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Genetic Testing and Risk Stratification for Brugada Syndrome

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COI Disclosure

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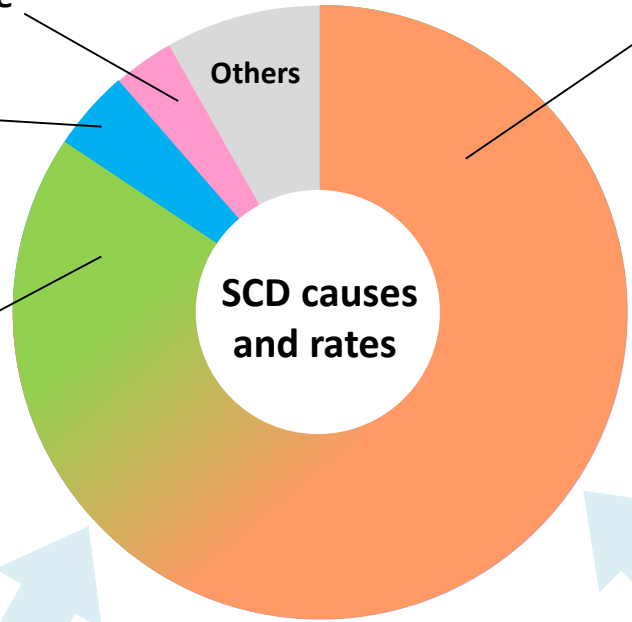
Causes of sudden cardiac death (SCD) and rates (A) and age of SCD onset (B)

(Hayashi M, Shimizu W, and Albert CM: Circ Res 2015;116:1887-1906, Textbook of Harrison Internal Medicine 2018)

(A)



Valvular heart disease
1-5%

Inherited arrhythmia syndrome
(LQTS, BrS, CPVT, ERS, etc)
1-2% in Western countries
10% in Japan

Cardiomyopathies
(NIDCM, HCM, ARVC, etc)
10-15% in Western countries
30-35% in Japan

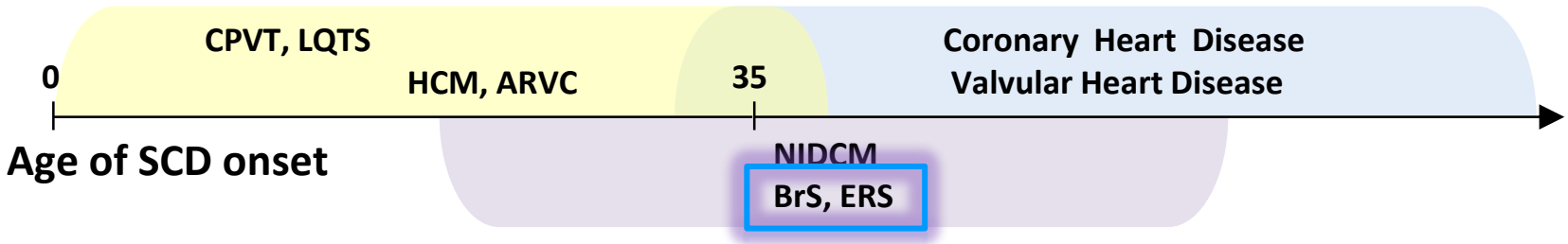
Coronary heart disease
~75% in Western countries (~50% in women and blacks)
50-60% in Japan

Substrates in myocardium
- Fibrosis
- Hypertrophy
- Ion channel functional modification
- Abnormal calcium handing

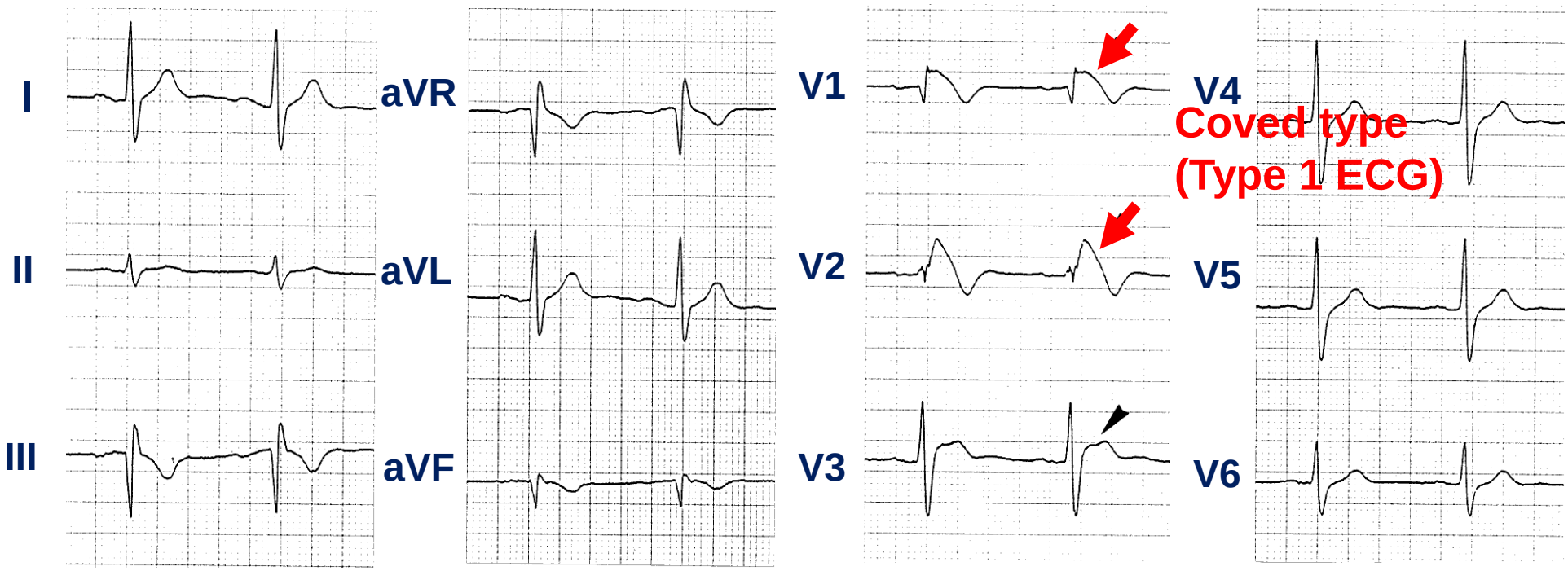
Predisposing factors and risks
- J wave / Repolarization abnormality
- Parasympathetic nerve dysfunction
- Male sex
- African descent
- Diabetes
- Smoking
- Genetics (Family history)
- Shortage of N-3 PUFA
- Atrial fibrillation
- Chronic kidney disease
- Obstructive sleep apnea

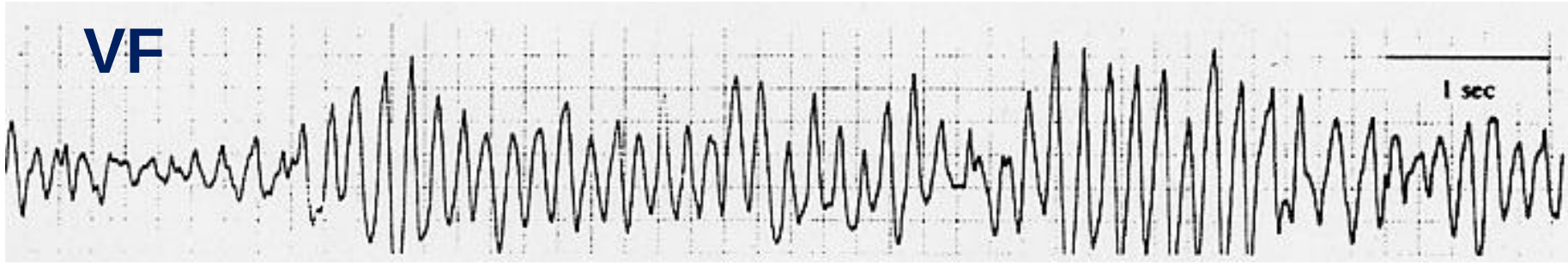
Triggers
- Heart failure / Stretch
- Ischemia
- Myocardial Inflammation
- Sympathetic nerve surge
- Electrolyte abnormality
- Environmental stress
- Psychological stress / Depression

