

Targeted Temperature Management (TTM) Update in Japan

Clinical Trials (B-HYPO, **COORARREST JP**) & Introduction of
New Device, Thermogard System

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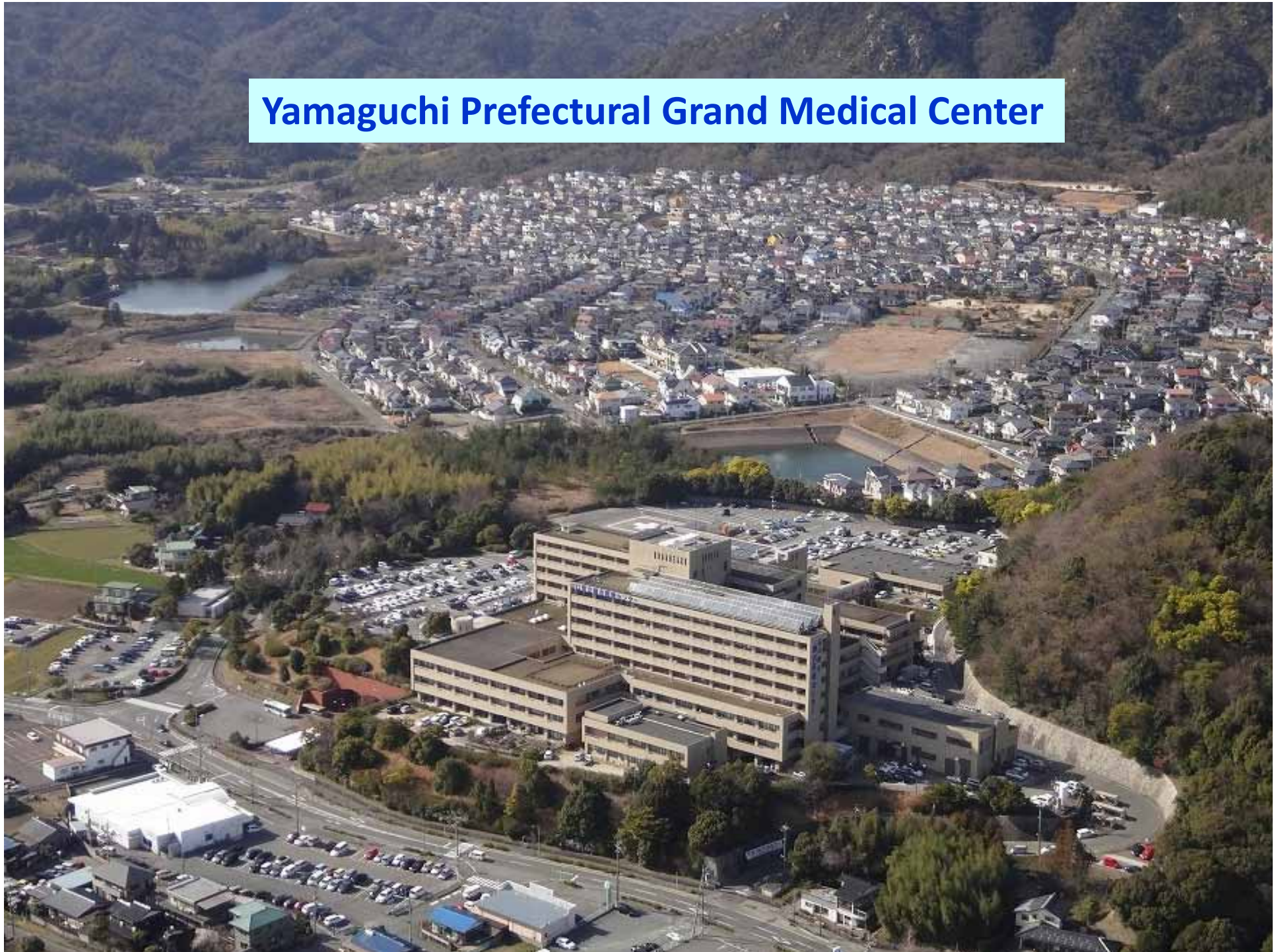
2016.03.19

Conflict of Interests

Presenter : Tsuyoshi Maekawa MD, PhD

- | | | |
|--|--------------------------------------|---|
| 1. Director's Remuneration * | <input checked="" type="radio"/> yes | . |
| no | | |
| 2. Benefit from Stock * (Stock > 5%) | <input type="radio"/> yes | 0 |
| no | | 0 |
| 3. Benefit from Patents * | <input type="radio"/> yes | 0 |
| no | | 0 |
| 4. Lecture Fee * | <input type="radio"/> yes | 0 |
| no | | 0 |
| 5. Manuscript Fee * | <input type="radio"/> yes | 0 |
| no | | 0 |
| 6. Research Grants * * | <input type="radio"/> yes | . |
| no | | |
| 7. Donation for Research | <input type="radio"/> yes | |
| no | | |
| 8. Staff of a Endowed Department | <input type="radio"/> yes | . |
| no | | |
- From a company / year : # > 0 * million yen, * > 1.0million yen, * * > 2.0million yen

