 例はわずかな神経学的後遺症を残すのみであった．一方，対照群ではわずか 1 例が完全回復したのみで，6 例は神経学的後遺症を残し，3 例が死亡し，このうちの 1 例は肺塞栓症であった．脳出血は，ヘパリン群 3 例，対照群 2 例にみられたが，ヘパリン群に新たな出血は起こらなかった．一方，対照群では 2 例に新たな出血がみられ，1 例に出血の増悪がみられた．これらの結果はヘパリン全身投与の有効性を示すものであり（$P<0.01$, modified Fisher's exact test），当初 60 例を目標にはじめた研究であったが，20 例の中間解析の後に，試験は中止となった．

結論：用量調節ヘパリン静注療法は CVST に有効であり，頭蓋内出血を伴うものも禁忌ではない．

論文の意義：これ以降 CVST に対するヘパリンの用量調節持続静注は有効と考えられるようになった．論文

中には同施設の無作為化していない過去の症例を含む102例のデータも報告されている．これによれば，治療開始前に頭蓋内出血があった43例中13例はヘパリンによる治療を受けておらず，その死亡率は69%（13例中9例）であったが，ヘパリン治療を受けた患者の死亡率は15%（27例中4例）と明らかに良好であった．本研究は1施設のデータでサンプルサイズも20例と少なく，治療開始までの時間が発症から1ヵ月程度と長く，十分精度が検証されていないスケール（SVT重症度スケール）を用いて転帰の判定をおこなった点などが問題であるが，本研究以降ヘパリンはたとえ脳出血を合併していたとしてもCVST患者に対して有効であると考えられるようになった歴史的意義は大きい．

2．de Bruijnら，1999年[12]

目的：CVST患者に対する低分子ヘパリン（ナドロパリン）皮下注と経口抗凝固療法の後療法の転帰改善効果の検証

試験デザイン：二重盲検プラセボ対照無作為化多施設共同群間比較試験

対象：脳血管撮影またはMRアンジオグラフィーで確定されたCVST．18歳未満，妊婦，ヘパリンを使用すべき明白な根拠または禁忌の存在，CVST以外に予後不良疾患があるものなどは除外した．

方法：初期3週間はナドロパリン（180 anti-factor Xa units/24時間）またはプラセボを皮下注（二重盲検期間），その後はナドロパリン割り付け群に対して国際感度指標（International normarized ratio：INR値）2.5～3.5を目標に経口抗凝固薬を10週間継続した（非盲検期間）．3週間後に，死亡またはBarthel index score＜15を転帰不良と定義して盲検下で評価し，3ヵ月後に，死亡またはOxford handicap scale score≧3を転帰不良と定義して非盲検下で評価してそれぞれ群間比較した．

結果：60例を登録し，追跡調査は全例おこなった．1例が無作為化後診断の誤りが確認されて除外した．3週間後の転帰不良例の率はナドロパリン群30例中6例（20%），プラセボ群29例中7例（24%）で，12週後のそれはナドロパリン群30例中4例（13%），プラセボ群29例中6例（21%）であったが，いずれも有意差はなかった．治療後に新たな脳出血はみられなかったが，ナドロパリン群で重篤な消化管出血が1例みられた．プラセボ群の1例が肺塞栓の臨床診断で死亡した．

結論：CVSTに対する抗凝固療法（経口抗凝固療法の後療法を伴う低分子ヘパリン皮下注）は，プラセボ群より良好な転帰をとったが，有意差はみられなかった．治療開始時に脳出血を伴う症例においても，抗凝固療法の安全性が証明された．

論文の意義：この研究では死亡率が低くプラセボ群に，より軽症例が多かったという問題があった．また，ナドロパリンの投与量は深部静脈血栓症の投与量を流用しており，この量がCVSTに適切であるかの証拠は十分ではない．1991年のEinhäuplら[11]の研究に引きつづき，CVSTに対する抗凝固療法の安全性を再確認する結果となった．

3．メタ解析

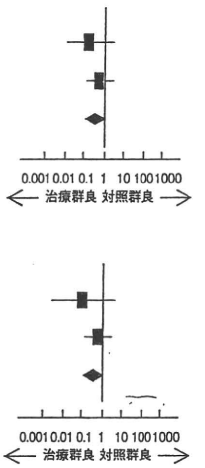
Stamら[13]は，Einhäuplら[11]の研究の転帰を標準的な評価法で再評価したうえで，上記2つの無作為化試験のメタ解析をおこなった．その結果，CVSTに対する抗凝固療法の施行は，有意ではないものの死亡の相対リスク（RRR 0.33，95% CI 0.08～1.21）を低下させ，死亡または非自立となるリスクを低下させる（RRR 0.46，95% CI 0.16～1.31）とされた（図❶）．

