Original Article

Investigation and treatment of pulmonary embolism as a potential etiology may be important to improve post-resuscitation prognosis in non-shockable out-of-hospital cardiopulmonary arrest: report on an analysis of the SOS-KANTO 2012 study

SOS-KANTO 2012 Study Group

Background: The prognosis of non-shockable out-of-hospital cardiac arrest is worse than that of shockable out-of-hospital cardiac arrest. We investigated the associations between the etiology and prognosis of non-shockable out-of-hospital cardiac arrest patients who experienced the return of spontaneous circulation after arriving at hospital.

Methods and Results: All subjects were extracted from the SOS-KANTO 2012 study population. The subjects were 3,031 adults: (i) who had suffered out-of-hospital cardiac arrest, (ii) for whom there were no pre-hospital data on ventricular fibrillation/pulseless ventricular tachycardia until arrival at hospital, (iii) who experienced the return of spontaneous circulation after arriving at hospital. We compared the patients' prognosis after 1 and 3 months between various etiological and presumed cardiac factors. The proportion of the favorable brain function patients that developed pulmonary embolism or incidental hypothermia was significantly higher than that of the patients with presumed cardiac factors (1 month, $P < 0.0001$ and $P < 0.0001$, respectively; 3 months, $P = 0.0018$ and $P < 0.0001$, respectively). In multiple logistic regression analysis, pulmonary embolism and incidental hypothermia were found to be significant independent prognostic factors for 1- and 3-month survival and the favorable brain function rate.

Conclusions: In patients who suffer non-shockable out-of-hospital cardiac arrest, but who experience the return of spontaneous circulation after arriving at hospital, the investigation and treatment of pulmonary embolism as a potential etiology may be important for improving post-resuscitation prognosis.

Key words: Cardiopulmonary arrest, cardiopulmonary resuscitation, non-shockable OHCA, out-of-hospital cardiac arrest (OHCA), pulmonary embolism

BACKGROUND

THE FREQUENCY OF the return of spontaneous circulation (ROSC) is lower after non-shockable out-of-hospital cardiopulmonary arrest (non-shockable OHCA), such as pulseless electrical activity (PEA) and asystole, than after ventricular fibrillation (VF)/pulseless ventricular tachycardia (VT)-related shockable out-of-hospital cardiopulmonary arrest (shockable OHCA), and hence, non-shockable OHCA exhibits a worse prognosis.^{1,2} It has been suggested that early electrical defibrillation might be important for

achieving ROSC after shockable OHCA.² After ROSC, it is relatively easy to determine whether a cardiac arrest has been caused by a disease with a clear VF-/pulseless VT-associated mechanism, such as acute coronary syndrome (ACS), long QT syndrome, and various electrolyte abnormalities, and it has been suggested that etiology-based treatment might lead to improvements in the prognosis of cardiac arrest patients.³

Whereas electrical defibrillation is used to treat shockable OHCA, there are no specific treatments for the management of non-shockable OHCA. Therefore, to restore the heart beat and improve prognosis, in many cases it might be necessary to investigate/overcome the cause of the cardiopulmonary arrest.^{2,4} As few diagnostic procedures can be carried out during cardiopulmonary resuscitation (CPR), it might be impossible to identify the etiology of non-shockable OHCA, except in cases in which the etiology is initially clear, such as those involving trauma or suffocation, which would affect the chance of the ROSC being achieved.

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In addition, even after ROSC has occurred, non-shockable OHCA itself is not indicative of particular etiological factors; therefore, the underlying causes of OHCA should be investigated to aid treatment.⁴ In the 2010 resuscitation guidelines, it is recommended that therapeutic hypothermia and early reperfusion therapy for ST-segment elevation myocardial infarction should be carried out during post-advanced cardiovascular life support–resuscitation care.⁵ However, it is unclear whether these procedures are sufficient in patients with non-shockable OHCA, whose etiologies can differ.

As specific etiology-based treatments might improve prognosis, it is important to examine the associations between etiology and prognosis in patients with non-shockable OHCA based on current treatments. Accordingly, patients in whom the etiology of non-shockable OHCA cannot be definitively determined might have a poor prognosis.

The purpose of this study was to clarify the association between the causes of non-shockable OHCA and prognosis after 1 and 3 months in patients who had ROSC after suffering a non-shockable OHCA compared with unknown etiology.