Yamaguchi Prefectural Grand Medical Center

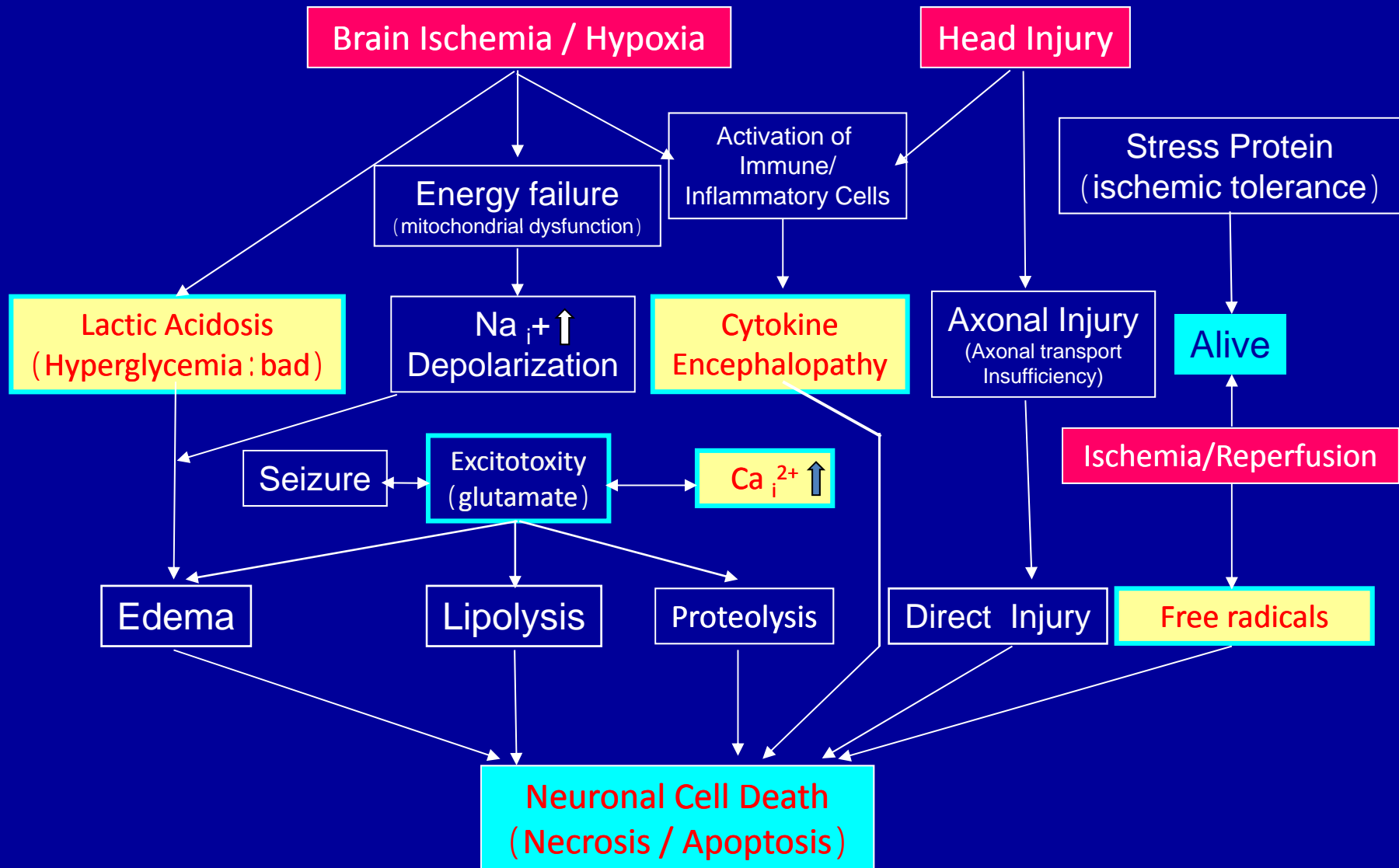


Pathophysiology of Acute Brain Insults

Brain Ischemia / Hypoxia, Traumatic Brain Injury

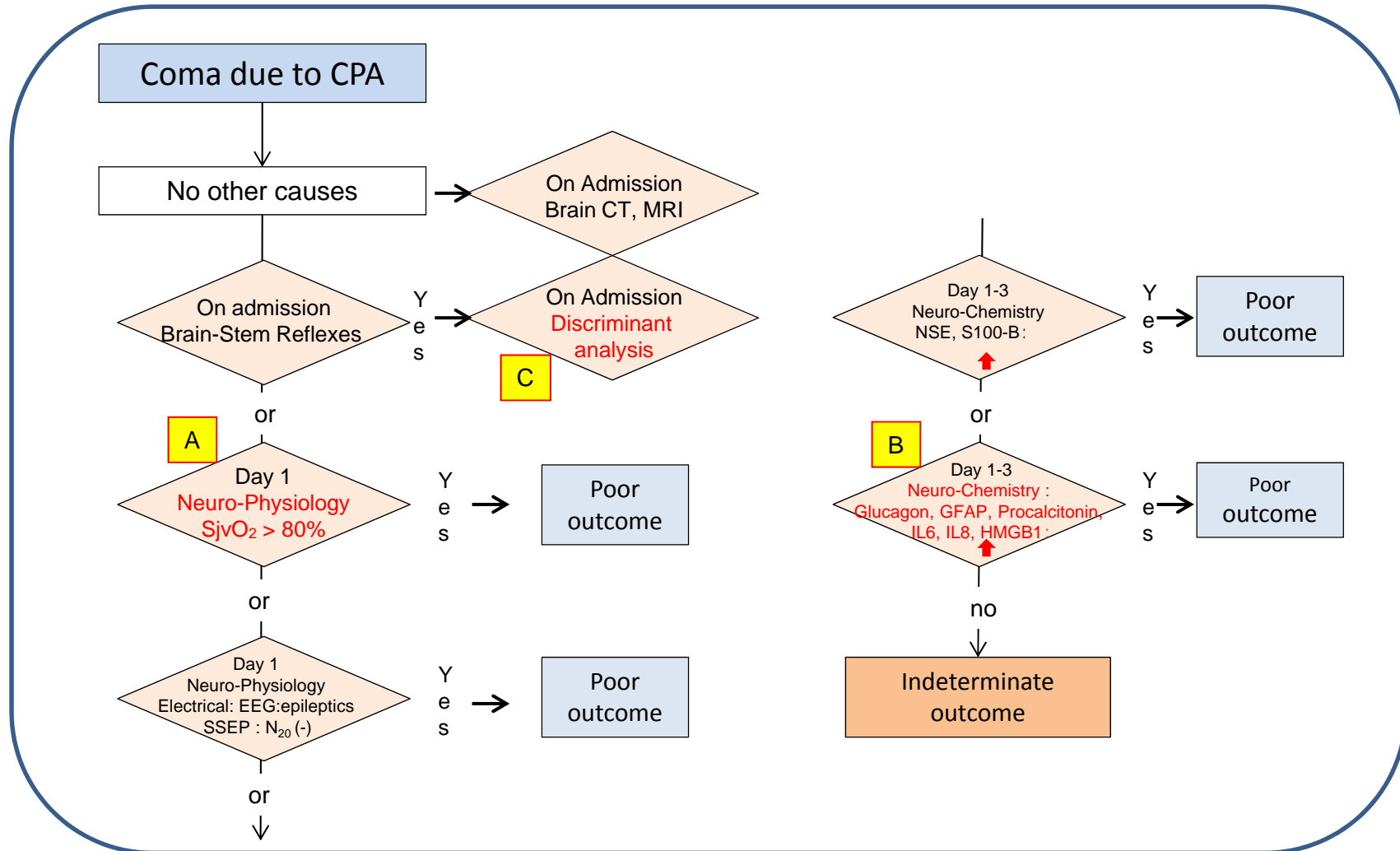
Mechanisms of Neuronal Cell Death

Caused by Brain Ischemia / Hypoxia or Traumatic Brain Injury



Predictability of Neurological Outcome for Cardiac Arrest Patients

Decision Algorithm for Use in Neurological Outcome Prediction in Comatose Survivors of Cardiac Arrest



Prediction of Neurological Outcome with Oxygen Saturation of Internal Jugular Venous Blood (SjvO₂) in Post Cardiac Arrest Patients

	SjvO ₂ (%)	SjvO ₂ range(%)
GR, MD (n=7)	50 +/- 12	35 - 64
SD,VS (n=7)	79 +/- 6	71 - 90
Death (n=6)	84 +/- 6	74 - 90

SjvO₂G: Oxygen saturation of internal jugular venous blood

GR: Good Recovery, MD: Moderate Disability,
SD: Severe Disability, VS: Vegetative State

7.0 hours after ROSC

SjvO₂ >80% Unfavorable Neurological outcome

Comparison of IL-8 and IL-6 in CSF and Serum between Control Subjects and Post Cardiac Arrest Patients

Variables	Controls (n=16)	Patients (n=13)	P-value
IL-8 (pg/ml)			
CSF	82 (69-116)	1311 (646-4007)	< 0.001
Serum	20 (17 - 22)	28 (18 - 73)	0.07
IL-6 (pg/ml)			
CSF	1 (1 - 2)	2040 (384 -16300)	< 0.001
Serum	3 (2 - 4)	120 (48 - 303)	< 0.001

48 hours after return of spontaneous circulation.

Values are the median (interquartile range).

CSF: cerebrospinal fluid

IL: Interleukin

CPR: cardiopulmonary resuscitation

**The Cutoff Values of IL-8 and IL-6 in CSF and Serum
with 100% Specificity for Predicting an Unfavorable Outcome
in Post Cardiac Arrest Patients**

Variables	Cutoff Value (pg/ml)	Sensitivity (%)	Specificity (%)	AUC
CSF				
IL-8	1423	86	100	0.88
IL-6	2708	86	100	0.90
Serum				
IL-8	117	14	100	0.60
IL-6	471	29	100	0.53

48 hours after return of spontaneous circulation.

ROC Analysis of Serum Procalcitonin for Unfavorable Neurological Outcome in Post Cardiac Arrest Patients

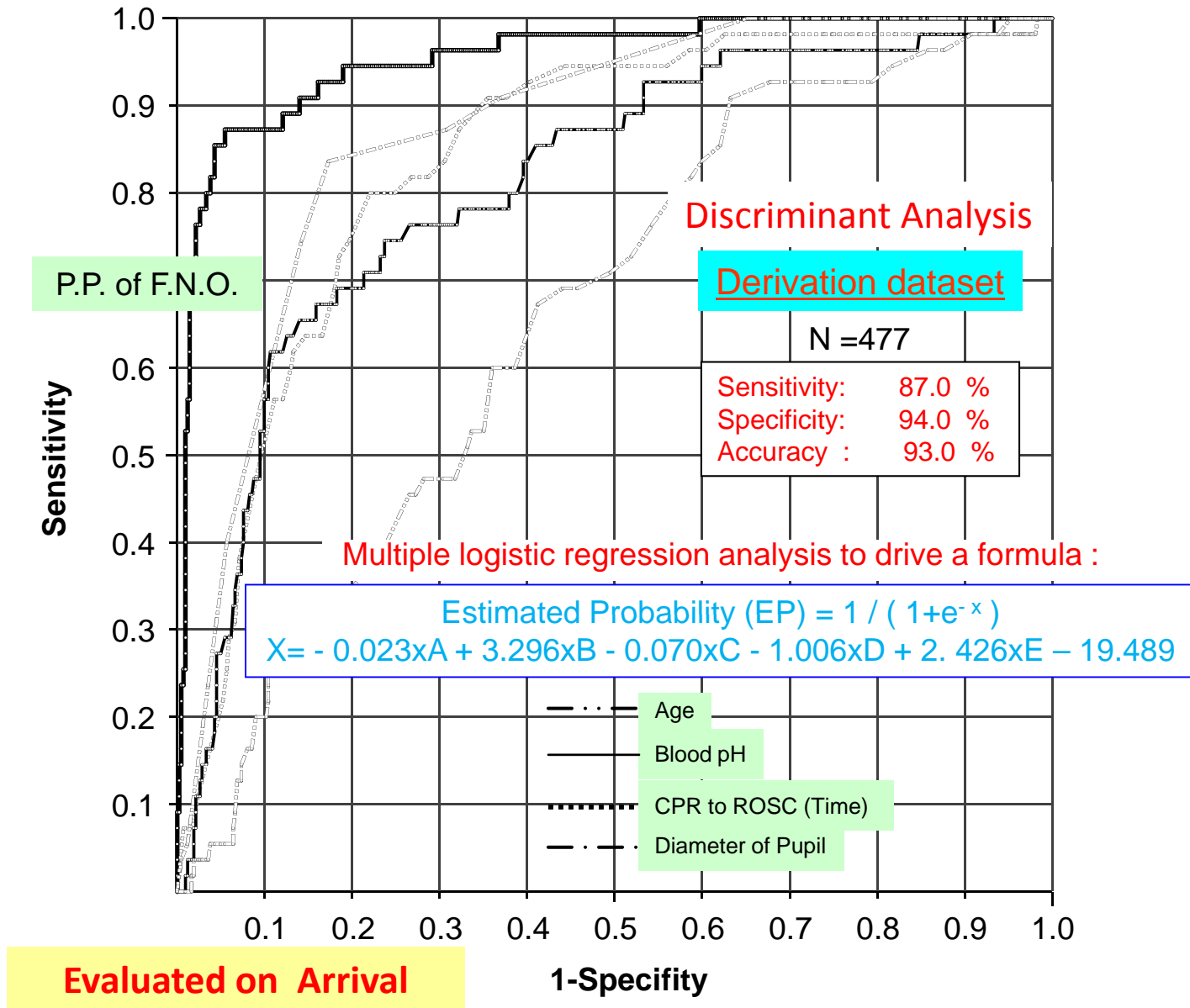
Variables	Hours	AUC (95% CI)	P value
PCT (ng/ml)	12	0.911 (0.78-1.04)	0.004
	24	0.939 (0.82-1.06)	0.002

Variables	Hours	Cutoff Value	Sensitivity (%)	Specificity (%)
PCT (ng/ml)	12	0.50	73.3	100
	24	0.50	100	83.3

