Journal Club
血管拡張性ショックに対する血圧管理目標

2018/03/13

聖マリアンナ医科大学救急医学
永冨彰仁

本日の論文

SYSTEMATIC REVIEW

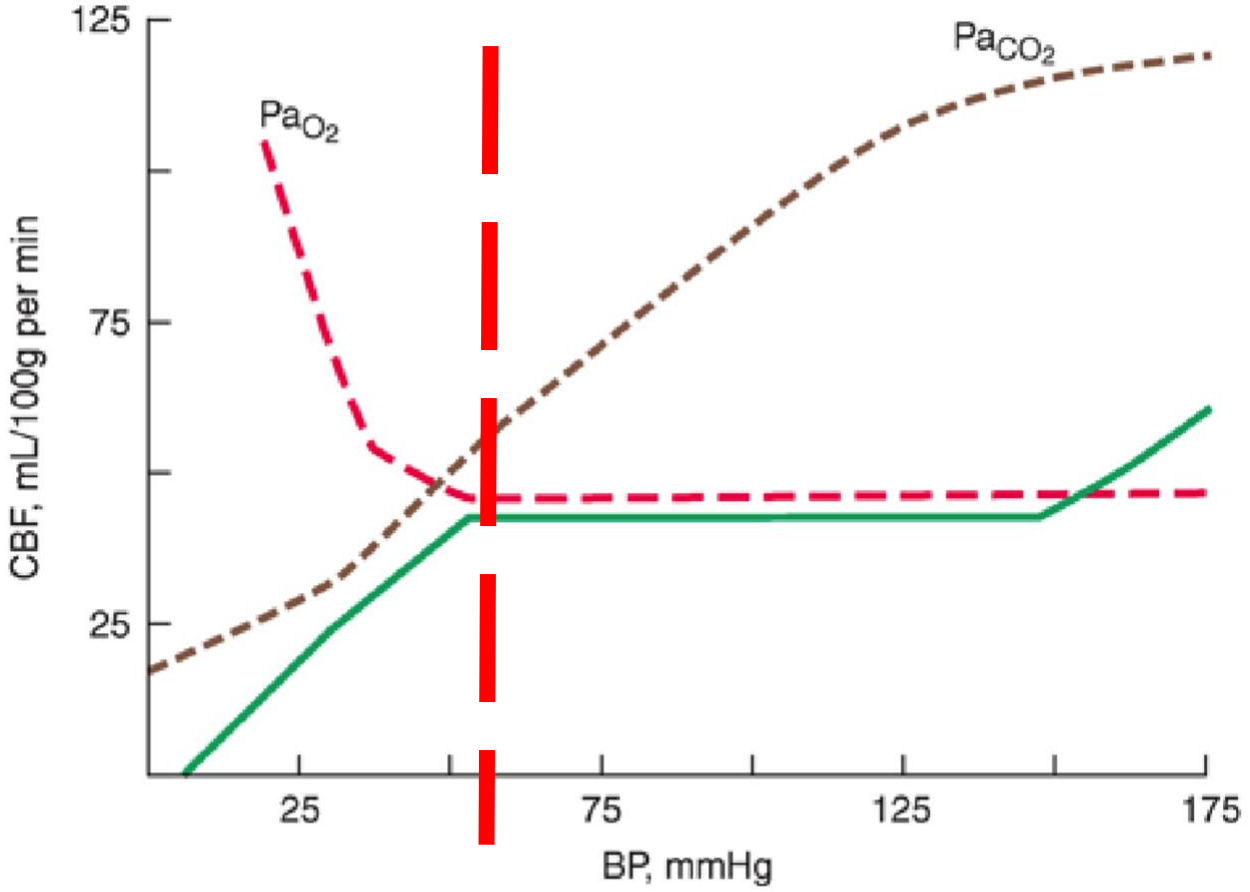
Pooled analysis of higher versus lower blood pressure targets for vasopressor therapy septic and vasodilatory shock

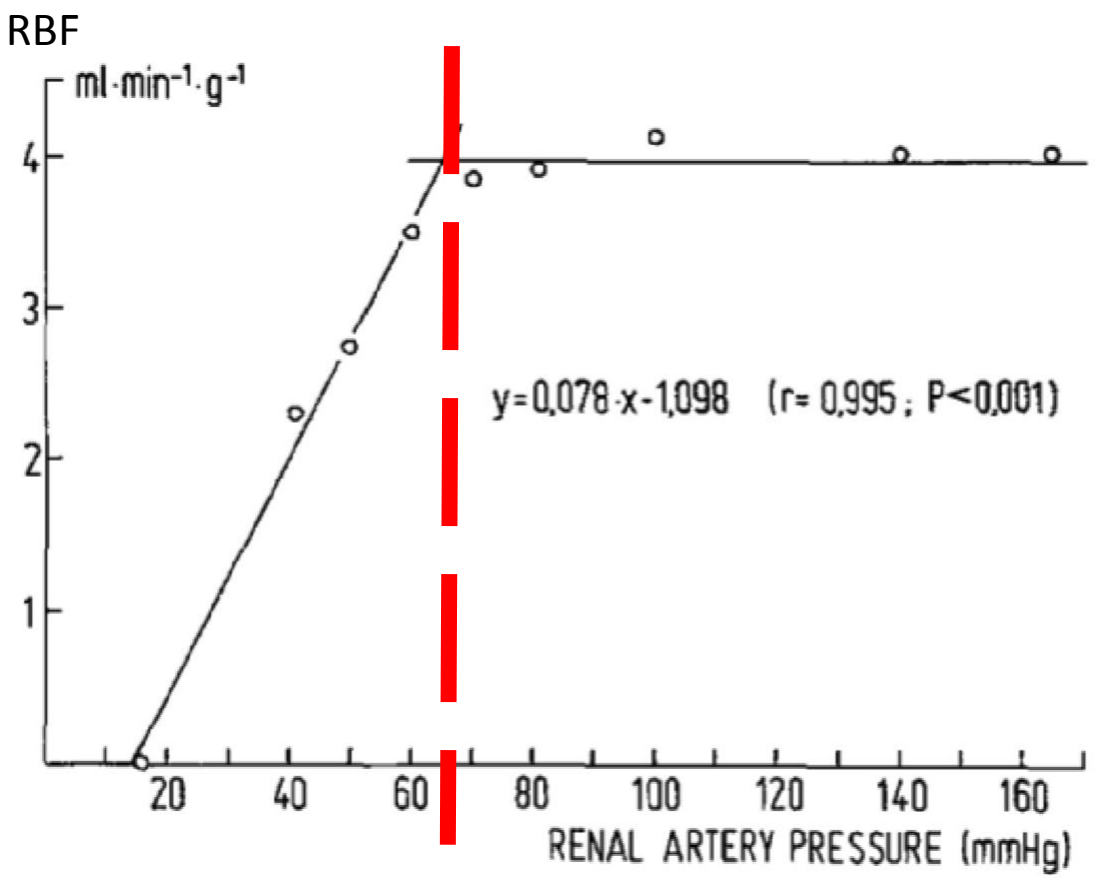
François Lamontagne[1,2*], Andrew G. Day[3], Maureen O. Meade[4,5], Deborah J. Cook[4,5], Gordon H. Guyatt[5], Mathieu Hylands[6], Peter Radermacher[7], Jean-Marie Chrétien[8], Nicolas Beaudoin[9], Paul Hébert[10], Frédérick D'Aragon[1,2], Ferhat Meziani[11] and Pierre Asfar[12]

Intensive Care Med (2018) 44:12–21

背景

脳血流・腎血流と血圧の関連





Phlugers Arch 1987;410-449

Source: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine, 18th Edition*: www.accessmedicine.com

Copyright © The McGraw-Hill Companies, Inc. All rights reserved.