METHODS

Study design

THE PRESENT STUDY analyzed the data from the SOS-KANTO 2012 study. The SOS-KANTO 2012 study was a prospective survey that aimed to collect the pre-/in-hospital data and follow-up records of cardiac arrest patients who were admitted to 67 emergency hospitals in the Kanto region between January 2012 and March 2013.⁶ This study was approved by the institutional review boards of all 67 institutions, which waived the requirement for informed patient consent to ensure the anonymity of the participants, which is stipulated in the guidelines for such studies produced by the Japanese government.⁶

Subjects

Of 16,452 patients for whom 3-month prognostic data were collected in the SOS-KANTO 2012 study, we excluded those who were aged 17 years or younger, those who suffered in-hospital cardiopulmonary arrest, those that were shocked with an automated external defibrillator by a bystander, those with cardiopulmonary arrest in whom there were records on VF/pulseless VT or electric shock by the emergency medical staff until arrival to hospital, those in whom ROSC was achieved until arrival, and those in whom the ROSC was not achieved after arrival, which resulted in 3,031 patients being included in this study (Fig. 1). Diagnostic procedures for

identifying the etiology of cardiopulmonary arrest might have been carried out more thoroughly in patients in whom the ROSC was achieved. Thus, this study only included patients in whom the ROSC was achieved after arrival for non-shockable OHCA.

Definitions and data collection

Cardiac arrest was defined as the cessation of cardiac mechanical activity; that is, the absence of a detectable pulse, responsiveness, and normal breathing.^{7,8} All cardiac arrest patients who were transported to the participating hospitals by emergency medical service (EMS) providers were included in the SOS-KANTO 2012 study.⁶ Pre- and in-hospital treatments were generally delivered by EMS personnel, physicians, and other healthcare providers in line with the national guidelines of the Japan Resuscitation Council, which are based on the international guidelines.⁹ The EMS providers collected pre-hospital information in the standardized Utstein style:^{7,8} the sex and age of the patients, the initial cardiac rhythm, and the time course of resuscitation. The latter included the time at which CPR was started by a bystander or EMS, the presence or absence of VF/pulseless VT, whether electrical shocking was carried out by the EMS providers, and the time of arrival at hospital. Additional information including whether the cardiac arrest was witnessed by a bystander, whether a bystander initiated CPR, and whether spontaneous circulation was restored before the patient arrived at hospital was also collected. The quality of CPR could not be assessed.

The causes of cardiac arrest were determined by the attending physicians caring for the patients in accordance with the SOS-KANTO 2012 survey form, which was produced in the standardized Utstein style.^{7,8} According to this classification, the patients were diagnosed with cardiac arrest due to a presumed cardiac factor (PCF) unless an obvious non-cardiac etiology, acute coronary syndrome (ACS), or a definite cardiogenic factor other than ACS was observed. So, patients that suffered cardiac arrests with no definitive etiology were classified into the PCF group. Non-cardiac etiologies were classified into extrinsic non-cardiogenic factors (trauma, burns, incidental hypothermia, hanging, drowning, suffocation, and poisoning), intrinsic non-cardiogenic factors (pulmonary embolism, acute aortic dissection, aortic aneurysmal rupture, subarachnoid hemorrhaging, and bronchial asthma), and other non-cardiogenic factors, including many minor etiological factors (e.g., sepsis, anaphylaxis).

Neurological outcomes were evaluated and reported using the Cerebral Performance Categories (CPC) scale, and responses were scored as follows: category 1, good cerebral performance; category 2, moderate cerebral disability; cat-

Fig. 1. Selection of study subjects. Of 16,452 patients for whom 3-month prognostic data were collected in the SOS-KANTO 2012 study, 3,031 subjects were extracted for this study after excluding those who were aged 17 years or younger, those who suffered an in-hospital cardiopulmonary arrest, those who were shocked with an automated external defibrillator (AED) by a bystander, those with cardiopulmonary arrest in whom there were records on pulseless ventricular tachycardia (VT)/ventricular fibrillation (VF) or electric shocks until arrival to hospital, those in whom the return of spontaneous circulation (ROSC) occurred before their arrival at hospital, and those in whom ROSC was not achieved after arrival. The numbers of patients that were followed-up at 1 and 3 months and that showed each etiological factor are shown. OHCA, out-of-hospital cardiac arrest.