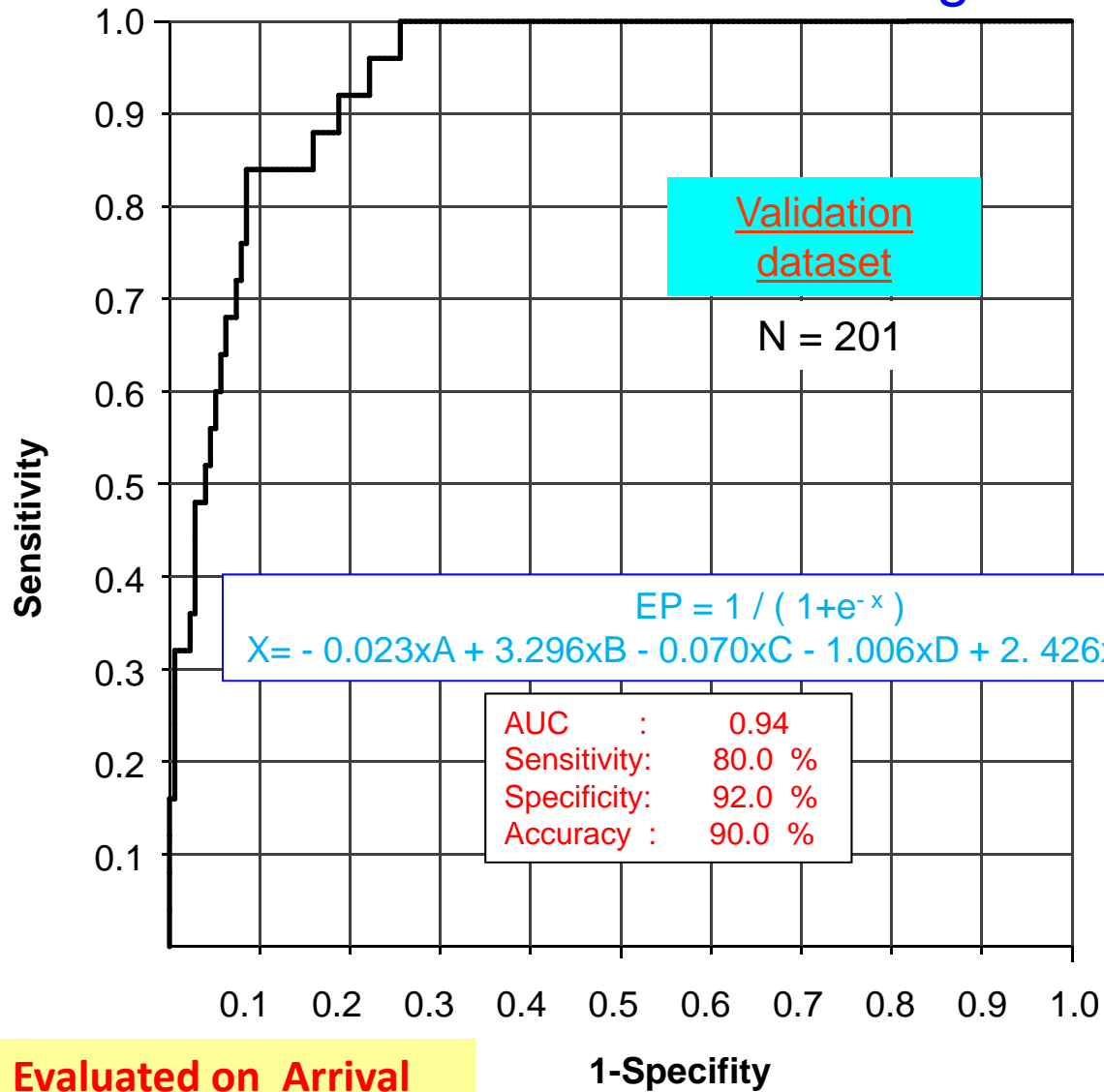
AUC: Area Under the ROC Curve, PCT: Procalcitonin

12 or 24 hours after return of spontaneous circulation.

ROC Curve for Favorable Neurological Outcome



ROC Curve for Favorable Neurological Outcome



A Full Recovery Patient Treated by Therapeutic Hypothermia

Date: 2003.10. 3

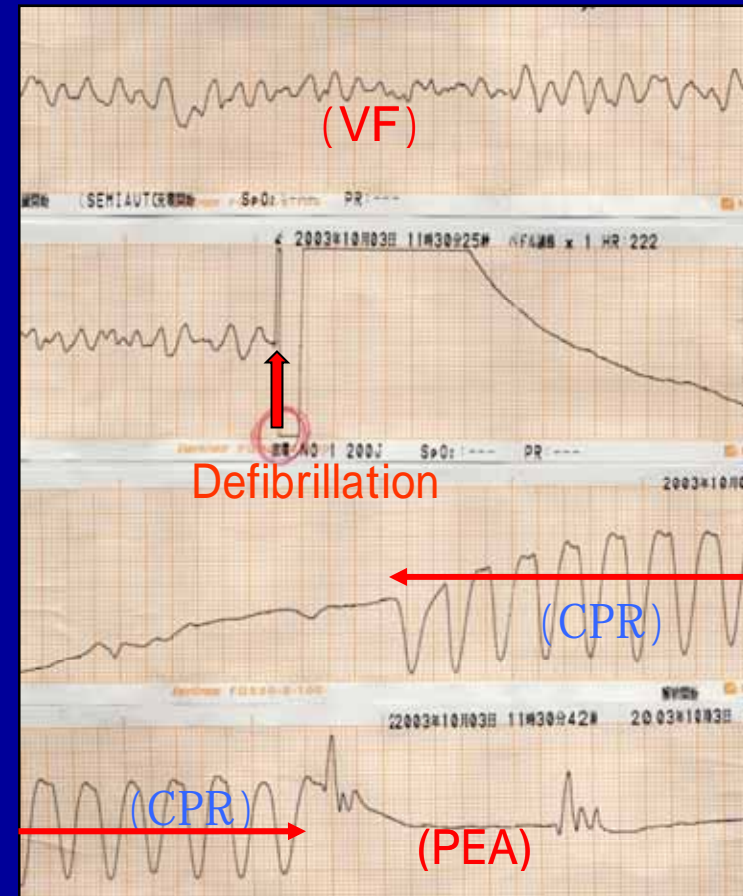
Clinical Course :

- 10: 20, Unconsciousness (CPA)
- 10: 22, Phone to Paramedic
- 10: 27, Paramedic **Arrival**
- 10: 28, Defibrillation by Paramedic
- 10: 34, Dr s Car **Arrival**
- 10: 35, Palpation of Carotid artery
- 10: 36, **Tracheal Intubation** (BP 109/79 mmHg)
- 10: 50, Arrive to Emergency Center
(JCS 200, BP 104/64 mmHg, HR 130 bpm, af)

Therapeutic Hypothermia

Full recovery on day 4

Case : 28y, Male



B-HYPO RCT

Intervals from Traumatic Brain Injury and Percent of Surgery

B-HYPO

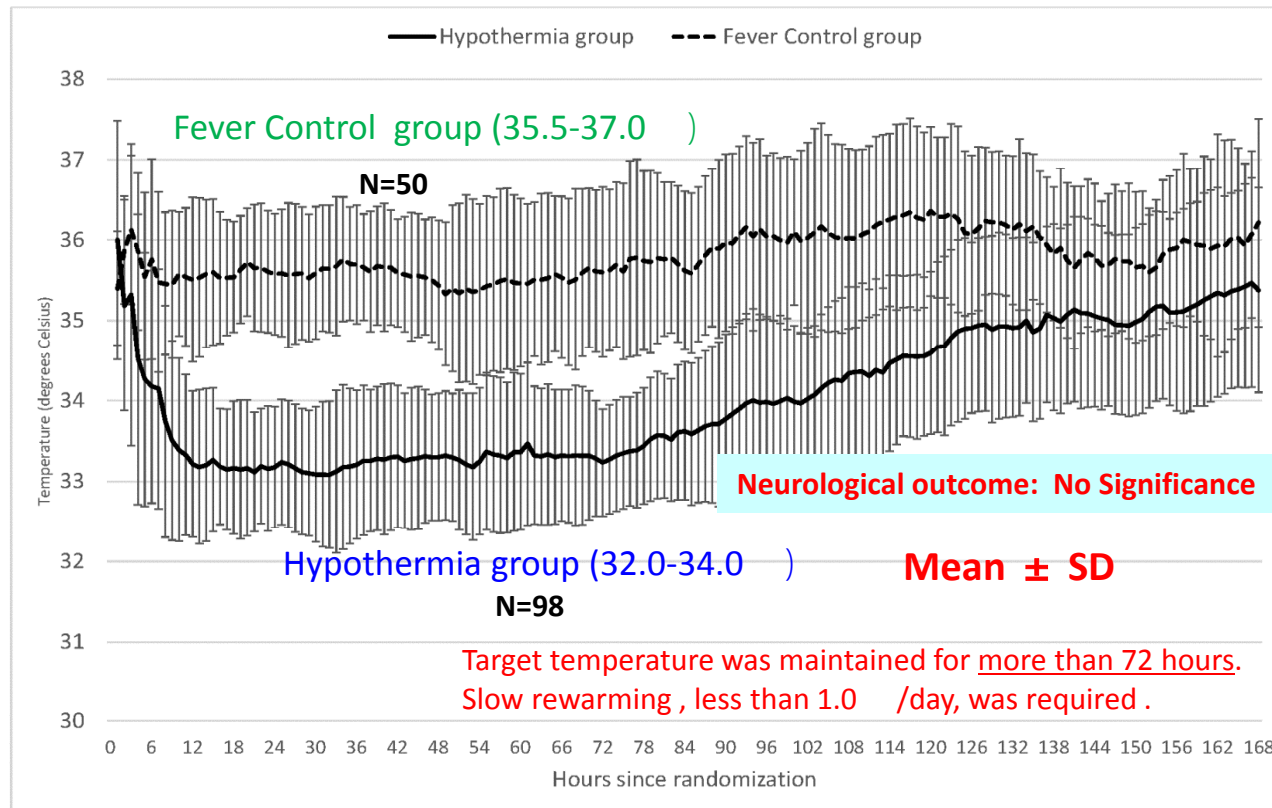
Variable (hrs)	Hypothermia (32.0-34.0 °C) n – 88	Fever Control (35.5-37.0 °C) n – 47	P value
To admission	0.7 (0.5-1.0)	0.8 (0.5-0.9)	0.780
To randomization	3.8 (2.7-5.1)	3.3(2.3-4.5)	0.906
To start cooling	3.0 (2.3-4.5)		
To 35.5 °C	5.2 (3.5-7.5)		
To 34.0 °	8.1(5.3-11.8)		