ショックの初期蘇生における平均血圧(MAP)目標値

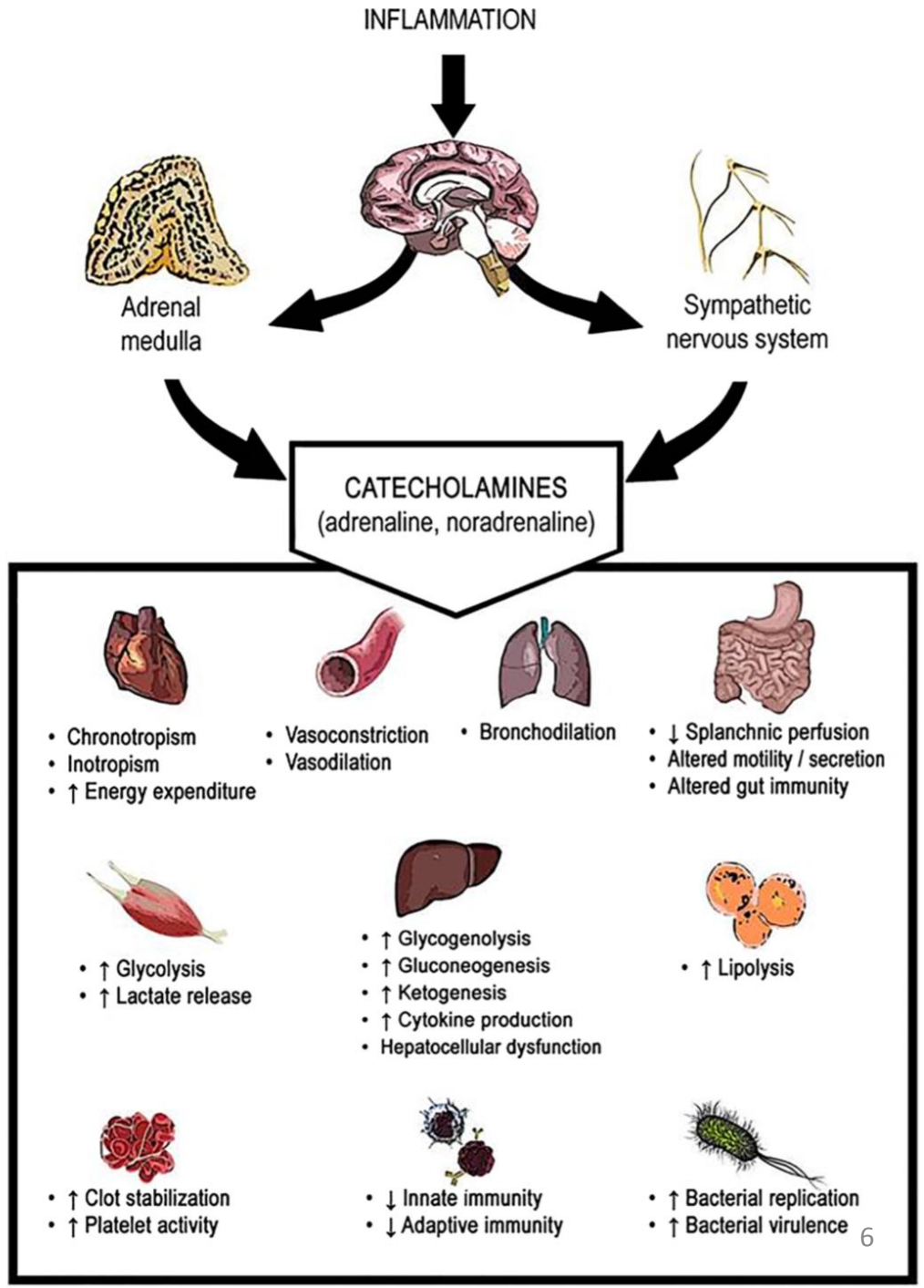
- ガイドラインでMAP≧65mmHgが推奨

Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med 41:580–637

Consensus on circulatory shock and hemodynamic monitoring. Task force of the European Society of Intensive Care Medicine. Intensive Care Med 40:1795–1815

ガイドライン上、もともと高血圧症や動脈硬化症がある患者は、より高い目標の方がいいかもしれないことが言及されていた

カテコラミン使用
による血管収縮
⇓
しばしば大量投与
⇓
臓器血流障害？
⇓
予後を悪化させる
可能性は？



Intensive Care Med 42:1387-1397.

血管拡張性ショックの蘇生における平均血圧目標は65mmHgで十分か？もっと高い方が良いか？

近年２件のRCTが発表

SEPSISPAM trial

敗血症性ショックにおける血圧目標

N Engl J Med 2014; 370:1583-1593

OVATION trial

血管拡張性ショックにおける血圧目標

Intensive Care Med (2016) 42:542–550

SEPSISPAM trial

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 24, 2014 VOL. 370 NO. 17

High versus Low Blood-Pressure Target in Patients with Septic Shock

Pierre Asfar, M.D., Ph.D., Ferhat Meziani, M.D., Ph.D., Jean-François Hamel, M.D., Fabien Grelon, M.D., Bruno Megarbane, M.D., Ph.D., Nadia Anguel, M.D., Jean-Paul Mira, M.D., Ph.D., Pierre-François Dequin, M.D., Ph.D., Soizic Gergaud, M.D., Nicolas Weiss, M.D., Ph.D., François Legay, M.D., Yves Le Tulzo, M.D., Ph.D., Marie Conrad, M.D., René Robert, M.D., Ph.D., Frédéric Gonzalez, M.D., Christophe Guitton, M.D., Ph.D., Fabienne Tamion, M.D., Ph.D., Jean-Marie Tonnelier, M.D., Pierre Guezennec, M.D., Thierry Van Der Linden, M.D., Antoine Vieillard-Baron, M.D., Ph.D., Eric Mariotte, M.D., Gaël Pradel, M.D., Olivier Lesieur, M.D., Jean-Damien Ricard, M.D., Ph.D., Fabien Hervé, M.D., Damien du Cheyron, M.D., Ph.D., Claude Guerin, M.D., Ph.D., Alain Mercat, M.D., Ph.D., Jean-Louis Teboul, M.D., Ph.D., and Peter Radermacher, M.D., Ph.D., for the SEPSISPAM Investigators*

N Engl J Med 2014; 370:1583-1593

SEPSISPAM trial

P	敗血症性ショック 776症例
I	High-Target Group(MAP80～85mmHg)
C	Low-Target Group (MAP65～70mmHg)
O	28日死亡率

結果

Primary outcome	28日死亡率　有意差（–）
Secondary outcome	90日死亡率　有意差（–） 慢性高血圧症例 Low-Target group　透析率↑
Adverse events	High-Target Group　心房細動↑

OVATION trial（本日の論文と同一の著者）

ORIGINAL

Higher versus lower blood pressure targets for vasopressor therapy in shock: a multicentre pilot randomized controlled trial

François Lamontagne[1,2,3*], Maureen O. Meade[4,5], Paul C. Hébert[6], Pierre Asfar[7], François Lauzier[8,9,25], Andrew J.E. Seely[10,11], Andrew G. Day[12], Sangeeta Mehta[13], John Muscedere[14], Sean M. Bagshaw[15], Niall D. Ferguson[13], Deborah J. Cook[4,5], Salmaan Kanji[11], Alexis F. Turgeon[9,25], Margaret S. Herridge[13], Sanjay Subramanian[16], Jacques Lacroix[17], Neill K.J. Adhikari[13,18], Damon C. Scales[13,18], Alison Fox-Robichaud[4], Yoanna Skrobik[19], Richard P. Whitlock[20,21], Robert S. Green[22], Karen K.Y. Koo[23], Teddie Tanguay[24], Sheldon Magder[19], Daren K. Heyland[12] and for the Canadian Critical Care Trials Group.