egory 3, severe cerebral disability; category 4, coma/vegetative state; category 5, brain death/death.^{7,8,10}

Classification and analysis of each etiological factor and prognosis

The subjects were grouped based on the etiological factors for cardiopulmonary arrest identified by the attending physicians after arrival according to the abovementioned SOS-KANTO 2012 Study classification (Fig. 1). The 1- and 3-month survival rates (CPC 1–4) and the proportion of patients who had favorable brain function (CPC 1–2) at these time points were compared between each group and a group of patients who showed PCF, but whose etiologies were unclear. In addition, multiple logistic regression analysis was carried out using the background and etiological factors as explanatory variables.

Statistics

We used StatFlex version 6.0 (Artech, Osaka, Japan) for all statistical analyses. Continuous variables are expressed as

mean $\pm$ SD values, and were compared using the Mann–Whitney *U*-test. When comparing discrete variables between two groups, the χ^2 -test was used, and Fisher's exact test was used when the number of samples was low. The independence of prognostic predictors was tested using multiple logistic regression analysis. *P*-values of <0.05 were regarded as statistically significant.

RESULTS

IN TOTAL, 3,031 patients were included in this study (Fig. 1), and the subjects' background data are presented in Table 1. The results of analyses are presented in Figures 2 and 3. The 1- and 3-month survival rates of the incidental hypothermia group were significantly higher than those of the PCF group, respectively (1 month: 50.0 vs. 3.1%, respectively, $P < 0.0001$; 3 months: 35.7 vs. 1.8%, respectively, $P < 0.0001$) (Fig. 2). In addition, body temperature on arrival at hospital were significantly lower in incidental hypothermia group than in others ($26.8 \pm 3.2^\circ\text{C}$ vs. $35.1 \pm 1.9^\circ\text{C}$, $P < 0.0001$). The 1-month survival rate of the

Table 1. Background data of subjects extracted from the SOS-KANTO 2012 study population

Number of patients	3,031
Age, years	73.0 ± 15.5
Female/male ratio	0.69
Presence of a witness	1,934 (63.8%)
CPR performed by a bystander	1,096 (36.2%)
Interval from the start of CPR by a bystander or EMS until arrival, min	22.1 ± 9.2
Interval from arrival until the ROSC, min	15.6 ± 11.5
1-month survival	124 (4.1%)
CPC 1–2 after 1 month	33 (1.1%)
3-month survival	70 (2.3%)
CPC 1–2 after 3 month	27 (0.9%)

Data are shown as absolute values, mean ± SD values, or ratios. CPC, Cerebral Performance Categories; CPR, cardiopulmonary resuscitation; EMS, emergency medical service; ROSC, return of spontaneous circulation.

suffocation group was significantly higher than that of the PCF group (5.8 vs. 3.1%, respectively, $P = 0.0170$) (Fig. 2). Concerning intrinsic non-cardiogenic factors, the 1- and 3-month survival rates of the pulmonary embolism group were significantly higher than those of the PCF group (1 month: 25.0 vs. 3.1%, respectively, $P < 0.0001$; 3 months: 15.0 vs. 1.8%, respectively, $P = 0.0002$) (Fig. 2). The proportions of patients who maintained favorable brain function at 1 and 3 months were significantly higher in the incidental hypothermia group than in the PCF group (1 month: 28.6 vs. 0.6%, respectively, $P < 0.0001$; 3 months: 28.6 vs. 0.4%, respectively, $P < 0.0001$) (Fig. 3). In the pulmonary embolism group, the proportions of patients who maintained favorable brain function after 1 and 3 months were also significantly higher than in the PCF group (1 month: 15.0 vs. 0.6%, respectively, $P < 0.0001$; 3 months: 7.5 vs. 0.4%, respectively, $P = 0.0018$) (Fig. 3).

Table 2 shows the background data in each etiological group that was associated with significant differences in the

* $P = 0.0170$, ** $P = 0.0002$, *** $P < 0.0001$, vs. PCF

Fig. 2. Survival rate after the return of spontaneous circulation according to the etiology of non-shockable out-of-hospital cardiac arrest. * $P = 0.0170$, ** $P = 0.0002$, *** $P < 0.0001$, vs. presumed cardiac factors (PCF).