TBI : Traumatic Brain Injury

Hypothermia Group : Cooling Period : 75.5 h (68.9 - 84.0 h)
 Re-warming period : 76.0 h (51.5 -113.5 h)

BHYPO in Japan for TBI
 Maekawa T, et al. J Neurotrauma: 2015, 32:422-429

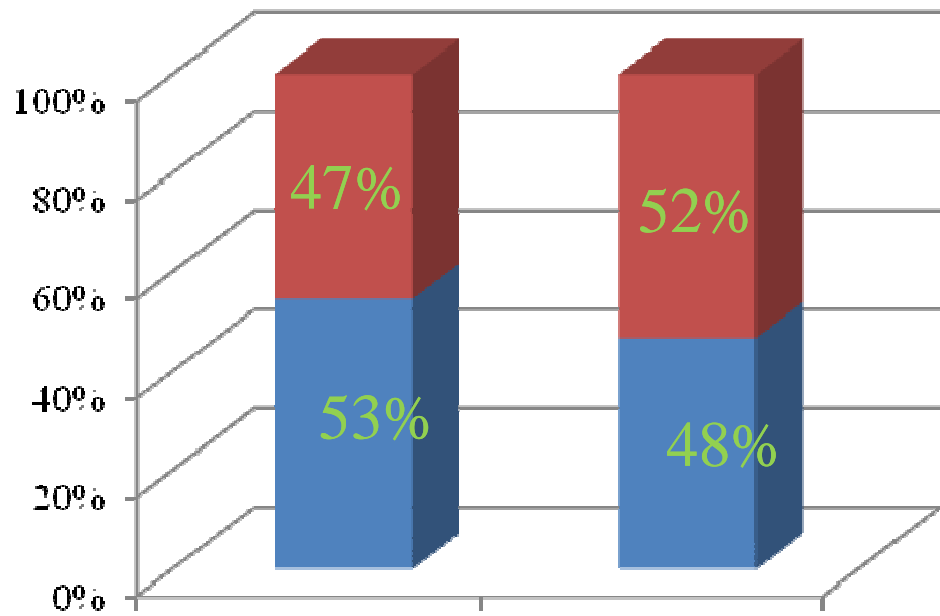
Core Body Temperature between The Two Groups



BHYPO in Japan for TBI
Maekawa T, et al. J Neurotrauma: 2015, 32:422-429

Neurological Outcome Evaluated by GOS at 6 Months

Favorable outcome



Hypothermia

(n = 94)

Fever Control

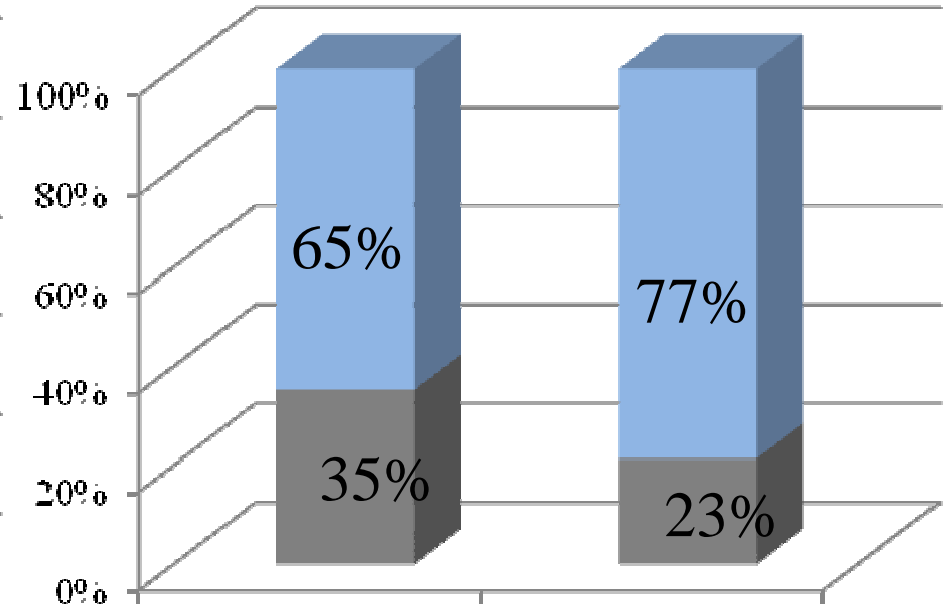
(n = 48)

$P = 0.597$

■ GR, MD

■ SD, VS, D

Mortality



Hypothermia

(n = 94)

Fever Control

(n = 48)

$P = 0.180$

■ Survive

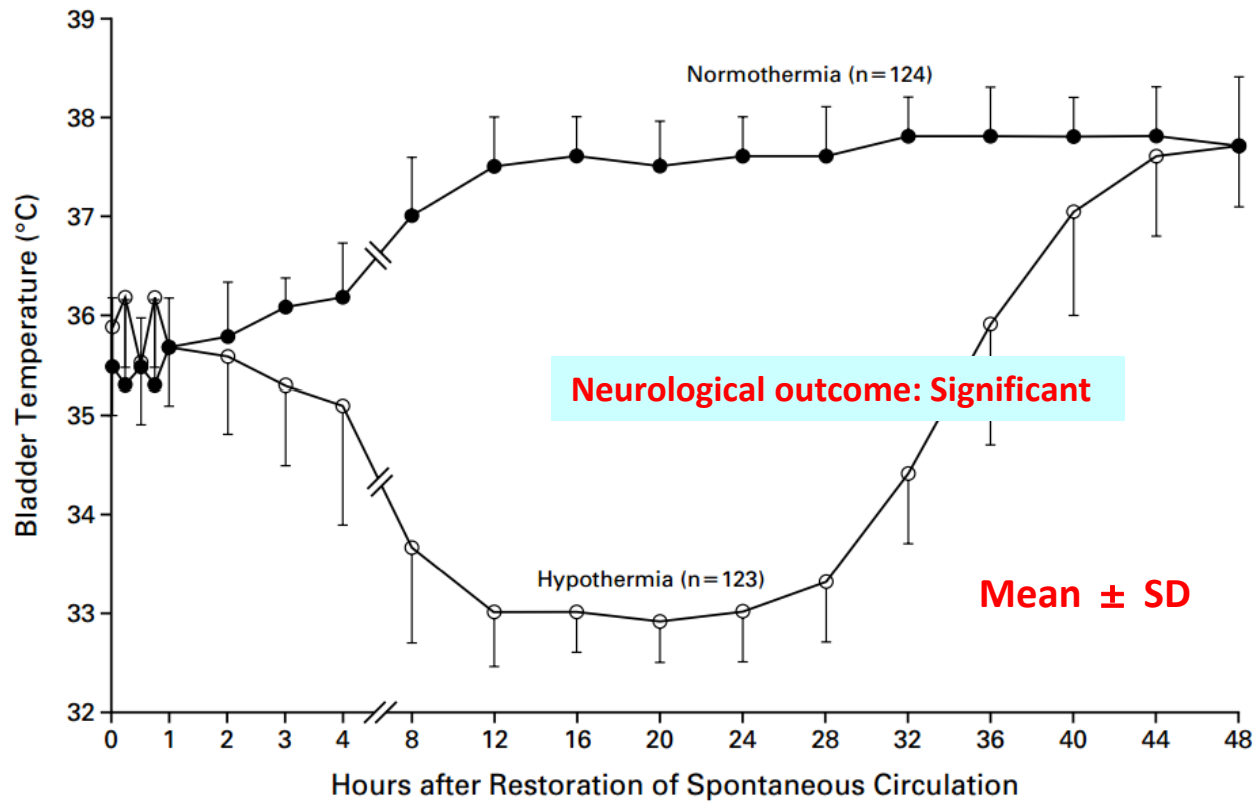
■ Death

Neurologically Good Outcome at that period : 30-35 %

BHYPO in Japan for TBI

Maekawa T, et al. J Neurotrauma: 2015, 32:422-429

Core Body Temperature between The Two Groups



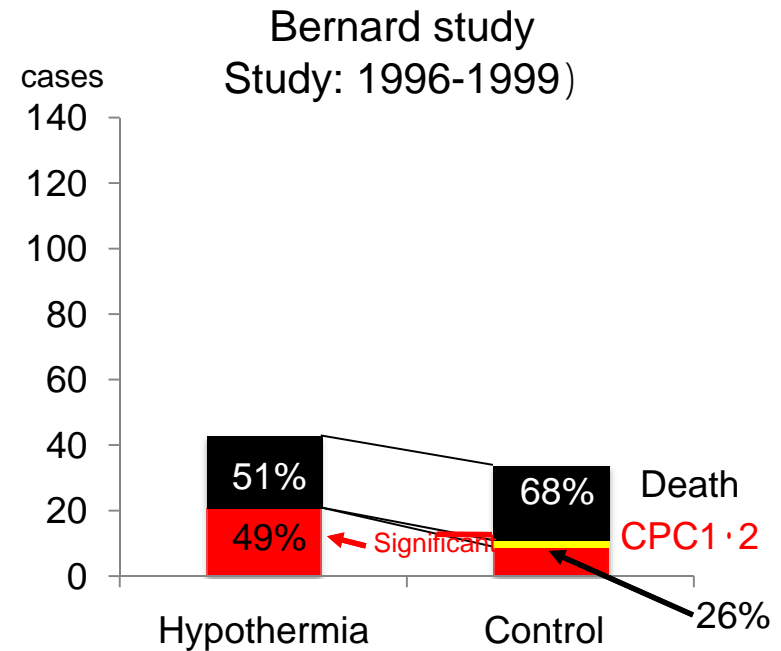
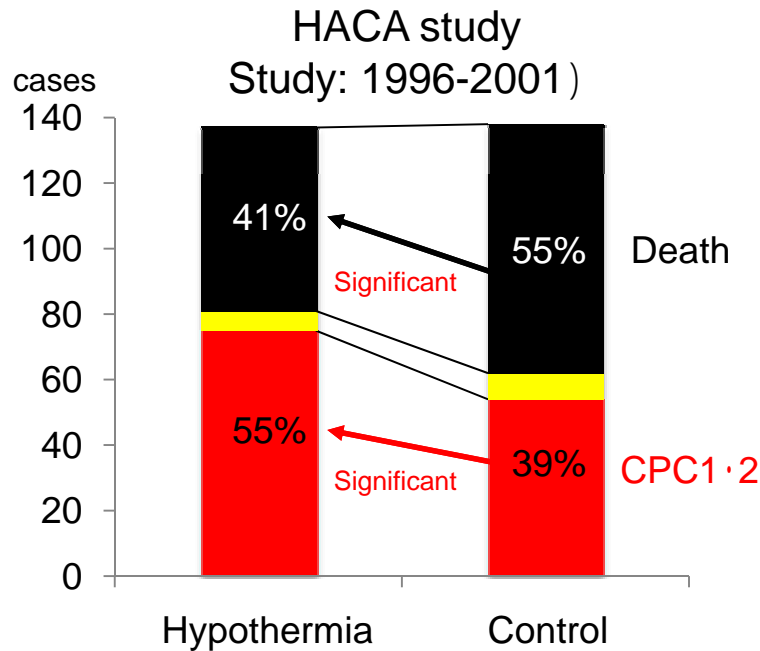
HACA study, 2002

