The NEW ENGLAND JOURNAL of MEDICINE

Duration of Device-Based Fever Prevention after Cardiac Arrest

N Engl J Med 2023;388:888-97.

＜心停止後脳損傷と低体温＞

- Hypothermia decreases the cerebral metabolic rate for oxygen ($CMRO_2$) by about 6% for each 1℃ reduction in core temperature and this reduces the release of excitatory amino acids and the production of free radicals.

Resuscitation 2015; 95: 202-22.

Bernard Study (2002)

INDUCED HYPOTHERMIA AFTER OUT-OF-HOSPITAL CARDIAC ARREST

TREATMENT OF COMATOSE SURVIVORS OF OUT-OF-HOSPITAL CARDIAC ARREST WITH INDUCED HYPOTHERMIA

N Engl J Med, Vol. 346, No. 8 · February 21, 2002

P: OHCA、VF
I: 33℃/12h、復温(～24h)
C: 37℃/24h
O: 退院時の神経学的転帰

Outcome*	Hypothermia (N=43)	Normothermia (N=34)
	number of patients	
Normal or minimal disability (able to care for self, discharged directly to home)	15	7
Moderate disability (discharged to a rehabilitation facility)	6	2
Severe disability, awake but completely dependent (discharged to a long-term nursing facility)	0	1
Severe disability, unconscious (discharged to a long-term nursing facility)	0	1
Death	22	23

HACA Study (2002)

The New England Journal of Medicine

MILD THERAPEUTIC HYPOTHERMIA TO IMPROVE THE NEUROLOGIC OUTCOME AFTER CARDIAC ARREST

FEBRUARY 21, 2002

P: 目撃ありOHCA、shockable
I: 32-34℃/24h、復温(8h以上)
C: normothermia
O: 6ヶ月後の神経学的転帰

TABLE 2. NEUROLOGIC OUTCOME AND MORTALITY AT SIX MONTHS.

Outcome	Normothermia	Hypothermia	Risk Ratio (95% CI)*	P Value†
	no./total no. (%)			
Favorable neurologic outcome‡	54/137 (39)	75/136 (55)	1.40 (1.08–1.81)	0.009
Death	76/138 (55)	56/137 (41)	0.74 (0.58–0.95)	0.02

※ いずれのStudyも ① Control群で多くの発熱を認める。
② 復温後の発熱予防は行っていない。

ILCOR Recommendations

On the basis of the published evidence to date, the Advanced Life Support (ALS) Task Force of the International Liaison Committee on Resuscitation (ILCOR) made the following recommendations in October 2002:

- Unconscious adult patients with spontaneous circulation after out-of-hospital cardiac arrest should be cooled to 32°C to 34°C for 12 to 24 hours when the initial rhythm was ventricular fibrillation (VF).
- Such cooling may also be beneficial for other rhythms or in-hospital cardiac arrest.

Recommendations for fever prevention for 72 hours were introduced in 2005.

European Resuscitation Council Guidelines for Resuscitation 2005
Section 4. Adult advanced life support

Jerry P. Nolan, Charles D. Deakin, Jasmeet Soar, Bernd W. Böttiger, Gary Smith

Resuscitation (2005) **67S1**, S39–S86

- 心停止後48時間以内は高体温(発熱)が起こりやすい。
- 体温37℃を超えると神経学的転帰不良のリスクが増える。
- 動物実験では虚血モデルに対する解熱薬投与や冷却法により梗塞容積が減少した。
- ヒトの観察研究で、臨床的脳死では入院72時間以内の腋窩温は高く、腋窩温が高い患者のほとんどは脳死と診断された。

↓

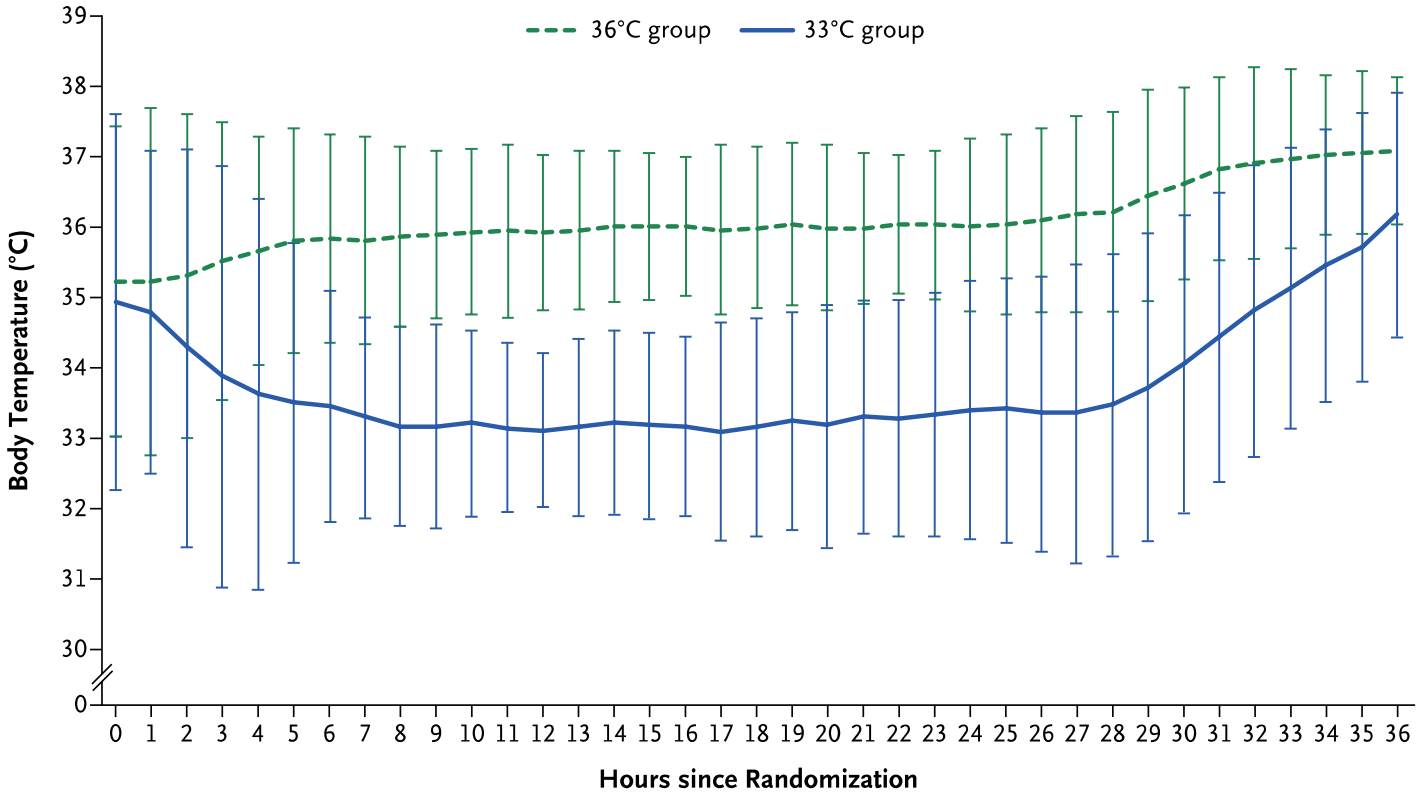
(だから) 心停止後「72時間」までの高体温は、解熱薬や冷却法により治療すべきである。

Targeted Temperature Management at 33°C versus 36°C after Cardiac Arrest

N Engl J Med 2013;369:2197-206.