* $P = 0.0018$, ** $P < 0.0001$, vs. PCF

Fig. 3. Frequency of favorable brain function (a Cerebral Performance Categories scale score of 1–2) after the return of spontaneous circulation according to the etiology of non-shockable out-of-hospital cardiac arrest. * $P = 0.0018$, ** $P < 0.0001$, vs. presumed cardiac factors (PCF).

Table 2. Relationships between background factors and etiological factors that were associated with significant differences in the 1-month survival rate, the presumed cardiac factor (PCF) group, and acute coronary syndrome (ACS) group in patients with out-of-hospital cardiopulmonary arrest

	PCF (n = 962)	Incidental hypothermia (n = 14)	Suffocation (n = 450)	Pulmonary embolism (n = 40)	ACS (n = 160)
Age, years	76.5 ± 12.7	66.5 ± 15.0**	77.3 ± 13.2	60.4 ± 16.9****	75.7 ± 12.0
Female/male ratio	0.694	0.750	0.737	1.667**	0.538
Presence of a witness, %	59.7	35.7	80.4****	75.0	65.0
CPR performed by a bystander, %	35.9	28.6	48.7****	30.0	35.6
Interval from the start of CPR by a bystander or EMS until arrival, min	22.4 ± 9.0	15.6 ± 11.3**	23.6 ± 9.2*	16.2 ± 9.3***	21.8 ± 10.6
Interval from arrival until the ROSC, min	16.1 ± 9.9	22.1 ± 17.3	14.3 ± 8.8****	21.7 ± 15.9	17.8 ± 11.0

Data are shown as mean ± SD values, ratios, or percentages. * $P = 0.0208$, ** $P = 0.0068$, *** $P = 0.0014$, **** $P < 0.0001$, vs. PCF. CPR, cardiopulmonary resuscitation; EMS, emergency medical service; ROSC, return of spontaneous circulation.

Table 3. Multiple logistic regression analysis of factors affecting 1- and 3-month survival in patients with non-shockable out-of-hospital cardiopulmonary arrest

Explanatory variables	1-month survival		3-month survival	
	Odds ratio	95% CI	Odds ratio	95% CI
Female	1.294	0.866–1.934	1.236	0.726–2.105
Age, $\Delta= +10$ years	<u>0.853</u>	<u>0.758–0.959</u>	<u>0.796</u>	<u>0.683–0.923</u>
Presence of witness	1.072	0.689–1.666	1.169	0.644–2.123
CPR performed by a bystander	0.827	0.540–1.267	0.823	0.466–1.454
Interval from start of CPR until arrival, $\Delta= +5$ min	<u>0.644</u>	<u>0.571–0.728</u>	<u>0.584</u>	<u>0.495–0.689</u>
Interval from arrival until ROSC, $\Delta= +5$ min	0.940	0.877–1.006	0.954	0.866–1.050
Acute coronary syndrome	1.835	0.842–4.001	1.655	0.561–4.876
<u>Pulmonary embolism</u>	<u>6.094</u>	<u>2.592–14.328</u>	<u>6.160</u>	<u>2.178–17.424</u>
<u>Incidental hypothermia</u>	<u>23.050</u>	<u>6.972–76.205</u>	<u>26.807</u>	<u>7.247–99.167</u>
<u>Suffocation</u>	<u>2.582</u>	<u>1.562–4.268</u>	<u>2.810</u>	<u>1.443–5.472</u>

The underlined explanatory variables are statistically significant; i.e., independent predictive variables. CI, confidence interval; CPR, cardiopulmonary resuscitation; ROSC, return of spontaneous circulation.

Table 4. Multiple logistic regression analysis of the factors affecting favorable brain function at 1 or 3 months (Cerebral Performance Categories 1–2) in patients with out-of-hospital cardiopulmonary arrest