© 2016 Springer-Verlag Berlin Heidelberg and ESICM

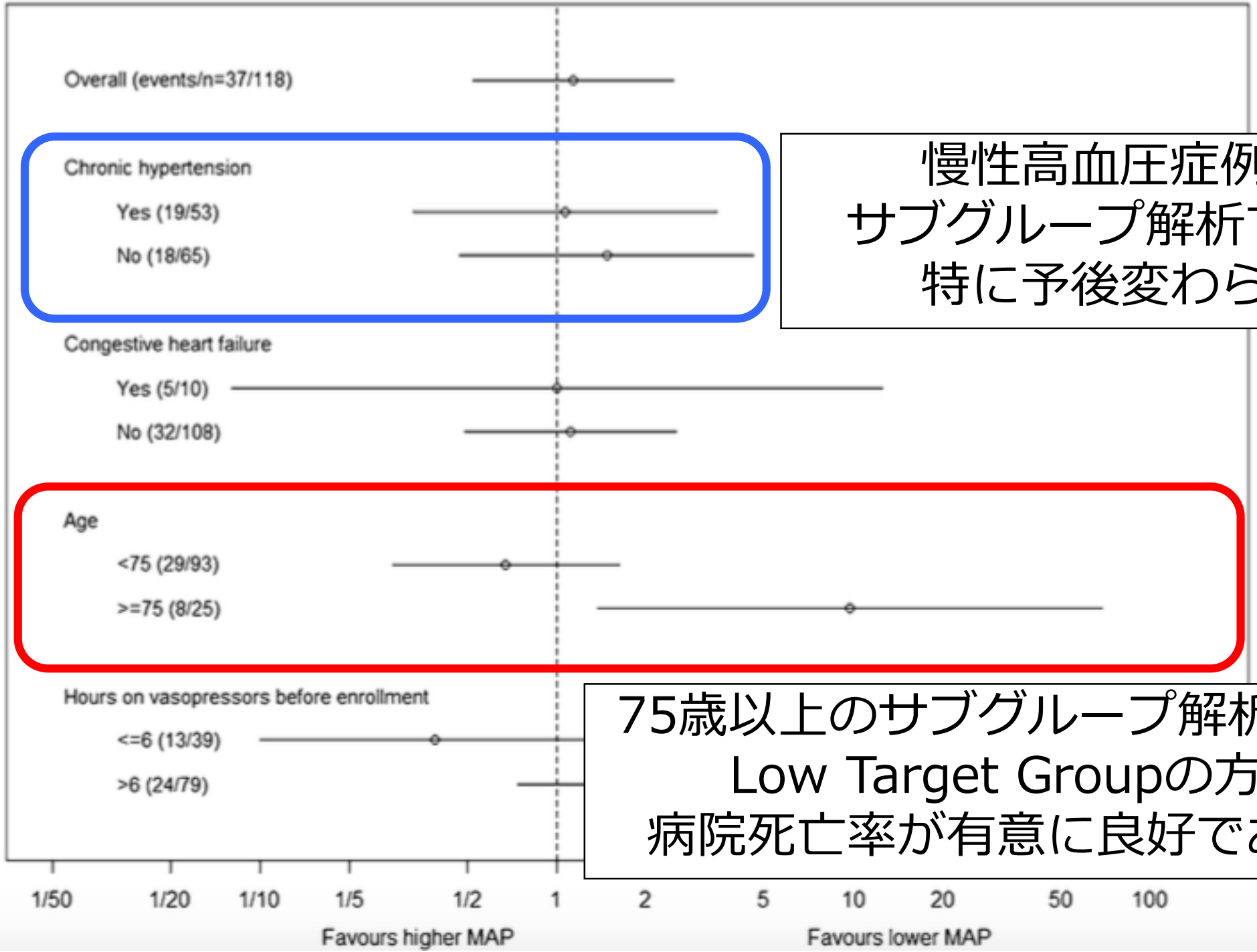
Intensive Care Med (2016) 42:542–550

OVATION trial

P	血管拡張性ショック 118症例 約70%が敗血症性ショック
I	High-Target Group(MAP:75～80mmHg)
C	Low-Target Group (MAP:60-65mmHg)
O	両群間のMAPの差（pilot trialのため）

結果

Primary outcome	両群間のMAPの差　9mmHg
Clinical outcome	ICU退室時死亡率 28日死亡率 退院時死亡率 6カ月死亡率 いずれも有意差（－）
Adverse effects	心房細動発症率有意差（－）



慢性高血圧症例の
サブグループ解析では、
特に予後変わらず

75歳以上のサブグループ解析では、
Low Target Groupの方が
病院死亡率が有意に良好であった

2件のRCT
目標血圧は患者属性で変えるべき
可能性があることを示唆

本日の論文

SYSTEMATIC REVIEW

Pooled analysis of higher versus lower blood pressure targets for vasopressor therapy septic and vasodilatory shock

François Lamontagne[1,2*], Andrew G. Day[3], Maureen O. Meade[4,5], Deborah J. Cook[4,5], Gordon H. Guyatt[5], Mathieu Hylands[6], Peter Radermacher[7], Jean-Marie Chrétien[8], Nicolas Beaudoin[9], Paul Hébert[10], Frédérick D'Aragon[1,2], Ferhat Meziani[11] and Pierre Asfar[12]

Intensive Care Med (2018) 44:12–21

CLINICAL QUESTIONS

成人ショック症例で血圧目標を変化させることで
28日死亡率を低減しうるか

患者属性に応じ血圧目標を変えることで
28日死亡率を減少させるか

Systematic reviewを行い
個人データを用いたmeta-analysisで調査する

方法

対象論文のPICO
以下を調べたRCTを対象として検索

P	血管拡張性ショック
I	Higher MAP target群
C	Lower MAP target群
O	28日死亡率

検索と選別基準

PROSPEROに登録 (CRD42016037482)

使用したサーチエンジン

MEDLINE(1946～2017年1月)

EMBASE(1980～2017年1月)

