Online Supplement

The practical "1-2-3-4-day" rule for starting direct oral anticoagulants after ischemic stroke with atrial fibrillation

Authors: Shunsuke Kimura, et al, for the SAMURAI, RELAXED, RAF, RAF-NOAC, CROMIS-2, NOACISP LONGTERM, Erlangen registry and Verona registry Investigators

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Table I. List for the Study Investigators

[Derivation]

A. SAMURAI Study Investigators

Principal investigator: Kazunori Toyoda, MD (National Cerebral and Cardiovascular Center: NCVC)

Investigators and Institutions: Kenichi Todo, MD (Kobe City Medical Center General Hospital); Kazumi Kimura, MD; Yoshiki Yagita, MD (Kawasaki Medical School); Eisuke Furui, MD; Ryo Itabashi, MD (Kohnan Hospital); Tadashi Terasaki, MD (Japanese Red Cross Kumamoto Hospital); Yoshiaki Shiokawa, MD; Teruyuki Hirano, MD (Kyorin University School of Medicine); Kenji Kamiyama, MD; Jyoji Nakagawara, MD (Nakamura Memorial Hospital); Shunya Takizawa, MD; Kazunari Homma, MD (Tokai University School of Medicine); Satoshi Okuda, MD (NHO Nagoya Medical Center); Yasushi Okada, MD; Keisuke Tokunaga, MD (NHO Kyushu Medical Center); Tomoaki Kameda, MD; Kazuomi Kario, MD (Jichi Medical University School of Medicine); Yoshinari Nagakane, MD (Kyoto Second Red Cross Hospital); Yasuhiro Hasegawa, MD; Hisanao Akiyama, MD (St Marianna University School of Medicine); Satoshi Shibuya, MD; Hiroshi Mochizuki, MD (South Miyagi Medical Center); Yasuhiro Ito, MD (TOYOTA Memorial Hospital); Takahiro Nakashima, MD; Hideki Matsuoka, MD (NHO Kagoshima Medical Center); Kazuhiro Takamatsu, MD (Ohta Memorial Hospital); Kazutoshi Nishiyama, MD (Kitasato University School of Medicine); Masatoshi Koga, MD (NCVC)

Central Office: Sohei Yoshimura, MD; Shoichiro Sato, MD; Shoji Arihiro, MD; Masatoshi Koga, MD; Hiroshi Yamagami, MD; Manabu Inoue, MD; Masahito Takagi, MD; Kanta Tanaka, MD; Masayuki Shiozawa, MD; Takeshi Yoshimoto, MD; Tetsuya Chiba, MD; Shunsuke Kimura, MD (NCVC)

Supervisory Advisor: Kazuo Minematsu, MD; Kazuyuki Nagatsuka, MD (NCVC)

B. RELAXED Study Investigators

Principal investigator: Kazuo Minematsu, MD

Supervisor: Takenori Yamaguchi, MD

Protocol committee: Masahiro Yasaka, MD (Chair); Kazunori Toyoda, MD (Vice-chair); Takehiko Nagao, MD; Hiroshi Yamagami, MD; Shinichi Yoshimura, MD

Steering committee: Yasuhiro Hasegawa, MD; Yoichiro Hashimoto, MD; Kiyohiro Houkin, MD; Kazumi Kimura, MD; Kazuo Kitagawa, MD; Masayasu Matsumoto, MD; Yasushi Okada, MD; Satoshi Okuda, MD; Norio Tanahashi, MD; Yasuo Terayama, MD; Shinichiro Uchiyama, MD

Clinical Events Committee: Etsuro Mori, MD (Chair); Yutaka Furukawa , MD; Takeshi Kimura, MD; Yoshiaki Kumon, MD; Ken Nagata, MD; Shigeru Nogawa, MD; Tomohiro Sakamoto, MD

MRI Imaging Evaluation Committee: Teruyuki Hirano, MD (Chair); Toshinori Hirai, MD; Kohsuke Kudo, MD; Makoto Sasaki, MD

Data Monitoring Committee: Shotai Kobayashi, MD

Statistical Analysis: Toshimitsu Hamasaki, PhD

[Validation]