Explanatory variables	1-month survival		3-month survival	
	Odds ratio	95% CI	Odds ratio	95% CI
Female	1.321	0.610–2.862	0.895	0.368–2.177
Age, $\Delta= +10$ years	<u>0.784</u>	<u>0.630–0.975</u>	<u>0.720</u>	<u>0.571–0.908</u>
Presence of witness	1.463	0.598–3.577	1.261	0.479–3.318
CPR performed by a bystander	1.121	0.494–2.541	1.227	0.495–3.045
Interval from start of CPR until arrival, $\Delta= +5$ min	<u>0.580</u>	<u>0.458–0.736</u>	<u>0.570</u>	<u>0.436–0.745</u>
Interval from arrival until ROSC, $\Delta= +5$ min	1.022	0.887–1.178	1.030	0.882–1.203
Acute coronary syndrome	2.557	0.708–9.237	3.340	0.892–12.506
<u>Pulmonary embolism</u>	<u>10.805</u>	<u>3.557–32.823</u>	<u>5.702</u>	<u>1.344–24.192</u>
<u>Incidental hypothermia</u>	<u>30.335</u>	<u>7.465–123.261</u>	<u>48.125</u>	<u>11.296–205.032</u>
<u>Suffocation</u>	0.806	0.180	1.068	0.232–4.914

The underlined explanatory variables are statistically significant; i.e., independent predictive variables. CI, confidence interval; CPR, cardiopulmonary resuscitation; ROSC, return of spontaneous circulation.

1-month survival rate, the PCF group, and ACS group. Because the background factors in other etiological groups did not influence prognosis, we did not analyze them. The mean ages of the pulmonary embolism and incidental hypothermia groups were significantly younger than those of the PCF group (60.4 ± 16.9 and 66.5 ± 15.0 vs. 76.5 ± 12.7 years, respectively, $P < 0.0001$ and $P = 0.0068$, respectively). In addition, the female-to-male patient ratio was significantly higher in the pulmonary embolism group than in the PCF group (1.67 vs. 0.69, respectively, $P = 0.0068$).

Furthermore, the interval from the start of CPR until arrival was significantly shorter in the pulmonary embolism and incidental hypothermia groups than in the PCF group (16.2 ± 9.3 and 15.6 ± 11.3 vs. 22.4 ± 9.0 min, respectively, $P = 0.0001$, $P = 0.0068$).

Results of multiple logistic regression analyses are shown in Tables 3 and 4. Age, the interval from the start of CPR until arrival, pulmonary embolism, incidental hypothermia, and suffocation were shown to be significant independent prognostic factors for the 1- and 3-month survival

rates after ROSC (Table 3) brain function at 1 and 3 months (Table 4).

DISCUSSION

THE PROGNOSIS OF non-shockable OHCA is worse than that of shockable OHCA.^{1,2} In many cases of non-shockable OHCA, it might be necessary to investigate and treat the etiology of the patient's condition to achieve ROSC.^{2,4} In the 2010 resuscitation guidelines,⁵ it is recommended that hypothermia therapy and early reperfusion therapy for ST-segment elevation myocardial infarction should be carried out during post-advanced cardiovascular life support–resuscitation care after the ROSC. However, it is unclear whether these procedures are sufficient.

In this study, the proportions of patients who showed favorable brain function after 1 or 3 months or survived for 1 or 3 months were significantly higher among ROSC patients that suffered non-shockable OHCA caused by pulmonary embolism or incidental hypothermia than among the PCF group, in other words, the unknown etiology group. Multivariate analysis showed that the abovementioned conditions were independent prognostic factors, as were age and the interval from the start of CPR until arrival. This suggests that non-shockable OHCA patients should be promptly transferred to hospital and that it is useful to clarify/manage the etiology of non-shockable OHCA even after the ROSC in order to improve patient prognosis.

However, there are some patients with non-shockable OHCA in whom the etiology of the condition is clear based on their clinical circumstances/course after arrival. In most of these cases, extrinsic factors are involved, and etiology-based therapy should be added to CPR, if possible, to achieve the ROSC.⁴ Of the etiological factors that were found to be associated with a better prognosis in this study, suffocation and incidental hypothermia might be representative conditions. In the patients that suffocated, airway management and artificial ventilation¹¹ were performed together with CPR. In those that suffered incidental hypothermia, rewarming¹² was carried out together with CPR. In addition, in patients with incidental hypothermia, the condition might help to protect the brain.¹¹ However, in most patients with non-shockable OHCA, the etiology of the condition is initially unclear after arrival, although it is speculated that non-shockable OHCA is associated with intrinsic factors. To achieve the ROSC, sufficient etiological investigations and CPR should be carried out,⁴ but such investigations are not always straightforward.