Cochrane Central Register of Controlled Trials

除外基準

クロスオーバー試験

通常用いられない昇圧薬

24時間未満の治療介入の研究は除外

言語での除外はしなかった

抽出したRCTの個人データから マスター・データベースを作成

eTable 4: Variable harmonization

Harmonized variables	Variables in SEPSISPAM	Variables in OVATION	Notes for combining variables from OVATION and SEPSISPAM
Baseline Characteristics			
Site	Site	Site	Site numbers are nominal integers and we ensured the site numbers from SEPSIPAM and and OVATION did not overlap
Age	Age	Age	No translation
Sex	Sex	Sex	No translation
Predicted probability of hospital mortality	SAPS	APACHE II	Calcuated from APACHE II for OVATION OR SAPS for SEPSIPAM
Admission Type	Admission Type	Admission Type	No translation
Hours on vasopressor prior to randomization	Hours on vasopressor prior to randomization	Hours on vasopressor prior to randomization	No translation
Pre-existing conditions			
Chronic hypertension	Chronic hypertension	Chronic hypertension	Collected from research teams from medical records
Chronic heart failure	Chronic heart failure	Chronic heart failure	Collected from research teams from medical records
Atherosclerotic disease	Atherosclerotic disease	Atherosclerotic disease	Collected from research teams from medical records
Arrhythmia	Not available	Arrhythmia	Reported for patients enrolled in OVATION only
Supraventricular arrhythmia	Not available	Supraventricular arrhythmia	Reported for patients enrolled in OVATION only
Ventricular arrhythmia	Not available	Ventricular arrhythmia	Reported for patients enrolled in OVATION only
Outcomes			
28-day mortality	28-day mortality collected	28-day mortality calculated from date of death	No translation
90-day mortality	90-day mortality	90-day mortality	No translation
Arrhythmia during first 5 days	Daily screening for arrhythmia for first 5 days	As reported by clinical teams up to day 28	Analysis limited to first five days in both trials
Myocardial injury	Myocardial infarction (typical electrocardiographic changes, with a concomitant increase in troponin, and segmental echocardiographic hypokinesia or akinesia, with the infarction confirmed, when possible, by means of coronary angiography) as reported by clinical teams	Myocardial injury (troponin elevation) as reported by clinical teams	Sum of myocardial infarction collected in SEPSISPAM and myocardial injury reported in OVATION
Digit ischemia or limb	Digital ischemia as reported by clinical teams	Digit or limb necrosis as reported by clinical teams	Sum of digital ischemia collected in SEPSISPAM and digit or limb necrosis collected in OVATION
Mesenteric ischemia	Mesenteric ischemia	Mesenteric ischemia	No translation
Major bleeding	Major bleeding	Major bleeding	Defined in both trials as bleeding requiring at least 2 units of packed red blood cells as reported by clinical teams
PODS at day 28	Calculated from daily data	Calculated from daily data	Calculated in both trials using the number of patients requiring mechanical ventilation, renal replacement therapy or vasopressors at days 28
PODS free days	Calculated from daily data	Calculated from daily data	Calculated from days alive and off mechanical ventilation, renal replacement therapy, and vasopressors at day 28
Daily Data			
Mechanical ventilation	Mechanical ventilation	Mechanical ventilation	No translation
Vasopressors	Vasopressors	Vasopressors	No translation
Renal Replacement	Renal Replacement	Renal Replacement	No translation

アウトカム

Primary Outcome	28日死亡率
Secondary Outcome	・90日死亡率 ・臓器機能不全(昇圧剤使用・人工呼吸器離脱困難・透析中)もしくは死亡した患者の割合 ・生存日数及び臓器不全のない日数 ・血管作動薬投与初期5日間での副作用 ・水分バランス ・平均MAP ・ノルアドレナリンの投与量

血管作動薬の
ノルアドレナリン投与量への換算

e-Table 1. Dose equivalents of vasopressors

Vasopressor	Norepinephrine equivalent dose
Norepinephrine	1
Epinephrine	1
Dopamine(E1, E2)	0.01
Vasopressin(E3)	5*
Phenylephrine(E4)	0.45

*Approximate conversion of vasopressin dose in units/min to equivalent norepinephrine dose in mcg/kg/min, normalized to 100kg body weight

Risk of bias

Cochrane Collaboration’s instrument修正版を用いて
risk of biasを評価

- 連続して隠されている割り付け
- 参加者とケア提供者が盲検である
- データ収集者が盲検である
- アウトカム評価が盲検である
- データ解析者が盲検
- 選別されている結果報告
- 計画で定められたサンプルサイズの前に割り付けが終了

統計

- 28日死亡率の一次アウトカムやその他の二次アウトカムは一般化線形(ロジスティック)混合モデルを用いて解析
  - 変量効果：治療施設　固定効果：治療介入
- 有害事象比較はFisher extract testを用いた
- 一次アウトカムの感度分析：一次アウトカムはあらかじめベースラインの変数を加え28日死亡率のオッズ比を調整
  - ベースラインの変数
    - 年齢・院内死亡率、ベースラインの高血圧、血管作動薬使用期間
- Kaplan-Meier曲線を用いて3か月以上の生存曲線を作成

以下のサブグループの設定

1. 高血圧の既往
2. うっ血性心不全の既往
3. 年齢
4. 血管作動薬を使用して
   目標血圧に達するまでの時間
   6時間以下 vs 以上

統計

- サブグループ解析は全てのアウトカムに関して実施
- カテゴリカルはダミー変数を用い年齢は連続変数とした
- 年齢は非線形変数であり効果調整を許容するため、40～80歳で等間隔の制御点を定義した制限3次スプラインを用いた
  - 5、10、20年間隔を定義し最小のＡＩＣスコアのモデルを選択
- ホスマー＝レメショー検定を用いてモデルの適格性を検証
- 欠損値を最小にするため一次解析は欠損値がない状態で実施
- 欠損データの複数の入力を繰り返して一次結果を確認