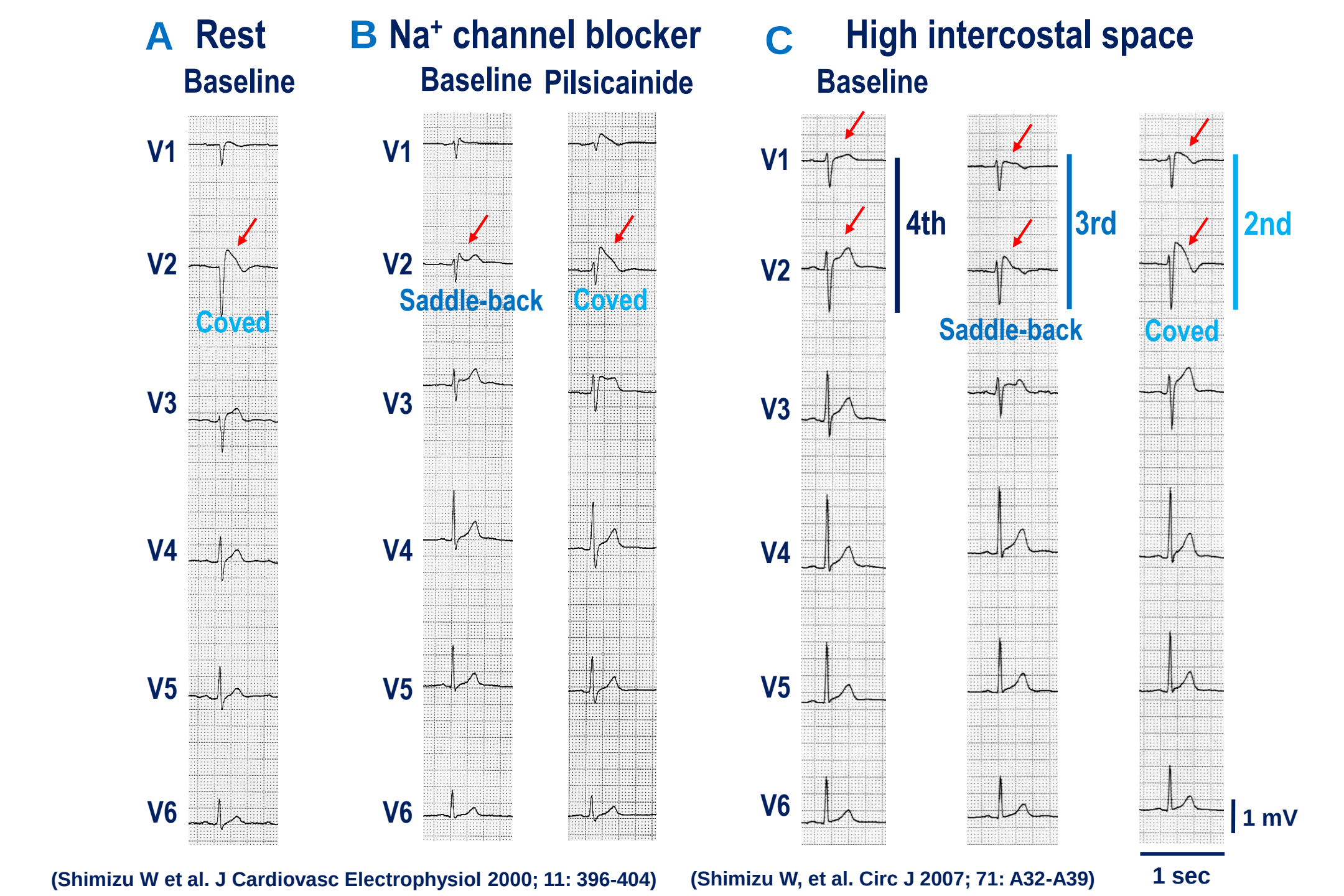
(B)



Brugada syndrome







(Shimizu W et al. J Cardiovasc Electrophysiol 2000; 11: 396-404)

(Shimizu W, et al. Circ J 2007; 71: A32-A39)

The 2013 Expert Consensus Statement on the Diagnosis and Management of Inherited Arrhythmias

Denver, Co

May 10, 2013

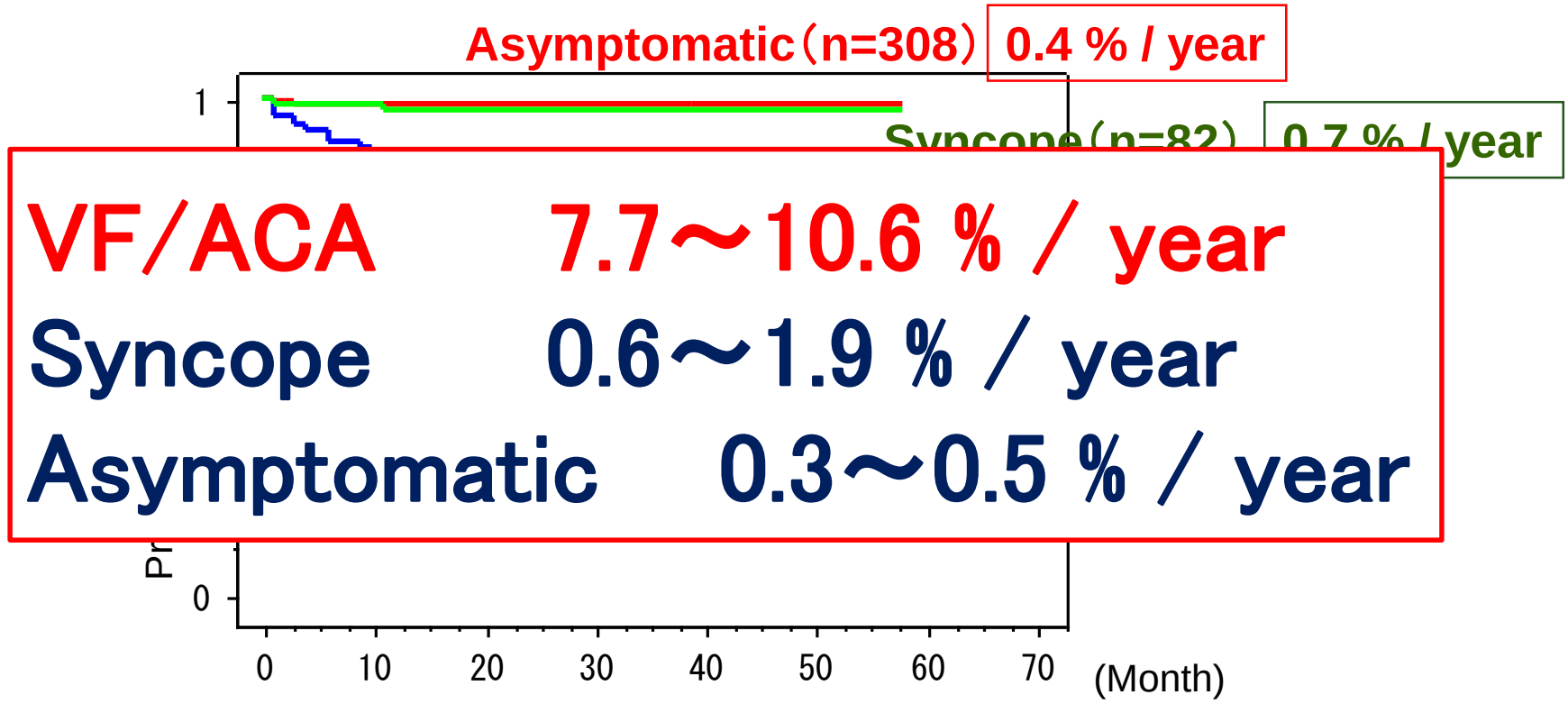
Recommendations on the Diagnosis and Management of Brugada Syndrome

Brugada Syndrome

Expert Consensus Recommendations on Diagnosis

1. BrS ***is diagnosed*** in patients with ST segment elevation with **type 1 morphology >= 2 mm in >= 1 lead** among the right precordial leads V1,V2, positioned **in the 2nd, 3rd or 4th intercostal space** occurring **either spontaneously *or* after provocative drug** test with intravenous administration of Class I antiarrhythmic drugs.
2. BrS ***is diagnosed*** in patients with type 2 or type 3 ST segment elevation in >= 1 lead among the right precordial leads V1,V2 positioned in the 2nd, 3rd or 4th intercostal space when a provocative drug test with intravenous administration of Class I antiarrhythmic drugs induces a type 1 ECG morphology

Lethal Cardiac Events in Japanese Brugada Registry



Kamakura S, Shimizu W, et al: Circ. Arrhythmia and Electrophysiol 2009;2:495-503

Predictors for Lethal Cardiac Events in Brugada Syndrome

Evidence Level B

- **VF, Aborted Cardiac Arrest (10% of recurrence of VF)**
- **Syncope**
- **Spontaneous Type 1 ECG**
- **Male**

Evidence Level B (Controversial)

- **Induction of VF**
  - **(Brugada J, et al. *Heart Rhythm.* 2011;8:1595–1597.)**
- **FH of SCD**
  - **(Kamakura S, et al. *Circulation. A & E*. 2009; 2: 495-503.)**

Evidence Level C

- ***SCN5A* mutation (Nishi N, et al. *Circ J.* 2010; 74: 2572–2578.)**
- **Late Potential in SAECG**
- **Atrial fibrillation etc.**

Clinical impact of the number of extrastimuli in programmed electrical stimulation in patients with Brugada type 1 electrocardiogram

Hisaki Makimoto, MD, Shiro Kamakura, MD, PhD, Naohiko Aihara, MD, Takashi Noda, MD, PhD, Ikutaro Nakajima, MD, Teruki Yokoyama, MD, Atsushi Doi, MD, PhD, Hiro Kawata, MD, Yuko Yamada, MD, Hideo Okamura, MD, Kazuhiro Satomi, MD, PhD, Takeshi Aiba, MD, PhD, Wataru Shimizu, MD, PhD

From the Division of Arrhythmia and Electrophysiology, Department of Cardiovascular Medicine, National Cerebral and Cardiovascular Center, Suita, Osaka, Japan.