TTM study (2013)

P: OHCA (目撃なしAsystole除く)
I: 33℃/28h → 37℃へ復温(0.5℃/h)
C: 36℃/28h → 37℃へ復温(0.5℃/h)
O: trial終了までの全死亡率
(両群とも72hまで <37.5℃ keep)



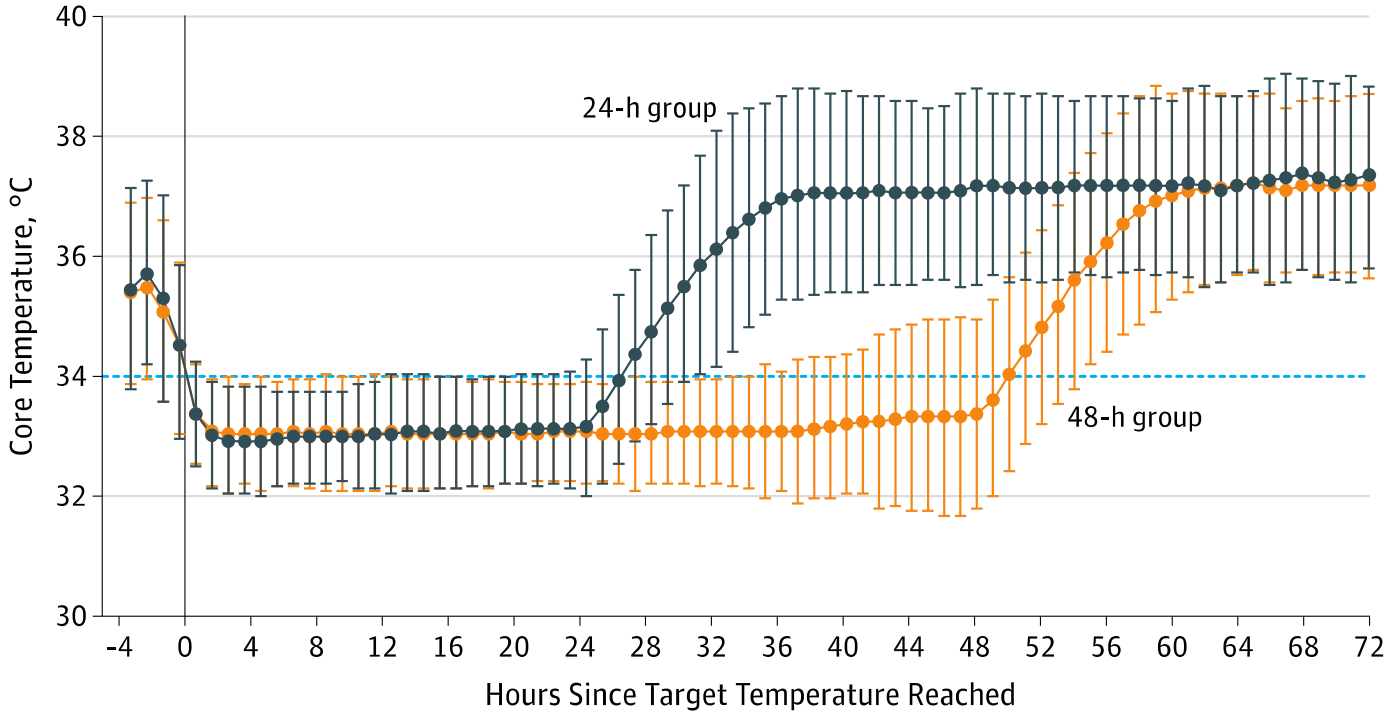
Outcome	33°C Group	36°C Group	Hazard Ratio or Risk Ratio (95% CI)*	P Value
	no./total no. (%)			
Primary outcome: deaths at end of trial	235/473 (50)	225/466 (48)	1.06 (0.89–1.28)	0.51
Secondary outcomes				
Neurologic function at follow-up†				
CPC of 3–5	251/469 (54)	242/464 (52)	1.02 (0.88–1.16)	0.78
Modified Rankin scale score of 4–6	245/469 (52)	239/464 (52)	1.01 (0.89–1.14)	0.87
Deaths at 180 days	226/473 (48)	220/466 (47)	1.01 (0.87–1.15)	0.92

Targeted Temperature Management for 48 vs 24 Hours and Neurologic Outcome After Out-of-Hospital Cardiac Arrest

A Randomized Clinical Trial

JAMA July 25, 2017 Volume 318, Number 4

P: OHCA (目撃なしAsystole除く)
I: 33(±1)℃/48h
C: 33(±1)℃/24h
O: 6ヶ月後の神経学的転帰
(両群とも72hまで37℃目標)



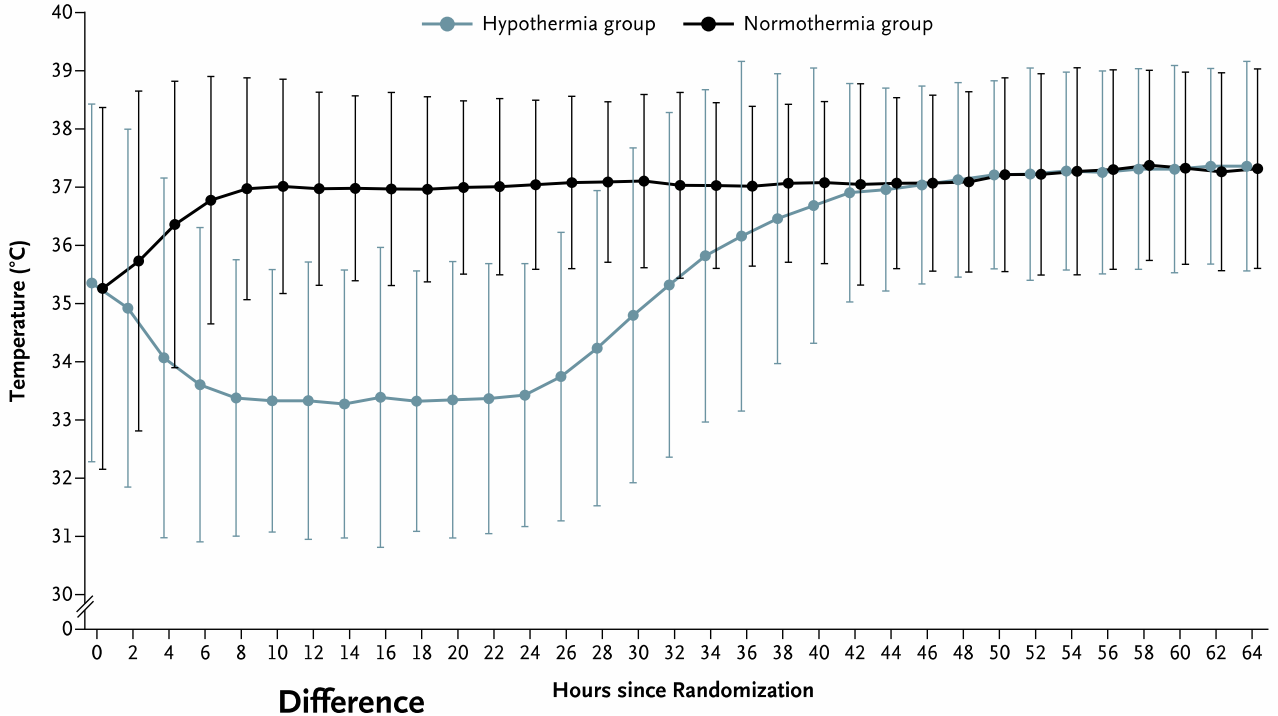
	No. (%) of Patients				
	48-Hour Group (n = 175)	24-Hour Group (n = 176)	Difference, % (95% CI)	RR (95% CI)	*P* Value
Primary outcome: CPC score of 1 or 2 at 6 mo	120 (69)	112 (64)	4.9 (−5 to 14.8)	1.08 (0.93 to 1.25)	.33
Secondary outcomes					
Mortality at 6 mo	48 (27)	60 (34)	−6.5 (−16.1 to 3.1)	0.81 (0.59 to 1.11)	.19
Any adverse event	169 (97)	161 (91)	5.6 (0.6 to 10.6)	1.06 (1.01 to 1.12)	.03

Targeted Temperature Management for Cardiac Arrest with Nonshockable Rhythm

N Engl J Med 2019;381:2327-37.

HYPERION study (2019)

P: OHCA/IHCA、non-shockable
I: 33(±0.5)℃/24h → 復温(0.25-0.5℃/h)
→ 37(±0.5)℃/24h
C: 37(±0.5)℃/48h
O: 90日後の神経学的転帰