統計

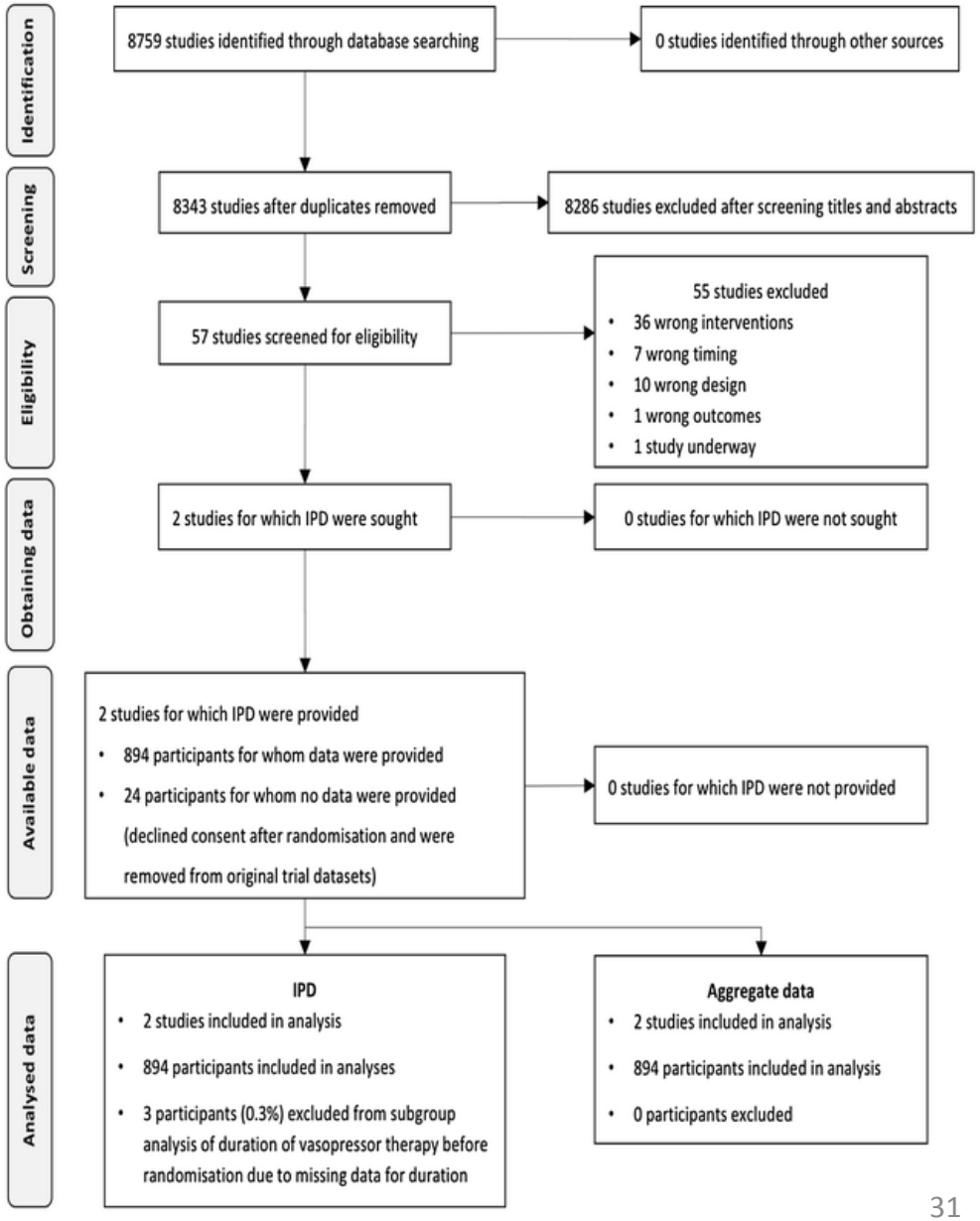
- Study開始後5日間の血圧と昇圧薬使用量を箱ひげ図で示した
- 治療開始28日間の臓器障害なしの期間をカウント
- 治療開始5日間の患者の平均MAP・血管作動薬使用量・血管作動薬使用量は対数変換を用い解析
- 水分バランスは正規分布していないため四分位値で示し、群間比較を行う際はウィルコクソン順位相関係数で比較

統計

- グループ間は95%ＣＩで評価
- 有意水準　$p < 0.05$
- 解析ソフト　SAS v.9.4

結果

8343件の文献
↓
文献57件が検索
↓
2件のRCTを組み込み
SEPSISPAM trial(n=776)
&
OVATION trial(n=118)



2つのRCTの比較

	SEPSISPAM (n=776)	OVATION (n=118)	P value
Age – yr	65.2±14.0	64.7±13.4	0.73
Male sex	517 (67%)	64 (54%)	0.009
APACHE II	NA	24.6±7.2	
SAPS-Ⅱ	58.7±18.9	NA	
SOFA score	10±3.1	Not all domains	
院内死亡率	0.59±0.28	0.52±0.22	0.003

その他、OVATIONで、予定術後入院が多い（8% vs 1%）
ランダム化前の血管作動薬使用時間が長い（10.6hr vs 3.6hr）

Baseline characteristics
Higher target vs Lower target

	Higher target *n* = 446	Lower target *n* = 448
Age, year	64.7 ± 13.4	65.5 ± 14.3
Male sex	300 (67%)	281 (63%)
APACHE II score[a]	24.7 ± 6.2	24.4 ± 8.0
ICU Admission Simplified Acute Physiology Score[b]	58.2 ± 18.7	59.3 ± 19.1
SOFA score[b]	10.7 ± 3.1	10.8 ± 3.1
Predicted probability of hospital mortality, %[c]	57 ± 27	58 ± 27
Admission type		
Medical	380 (85%)	383 (85%)
Surgical elective	9 (2%)	6 (1%)
Surgical emergency	57 (13%)	59 (13%)
Hours on vasopressors prior to randomization, median [Q1, Q3]	3.8 [1.9, 5.5]	4.0 [2.0, 5.7]
> 6 h	55 (12%)	67 (15%)

Baseline characteristics
Higher target vs Lower target

	Higher target *n* = 446	Lower target *n* = 448
Pre-existing conditions		
Chronic hypertension	186 (42%)	207 (46%)
Chronic heart failure	65 (15%)	57 (13%)
Atherosclerotic disease	48 (11%)	50 (11%)
Arrhythmia[a]	56 (13%)	47 (10%)
Supraventricular arrhythmia[a]	55 (12%)	45 (10%)
Ventricular arrhythmia[a]	3 (0.7%)	2 (0.5%)