BACKGROUND Use of programmed electrical stimulation (PES) for risk stratification of Brugada syndrome (BrS) is controversial.

OBJECTIVE To elucidate the role of the number of extrastimuli during PES in patients with BrS.

METHODS Consecutive 108 patients with type 1 electrocardiogram (104 men, mean age 46 ± 12 years; 26 with ventricular fibrillation [VF], 40 with syncope, and 42 asymptomatic) underwent PES with a maximum of 3 extrastimuli from the right ventricular apex and the right ventricular outflow tract. Ventricular arrhythmia (VA) was defined as VF or nonsustained polymorphic ventricular tachycardia >15 beats. Patients with VA induced by a single extrastimulus or double extrastimuli were assigned to group SD (Single/Double), by triple extrastimuli to group T (Triple), and the remaining patients to group N.

RESULTS VA was induced in 81 patients (VF in 71 and polymorphic ventricular tachycardia in 10), in 4 by a single extrastimulus, in 41 by double extrastimuli, and in 36 by triple extrastimuli. During 79 ± 48 months of follow-up, 24 patients had VF events. Although the overall inducibility of VA was not associated with an increased risk of VF (log-rank $P = .78$), group SD had worse prognosis than did group T ($P = .004$). Kaplan–Meier analysis in patients without prior VF also showed that group SD had poorer outcome than did group T and group N ($P = .001$). Positive and negative predictive values of VA induction with up to 2 extrastimuli were, respectively, 36% and 87%, better than those with up to 3 (23% and 81%, respectively).

CONCLUSIONS The number of extrastimuli that induced VA served as a prognostic indicator for patients with Brugada type 1 electrocardiogram. Single extrastimulus or double extrastimuli were adequate for PES of patients with BrS.

KEYWORDS Brugada syndrome; Programmed electrical stimulation; Number of extrastimuli; Risk stratification; Sudden death

ABBREVIATIONS **BrS** = Brugada syndrome; **ECG** = electrocardiogram; **ICD** = implantable cardioverter-defibrillator; **LAS40** = duration of low-amplitude signals <40 μV of the filtered QRS complexes; **NPV** = negative predictive value; **PES** = programmed electrical stimulation; **PPV** = positive predictive value; **PVT** = polymorphic ventricular tachycardia; **RVA** = right ventricular apex; **RVOT** = right ventricular outflow tract; **RMS40** = root mean square voltage of the terminal 40 ms of the filtered QRS complexes; **VA** = ventricular arrhythmia; **VF** = ventricular fibrillation

(Heart Rhythm 2012;9:242–248)

Programmed Ventricular Stimulation for Risk Stratification in the Brugada Syndrome

A Pooled Analysis

Jakub Sroubek, MD, PhD; Vincent Probst, MD, PhD; Andrea Mazzanti, MD; Pietro Delise, MD; Jesus Castro Hevia, MD; Kimie Ohkubo, MD; Alessandro Zorzi, MD; Jean Champagne, MD; Anna Kostopoulou, MD; Xiaoyan Yin, PhD; Carlo Napolitano, MD, PhD; David J. Milan, MD; Arthur Wilde, MD; Frederic Sacher, MD, PhD; Martin Borggrefe, MD, PhD; Patrick T. Ellinor, MD, PhD; George Theodorakis, MD; Isabelle Nault, MD; Domenico Corrado, MD, PhD; Ichiro Watanabe, MD; Charles Antzelevitch, PhD; Giuseppe Allocca, MD; Silvia G. Priori, MD, PhD; Steven A. Lubitz, MD, MPH

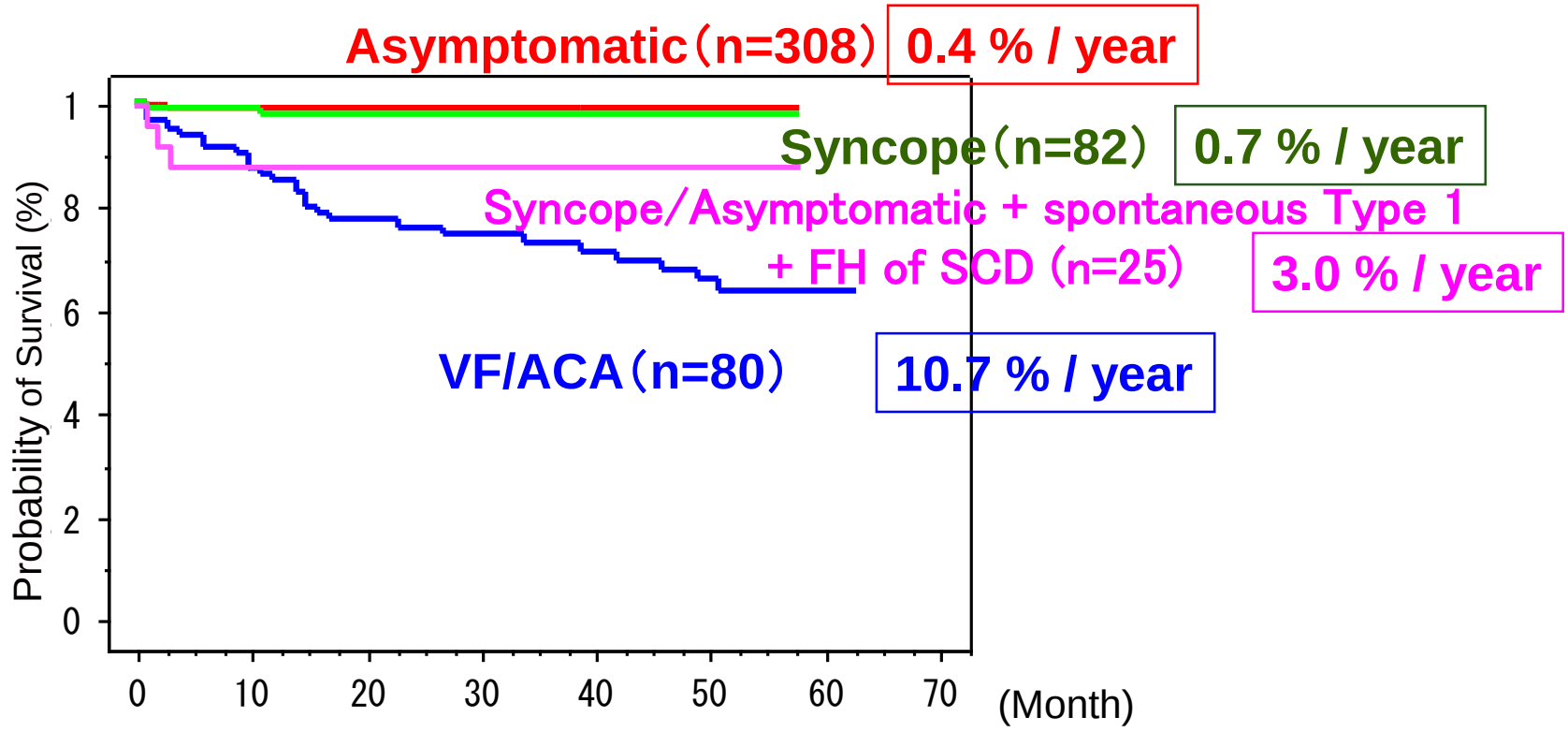
Background—The role of programmed ventricular stimulation in identifying patients with Brugada syndrome at the highest risk for sudden death is uncertain.