C. RAF and RAF-NOAC

Michela Giustozzi MD, Monica Acciarresi MD, Giancarlo Agnelli MD, Valeria Caso MD, PhD, Fabio Bandini MD, Georgios Tsivgoulis MD, Shadi Yaghi MD, Karen L. Furie MD, Prasanna Tadi MD, Cecilia Becattini MD, Marialuisa Zedde MD, Azmil H Abdul-Rahim MD, Kennedy R Lees MD, Andrea Alberti MD, Michele Venti MD, PhD, Cataldo D'Amore MD, Maria Giulia Mosconi MD, Ludovica Anna Cimini MD, Paolo Bovi MD, Monica Carletti MD, Alberto Rigatelli MD, Manuel Cappellari MD, Jukka Putaala MD, Liisa Tomppo MD, Turgut Tatlisumak MD, Simona Marcheselli MD, Alessandro Pezzini MD, Loris Poli MD, Alessandro Padovani MD, PhD, Vieri Vannucchi MD, Sung-Il Sohn MD, PhD, Gianni Lorenzini MD, Rossana Tassi MD, Francesca Guideri MD, Maurizio Acampa MD, Giuseppe Martini MD, George Ntaios MD, George Athanasakis MD, Konstantinos Makaritsis MD, Efstathia Karagkiozi MD, Konstantinos Vadikolias MD, Chrissoula Liantinioti MD, Maria Chondrogianni MD, Nicola Mumoli MD, Franco Galati MD, Simona Sacco MD, Cindy Tiseo MD, Francesco Corea MD, PhD, Walter Ageno MD, Marta Bellesini MD, Giovanna Colombo MD, Giorgio Silvestrelli MD, PhD, Alfonso Ciccone MD, Alessia Lanari MD, Umberto Scoditti MD, Licia Denti MD, Michelangelo Mancuso MD, Miriam Maccarrone MD, Leonardo Ulivi MD, Giovanni Orlandi MD, Nicola Giannini MD, Tiziana Tassinari MD, Maria Luisa De Lodovici MD, Christina Rueckert MD, Antonio Baldi MD, Danilo Toni MD, PhD, Federica Letteri MD, Martina Giuntini MD, Enrico Maria Lotti MD, Yuriy Flomin MD, Alessio Pieroni MD, Odysseas Kargiotis MD, Theodore Karapanayiotides MD, PhD, Serena Monaco MD, Mario Maimone Baronello MD, Laszló Csiba MD, Lilla Szabó MD, Alberto Chiti MD, Elisa Giorli MD, Massimo Del Sette MD, Davide Imberti MD, Dorjan Zabzuni MD, Boris Doronin MD, Vera Volodina MD, Patrik Michel, PD-MER, Peter Vanacker MD, Kristian Barlinn MD, Lars-Peder Pallesen MD, Jessica Barlinn MD, Dirk Deleu, MD, PhD, Gayane Melikyan MD, Faisal Ibrahim MD, Naveed Akhtar MD, Vanessa Gourbali MD, Luca Masotti MD

D. CROMIS-2

Adrian Parry-Jones, MD; Chris Patterson, MD; Christopher Price, MD; Abduelbaset Elmarimi, MD; Anthea Parry, MD; Arumug Nallasivam, MD; Azlisham Mohd Nor, MD; Bernard Esis, MD; David

Bruce; Christine Roffe, MD; Clare Holmes, MD; David Cohen, MD; David Hargroves, MD; David Mangion, MD; Dinesh Chadha, MD; Djamil Vahidassr, MD; Dulka Manawadu, MD; Elio Giallombardo, MD; Elizabeth Warburton, MD; Enrico Flossman, MD; Gunaratam Gunathilagan, MD; Harald Proschel, MD; Hedley Emsley, MD; Ijaz Anwar, MD; James Okwera, MD; Janet Putterill, MD; Janice O'Connell, MD; John Bamford, MD; John Corrigan, MD; Jon Scott; Jonathan Birns, MD; Karen Kee, MD; Kari Saastamoinen, MD; Kath Pasco, MD; Krishna Dani, MD; Lakshmanan Sekaran, MD; Lillian Choy, MD; Liz Iveson, MD; Maam Mamun, MD; Mahmud Sajid, MD; Martin Cooper, MD; Matthew Burn, MD; Matthew Smith, MD; Michael Power, MD; Michelle Davis, MD; Nigel Smyth, MD; Roland Veltkamp, MD; Pankaj Sharma, MD; Paul Guyler, MD; Paul O'Mahony, MD; Peter Wilkinson, MD; Prabel Datta, MD; Prasanna Aghoram, MD; Rachel Marsh, MD; Robert Luder, MD; Sanjeevikumar Meenakishundaram, MD; Santhosh Subramonian, MD; Simon Leach, MD; Sissi Ispoglou, MD; Sreeman Andole, MD; Timothy England, MD; Aravindakshan Manoj, MD; Frances Harrington, MD; Habib Rehman, MD; Jane Sword, MD; Julie Staals, MD; Karim Mahawish, MD; Kirsty Harkness, MD; Louise Shaw, MD; Michael McCormich, MD; Nikola Sprigg, MD; Syed Mansoor, MD; Vinodh Krishnamurthy, MD