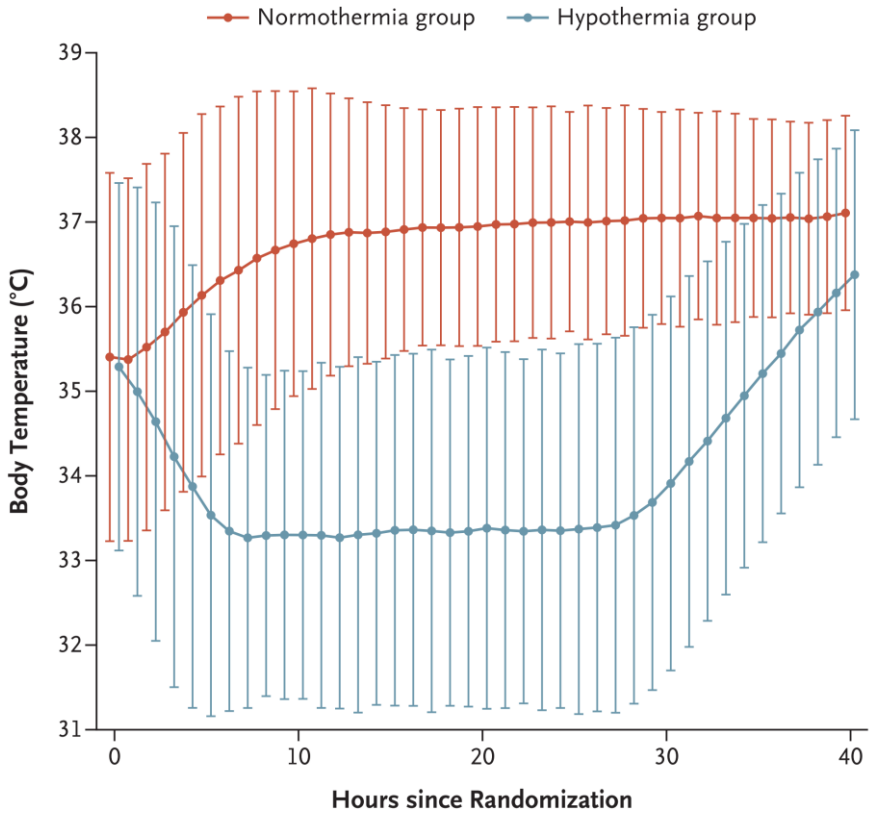
Outcome	Hypothermia (N=284)	Normothermia (N=297)	Difference or Hazard Ratio (95% CI)
CPC score of 1 or 2 on day 90 — no. (%)	29 (10.2)	17 (5.7)	4.5 (0.1 to 8.9)†
Cause of cardiac arrest — no. (%)			
Asphyxia	158 (55.6)	162 (54.5)	
Cardiac cause	79 (27.8)	79 (26.6)	
Anaphylaxis	4 (1.4)	5 (1.7)	
Neurologic cause	7 (2.5)	6 (2.0)	
Pulmonary embolism	10 (3.5)	12 (4.0)	
Other medical cause	20 (7.0)	22 (7.4)	
Trauma	1 (0.4)	2 (0.7)	
Drug poisoning	1 (0.4)	7 (2.4)	
Drowning	4 (1.4)	2 (0.7)	

Hypothermia versus Normothermia after Out-of-Hospital Cardiac Arrest

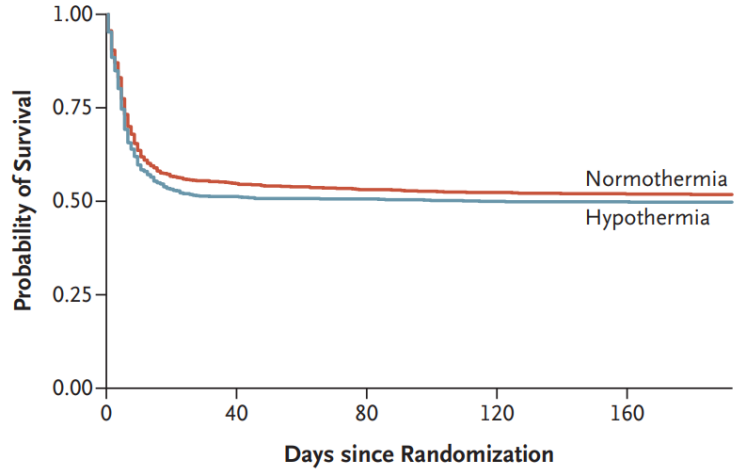
N Engl J Med 2021;384:2283-94.

TTM2 study (2021)

P：OHCA (目撃なしAsystole除く)
Ⅰ：33℃/28h → 37℃へ復温(0.33℃/h)
C：<37.8℃/40h
O：6ヶ月後の全死亡率
(両群とも72hまで 36.5-37.7℃ keep)



Outcome or Event	Hypothermia (N=930)	Normothermia (N=931)	Relative Risk (95% CI)*	P Value
Primary outcome: death from any cause at 6 mo — no./total no. (%)	465/925 (50)	446/925 (48)	1.04 (0.94–1.14)	0.37
Main secondary outcome — no./total no. (%)				
Score of 4–6 on modified Rankin scale at 6-mo follow-up†	488/881 (55)	479/866 (55)	1.00 (0.92–1.09)	
Serious adverse events — no./total no. (%)				
Arrhythmia resulting in hemodynamic compromise	222/927 (24)	152/921 (16)	1.45 (1.21–1.75)	<0.001



No. at Risk

Normothermia	925	506	491	484	480
Hypothermia	925	474	468	462	461

Individual differences in normal body temperature: longitudinal big data analysis of patient records

BMJ 2017;359:j5468

- コホート研究
- 2009-2014年
- アメリカ北東部の大学病院の外来患者
- 救急外来患者を除く
- 非感染症の診断で抗生剤非投与の患者
- 35,488名（平均年齢52.9歳、女性64%、白人59%）
- 計243,506回の体温測定
- 口腔内88.2%、側頭部3.5%、鼓膜3.0%、腋窩0.1%
- 平均体温36.6℃（95%CI 35.7-37.3℃、99%CI 35.3-37.7℃）

European Resuscitation Council and European Society of Intensive Care Medicine Guidelines 2021: Post-resuscitation care☆

RESUSCITATION 161 (2021) 220–269

Temperature control

- We recommend targeted temperature management (TTM) for adults after either OHCA or in-hospital cardiac arrest (IHCA) (with any initial rhythm) who remain unresponsive after ROSC.
- Maintain a target temperature at a constant value between 32 °C and 36 °C for at least 24 h.
- Avoid fever (>37.7 °C) for at least 72 h after ROSC in patients who remain in coma.
- Do not use pre-hospital intravenous cold fluids to initiate hypothermia.

ERC-ESICM guidelines on temperature control after cardiac arrest in adults ☆

RESUSCITATION 172 (2022) 229–236

Table 2 – ERC-ESICM Recommendations for temperature control after cardiac arrest in adults.

We recommend continuous monitoring of core temperature in patients who remain comatose after ROSC from cardiac arrest (good practice statement).
We recommend actively preventing fever (defined as a temperature > 37.7 °C) in post-cardiac arrest patients who remain comatose (weak recommendation, low-certainty evidence).
We recommend actively preventing fever for at least 72 hours in post-cardiac arrest patients who remain comatose (good practice statement).
Temperature control can be achieved by exposing the patient, using anti-pyretic drugs, or if this is insufficient, by using a cooling device with a target temperature of 37.5 °C (good practice statement).
There is currently insufficient evidence to recommend for or against temperature control at 32–36 °C in sub-populations of cardiac arrest patients or using early cooling, and future research may help elucidate this. We recommend not actively rewarming comatose patients with mild hypothermia after ROSC to achieve normothermia (good practice statement).
We recommend not using prehospital cooling with rapid infusion of large volumes of cold IV fluid immediately after ROSC (strong recommendation; moderate certainty evidence).

L008-2

「低体温療法」は「体温維持療法」に変わります

「L008-2 低体温療法」は「**L008-2 体温維持療法**」に名称を変え、
算定条件の目標温度が 35℃以下から **36℃**以下に、
維持時間が 12 時間以上から **24 時間**以上に変更となりました。

診療報酬改定について

改定前

L008-2

低体温療法（1 日につき）

12,200 点

(1) 低体温療法は、心肺蘇生後の患者に対し、直腸温 **35℃**以下で **12 時間**以上維持した場合に、開始日から3日間に限り算定する。

(2) 重度脳障害患者への治療的低体温の場合は算定できない。

(3) 当該点数を算定するに当たり、必ずしも手術を伴う必要はない。

2022 年 4 月　改定後

L008-2

体温維持療法（1 日につき）

12,200 点

(1) **体温維持療法**は、心肺蘇生後の患者に対し、直腸温 **36℃**以下で **24 時間**以上維持した場合に、開始日から3日間に限り算定する。

(2) 重度脳障害患者への治療的低体温の場合は算定できない。

(3) 当該点数を算定するに当たり、必ずしも手術を伴う必要はない。

令和 4 年厚生労働省告示第 54 号 診療報酬の算定方法の一部を改正する件別表第一 , 300P
令和 4 年 3 月 4 日保医発 0304 第 1 号 診療報酬の算定方法の一部改正に伴う実施上の留意事項について（通知）別添 1, 601P

The NEW ENGLAND JOURNAL of MEDICINE

Duration of Device-Based Fever Prevention after Cardiac Arrest

N Engl J Med 2023;388:888-97.

BOX trial (2022)

Blood-Pressure Targets in Comatose Survivors of Cardiac Arrest

N Engl J Med 2022;387:1456-66.

P: OHCA (目撃なしAsystole除く)
I: mABP 63mmHg (lower blood pressure)
C: mABP 77mmHg (higher blood pressure)
O: 90日以内の全死亡or退院時神経転帰不良

n = 789

Oxygen Targets in Comatose Survivors of Cardiac Arrest

N Engl J Med 2022;387:1467-76.