Methods and Results—We performed a systematic review and pooled analysis of prospective, observational studies of patients with Brugada syndrome without a history of sudden cardiac arrest who underwent programmed ventricular stimulation. We estimated incidence rates and relative hazards of cardiac arrest or implantable cardioverter-defibrillator shock. We analyzed individual-level data from 8 studies comprising 1312 patients who experienced 65 cardiac events (median follow-up, 38.3 months). A total of 527 patients were induced into arrhythmias with up to triple extrastimuli. Induction was associated with cardiac events during follow-up (hazard ratio, 2.66; 95% confidence interval [CI], 1.44–4.92, $P<0.001$), with the greatest risk observed among those induced with single or double extrastimuli. Annual event rates varied substantially by syncope history, presence of spontaneous type 1 ECG pattern, and arrhythmia induction. The lowest risk occurred in individuals without syncope and with drug-induced type 1 patterns (0.23%, 95% CI, 0.05–0.68 for no induced arrhythmia with up to double extrastimuli; 0.45%, 95% CI, 0.01–2.49 for induced arrhythmia), and the highest risk occurred in individuals with syncope and spontaneous type 1 patterns (2.55%, 95% CI, 1.58–3.89 for no induced arrhythmia; 5.60%, 95% CI, 2.98–9.58 for induced arrhythmia).

Conclusions—In patients with Brugada syndrome, arrhythmias induced with programmed ventricular stimulation are associated with future ventricular arrhythmia risk. Induction with fewer extrastimuli is associated with higher risk. However, clinical risk factors are important determinants of arrhythmia risk, and lack of induction does not necessarily portend low ventricular arrhythmia risk, particularly in patients with high-risk clinical features. **(*Circulation*. 2016;133:622-630. DOI: 10.1161/CIRCULATIONAHA.115.017885.)**

and therefore of limited clinical utility. Our observations are consistent with a prior single-center study in an independent group of 108 patients by Makimoto et al.[28] Thus, in patients with Brugada syndrome undergoing electrophysiology study, we submit that programmed ventricular stimulation is most informative when limited to protocols including up to double extrastimuli.

Lethal Cardiac events in Japanese Brugada Registry



Kamakura S, Shimizu W, et al: Circ. Arrhythmia and Electrophysiol 2009;2:495-503

Journal of the American Heart Association

SYSTEMATIC REVIEW AND META-ANALYSIS

Does the Age of Sudden Cardiac Death in Family Members Matter in Brugada Syndrome?

Pattara Rattanawong, MD; Jakrin Kewcharoen, MD; Chanavuth Kanitsoraphan, MD; Timothy Barry, MD; Anusha Shanbhag, MD; Nway L. Ko Ko, MD; Wasawat Vutthikraivit, MD; Madhurima Home, MD; Pradyumna Agasthi, MD; Hasan Ashraf, MD; Wataru Shimizu, MD, PhD; Win-Kuang Shen, MD

BACKGROUND: Brugada syndrome is an inherited cardiac channelopathy associated with major arrhythmic events (MAEs). The presence of a positive family history of sudden cardiac death (SCD) as a risk predictor of MAE remains controversial. We aimed to examine the association between family history of SCD and MAEs stratified by age of SCD with a systematic review and meta-analysis.

METHODS AND RESULTS: We searched the databases of MEDLINE and EMBASE from January 1992 to January 2020. Data from each study were combined using the random-effects model. Fitted metaregression was performed to evaluate the association between the age of SCD in families and the risk of MAE. Twenty-two studies from 2004 to 2019 were included in this meta-analysis involving 3386 patients with Brugada syndrome. The overall family history of SCD was not associated with increased risk of MAE in Brugada syndrome (pooled odds ratio [OR], 1.11; 95% CI, 0.82–1.51; P=0.489, I^2=45.0%). However, a history of SCD in family members of age younger than 40 years of age did increase the risk of MAE by ≈2-fold (pooled OR, 2.03; 95% CI, 1.11–3.73; P=0.022, I^2=0.0%). When stratified by the age of cut point at 50, 45, 40, and 35 years old, a history of SCD in younger family member was significantly associated with a higher risk of MAE (pooled OR, 0.49, 1.30, 1.51, and 2.97, respectively; P=0.046).

CONCLUSIONS: A history of SCD among family members of age younger than 40 years was associated with a higher risk of MAE.