E. NOACISP-LONGTERM

Stefan T Engelter, Philippe A Lyrer, Leo H Bonati, David J Seiffge , Christopher Traenka, Alexandros A Polymeris , Annaelle Zietz, Nils Peters, Gian Marco De Marchis, Sebastian Thilemann, Nikolaos S Avramiotis, Henrik Gensicke, Lisa Hert, Benjamin Wagner, Fabian Schaub, Louisa Meya, Joachim Fladt, Tolga Dittrich, Urs Fisch

F. Verona registry

Bruno Bonetti, MD, PhD; Paolo Bovi, MD; Giampaolo Tomelleri, MD; Nicola Micheletti, MD; Cecilia Zivelonghi, MD; Andrea Emiliani, MD.

G. Erlangen registry

Bernd Kallmünzer, Kosmas Macha, Gabriela Siedler, Svenja Stoll, Ruihao Wang, Bastian Volbers, Stefan Schwab, David Haupenthal, Luise Gaßmann

Table II. Inclusion and exclusion criteria for the included studies

A. SAMURAI

Inclusion criterion:

Patients who were hospitalized (or initiated acute management at the outpatient clinic) within 7 days after onset of acute ischemic stroke (AIS) or transient ischemic attack (TIA) and were diagnosed as having nonvalvular atrial fibrillation (NVAF)

Exclusion criteria:

1. Rheumatic mitral valve disease
2. A history of prosthetic valve replacement or mitral valve surgical repair
3. Active infective endocarditis
4. Patient, family member or legally responsible person does not have given informed consent
5. Inappropriate patient's conditions for study enrollment in the opinion of the investigator

B. RELAXED

Inclusion criterion:

Patients with NVAF complicated with AIS or TIA who fulfill the following criteria

1. Hospitalized or visited the hospital as outpatients within 48 hours of the onset of AIS or TIA
2. Having an infarct (a symptom in those with TIA) in the middle cerebral artery area
3. Treated with rivaroxaban within 30 days of the onset of AIS or TIA
4. Those who or those whose family or other representatives agree to participate in the study

Exclusion criteria:

1. Hypersensitivity to rivaroxaban
2. Clinically significant hemorrhage, including gastrointestinal hemorrhage
3. Liver disease with a coagulation disorder
4. A moderate or severe liver disorder (Child-Pugh Class B or C)
5. Renal failure (creatinine clearance: <15 mL/minute)
6. Poorly controlled hypertension (> 180/100 mmHg)
7. Women who are or are likely to be pregnant
8. Treated with HIV protease inhibitors including ritonavir, atazanavir, and indinavir
9. Treated with an oral or injectable formulation of azole antifungal drugs, including itraconazole, voriconazole, and ketoconazole, and excluding fluconazole
10. Acute bacterial endocarditis

11. Anticoagulation is initiated with dabigatran, apixaban, or edoxaban and is substituted by rivaroxaban.
12. The investigator in charge judges not eligible for the study

C. RAF

Inclusion criterion:

Patients with AIS and known or newly diagnosed atrial fibrillation (NVAF).

Exclusion criteria:

Contraindications to anticoagulation.

D. RAF-NOAC

Inclusion criterion:

Patients with AIS and known or newly diagnosed AF.

Exclusion criteria:

1. Contraindications to anticoagulation with direct oral anticoagulants (DOACs).
2. High risk of bleeding, defined as clinically significant liver disease (acute or chronic hepatitis, cirrhosis, or alanine aminotransferase level >3 times the upper limit of normal), creatinine clearance <30 mL/min (for apixaban, the threshold was 25 mL/min)
3. Life expectancy of <3 to 6 months, 3) use of interacting medications
4. Uncontrolled hypertension.

E. CROMIS-2

Inclusion criterion:

Adults (ie, ≥18 years of age) with electrocardiogram-confirmed NVAF who presented to participating hospitals with AIS or TIA and were identified by their treating physician for anticoagulation treatment.

Exclusion criteria:

1. Could not undergo MRI
2. Definite contraindication to anticoagulation
3. Previously received therapeutic anticoagulation

F. Single-center study from Basel

Inclusion criterion:

1. At least 18 years old
2. Hospitalization between April 2013 and September 2015 for AIS or TIA
3. Diagnosis of NVAF, either preexisting or in-hospital
4. Oral anticoagulation with DOAC or vitamin K antagonists continued (for those already on anticoagulation) or started or restarted within 6 months after the index event.

Exclusion criteria:

Patients with mechanical heart valves and those in whom anticoagulation was started more than 6 months after the index event.