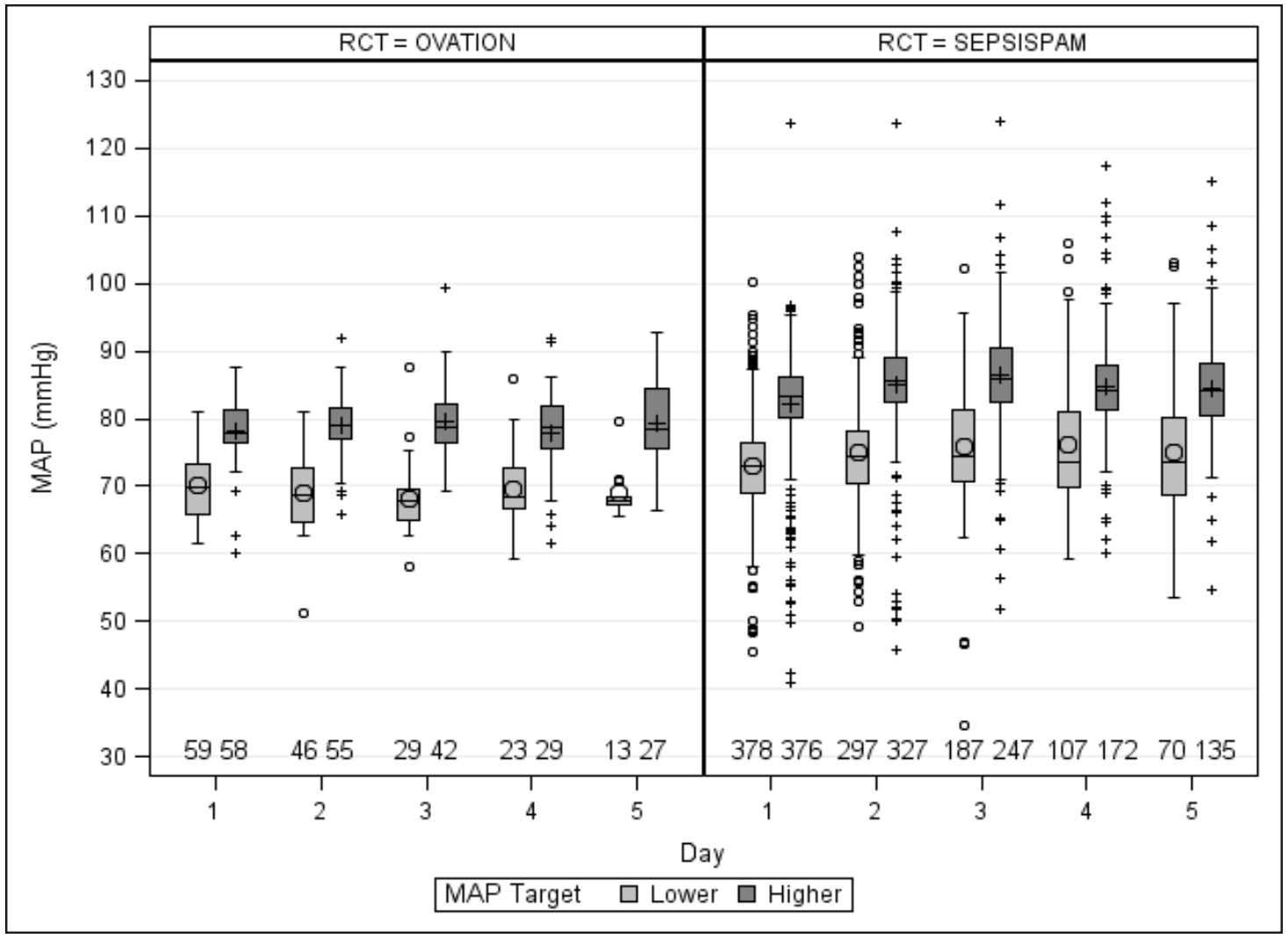
Risk of bias

2件のRCTとも

治療者が非盲検である

Overall risk of biasは高いと判断

治療開始５日間の平均血圧の推移



OVATION study
Higher target 79.2mmHg
Lower target 70.2mmHg

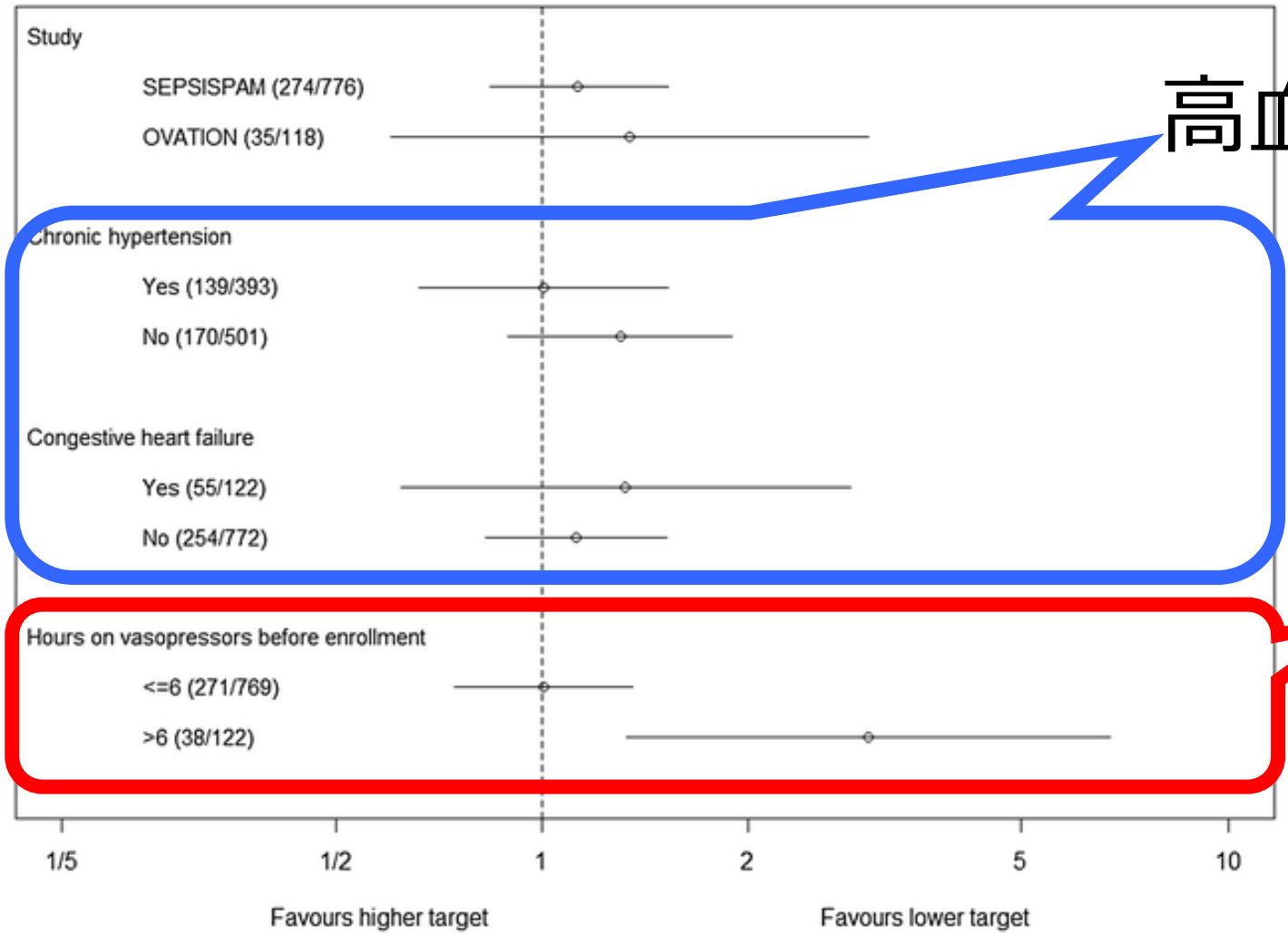
SEPSISPAM study
Higher target 83.2mmHg
Lower target 74.3mmHg

28日および90日死亡率
→特に有意差は認められず

	Higher Target	Lower Target	OR (95% CI)	p-value
28-day mortality				
SEPSISPAM	142/388 (37%)	132/388 (34%)	1.13 (0.84-1.53)	0.41
OVATION	19/58 (33%)	16/60 (27%)	1.34 (0.60-2.99)	0.47
Pooled	161/446 (36%)	148/448 (33%)	1.15 (0.87-1.52)	0.31
90-day mortality				
SEPSISPAM	170/388 (44%)	164/388 (42%)	1.08 (0.81-1.44)	0.61
OVATION	23/58 (40%)	20/60 (33%)	1.31 (0.62-2.81)	0.48
Pooled	193/446 (43%)	184/448 (41%)	1.10 (0.84-1.44)	0.47