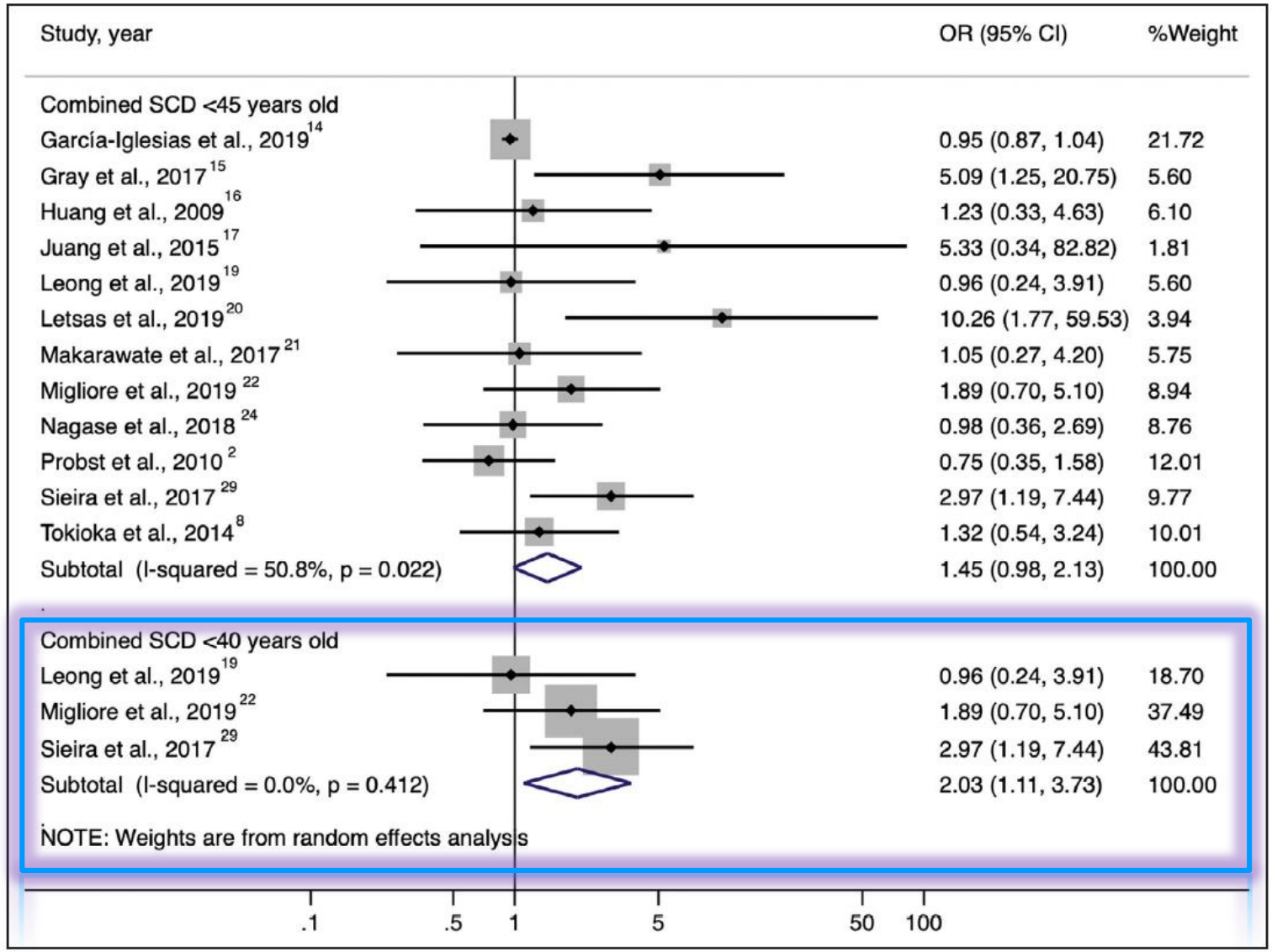


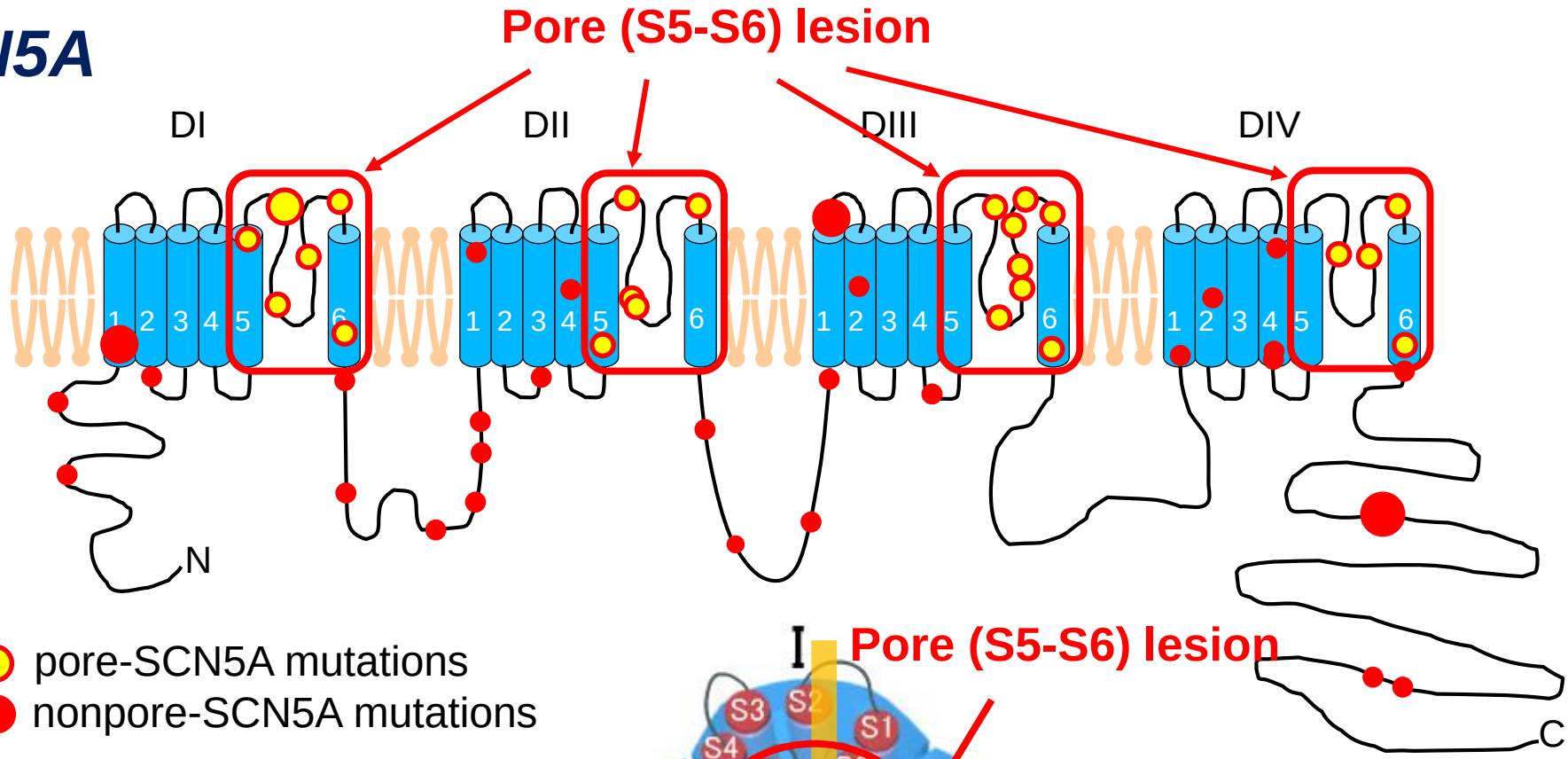
Figure 3. Forest plot demonstrating the association of family history of sudden cardiac death at age <45 and <40 years old and major arrhythmic event in patients with Brugada syndrome.

OR indicates odds ratio; and SCD, sudden cardiac death.

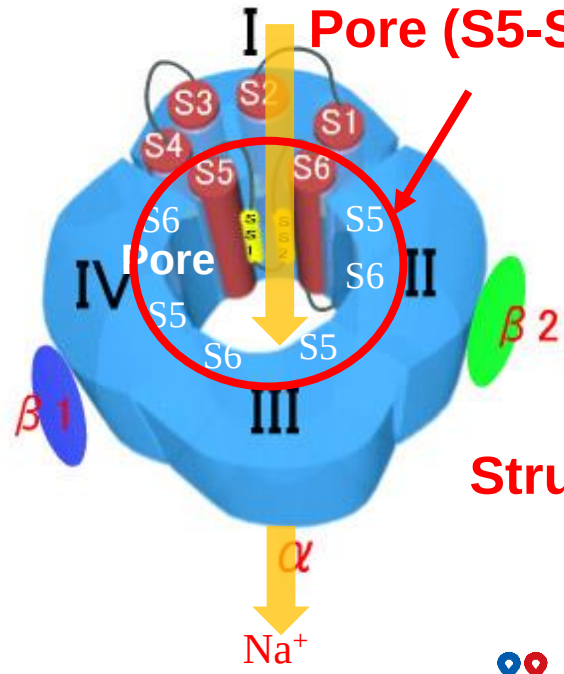
Ion Channel Defect Responsible for Brugada Syndrome

Loci	Chromosome	Gene	Ion Channel
BrS1	3 (3p 21-24)	*SCN5A*	I_{Na} ↓
BrS2	3 (3p21)	*GPD1-L*	I_{Na} ↓
BrS3	12 (12p13.3)	*CACNA1C*	$I_{Ca\text{-}L}$ ↓
BrS4	10 (10P12.33)	*CACNB2*	$I_{Ca\text{-}L}$ ↓
BrS5	19 (19q13.1)	*SCN1B*	I_{Na} ↓
BrS6	11 (11q13-q14)	*KCNE3*	I_{to} ↑
BrS7	11 (11q23.3)	*SCN3B*	I_{Na} ↓
BrS8	12 (12p11.23)	*KCNJ8*	$I_{K\text{-}ATP}$ ↑
BrS9	7 (7q21-q22)	*CACNA2D1*	$I_{Ca\text{-}L}$ ↓
BrS10	1 (1p13.3)	*KCND3*	I_{to} ↑
BrS11	17 (17p13.1)	*MOG1*	I_{Na} ↓
BrS12	3 (3p21.2-p14.3)	*SLMAP*	I_{Na} ↓
BrS14	11 (11q23)	*SCN2B*	I_{Na} ↓

SCN5A



- pore-SCN5A mutations
- nonpore-SCN5A mutations



Structure of Na channel

Genotype-Phenotype Correlation of *SCN5A* Mutations for the Clinical and Electrocardiographic Characteristics of Probands with Brugada Syndrome: A Japanese Multicenter Registry

Japanese Brugada Multicenter Registry

by the Minister of Health, Labour and Welfare

Circulation 2017; 135(23): 2255-2270

Kenichiro Yamagata,
Minoru Horie, Takeshi Aiba, Satoshi Ogawa, Yoshifusa Aizawa, Tohru Ohe, Masakazu Yamagishi, Naomasa Makita, Harumizu Sakurada, Toshihiro Tanaka, Akihiko Shimizu, Nobuhisa Hagiwara, Ryoji Kishi, Yukiko Nakano, Masahiko Takagi, Takeru Makiyama, Seiko Ohno, Keiichi Fukuda, Hiroshi Watanabe, Hiroshi Morita, Kenshi Hayashi, Kengo Kusano, Shiro Kamakura, Satoshi Yasuda, Hisao Ogawa, Yoshihiro Miyamoto, Jamie D. Kapplinger, Michael J. Ackerman,
Wataru Shimizu