Therapeutic Hypothermia for Patients of Out of Hospital Cardiac Arrest / ROSC

RCT

Six Month. Outcome

Outcome at Discharge



$P < 0.009$

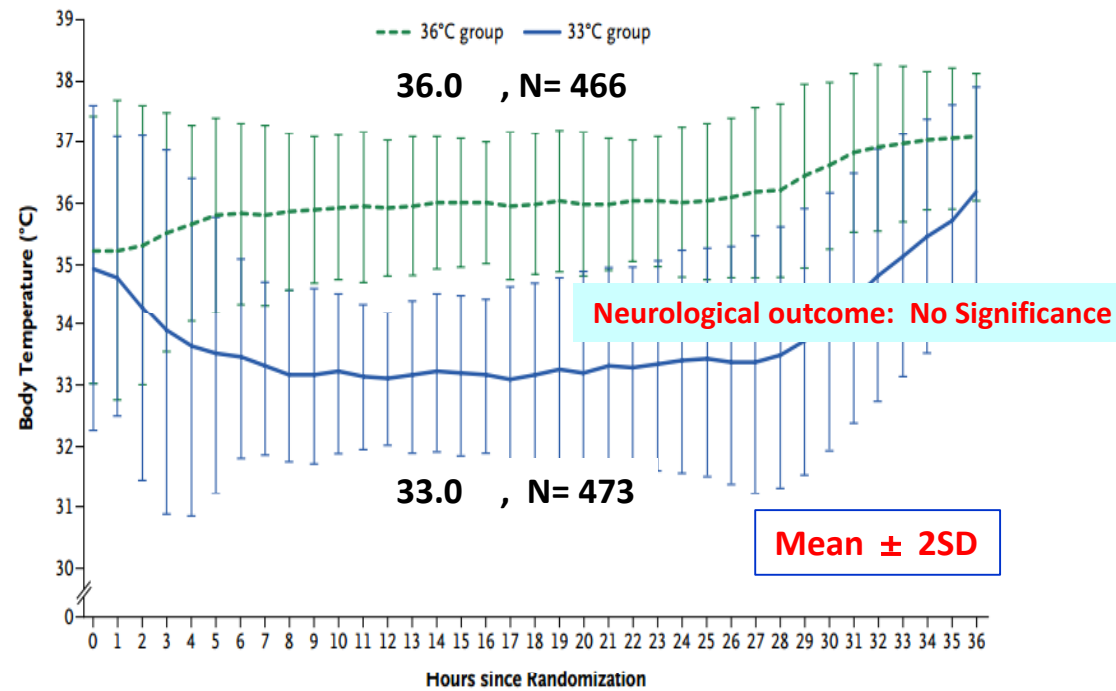
Post-ROSC Cooling

$P < 0.046$

32-34 : Duration:24 Hrs

33 : Duration:12 Hrs

Core Body Temperature between The Two Groups



Nielsen N, et al. N Engl J Med 369:2197-206, 2013.

COORARREST-JP

Intra-vascular Cooling from Inguinal (Femoral) Vein



Intra-vascular catheter



Intra-Vascular Cooling Device

Mild Therapeutic Hypothermia in Out of Hospital Cardiac Arrest Patients COOL-ARREST JP (Intra-vascular cooling)

Indication

- One arm prospective study
- Multi(10 GCP)-center study
- 25 cases
- Out-of hospital CPA / ROSC
- 18 y - 70 yo, male / female
- ECG : VF· VT /witnessed CPA
- CPR duration < 30min

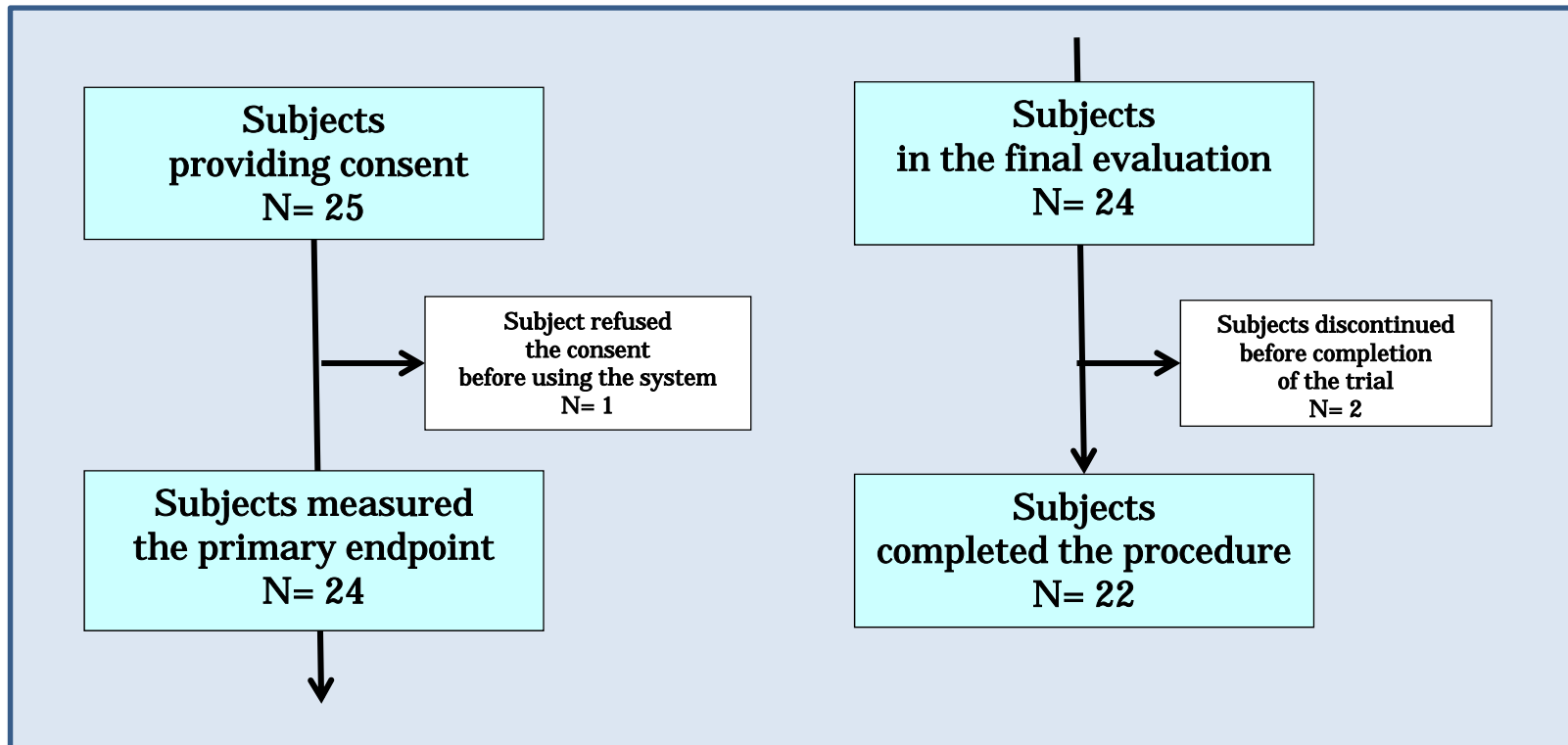
Protocol

- **Thermo-gurd XP System™**
Catheter: IC-3893™,
IC-4593™
Start-Up Kit (SUK)™

Primary /secondary End Points

- < 3 hours : to be 32-34
- Safety · Efficacy of cooling
- Neurological outcome: 14 days CPC

Diagram Representing the Number of PCAS Patients for Therapeutic Hypothermia



Intention to treat analysis, n = 24

Patient Characteristics, Physiological Parameters and Laboratory Data on Admission

Age (year)	60 (43-70)	Mean BP (mmHg)	98 (64 - 123)
Male	21 (87.5%)	HR (bpm)	110 (74 - 123)
Height (cm)	170 (162-174)	PaO ₂ (mmHg)	128 (64 - 316)
Weight (kg)	70 (60-75)	PaCO ₂ (mmHg)	47.9 (37.1 - 53.3)
BMI (kg/m ²)	24.4 (23.2-25.3)	pH	7.25 (7.18- 7.30)
BSA (m ²)	1.75 (1.63-1.85)	BE (mEq/L)	-8.4 (-11.5 - -5.1)
Characteristics of Cardiac Arrest		Lactate (mg/dL)	50.4 (32.0 - 70.0)
Out of Hospital	24 (100%)	Glucose (mg/dL)	244 (200 - 323)
Witnessed	21 (87.5%)	CRP (mg/dL)	0.11 (0.09 - 0.22)
VT • VF / PEA	18 (75%) / 6 (25%)	Procalcitonin	0.06 (0.04 - 0.12)

Modified Intention to Treat Population

median (IQR) of 24 patients or n (%)

Duration, GCS, Volume of Cold fluid in the Modified Intention to Treat Population

Duration

Cardiac arrest to admission (min)	32 (26-120)
Cardiac arrest to ROSC (min)	20 (14-35)
Cardiac arrest to start cooling(min)	274 (242-359)
ROSC to start cooling (min)	249 (216-342)

GCS and Fluid Volume

GCS on admission	3 (3-6)
Cold fluid transfusion (ml/kg)	21 (14-27)

ROSC, return of spontaneous circulation; GCS, Glasgow Coma Scale.
N=24, Values are expressed as **median (interquartile range)**.