28日死亡率のサブグループ解析

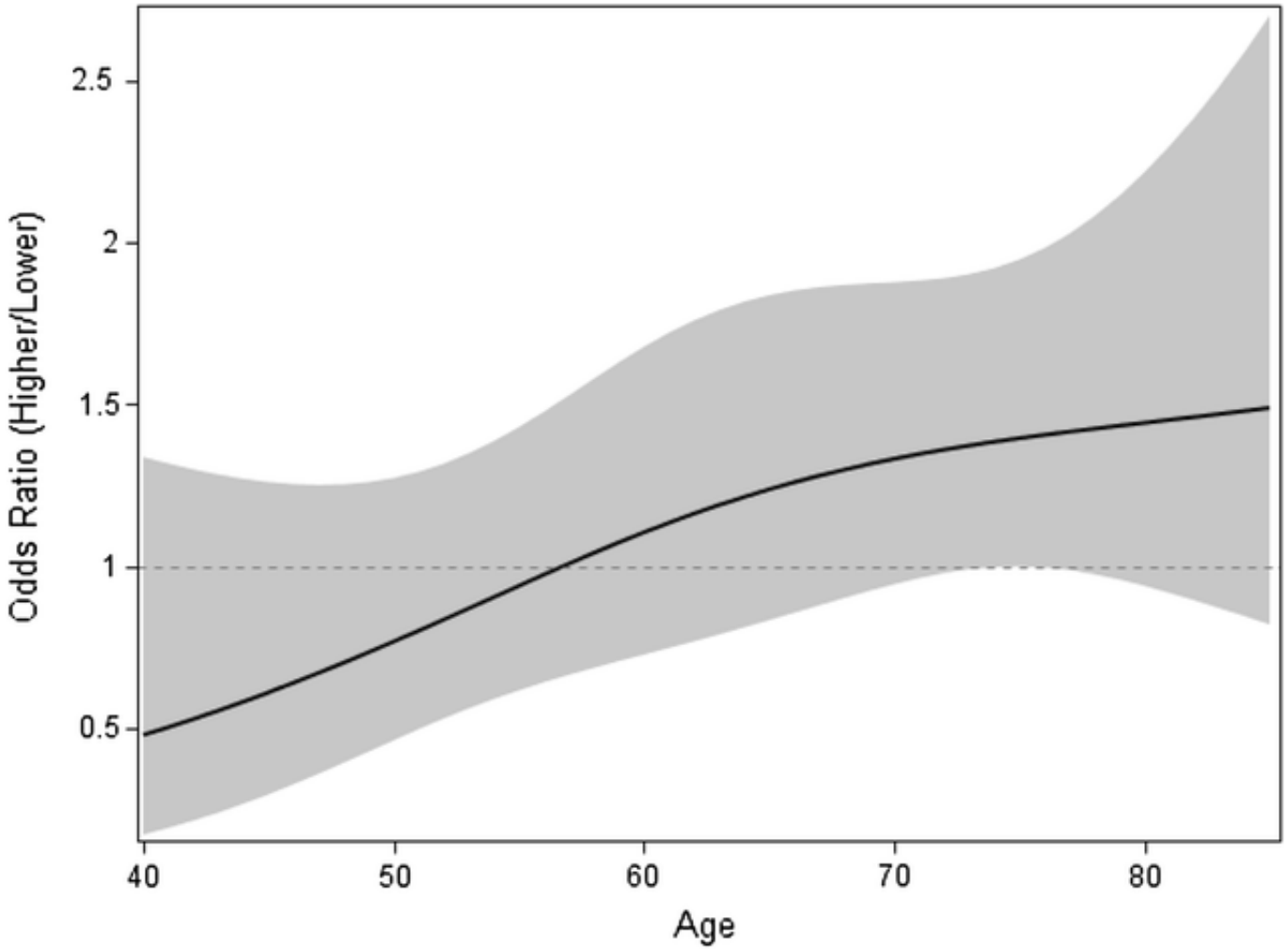
Figure 2



高血圧・心不全は無関係

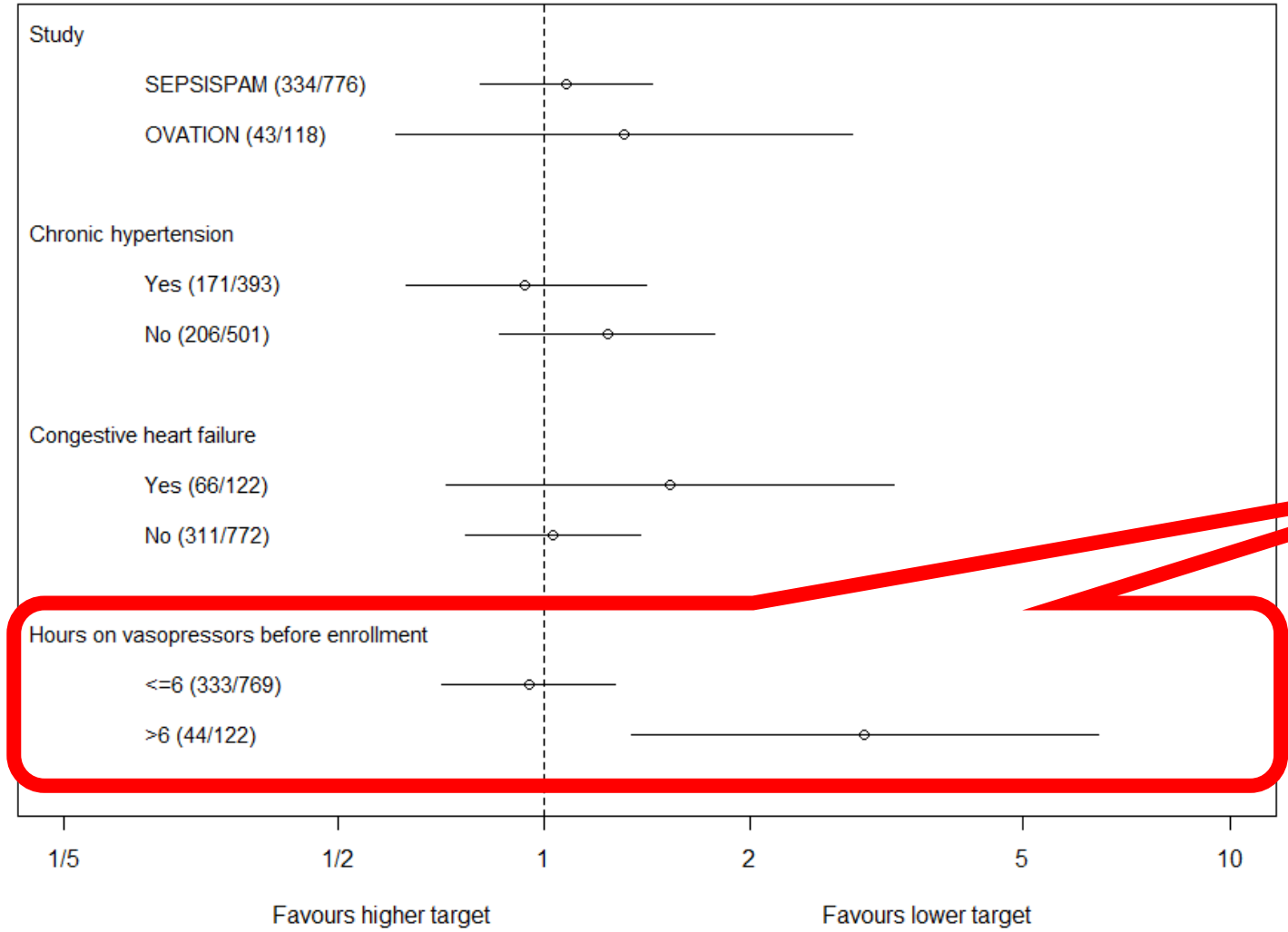
目標血圧到達＞6時間
Higher target群
２８日死亡率↑

28日死亡率のサブグループ解析



年齢調整でのオッズ比
関連なし

90日死亡率でのサブグループ解析



目標血圧到達＞６時間
Higher target群
９０日死亡率↑

28日死亡率と臓器不全遷延率を合わせて解析

Table 2 Summary of effects

Outcome	Subgroup	Higher MAP arm event/*n* (%)	Lower MAP arm event/*n* (%)	Odds ratio (95% CI)	*p* value	% absolute risk difference (95% CI)	Quality of evidence
28-day mortality	≤ 6 h	137/390 (35%)	134/379(35%)	1.01 (0.75–1.36)	0.97	0 (− 7 to 7)	Low due to risk of bias, imprecision, and inconsistency
	> 6 h	24/55 (44%)	14/67(21%)	3.00 (1.33–6.74)	< 0.01	23 (6 to 39)	Low due to risk of bias and inconsistency
90-day mortality	≤ 6 h	166/390 (43%)	167/379(44%)	0.95 (0.71–1.27)	0.74	− 1 (− 8 to 6)	Low due to risk of bias, imprecision, and inconsistency
	> 6 h	27/55 (49%)	17/67(25%)	2.93 (1.34–6.42)	< 0.01	24 (7 to 41)	Low due to risk of bias and inconsistency
28-day death or persistent organ dysfunction	≤ 6 h	151/390 (39%)	155/379(41%)	0.92 (0.69–1.24)	0.59	− 2 (− 9 to 5)	Low due to risk of bias, imprecision, and inconsistency
	> 6 h	30/55 (55%)	21/67(31%)	2.61 (1.23–5.53)	0.01	23 (6 to 40)	Low due to risk of bias and inconsistency
Supraventricular arrhythmia during the first 5 days of vasopressor therapy[a]	Overall	40/446 (9%)	17/448(4%)	2[illegible]	< 0.01	5 (− 1 to 12)	Moderate due to risk of bias
Myocardial injury during the first 5 days of vaso-	Overall	16/446 (4%)	11/[illegible]				due to risk of [illegible]eci-

目標血圧到達＞6時間
Higher target群
28日死亡率＋臓器不全遷延↑

Outcome	Subgroup	Higher MAP arm event/*n* (%)	Lower MAP arm event/*n* (%)	Odds ratio (95% CI)	*p* value	% absolute risk difference (95% CI)	Quality of evidence
28-day death or persistent organ dysfunction	≤ 6 h	151/390 (39%)	155/379(41%)	0.92 (0.69–1.24)	0.59	− 2 (− 9 to 5)	Low due to risk of bias, imprecision, and inconsistency
	> 6 h	30/55 (55%)	21/67(31%)	2.61 (1.23–5.53)	0.01	23 (6 to 40)	Low due to risk of bias and inconsistency

28日間の臓器代替療法非使用生存日数

Table 2 Summary of effects

Outcome	Subgroup	Higher MAP arm event/*n* (%)	Lower MAP arm event/*n* (%)	Odds ratio (95% CI)	*p* value	% absolute risk difference (95% CI)	Quality of evidence
28-day mortality	≤ 6 h	137/390 (35%)	134/379(35%)	1.01 (0.75–1.36)	0.97	0 (− 7 to 7)	Low due to risk of bias, imprecision, and inconsistency
	> 6 h	24/55 (44%)	14/67(21%)	3.00 (1.33–6.74)	< 0.01	23 (6 to 39)	Low due to risk of bias and inconsistency
90-day mortality	≤ 6 h	166/390 (43%)	167/379(44%)	0.95 (0.71–1.27)	0.74	− 1 (− 8 to 6)	Low due to risk of

Outcome	Subgroup	Mean (SD)	Mean (SD)	Mean difference (95% CI)	*p* value	Quality of evidence