P: OHCA (目撃なしAsystole除く)
I: PaO_2 68-75mmHg (lower oxygenation)
C: PaO_2 98-105mmHg (higher oxygenation)
O: 90日以内の全死亡or退院時神経転帰不良

n = 789

先行の　Blood pressure × Oxygenation　による　２×２要因試験

⇩

今日の文献は、これに従属したROSC後の発熱予防期間に関する介入研究

- 2017年3月～2021年12月
- Denmark の cardiac arrest center 2施設
  (Odense University Hospital ＆ Rigshospitalet Copenhagen University Hospital)

P：OHCA (目撃なしAsystole除く)
　(ROSC後、機械的device導入による中枢温の管理)
I：36℃/24h → 37℃/12h (or 覚醒するまで)
C：36℃/24h → 37℃/48h (or 覚醒するまで)
　(いずれも37℃までは0.5℃/hで復温)
O：90日以内の全死亡or退院時神経転帰不良

＜Inclusion＞

- 18歳以上
- 心原性と推測されるOHCA
- 20分以上にわたり胸骨圧迫を要さず、循環維持できている
- GCS＜8、従命不可

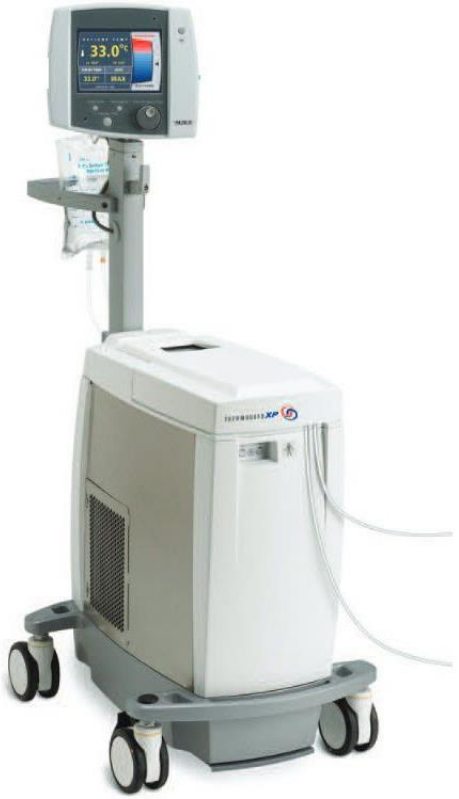
＜Exclusion＞

- 目撃なし心静止
- 頭蓋内出血や脳梗塞が疑われる

＜Randomization＞

- Web-based system
- Random permuted blocks of 2, 4 and 6 participants

OR



Criticool® and Allon®

(Belmont Medical Technologies)

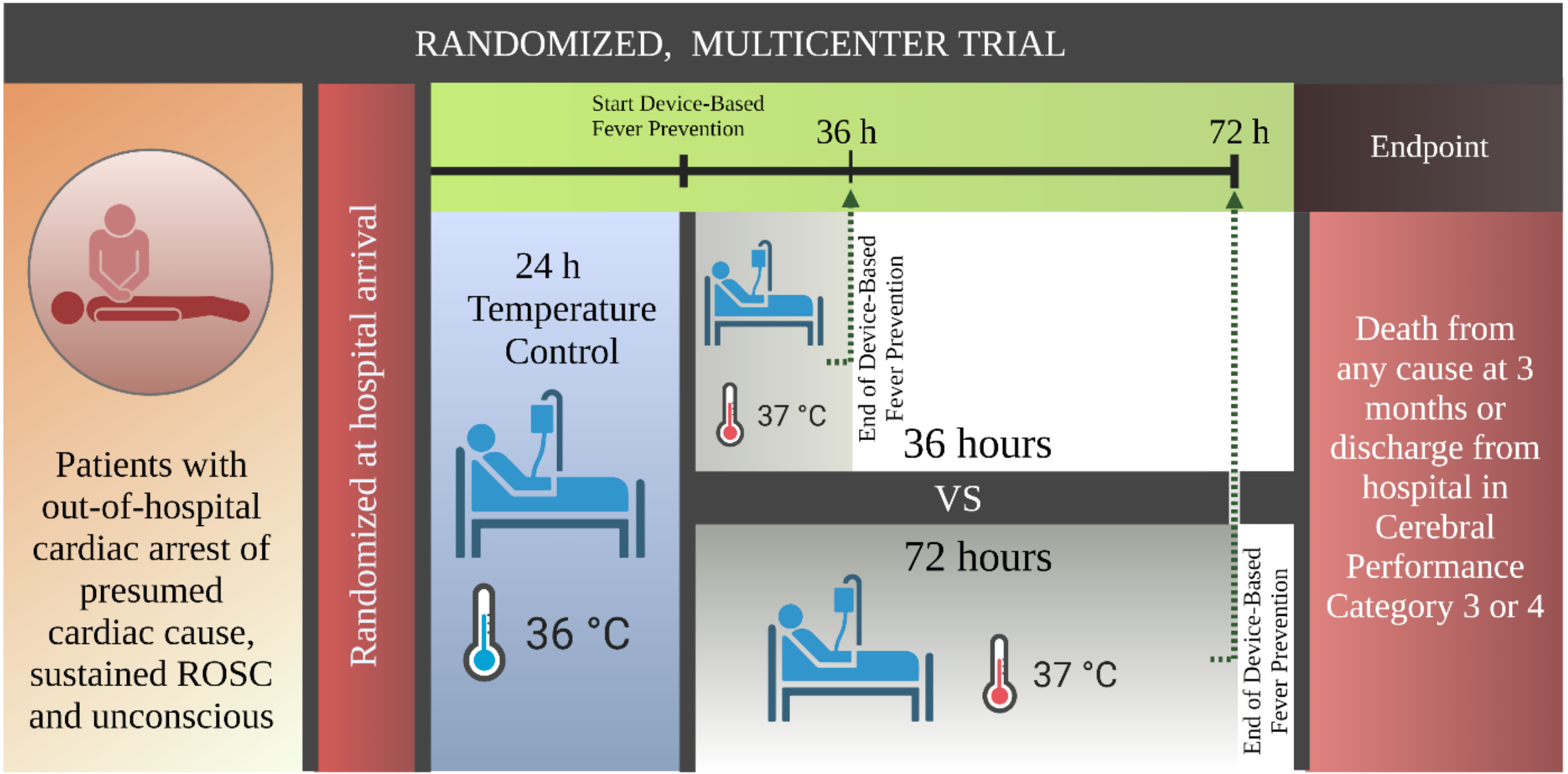
surface cooling

Thermogard XP® and Cool Line®

(Zoll)

intravenous cooling

BOX TRIAL - DEVICE-BASED FEVER PREVENTION



- 患者が覚醒すれば冷却は終了
- デバイスに拠らない発熱(＞37.7℃)への対応
  - pharmacologic (paracetamol)
  - uncovering the body

→医師の裁量で行う（ただし ice pack/ice pad は使わない）

＜Primary outcome＞

ランダム化90日以内での

- 全死亡　　または
- Cerebral Performance Category (CPC) = 3 or 4

成人用脳機能カテゴリースケール（Cerebral Performance Category Scale［Adult］）*

スコア	カテゴリー	説明
1	正常（脳機能良好）	意識清明で，労働が可能であり，普通の生活を送ることができる。 軽度の心理的問題または神経脱落症状を有することがある（例，軽度の嚥下困難，機能障害を伴わない不全片麻痺，軽微な脳神経の異常）。
2	中等度障害（身体障害はあるが介助は要さない）	意識があり，保護された環境でのパートタイム勤務または介助なしで日常生活動作（例，着衣，公共交通機関での移動，食事の準備）を行うのに十分な脳機能を有する。 片麻痺，痙攣発作，運動失調，構音障害，失語，または永続的な記憶障害もしくは精神状態の変化がみられることがある。
3	高度障害（意識はあるが身体障害があり介助を要する）	意識はあるが，日常生活に他者の介助を必要とする（施設内または自宅の場合には家族の並外れた努力の下で）。少なくとも制限された認知能力がある。 このカテゴリーには，広範囲の神経機能障害が含まれ，歩行可能であるが重度の記憶障害または認知症があり介助なしの生活ができない患者から，麻痺があり眼でしか意思疎通ができない患者（閉じ込め症候群でみられるような状態）に至るまで，幅がある。
4	意識がない（昏睡または植物状態）	意識がなく，周囲の状況を認識できず，認知能力がない。周囲環境との言語的または心理的な相互作用がない。
5	脳死	脳死の基準を満たしているか，従来の基準に基づき死亡している状態