G. Single-center study from Verona

Inclusion criterion:

DOAC-naïve patients who had infarct with or without asymptomatic HT classified according to European Cooperative Acute Stroke Study (ECASS) on pre-DOAC CT scan, and started DOAC within 7 days after stroke onset.

Exclusion criteria:

Started DOAC after 8 days of stroke onset.

H. Single-center study from Erlangen

Inclusion criterion:

1. AF-associated acute ischemic event
2. Treatment with DOACs during in-patient hospital stay.

Exclusion criteria:

1. Received several different anticoagulation regimens
2. Early cessation of DOAC therapy for other reasons than intracranial hemorrhage.

Table III. Baseline characteristics of patients in each subgroup of the derivation cohort by stroke severity

	TIA (n=67)	Ischemic stroke			P
		Minor (n=899)	Moderate (n=370)	Severe (n=461)	
Age, y	72 [65–80]	76 [70–82]	77 [69–84]	80 [73–86]	0.005
Women	23 (34)	326 (36)	152 (41)	229 (50)	<0.001
Premorbid modified Rankin Scale score	0 [0–0]	0 [0–0]	0 [0–1]	0 [0–2]	<0.001
Hypertension	41 (61)	605 (67)	256 (69)	310 (67)	0.632
Diabetes mellitus	12 (18)	166 (18)	58 (16)	73 (16)	0.524
Dyslipidemia	27 (40)	292 (32)	98 (26)	130 (28)	0.034
History of acute coronary syndrome	1 (1)	61 (7)	30 (8)	33 (7)	0.270
History of stroke/TIA before index event	16 (24)	180 (20)	59 (16)	80 (17)	0.202
Premorbid oral anticoagulation	13 (19)	188 (21)	68 (18)	108 (23)	0.351
Premorbid oral antiplatelet use	15 (22)	179 (20)	82 (22)	88 (19)	0.688
Paroxysmal AF	39 (58)	380 (42)	155 (42)	174 (38)	0.014
AF documented before index event	38 (57)	458 (51)	172 (46)	224 (49)	0.304
CHADS2 score	2 [1–2]	2 [1–3]	2 [1–2]	2 [1–3]	0.028
CHADS2-VASc score	3 [2–4]	3 [2–4]	3 [2–4]	4 [3–4]	<0.001
HAS-BLED score	2 [1–3]	2 [1–3]	2 [1–2]	2 [1–3]	0.315
NIHSS score at admission	0 [0–2]	3 [1–5]	12 [9–14]	20 [18–24]	<0.001
Small infarct	67 (100)	317 (35)	34 (9)	28 (6)	<0.001
Infarct only in the vertebrobasilar arterial territory	2 (3)	76 (8)	6 (2)	7 (2)	<0.001
Hemorrhagic transformation	0 (0)	58 (6)	37 (10)	58 (13)	<0.001
intravenous thrombolysis	1 (1)	114 (13)	140 (38)	193 (42)	<0.001
Mechanical thrombectomy	0 (0)	18 (2)	69 (19)	147 (32)	<0.001
Antiplatelet therapy after index event	9 (13)	171 (19)	45 (12)	35 (8)	<0.001
Days from onset to DOAC initiation, d	2 [1–5]	3 [2–7]	4 [2–7]	5 [2–9]	<0.001
Type of DOACs at initiation					<0.001
Dabigatran	11 (16)	144 (16)	32 (9)	24 (5)	
Rivaroxaban	55 (82)	741 (82)	332 (90)	433 (94)	
Apixaban	1 (1)	14 (2)	6 (2)	4 (1)	

N (%) or median [interquartile range].

AF indicates atrial fibrillation; DOAC, direct oral anticoagulant; NIHSS, National Institutes of Health Stroke Scale; TIA, transient ischemic attack.

Table IV. Outcomes in four subgroups of the derivation cohort by neurological severity