Brain Oriented Intensive Care for Therapeutic Hypothermia

Anesthesia : droperidol · fentanyl, muscle relaxant
Vaso-dilation / volume load

Respiration : PaO₂ (FiO₂ ;1.0 ?), PaCO₂ ; 35 ~ 40 mmHg

Circulation : **Cardiac index** 3.0 L / min / m²

Cerebral perfusion pressure (CPP) ; 60 ~ 70 mmHg

Intracranial pressure (ICP) ; < 20 mmHg

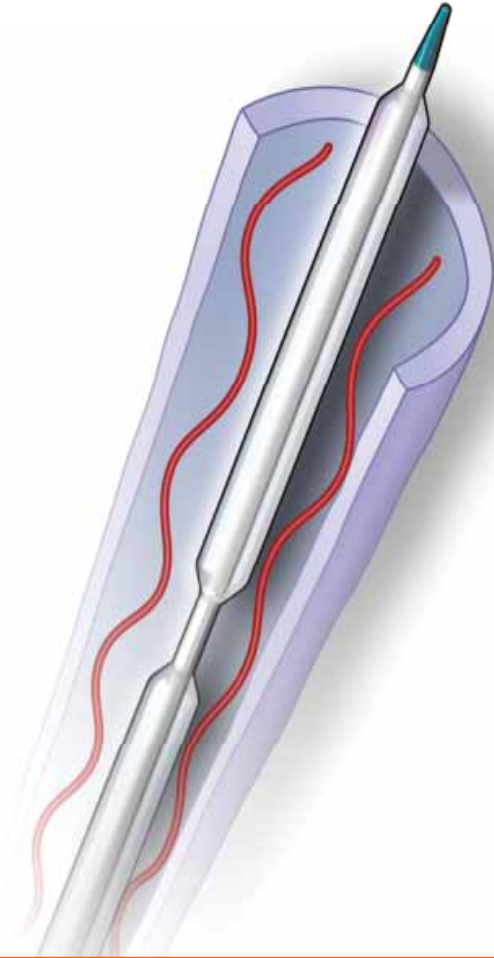
Metabolism : blood sugar (BS) ; 100 ~ 150 mg / dl

Internal Jugular Venous Blood Oxygen Saturation
(SjvO₂) 50 ~ 60 %

Electrolyte : serum K⁺ ; 3.5 ~ 4.5 mEq / l

Blood : platelets ; 5 x 10⁴ / μl

Rewarming : **slow (1 / day)** ; prevent free radical production



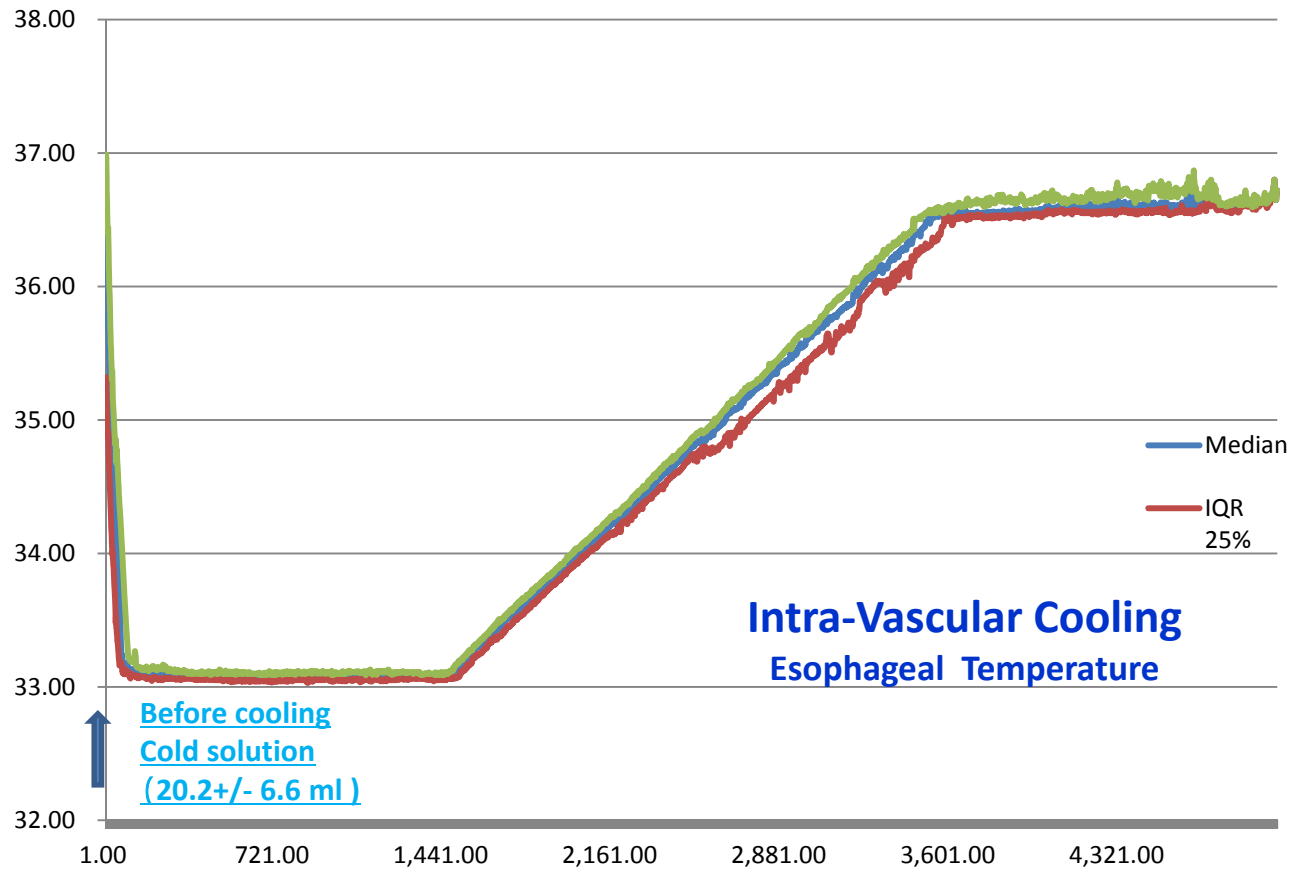
Intra-vascular catheter

Reach to 34.0 within 3.0 hours
Primary Endpoint Achievement

	n (%)
Reach to 34.0 <180 min	24 (100 %)
Reach to 34.0 (Range of duration)	
0 ~ 30 min	6 (25.0 %)
31 ~ 60 min	10 (41.7 %)
61 ~ 120 min	7 (29.2 %)
121 ~ 180 min	1 (4.2 %)

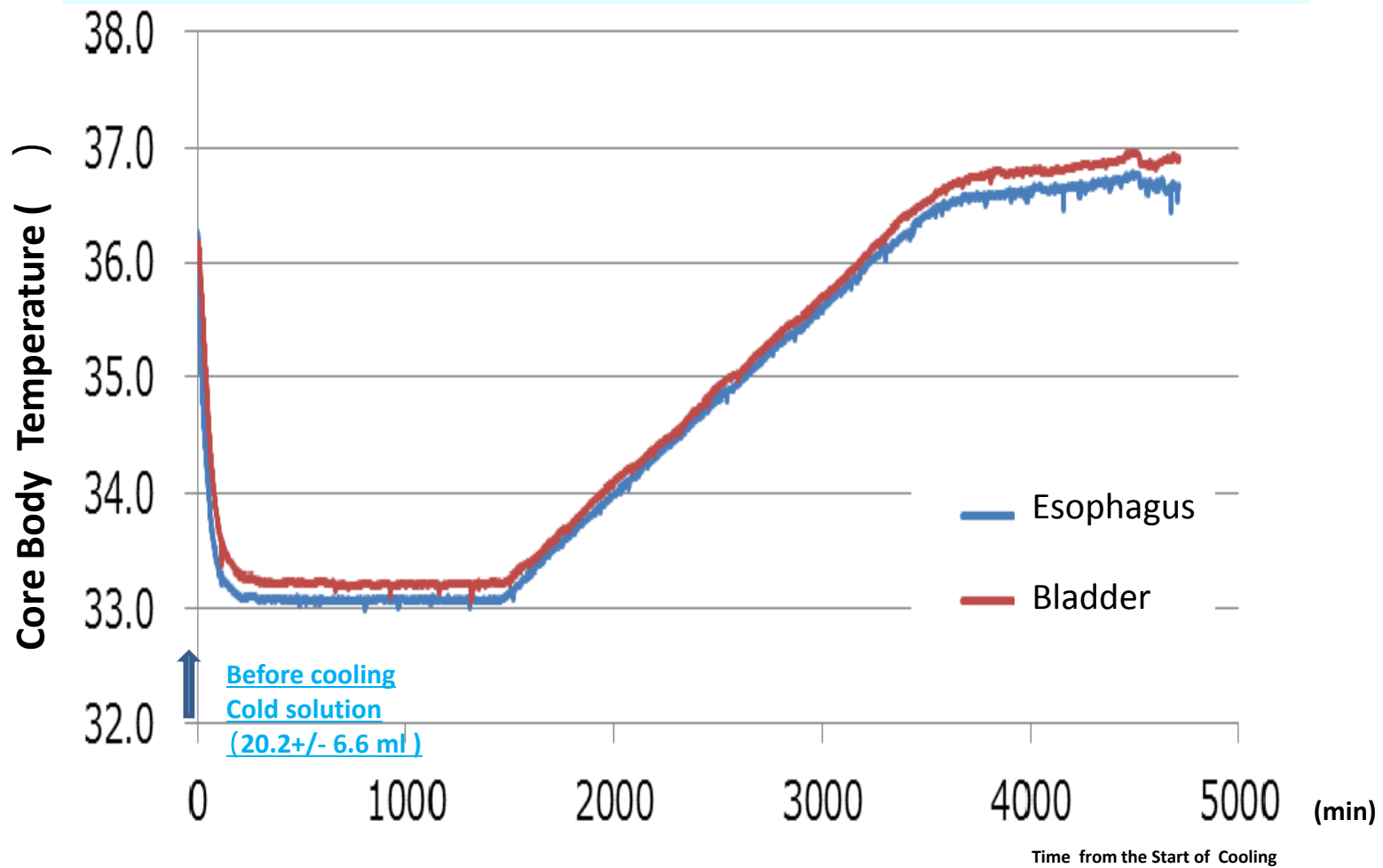
Infused cold fluid before cooling : 21 (14-27) (ml/kg)
36.4 (35.2 36.8)

Core Body Temperature in PCAS Patients



There was not any device related complication.