*分類の際は，どの基準においても最も悪い値を用いる。神経疾患が原因の場合についてのみ，障害をスコア化する。評価は診療録または保護者との面接に基づいて行う。

＜Secondary outcome＞

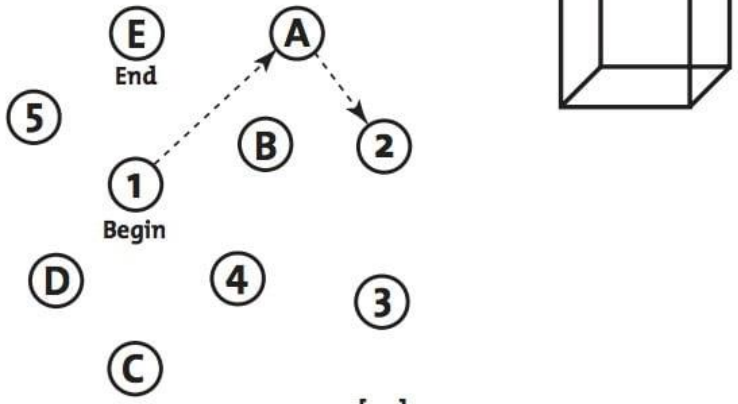
3ヶ月時点での

- Montreal Cognitive Assessment score (MoCA)
- modified Rankin Scale score (mRS)
- Cerebral Performance Category (CPC)

MONTREAL COGNITIVE ASSESSMENT (MOCA)

NAME :
Education :
Sex :
DATE :

VISUOSPATIAL / EXECUTIVE



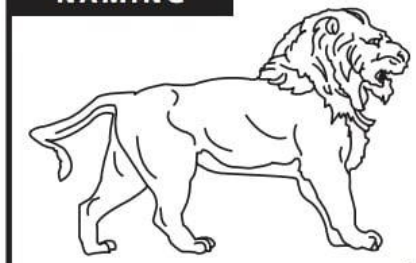
Copy cube [ ]

Draw CLOCK (Ten past eleven) (3 points) [ ]

POINTS

Contour [ ] Numbers [ ]

NAMING



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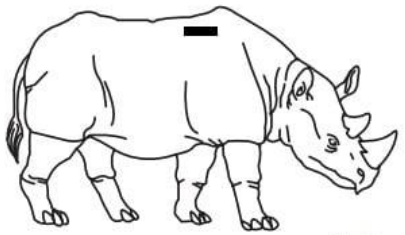

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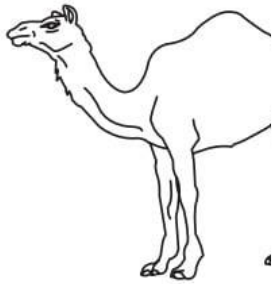


MEMORY	Read list of words, subject must repeat them. Do 2 trials. Do a recall after 5 minutes.		FACE	VELVET	CHURCH	DAISY	RED
		1st trial					
		2nd trial					

No points

ATTENTION Read list of digits (1 digit/ sec.). Subject has to repeat them in the forward order [ ] 2 1 8 5 4
Subject has to repeat them in the backward order [ ] 7 4 2 __/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors
[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B __/1

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65
4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt** __/3

LANGUAGE Repeat : I only know that John is the one to help today. [ ]
The cat always hid under the couch when dogs were in the room. [ ] __/2

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] ____ (N ≥ 11 words) __/1

ABSTRACTION Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler __/2

DELAYED RECALL	Has to recall words WITH NO CUE	FACE [ ]	VELVET [ ]	CHURCH [ ]	DAISY [ ]	RED [ ]	Points for UNCUED recall only
Optional	Category cue						
	Multiple choice cue						

__/5

ORIENTATION [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City __/6

 Version November 7, 2004

www.mocatest.org

Normal ≥ 26 / 30

TOTAL __/30

Add 1 point if ≤ 12 yr edu

MoCA score：

- 0～30点
- 26点以上で認知機能正常 の判定

Modified Rankin Scale	
0	No symptoms
1	No significant disability. Able to carry out all usual activities, despite some symptoms.
2	Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities.
3	Moderate disability. Requires some help, but able to walk unassisted.
4	Moderate severe disability. Unable to attend to own bodily needs without assistance, and unable to walk unassisted.
5	Severe disability. Requires constant nursing care and attention, bedridden, incontinent.
6	Dead

＜Statistical analysis＞

BOX trial (2022)

Blood-Pressure Targets in Comatose Survivors of Cardiac Arrest

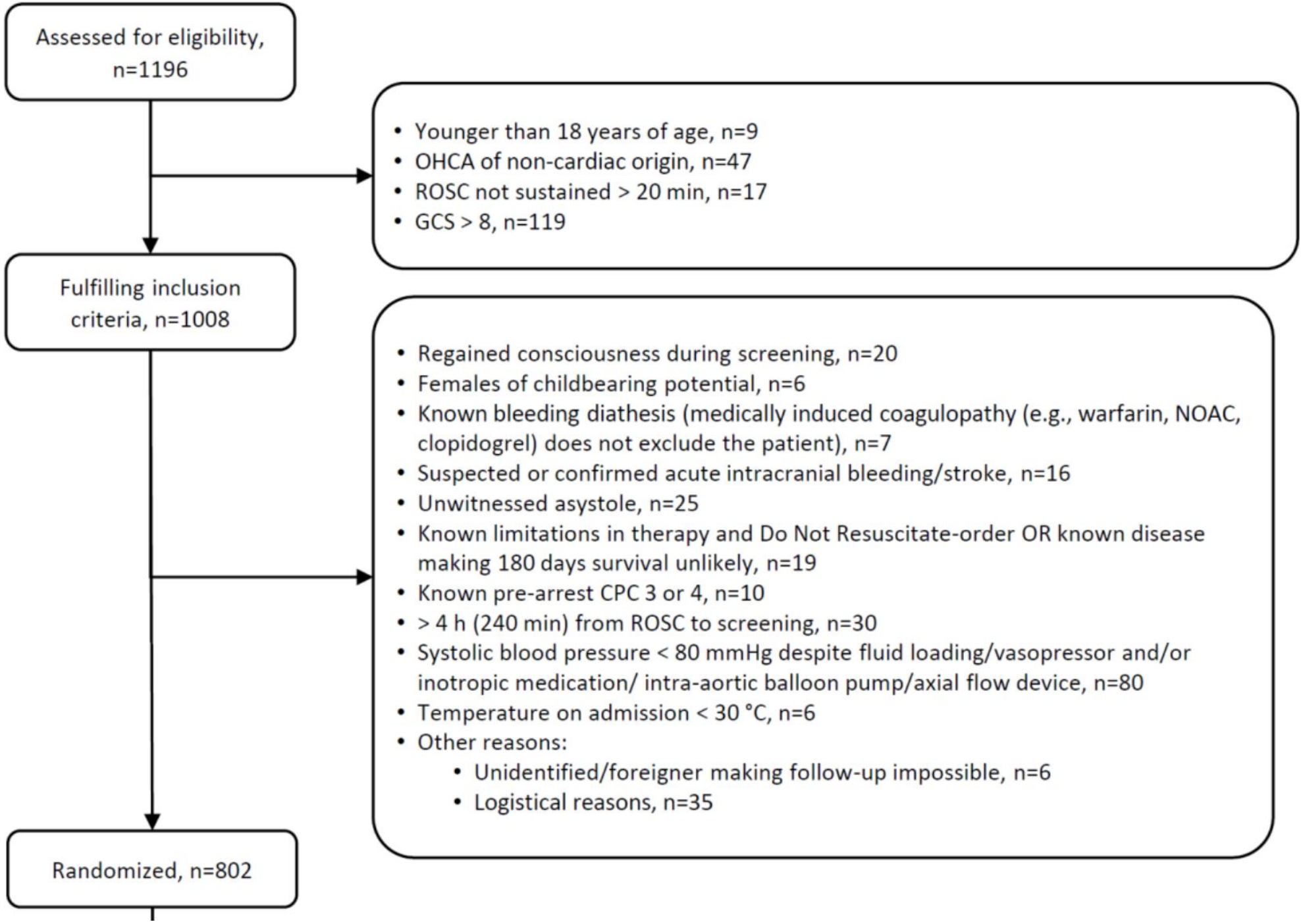
Oxygen Targets in Comatose Survivors of Cardiac Arrest

⇨

死亡率の差を10%に設定
⇩
サンプルサイズ 800 目標
⇩
802 patients enrolled

上記に従属した研究における本文献では、上記サンプルサイズにおいて

2群の差 27.5% を検出するのに、α値 0.05、検出力 80% を持つ計算


Assessed for eligibility, n=1196
• Younger than 18 years of age, n=9
• OHCA of non-cardiac origin, n=47
• ROSC not sustained > 20 min, n=17
• GCS > 8, n=119
Fulfilling inclusion criteria, n=1008
• Regained consciousness during screening, n=20
• Females of childbearing potential, n=6
• Known bleeding diathesis (medically induced coagulopathy (e.g., warfarin, NOAC, clopidogrel) does not exclude the patient), n=7
• Suspected or confirmed acute intracranial bleeding/stroke, n=16
• Unwitnessed asystole, n=25
• Known limitations in therapy and Do Not Resuscitate-order OR known disease making 180 days survival unlikely, n=19
• Known pre-arrest CPC 3 or 4, n=10
• > 4 h (240 min) from ROSC to screening, n=30
• Systolic blood pressure < 80 mmHg despite fluid loading/vasopressor and/or inotropic medication/ intra-aortic balloon pump/axial flow device, n=80
• Temperature on admission < 30 °C, n=6
• Other reasons:
• Unidentified/foreigner making follow-up impossible, n=6
• Logistical reasons, n=35
Randomized, n=802