National Cerebral and Cardiovascular Center

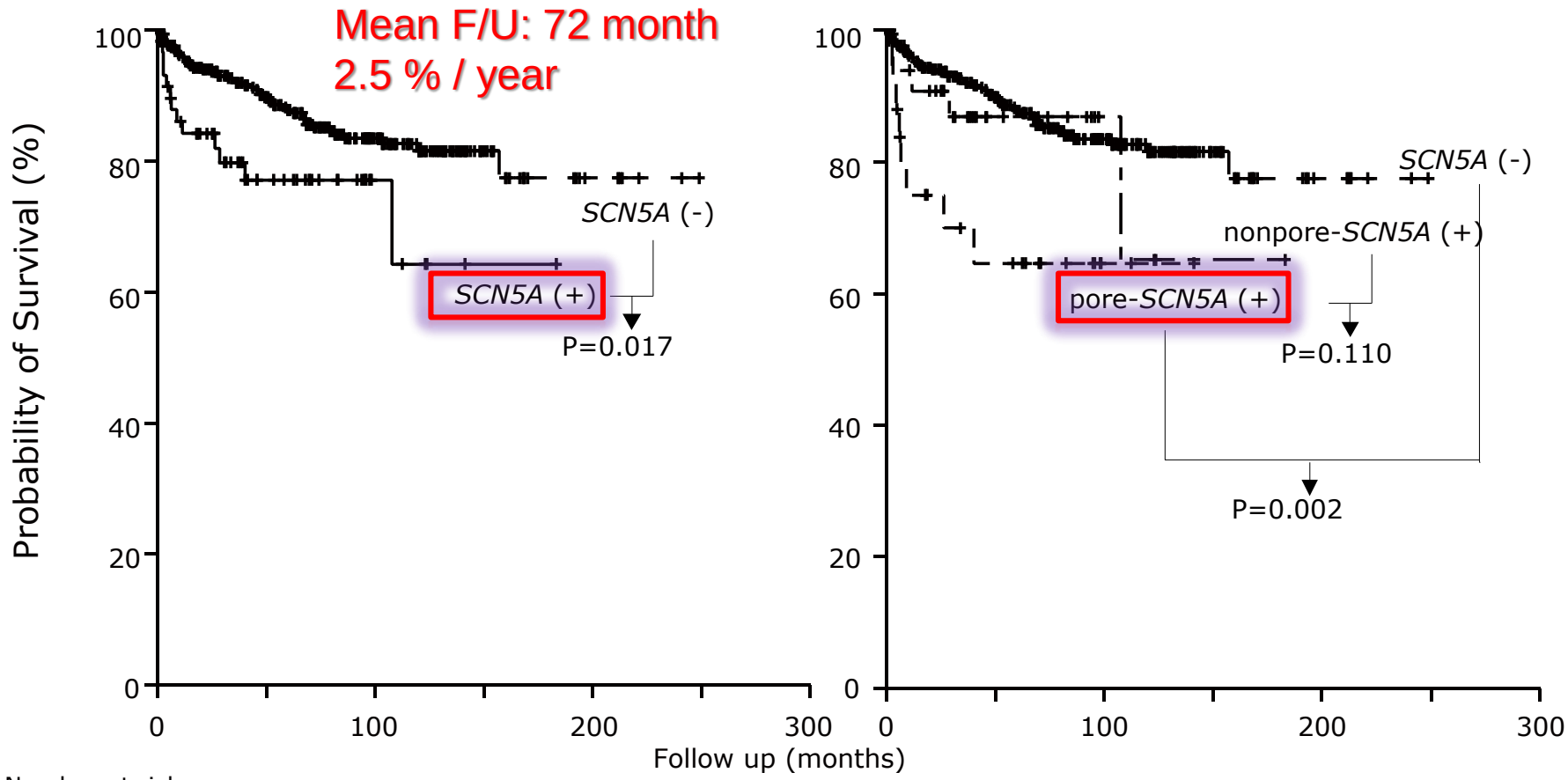
Population

- 415 Brugada probands
  (M: 403 pts, Average age: 46 y.o.)

- *SCN5A* mutation
  Positive 60 pts (14%): *SCN5A*(+)
  Negative 355 pts (86%): *SCN5A*(−)

Overall Survival among All 415 probands

(Yamagata K, Shimizu W, et al: Circulation 2017; 135(23): 2255-2270)



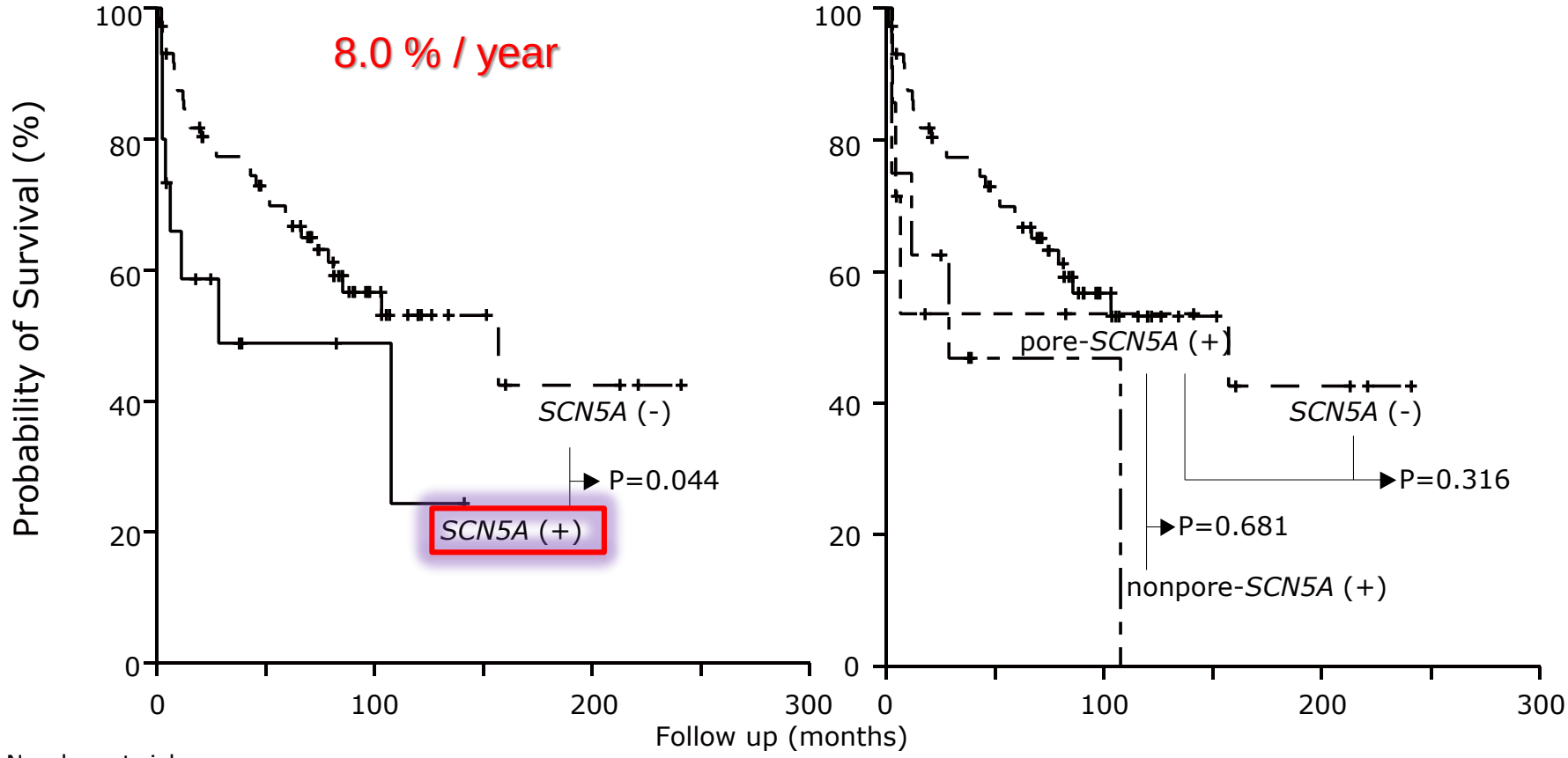
Number at risk

SCN5A(-)	355	236	108	26	7	0
SCN5A(+)	60	25	6	1	0	0

SCN5A(-)	355	236	108	26	7	0
nonpore-*SCN5A*(+)	35	13	4	1	0	0
pore-*SCN5A*(+)	25	12	2	0	0	0

Overall Survival among 88 ACA probands

(Yamagata K, Shimizu W, et al: Circulation 2017; 135(23): 2255-2270)