	Early Group	Late Group	*P*
Transient ischemic attack	n=26	n=41	
Stroke / systemic embolism	0	1 (2.4)	0.422
Ischemic stroke	0	1 (2.4)	0.422
Death	0	0	-
Major bleeding	0	1 (2.4)	0.422
Intracranial hemorrhage	0	0	-
Mild ischemic stroke	n=369	n=530	
Stroke / systemic embolism	10 (2.7)	23 (4.3)	0.201
Ischemic stroke	10 (2.7)	19 (3.6)	0.465
Death	4 (1.1)	2 (0.4)	0.201
Major bleeding	0	5 (0.9)	0.061
Intracranial hemorrhage	0	3 (0.6)	0.148
Moderate ischemic stroke	n=169	n=201	
Stroke / systemic embolism	1 (0.6)	4 (2.0)	0.246
Ischemic stroke	0	3 (1.5)	0.111
Death	1 (0.6)	4 (2.0)	0.246
Major bleeding	3 (1.8)	1 (0.5)	0.237
Intracranial hemorrhage	1 (0.6)	0	0.275
Severe ischemic stroke	n=221	n=240	
Stroke / systemic embolism	4 (1.8)	11 (4.6)	0.094
Ischemic stroke	3 (1.4)	9 (3.8)	0.107
Death	10 (4.5)	9 (3.8)	0.518
Major bleeding	3 (1.4)	3 (1.3)	0.919
Intracranial hemorrhage	1 (0.5)	1 (0.4)	0.953

Table V. Baseline characteristics of patients in the validation cohort

	Total (n=2036)	Early Group (n=547)	Late Group (n=1489)	P
Age, y	78 [71–84]	79 [73–85]	78 [71–84]	0.005
Women	1039 (51)	283 (52)	756 (51)	0.700
Hypertension, n (%)	1566 (77)	424 (78)	1142 (77)	0.688
Diabetes mellitus	432 (21)	103 (19)	329 (22)	0.110
Dyslipidemia	499 (41)	155 (39)	344 (42)	0.293
History of stroke/TIA before index event	483 (24)	141 (26)	342 (23)	0.187
Premorbid oral anticoagulation	414 (20)	153 (28)	261 (18)	<0.001
Concomitant oral antiplatelet use	633 (40)	134 (37)	499 (40)	0.331
Paroxysmal AF	273 (13)	83 (15)	190 (13)	0.157
AF documented before index event	730 (36)	286 (52)	444 (30)	<0.001
CHADS2-VASc score	5 [4–6]	5 [4–6]*	5 [4–6]*	0.004
HAS-BLED score	3 [2–4]	3 [2–3]	3 [2–4]	0.017
NIHSS score at admission	5 [2–10]	4 [2–10]	5 [2–10]	<0.001
Days from onset to DOAC initiation, d	6 [3–12]	2 [1–2]	8 [5–14]	<0.001
Intravenous thrombolysis	518 (26)	160 (29)	358 (24)	0.016
Type of DOACs at initiation				0.006
Dabigatran	654 (32)	154 (28)	500 (34)	
Rivaroxaban	514 (25)	145 (27)	369 (25)	
Apixaban	533 (26)	161 (29)	372 (25)	
Edoxaban	11 (1)	7 (1)	4 (0)	
Unknown	324 (16)	80 (15)	244 (16)	

N (%) or median [interquartile range].

* Mean ± standard deviation: 5.1±1.4 (Early) versus 4.9±1.6 (Late)

2 patients (1 in Early Group and 1 in Late Group) are missing data for age; 7 (2 and 5, respectively) for hypertension; 4 (1 and 3, respectively) for diabetes mellitus; 812 (146 and 666, respectively) for dyslipidemia; 435 (188 and 247, respectively) for concomitant oral antiplatelet use; 8 (1 and 7, respectively) for CHADS-VASc score; 1092 (235 and 857, respectively) for HAS-BLED score; and 12 (4 and 8, respectively) for intravenous thrombolysis.

AF indicates atrial fibrillation; DOAC, direct oral anticoagulant; NIHSS, National Institutes of Health Stroke Scale; TIA, transient ischemic attack.

Table VI. Outcomes in four subgroups of the validation cohort by neurological severity

	Early Group	Late Group	*P*
Transient ischemic attack	n=27	n=43	
Ischemic stroke	0 (0)	0 (0)	-
Death	0 (0)	2 (4.7)	0.256
Intracranial hemorrhage	0 (0)	1 (2.3)	0.425
Mild ischemic stroke	n=337	n=903	
Ischemic stroke	9 (2.7)	19 (2.1)	0.550
Death	5 (1.5)	10 (1.1)	0.590
Intracranial hemorrhage	1 (0.3)	2 (0.2)	0.922
Moderate ischemic stroke	n=117	n=357	
Ischemic stroke	2 (1.7)	6 (1.7)	0.983
Death	3 (2.6)	8 (2.2)	0.840
Intracranial hemorrhage	0 (0)	4 (1.1)	0.250
Severe ischemic stroke	n=66	n=186	
Ischemic stroke	2 (3.0)	8 (4.3)	0.650
Death	4 (6.1)	12 (6.5)	0.911
Intracranial hemorrhage	0 (0)	2 (1.1)	0.398

Figure I. Scatter plots of age and the National Institutes of Health Stroke Scale scores