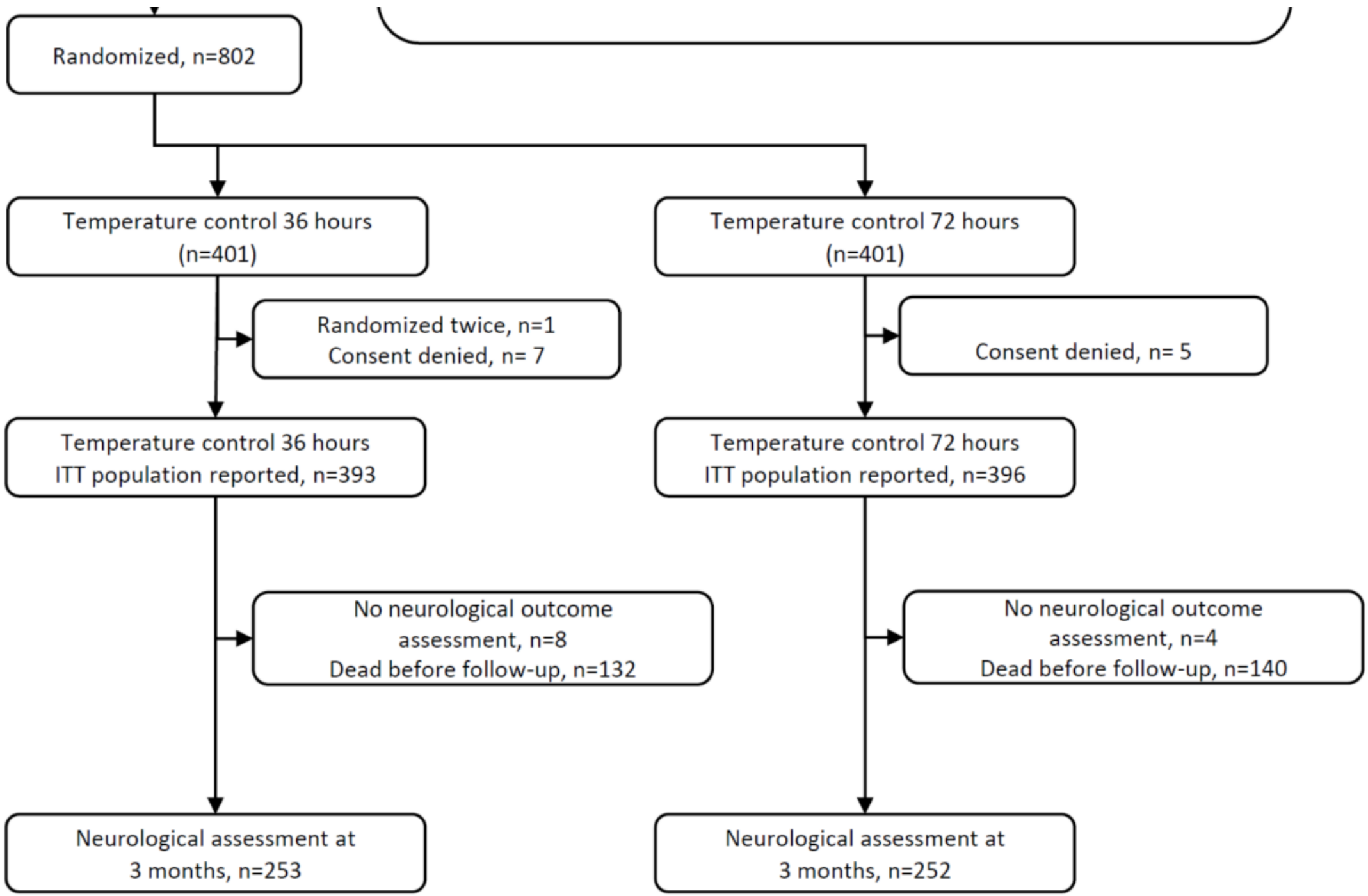
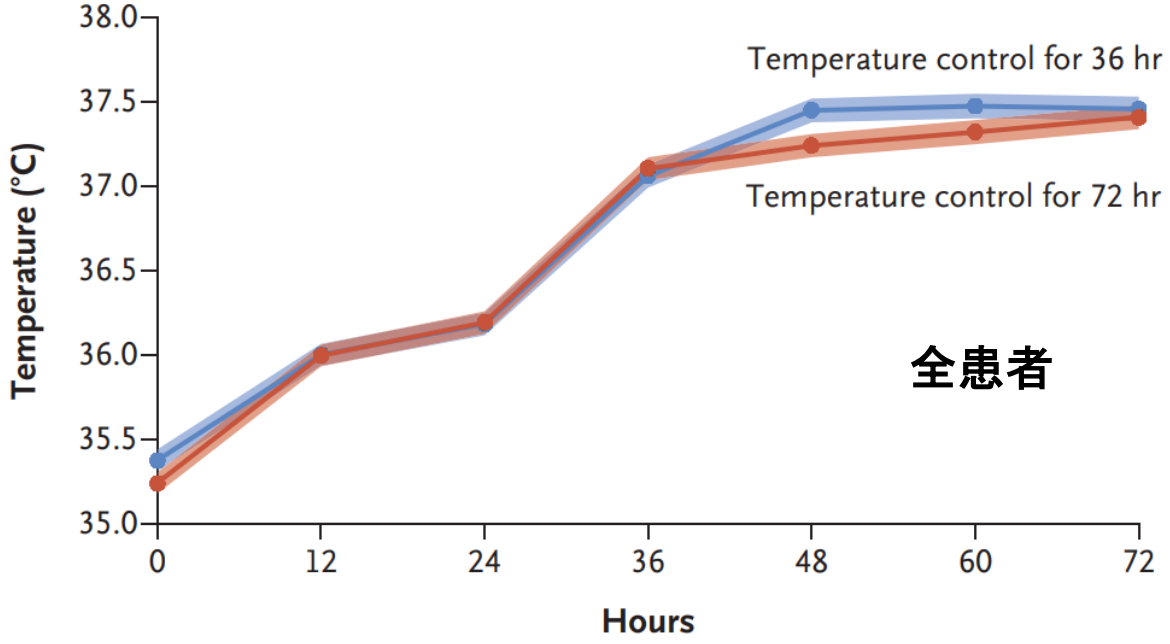

Randomized, n=802
Temperature control 36 hours
(n=401)
Temperature control 72 hours
(n=401)
Randomized twice, n=1
Consent denied, n= 7
Consent denied, n= 5
Temperature control 36 hours
ITT population reported, n=393
Temperature control 72 hours
ITT population reported, n=396
No neurological outcome
assessment, n=8
Dead before follow-up, n=132
No neurological outcome
assessment, n=4
Dead before follow-up, n=140
Neurological assessment at
3 months, n=253
Neurological assessment at
3 months, n=252

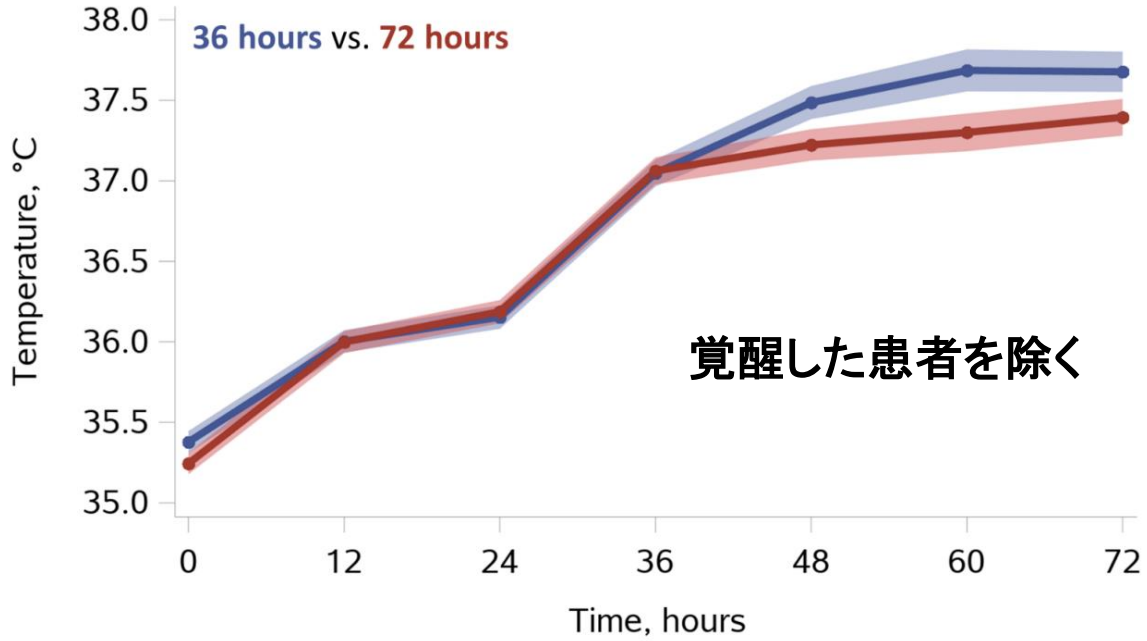
Table 1. Baseline Characteristics of the Patients.*