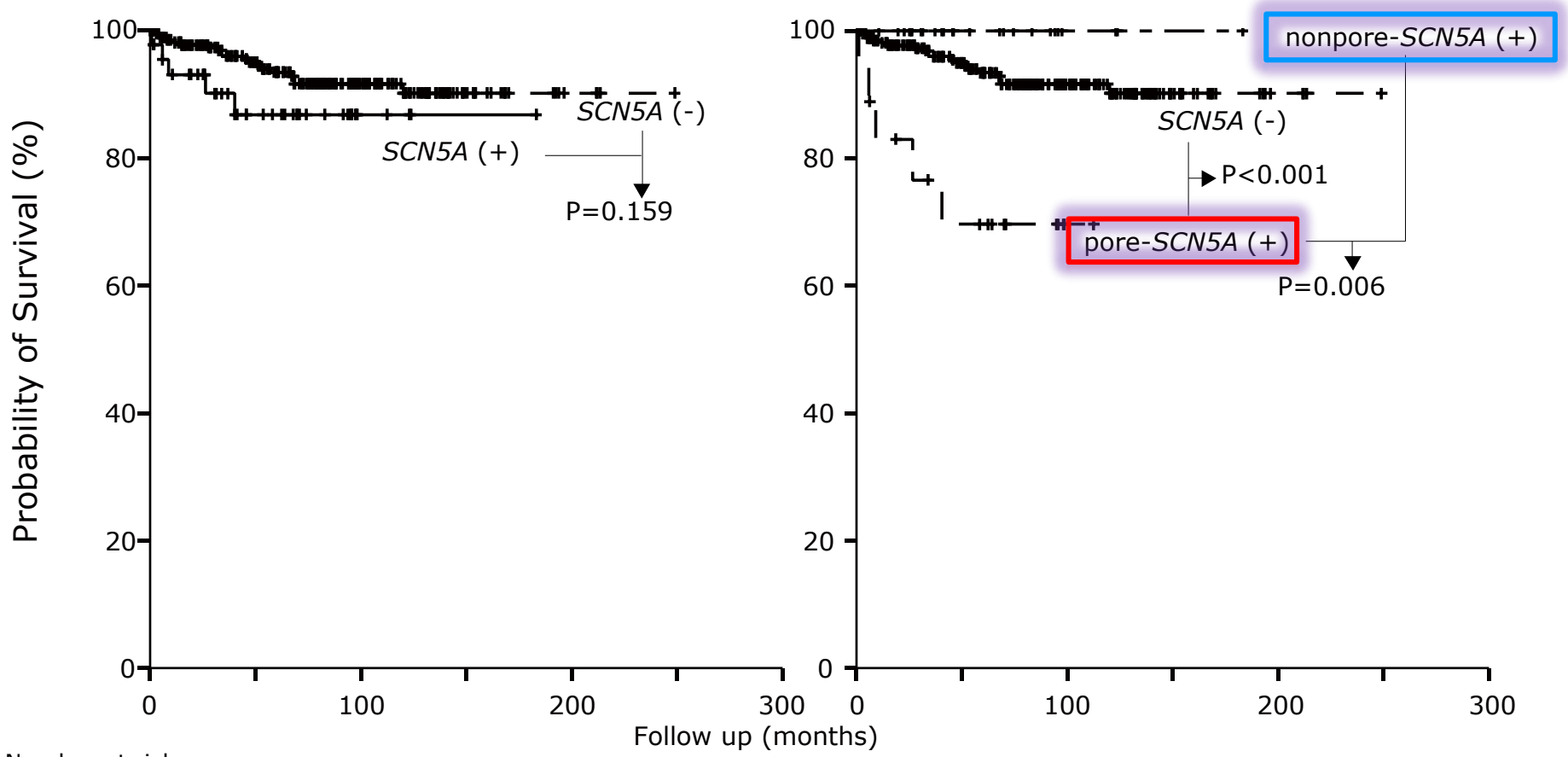
Number at risk

SCN5A(-)	73	46	17	6	3	0
SCN5A(+)	15	3	2	0	0	0

SCN5A(-)	73	46	17	6	3	0
nonpore-*SCN5A*(+)	8	1	1	0	0	0
pore-*SCN5A*(+)	7	2	1	0	0	0

Overall Survival among 327 non-ACA probands (Syncope + Asymptomatic)

(Yamagata K, Shimizu W, et al: Circulation 2017; 135(23): 2255-2270)



Number at risk

SCN5A(-)	282	190	91	20	4	0
SCN5A(+)	45	20	4	1	0	0

SCN5A(-)	282	190	91	20	4	0
nonpore-*SCN5A*(+)	27	12	3	1	0	0
pore-*SCN5A*(+)	18	10	1	0	0	0

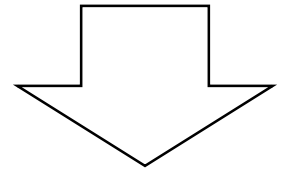
Multivariate Analyses
Comparing *SCN5A* (+) vs. *SCN5A* (-)

(Yamagata K, Shimizu W, et al: Circulation 2017; 135(23): 2255-2270)

	Hazard Ratio	95% CI	P value
History of ACA	6.46	3.79-11.02	<0.001
***SCN5A* mutation**	1.96	1.01-3.78	0.045
QRS V2 ≥ 120 ms	1.43	0.76-2.71	0.268
Atrial fibrillation	0.96	0.52-1.77	0.895

Conclusions

- **Probands with *SCN5A*-mediated BrS exhibited higher risk for future cardiac events.**
- **Probands with no history with ACA seems to be at high risk only if the *SCN5A* mutation is located in the pore region.**



- **Genetic screening may be useful in Brugada syndrome probands.**

ESC European Society of Cardiology

European Heart Journal (2021) **42**, 2854–2863
doi:10.1093/eurheartj/ehab254

TRANSLATIONAL RESEARCH
Arrhythmias

Functionally validated *SCN5A* variants allow interpretation of pathogenicity and prediction of lethal events in Brugada syndrome

Taisuke Ishikawa [1†], Hiroki Kimoto[2†], Hiroyuki Mishima[3], Kenichiro Yamagata [4], Soshiro Ogata[5], Yoshiyasu Aizawa [6], Kenshi Hayashi [7], Hiroshi Morita [8], Tadashi Nakajima [9], Yukiko Nakano[10], Satoshi Nagase[11], Nobuyuki Murakoshi[12], Shinya Kowase [13], Kimie Ohkubo[14], Takeshi Aiba[15], Shimpei Morimoto [16], Seiko Ohno[17], Shiro Kamakura[4], Akihiko Nogami [12], Masahiko Takagi[18], Matilde Karakachoff[19], Christian Dina [20], Jean-Jacques Schott [20], Koh-Ichiro Yoshiura[3], Minoru Horie [21], Wataru Shimizu [22], Kunihiro Nishimura[5], Kengo Kusano [4], and Naomasa Makita [1*]

Flowchart of the Study

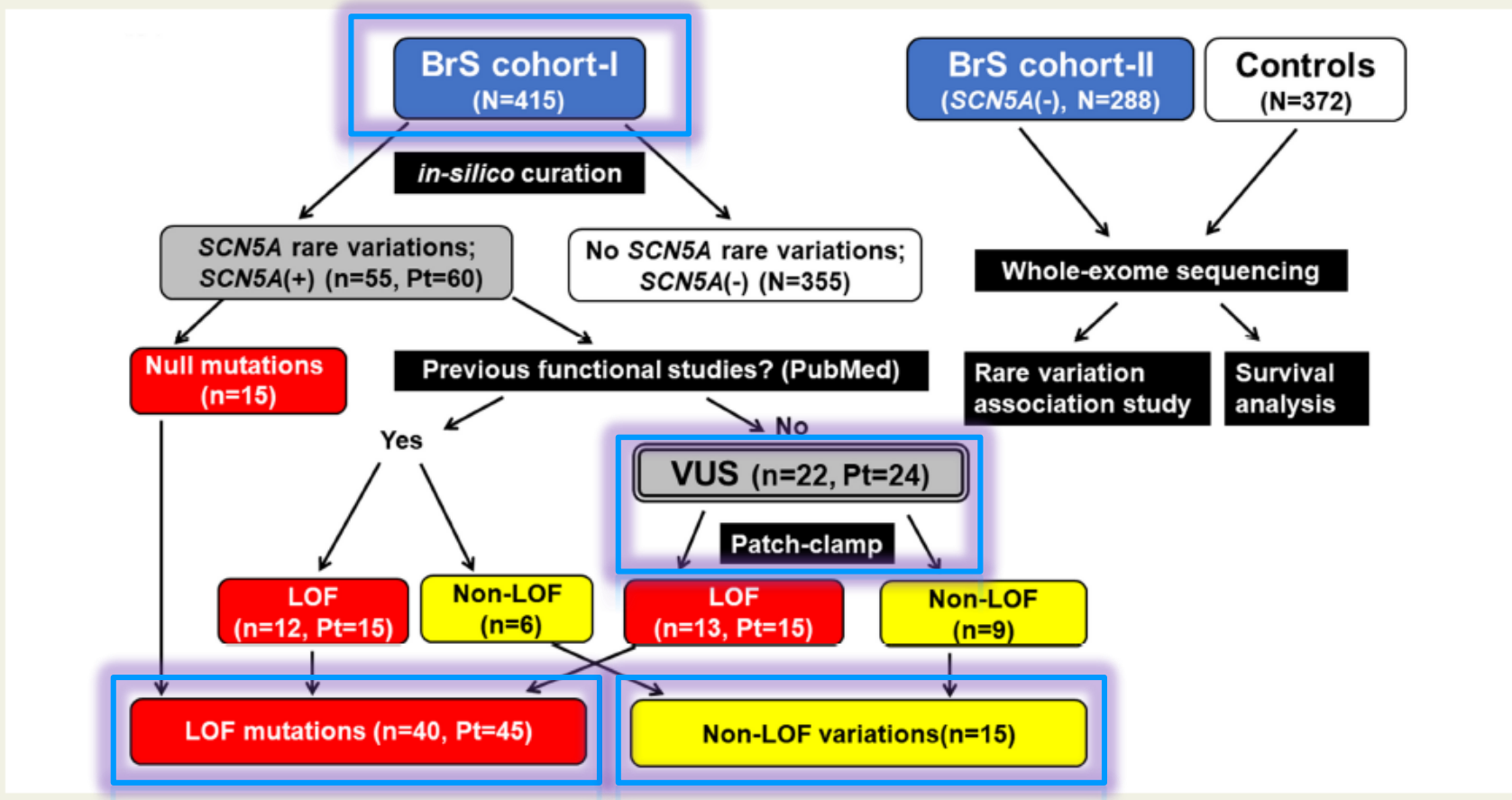
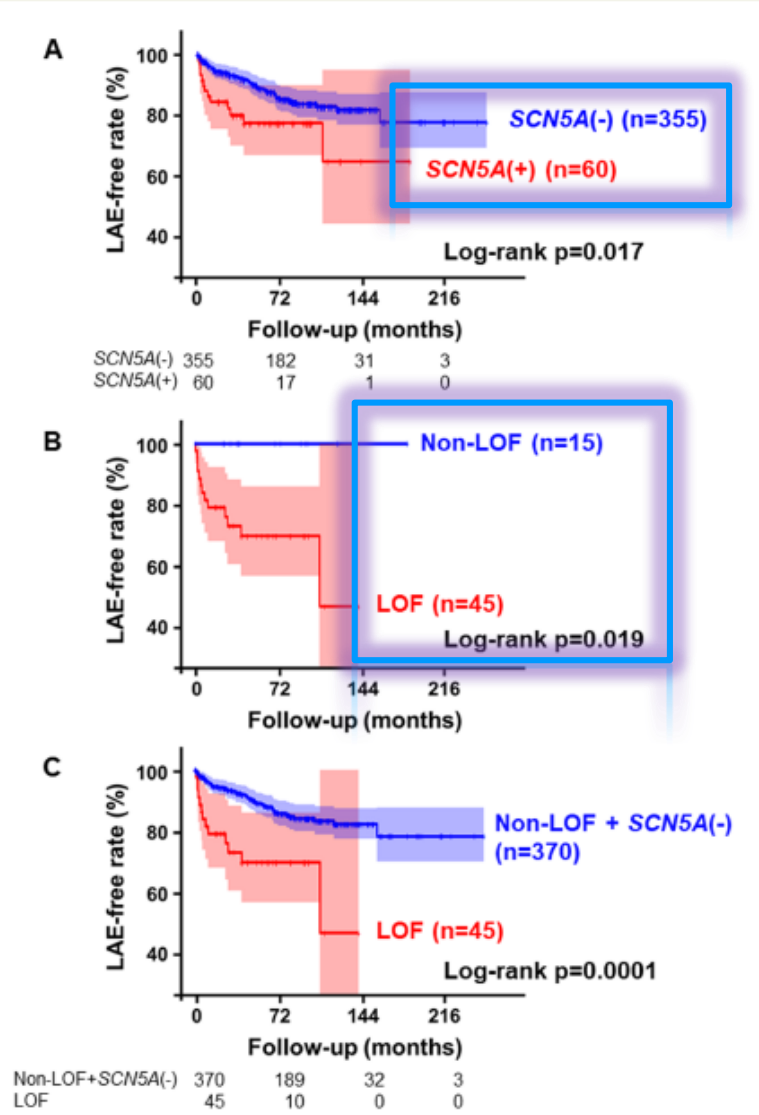