Core Body Temperature in PCAS Patients



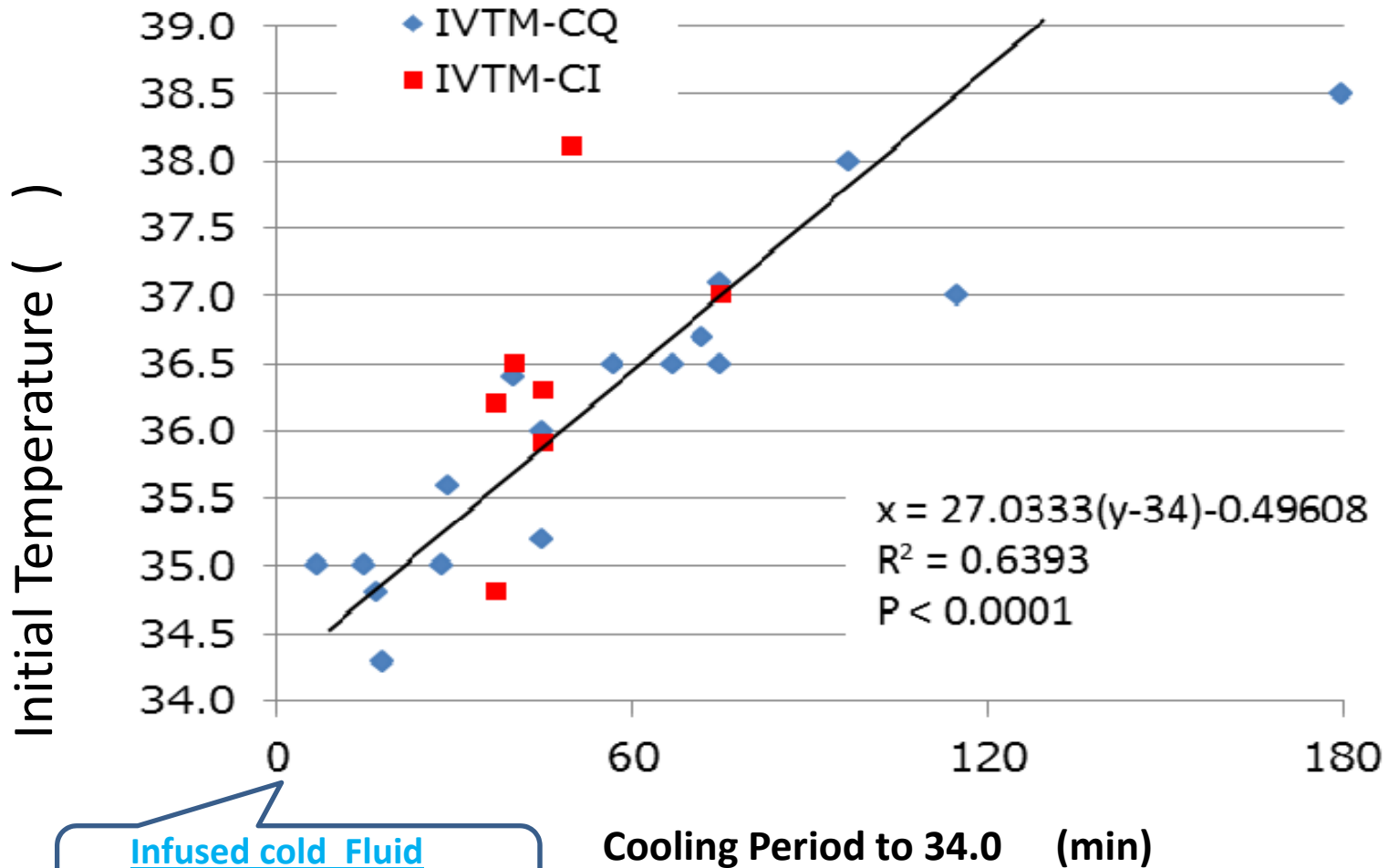
There was not any device related complication.

Core Body Temperature, Duration and Speed to Reach Certain Targeted Temperature

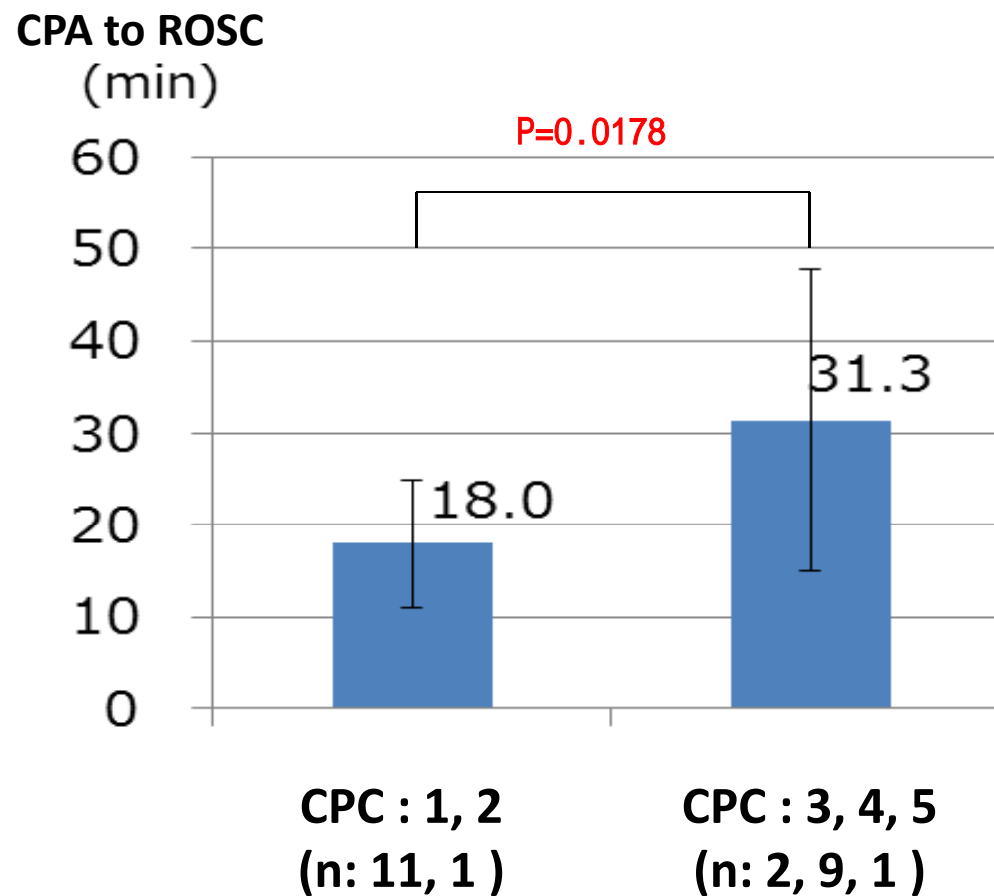
	All Patients (n=24)
Body temperature (°C)	
At registration	36.1 (35.6 - 37.0)
Just before cooling	36.4 (35.2 - 36.8)
Beginning of maintenance phase	34.0 (33.9 - 34.0)
8 hrs after reaching target temp.	33.1 (33.1 - 33.1)
24 hrs after reaching target temp.	33.1 (33.1 - 33.1)
At the time of reaching normal body temp.	36.0 (36.0 - 36.0)
8 hrs after reaching normal temp.	36.6 (36.5 - 36.6)
24 hrs after reaching normal temp.	36.7 (36.6 - 36.9)
Duration or speed	
Cooling to 34 °C (min)	45 (35 - 73)
Cooling speed to 33 °C (/hr)	2.7 (2.4 - 3.6)

median (IQ range)

Correlation between Initial Temp. and Cooling Period to Reach Targeted Temp. (34.0)



Neurological Outcome (CPC 1-2 vs CPC 3-5) and Duration from CPA to ROSC Secondary Endo-point



Facts to be Solve

Facts to be Solved in Therapeutic Hypothermia

- **Protective mechanisms of therapeutic hypothermia**
- **Immuno-suppression**

Pro : Normalization of excessive production of cytokines and free radicals

Con: Infection (ex; pneumonia)

- **Induction Phase :** Rapid induction to 32 - 34
- **Maintenance Phase :** Prolongation; 24-72hours or more ?
- **Recovery Phase :** Slow rewarming ; How long ?

⇒ **Thermo-controller :**

Powerful enough to perform rapid induction and stable maintenance to keep long term therapeutic hypothermia

Thank you very much to join this session with your cool and sharp brain.