Characteristic	Temperature Control for 36 Hr (N=393)	Temperature Control for 72 Hr (N=396)
Age — yr	62±13	63±14
Range	18–90	18–89
Male sex — no. (%)	320 (81)	316 (80)
Medical history — no./total no. (%)		
Hypertension	186/393 (47)	176/394 (45)
Diabetes	47/392 (12)	53/395 (13)
Myocardial infarction	93/391 (24)	79/396 (20)
Atrial fibrillation	72/390 (18)	55/395 (14)
Heart failure	71/391 (18)	66/396 (17)
Chronic obstructive pulmonary disease	26/391 (7)	37/396 (9)
Stroke	25/392 (6)	34/396 (9)
Chronic kidney disease†	20/392 (5)	19/396 (5)
Renal-replacement therapy	1/392 (<1)	3/396 (1)
Characteristics of the cardiac arrest		
Shockable rhythm — no./total no. (%)	334/392 (85)	333/395 (84)
Pulseless electrical activity — no./total no. (%)	17/392 (4)	18/395 (5)
Witnessed asystole — no./total no. (%)	15/392 (4)	15/395 (4)
Witnessed arrest — no./total no. (%)	338/392 (86)	334/396 (84)
Bystander cardiopulmonary resuscitation — no./total no. (%)	340/385 (88)	339/391 (87)
First defibrillation by automated external defibrillator — no./total no. (%)	92/386 (24)	90/390 (23)
Time to return of spontaneous circulation — min‡	21±13	21±15
Findings and procedures at hospital arrival		
pH§	7.20±0.13	7.21±0.13
Lactate level — mmol/liter¶	5.9±3.8	5.8±3.9
ST-segment elevation in ECG — no./total no. (%)	172/388 (44)	178/385 (46)
Immediate coronary angiography performed — no. (%)	359 (91)	363 (92)
PCI performed — no./total no. (%)	161/359 (45)	175/361 (48)

A


Temperature control for 36 hr
Temperature control for 72 hr
全患者
Temperature (°C)
38.0
37.5
37.0
36.5
36.0
35.5
35.0
0
12
24
36
48
60
72
Hours

A


36 hours vs. 72 hours
覚醒した患者を除く
Temperature, °C
38.0
37.5
37.0
36.5
36.0
35.5
35.0
0
12
24
36
48
60
72
Time, hours

B

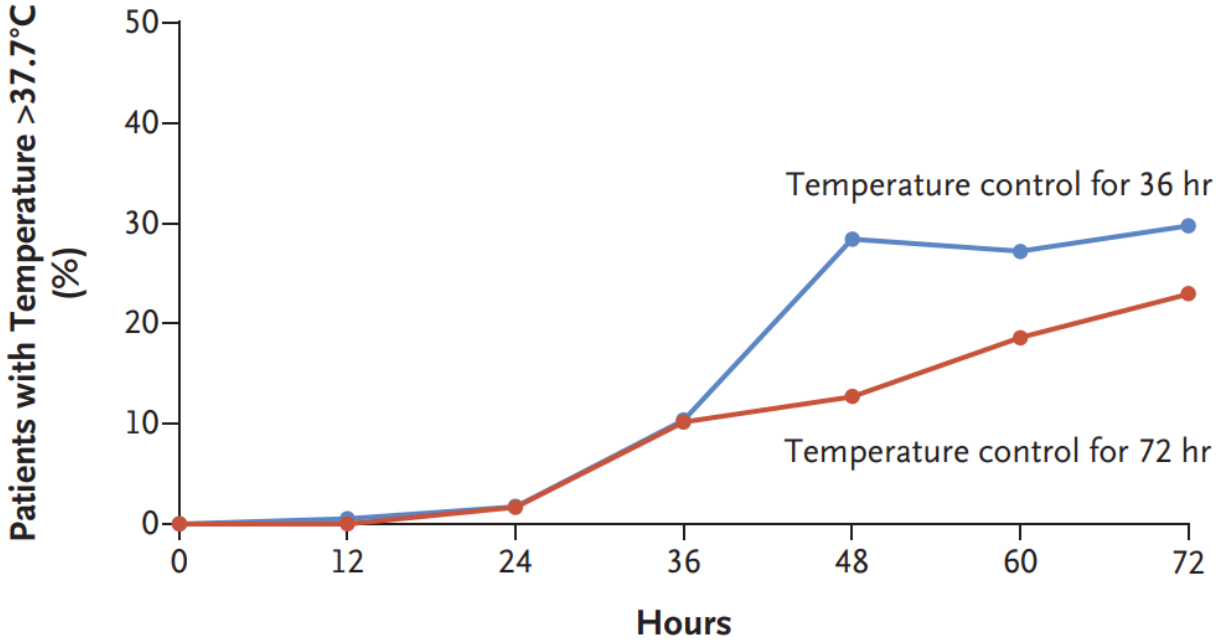
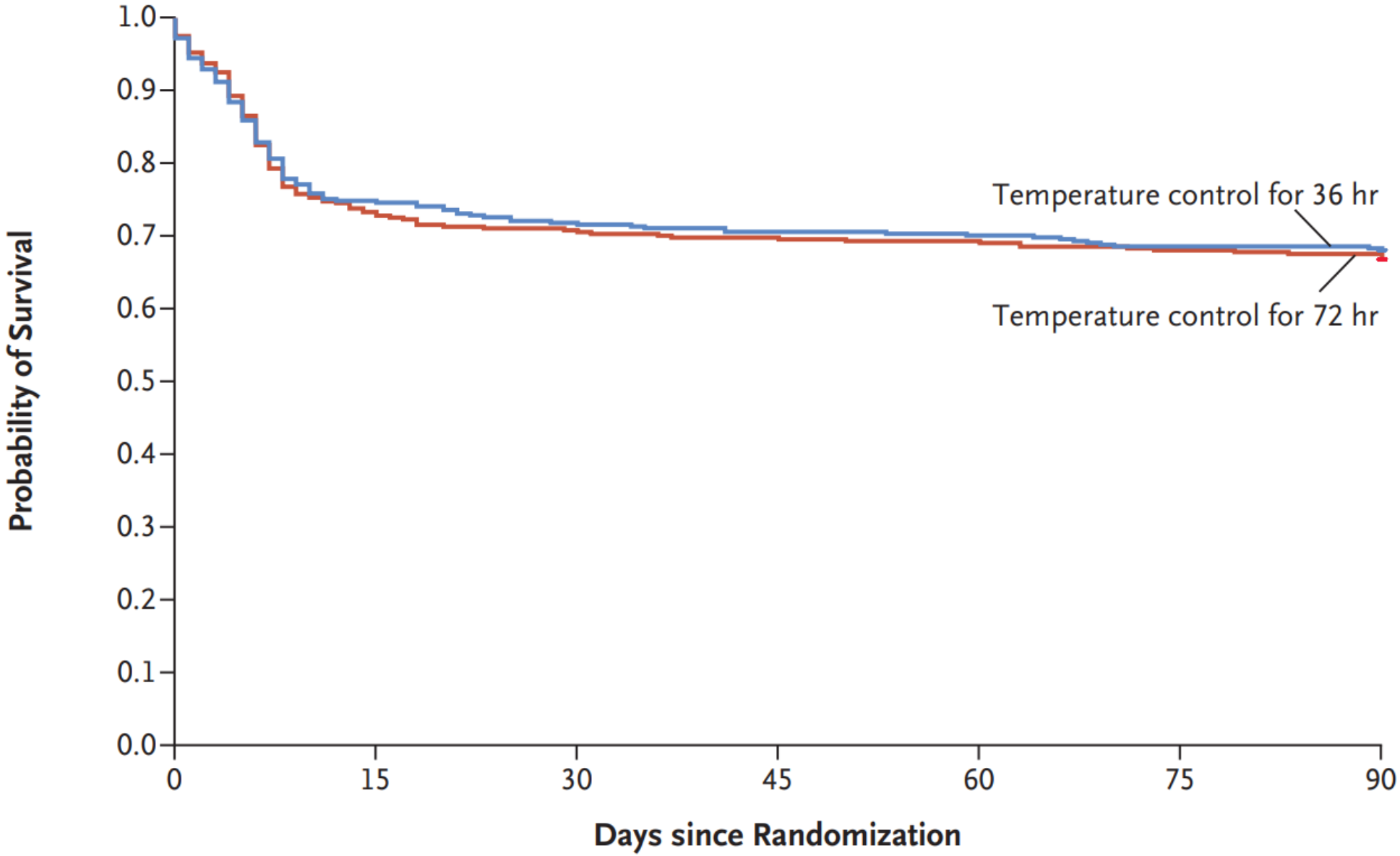