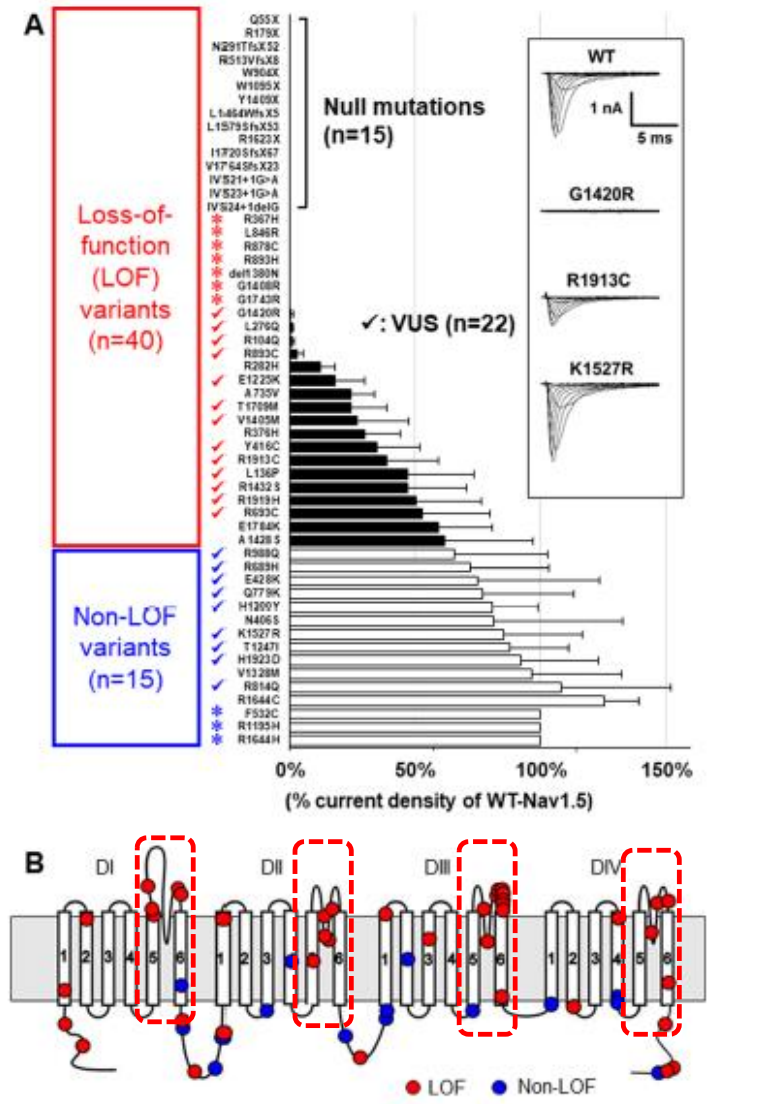
Figure 1 Flowchart of this study. Patients of Brugada syndrome (BrS) cohort-I were assigned to groups of loss-of-function (LOF) *SCN5A* mutation carriers ($N = 45$), non-loss-of-function *SCN5A* variation carriers ($N = 15$), and *SCN5A*-mutation negative patients (*SCN5A*(-), $N = 355$) by *in silico* curation, PubMed search and functional evaluation using patch clamp. Numbers of unique variations (n) and patients (Pt) are shown where a duplication was identified. Brugada syndrome cohort-II consists of independent Brugada syndrome probands carrying no *SCN5A* rare variations.

Eur Heart J 2021; 42: 2854-2863

Lethal arrhythmic event-free survival



Functional classification and location of 55 *SCN5A* variants



Eur Heart J 2021; 42: 2854-2863

Predictors for Lethal Cardiac Events in Brugada Syndrome

(Revised)

Evidence Level B (A)

- **VF, Aborted Cardiac Arrest (10% of recurrence of VF)**
- **Syncope**
- **Spontaneous Type 1 ECG**
- **Male**
- **Induction of VF with up to 2 ventricular extrastimuli**
  (Sroubek J, et al. Circulation. 2016;133:622-30.)
- **FH of SCD**
  (Rattanawong P, et al. JAHA. 2021;10:e019788.)
- ***SCN5A* mutation**
  (Yamagata K, et al. Circulation. 2017;135:2255-2270.)

Evidence Level C

- **Late Potential in SAECG**
- **Atrial fibrillation etc.**

Conclusions: Brugada syndrome

(1) The diagnosis of Brugada syndrome is an electrocardiographic diagnosis.

(2) The annual rate of recurrence of VF in Brugada patients with a history of VF/ACA is approximately 10%, strongly suggesting the indication of ICD (Class 1, Secondary prevention).

(3) The indication of ICD for Primary prevention in Brugada patients with a history of syncope and asymptomatic patients is determined in consideration of clinical findings (Syncope, FH of SCD, Induction of VF, *SCN5A* mutation) and/or electrocardiographic findings (QRS spike, ER pattern, etc).

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- Shiga Univ. School of Medical Science
  - Minoru Horie, Seiko Ohno
  - Hiroshi Matsuura, Futoshi Toyoda
- Keio University
  - Keiichi Fukuda, Satoshi Ogawa
  - Shinsuke Yuasa, Yoshiyasu Aizawa
- Nagasaki University
  - Naomasa Makita
- Tokyo Medical and Dental University
  - Tetsushi Furukawa
  - Toshihiro Tanaka
- Niigata University
  - Hiroshi Watanabe, Yoshifusa Aizawa
- Tokyo Womens Medical University
  - Nobuhisa Hagiwara
- Nihon University
  - Naokata Sumitomo
- Kanazawa University
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  - Akihiro Sekine
  - Isao Shiraishi
  - Hisaki Makimoto
  - Hiro Kawata
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Thank you for your attention