Possible Mechanisms Underlying Brain Protective Effects of Hypothermia

Explanation	Time Frame	Evidence of Efficacy by Hypothermia
1. Proteolysis by Calpain	Hs ~ Ws	Prevent proteolysis
2. Mitochondrial dysfunction	Hs ~ Ds	Improve mitochondrial dysfunction Improved energy homeostasis
3. O ₂ · ⁻ , ONOO ⁻ , H ₂ O ₂ , OH [·]	Hs ~ Ds	Suppress free radical production
4. Reperfusion injury	Hs ~ Ds	Prevent reperfusion injury
5. BBB destruction Increase vessel permeability	Hs ~ Ds	Prevent BBB dysfunction Suppress edema
6. Increase membrane permeability, Acidosis, DNA injury	Hs ~ Ds	Suppress membrane and nuclear membrane permeability, Mitigate DNA injury

Hs: Hours Ds: Days Ws: Weeks

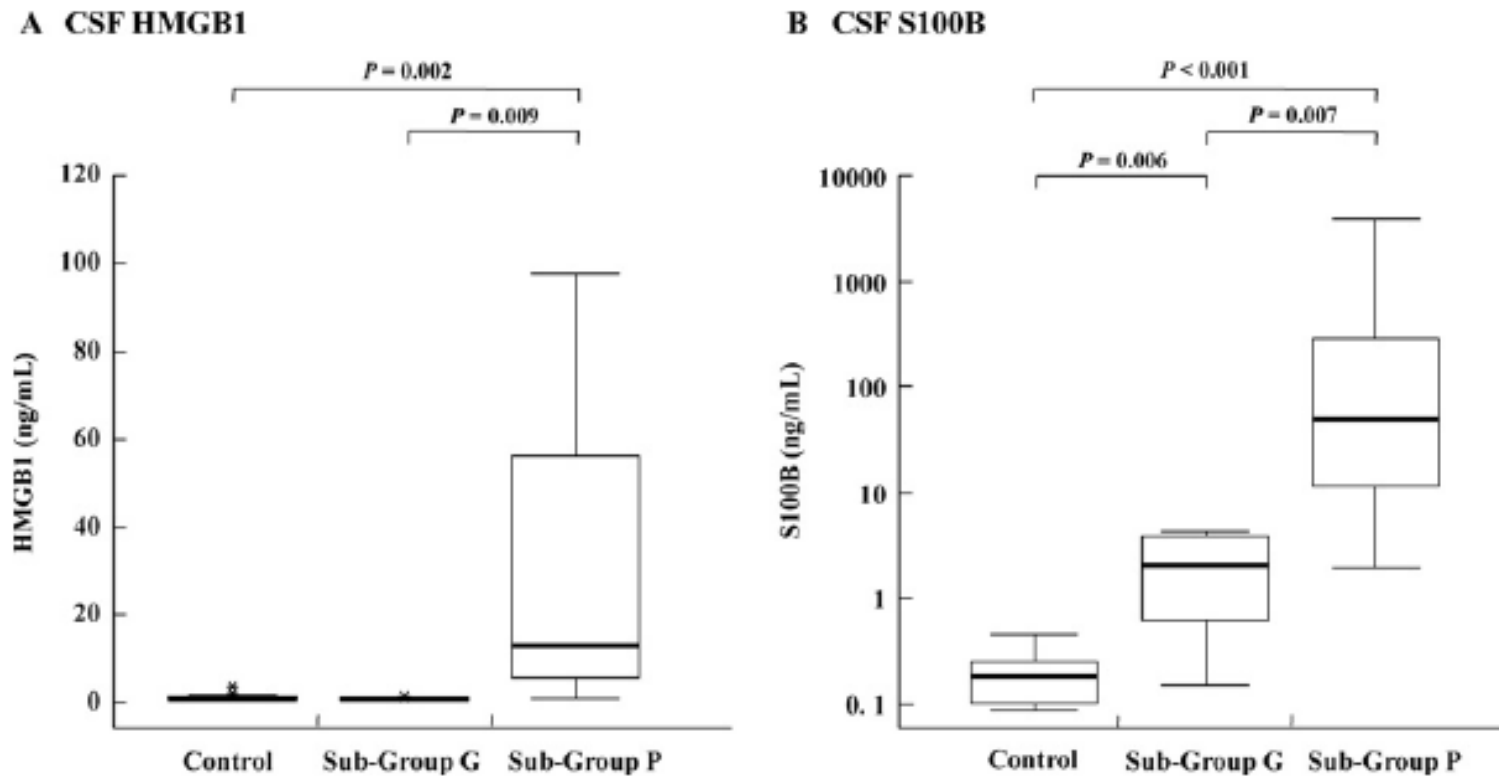
Polderman KH : Lancet 371 : 1955-69, 2008

Possible Mechanisms Underlying Brain Protective Effects of Hypothermia

Explanation	Time Frame	Evidence of Efficacy by Hypothermia
7. Glutamate · Ca _i ²⁺ ↑ Excito-toxicity, ↑ <u>Enzyme activity</u> ↑	First Min ~ 72Hs	Improved Ion homeostasis Suppress enzyme activity
8. Oxygen debt ↑ Glucose consumption ↑	Hs ~ Ds	Suppress metabolism (5 ~ 8% /)
9. Inflammation, Cytokine ↑ Continuous inflammation	First H ~ 5Ds	Suppress over-shot Immunity and inflammation
10. Cerebral thermo-pooling (TBI : 2 ~ 3)	Mins ~ Ds	Reduction in cerebral thermo-pooling
11. Micro thrombi after ROSC	Mins ~ Ds	Anti-coagulant effect
12. Epileptic activity / seizure	Hs ~ Ds	Mitigate epileptic activity

Mins: Minutes Hs: Hours Ds: Days

Prediction of Neurological Outcome with HMGB1 and S100-B in Post Cardiac Arrest Patients

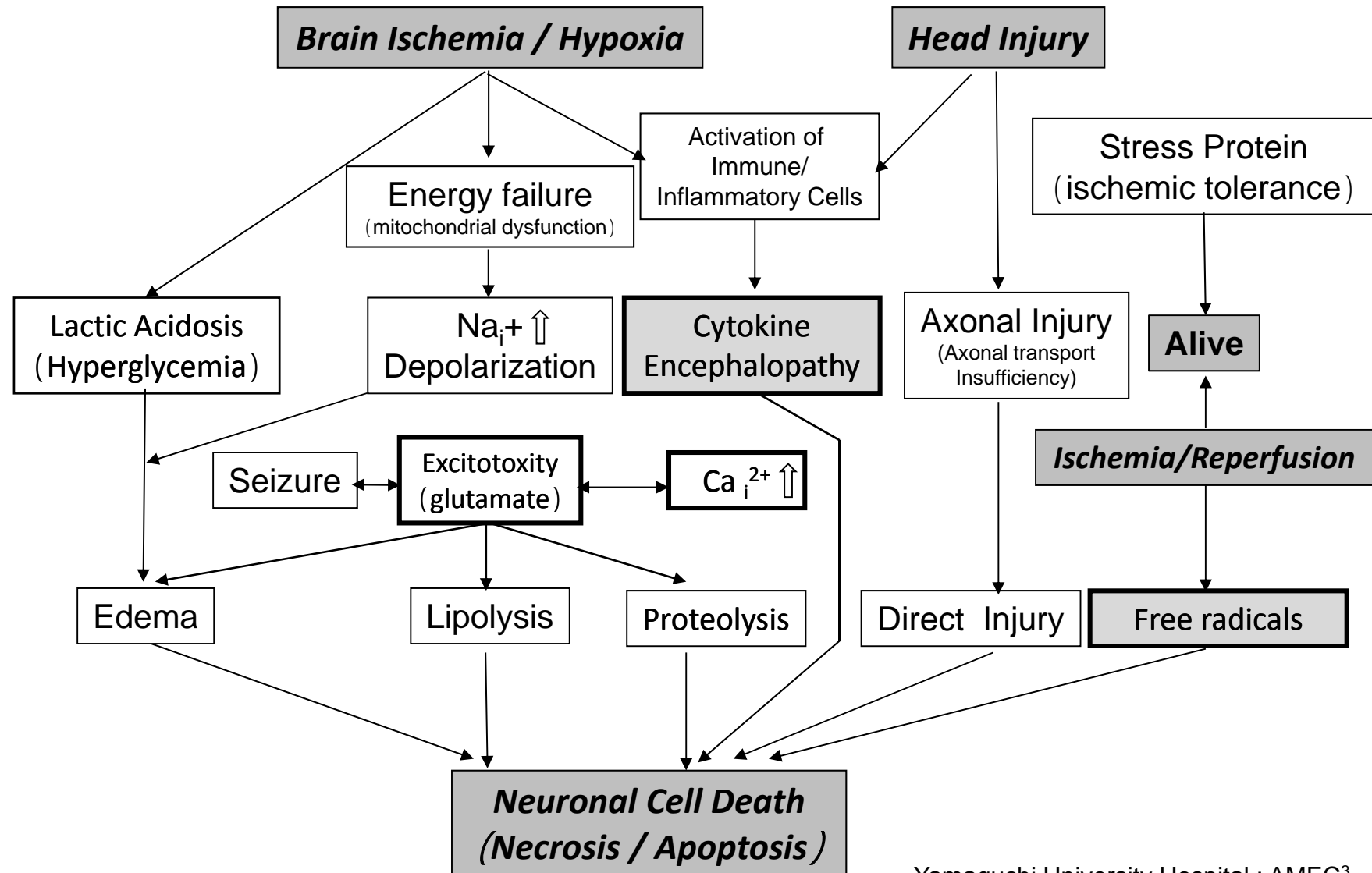


G: Good Outcome (n=6)

P: Poor Outcome (n=8)

Mechanisms of Neuronal Cell Death

Caused by Brain Ischemia / Hypoxia or Traumatic Brain Injury



Decision Algorithm for Use in Neurological Outcome Prediction in Comatose Survivors of Cardiac Arrest