This study involved patients with non-shockable OHCA in whom the ROSC was achieved after arrival. However, with respect to intrinsic factors the 1- and 3-month survival rates

and the proportions of patients who showed favorable brain function after 1 and 3 months were significantly higher in the pulmonary embolism group than in the presumed cardiogenic group. From the results of the univariate analysis, the interval from the start of CPR by a bystander or EMS until arrival at hospital might have some effect on the prognosis of pulmonary embolism, but the multivariate analysis also showed that these parameters were independent prognostic factors. The results of this study were obtained under the 2010 guidelines for resuscitation, in which therapeutic hypothermia, the detection of acute coronary syndrome, especially ST elevation-type myocardial infarction, and reperfusion therapy are strongly recommended for non-shockable OHCA patients in whom ROSC and stable respiratory/circulatory state is achieved.⁵ If, for example, contrast-enhanced CT under a tentative diagnosis of pulmonary embolism and subsequent thrombolytic therapy/surgical or catheter-mediated thrombus removal are recommended for such patients, it may contribute to an improvement in the prognosis of non-shockable OHCA patients.

Acute pulmonary embolism-related OHCA may suddenly occur with rapid, extensive occlusion of the pulmonary vascular floor, but the circulating blood volume and oxygen content of blood may be maintained early after onset. Therefore, a favorable prognosis may be achieved by undertaking adequate resuscitation, including chest compression, and appropriate treatments, such as assisted circulation/thrombolytic therapy/surgical thrombus removal/catheter-mediated thrombus removal.¹³ We also reviewed published reports on pulmonary embolism-related cardiopulmonary arrest. Krkciyan *et al.* retrospectively investigated 1,246 patients who suffered cardiac arrests and reported that pulmonary emboli were detected in 60 patients (4.8%). They indicated that 38 of the 60 patients exhibited PEA, 30 of whom were clinically diagnosed with pulmonary embolism. In addition, 15 patients underwent thrombolytic therapy, and 2 of them survived, whereas all 15 of the patients who did not undergo thrombolytic therapy died.¹⁴ Courtney *et al.* reported that the sensitivity and specificity of pulmonary embolism were 67.6 and 94.5%, respectively, when the condition was limited to witnessed PEA among patients with intrinsic cardiac arrest.¹⁵ In the 2010 American Heart Association Guidelines for CPR and emergency cardiovascular care, administration of fibrinolytics is recommended as class IIa in patients with cardiac arrest due to presumed or known pulmonary embolism.⁴ Even after ROSC, pulmonary embolism must be considered as a possible cause of cardiac arrests.

In this study, we also compared the outcomes of patients with ACS, which the 2010 resuscitation guidelines recommend should be considered as a potential etiology/treated

after the ROSC,⁵ with those of patients with PCF. However, there was no significant difference in the prognosis of these two groups. Therefore, pulmonary embolism could be given priority over ACS, in cases of non-shockable OHCA after ROSC.

The present study had the following limitations. First, it was a retrospective, observational study. Second, it is unclear whether the results of this study are indicative of the prognosis of all cardiopulmonary arrest patients. Third, the presence/absence of a diagnosis before ROSC might have biased the subject enrolment process. Fourth, the etiology of each cardiopulmonary arrest was evaluated by the attending physician, and no detailed information about the diagnostic process was obtained in the SOS-KANTO 2012 study; thus, it is impossible to evaluate the accuracy/usefulness of diagnosis. Theoretically, all non-cardiogenic and definite cardiogenic factors might be included in PCF. Thus, the fact that the identification of the etiology of non-shockable OHCA was completely dependent on the discretion of the attending physicians is an important limitation of the present study. Finally, no data on concomitant diseases were collected, and so their influence cannot be evaluated.

CONCLUSION

AMONG PATIENTS WHO suffered non-shockable OHCA and then achieved ROSC after arriving at hospital, those who suffered incidental hypothermia or pulmonary embolism had better prognoses than those in the PCF group with unknown etiology. In particular, our results obtained under the 2010 resuscitation guidelines suggest that the investigation and treatment of pulmonary embolism as a potential etiology may be important for improving patients' post-resuscitation prognosis.

Part of this study was presented at the 42nd Annual Scientific Meeting of the Japanese Association for Acute Medicine, Fukuoka, in October 2014.

CONFLICTS OF INTEREST

None.

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