3 急性期治療のガイドライン

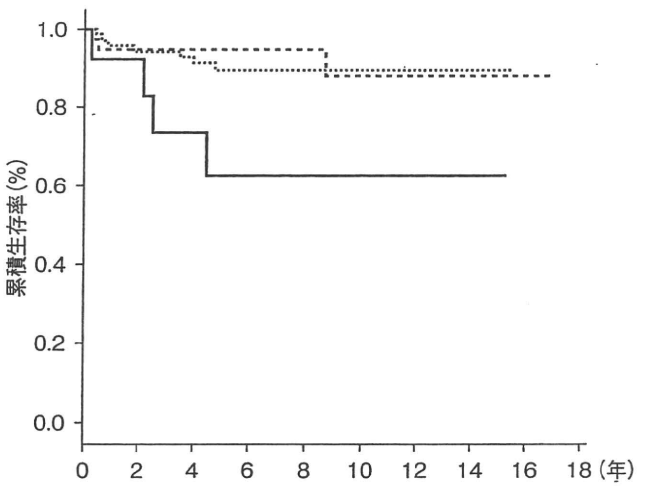
以上のようなエビデンスをふまえ，わが国の脳卒中治療ガイドライン2009[14]でも，抗凝固療法が第一選択であること，出血を伴う例でもヘパリンの使用は禁忌ではないことが記載されている．また，ヘパリンはAPTT値が約2倍程度になるように用量を調節し，約2週間のヘパリン持続静注後，経口投与に切り替えることを推奨している[14]．さらに重症例あるいは抗凝固療法によって改善のみられない症例に血栓溶解薬［ウロキナーゼあるいは組織プラスミノーゲンアクチベータ（tissue plasminogen activator：t-PA）］の局所投与を試みてもよいが，頭蓋内出血を伴う例では，ヘパリンとt-PAの併用は出血を助長する危険があり，使用すべきではない（グレードD）としている[14]．

血栓溶解療法の効果は全身投与であれ局所投与であれ，効果と安全性には十分な根拠がない．日常臨床でおこなわれるとすれば，適切な抗凝固療法にもかかわらず増悪

研究	治療群 n/N	対照群 n/N	リスク比 M-H, Fixed, 95%CI	weight	リスク比 M-H, Fixed, 95%CI
◆ 死亡					
Einhäupl ら,1991年	0/10	3/10		46.2%	0.14 [0.01, 2.45]
de Bruijn ら,1999年	2/30	4/29		53.8%	0.48 [0.10, 2.44]
計(95%CI)	40	39		100.0%	0.33 [0.08, 1.28]
◆ 死亡または非自立					
Einhäupl ら,1991年	0/10	3/10		36.5%	0.14 [0.01, 2.45]
de Bruijn ら,1999年	4/30	6/29		63.5%	0.64 [0.20, 2.05]
計(95%CI)	40	39		100.0%	0.46 [0.16, 1.31]



図❶ コクライングループによるメタ解析結果
(Stam J *et al*, 2002[13]より改変引用)



図❷ 脳静脈・静脈洞血栓症発症後の血栓性素因別カプランマイヤー曲線
(Martinelli I *et al*, 2010[19]より引用)
血栓症イベントなしでの累積生存曲線をカプランマイヤー法によりリスク別に示した.
血栓性素因なし(点線), 軽度血栓性素因あり(破線), 高度血栓性素因あり(実線)

し, 血栓形成以外に増悪の根拠がみつからず, 大きな頭蓋内出血がないといったかぎられた症例について選択されうるものと思われる.

4 急性期治療後の抗凝固療法

急性期治療後の抗凝固療法の目標 INR 値や治療期間については大小さまざまな臨床研究があるが[4)15)16)], 明確な指針を得ることのできるほどの研究はなく, 各国のガイドラインも静脈血栓症の治療指針[17)]を流用している

ものがほとんどである．CVST 発症後の再発防止には，CVST を生じた基礎疾患の評価が重要となるが，明らかな原因を確定できない症例も 15～20%存在する[18]．

Martinelli ら[19]は初回 CVST 患者 145 例を抗凝固療法中止後，中央値 6 年間を追跡した成績を報告している．CVST の再発は 5 例（3%）で他の静脈血栓症は 10 例（7%），これら 2 つの再発率は 100 人・年あたり 2.03（95% CI 1.16～3.14）で，CVST のみの再発率は 100 人・年あたり 0.53（95% CI 0.16～1.10）であった．再発の半数は抗凝固中止 1 年以内に起こり，再発リスクは男性，CVST 以外の血栓症，重度の血栓性素因（アンチトロンビンⅢ欠損症，プロテイン C 欠損症，プロテイン S 欠損症，抗リン脂質抗体）で高かった．CVST の再発リスク自体は高いものではないが，抗凝固療法中断 1 年以内に，とくに男性で起こりやすく，重度の血栓性素因では CVST の再発，静脈血栓症や肺塞栓症のリスクが高いと結論している（図❷）．

2010 年 4 月に公表された欧州のガイドライン[20]でも，急性期治療後の経口抗凝固療法の適切な期間は不明であるとされているが，背景となるリスクに応じた推奨期間を示しており参考となる．経口抗凝固療法の期間は，CVST が一時的なリスクにより生じたものであれば 3 ヵ月，原因不明あるいは軽度の血栓性素因（leiden V 因子ヘテロ，プロトロンビン G20210A 変異，第Ⅷ因子高値）では 6～12 ヵ月，CVST を再発するものや 1 回の CVST であっても重度の血栓性素因のあるもの（アンチトロンビンⅢ欠損症，プロテイン C 欠損症，プロテイン S 欠損症，leiden V 因子ヘテロ，プロトロンビン G20210A 変異，抗リン脂質抗体など）では永久につづけることを推奨している．

おわりに

CVST に対する抗凝固療法の有効性と安全性に関するこれまでの研究と治療のコンセンサスについて概説した．

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