Temperature control for 36 hr
Temperature control for 72 hr
Patients with Temperature >37.7°C (%)
50
40
30
20
10
0
0
12
24
36
48
60
72
Hours

Table 2. Outcomes and Adverse Events.*

Outcome or Event	Temperature Control for 36 Hr (N=393)	Temperature Control for 72 Hr (N=396)	Hazard Ratio (95% CI)	P Value
Primary outcome				
Death from any cause or CPC of 3 or 4 at discharge within 90 days — no. (%)†	127 (32.3)	133 (33.6)	0.99 (0.77–1.26)	0.70
Secondary outcomes				
Death from any cause within 90 days — no. (%)	116 (29.5)	120 (30.3)	0.97 (0.75–1.26)	
Median CPC among patients alive at 3 mo (IQR)†	1 (1–5)	1 (1–5)		
Median modified Rankin scale score among patients alive at 3 mo (IQR)‡	1 (0–6)	1 (0–6)		
Median Montreal Cognitive Assessment score among patients alive at 3 mo (IQR)§	26 (24–29)	27 (24–28)		
			Relative Risk (95% CI)	
Adverse events — no. (%)				
Infection in ICU¶	102 (26.0)	110 (27.8)	0.96 (0.82–1.11)	0.56
Arrhythmia in ICU‖	62 (15.8)	47 (11.9)	1.19 (0.95–1.50)	0.11
Any bleeding**	84 (21.4)	90 (22.7)	0.96 (0.82–1.13)	0.65
Uncontrolled bleeding**	17 (4.3)	21 (5.3)	0.90 (0.67–1.21)	0.52
Acute kidney injury with renal-replacement therapy	39 (9.9)	42 (10.6)	0.96 (0.77–1.20)	0.75
Electrolyte disorder††	30 (7.6)	27 (6.8)	1.06 (0.80–1.41)	0.66
Metabolic disorder‡‡	34 (8.7)	28 (7.1)	1.12 (0.84–1.49)	0.41
Seizure§§	84 (21.4)	80 (20.2)	1.04 (0.87–1.24)	0.69



No. at Risk

Temperature control for 36 hr	393	293	281	276	274	268	267
Temperature control for 72 hr	396	289	279	275	273	268	266

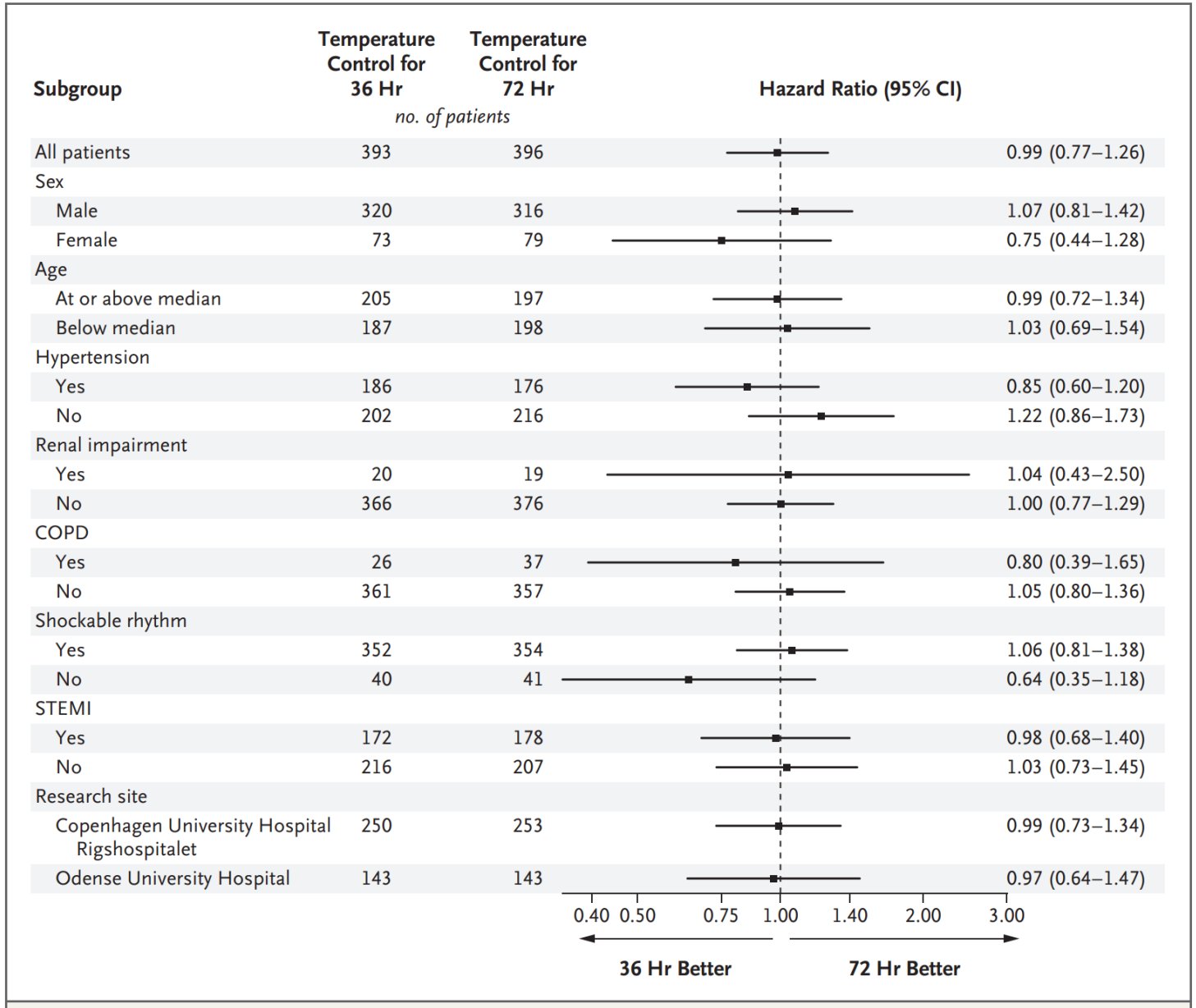


Figure 3. Subgroup Analysis of the Primary Outcome.

Data are from prespecified subgroup analyses of the primary outcome (death from any cause or discharge from hospital with a Cerebral Performance Category of 3 or 4). The forest plot shows the hazard ratios with 95% confidence intervals. COPD denotes chronic obstructive pulmonary disease, and STEMI ST-segment elevation myocardial infarction.

＜Discussion＞

- 介入期間に覚醒した患者（その時点で体温管理は終了）について、いずれかの device-based fever prevention により利があったかどうかについて、調査は行っていない。
- 「36時間」という時間は、冷却-維持-復温という工程が全患者で遂行されるのに必要な時間と考え、設定した。
- 発熱（＞37.7℃）を避けるために antipyretics や uncovering も併用するプロトコルだったが、これらの処置の効果は限定的かもしれず、神経学的不良転帰に対するエビデンスは乏しい。

＜Limitation＞

- 体温介入はマスクされていない。
- 微熱の予防に対しての効果はごく僅か。
- COVID-19 pandemic による制約のため、外来通院の一時停止や、その後も患者が病院へ行くのを避けるなどして追跡が難しくなり、認知機能テストの評価数が想定より少ない。
- 約85%の初期波形が shockable rhythm、約90%がbystander CPR を受けており、本trialでは、比較的良好な予後が期待できる患者が対象。（より重症な脳損傷の集団ではどうか。）
- 統計手法やサンプルサイズが独立したものでなく(先のBOX trial)、わずかな効果に対しては検出力が限られている可能性がある。

＜Conclusion＞

Active device-based fever prevention for 72 hours or 36hours

after cardiac arrest did not result in significantly different

percentages of patients dying or having severe disability or coma.