Number of days alive and without organ dysfunction up to day 28	≤ 6 h	13.4 (11.4)	13.3 (11.6)	0.1 (− 1.5 to 1.6)	0.95	Low due to risk of bias, imprecision, and inconsistency
	> 6 h	8.4 (10.6)	15.6 (11.2)	− 6.8 (− 10.9 to − 2.8)	< 0.01	Low due to risk of bias and inconsistency

pressor therapy[a]

Digit or limb ischemia during the first 5 days of vasopressor therapy[a]	Overall	11/446 (2%)				Low due to risk of bias and imprecision
Mesenteric ischemia during first 5 days[a]	Overall	9/446 (2%)	10/448		0 (− 7 to 6)	Low due to risk of bias and imprecision
Major bleeding during first 5 days[a]	Overall	33/446 (7%)	43/448 (10%)	1.24) 0.28	− 2 (− 9 to − 4)	Low due to risk of bias and imprecision

Outcome	Subgroup	Mean (SD)	Mean (SD)	Mean difference (95% CI)	*p* value	Quality of evidence
Number of days alive and without organ dysfunction up to day 28	≤ 6 h	13.4 (11.4)	13.3 (11.6)	0.1 (− 1.5 to 1.6)	0.95	Low due to risk of bias, imprecision, and inconsistency
	> 6 h	8.4 (10.6)	15.6 (11.2)	− 6.8 (− 10.9 to − 2.8)	< 0.01	Low due to risk of bias and inconsistency

Outcome	Subgroup	Median [Q1, Q3]	Median [Q1, Q3]	Ratio of geometric means (95% CI)	*p* value	Quality of evidence
Total daily norepinephrine equivalent received over the first 5 days of vasopressor therapy	≤ 6 h	101 [43, 230	44 [16, 159]	2.1 (1.7–2.6)	< 0.01	Moderate due to risk of bias
	> 6 h	69 [37, 171]	21 [5, 77]	3.7 (2.2–6.2)	< 0.01	Moderate due to risk of bias

Outcome	Subgroup	Median [Q1, Q3]	Median [Q1, Q3]	Ratio of medians	*p* value	Quality of evidence
Fluid balance over first 5 days on vasopressors	Overall	1332 [421, 2252]	1455 [679, 2435]	0.92	0.07	Low due to risk of bias and imprecision

CI confidence interval, *SD* standard deviation, *Q1* first quartile, *Q3* third quartile

[a] Due to small numbers the odds ratios and % absolute difference are unadjusted with exact confidence intervals

目標血圧到達＞6時間
Higher target群
28日間の臓器代替療法非使用生存日数↓

治療開始５日間の血管作動薬使用量と水分量

Table 2 Summary of effects

Outcome	Subgroup	Higher MAP arm event/*n* (%)	Lower MAP arm event/*n* (%)	Odds ratio (95% CI)	*p* value	% absolute risk difference (95% CI)	Quality of evidence
28-day mortality	≤ 6 h	137/390 (35%)	134/379(35%)	1.01 (0.75–1.36)	0.97	0 (− 7 to 7)	Low due to risk of bias, imprecision, and inconsistency
	> 6 h	24/55 (44%)	14/67(21%)	3.00 (1.33–6.74)	< 0.01	23 (6 to 39)	Low due to risk of bias and inconsistency
90-day mortality	≤ 6 h	166/390 (43%)	167/379(44%)	0.95 (0.71–1.27)	0.74	− 1 (− 8 to 6)	Low due to risk of bias, imprecision, and inconsistency
	> 6 h	27/55 (49%)	17/67(25%)	2.93 (1.34–6.42)	< 0.01	24 (7 to 41)	Low due to risk of bias and inconsistency
28-day death or persistent organ dysfunction	≤ 6 h	151/390 (39%)	155/379(41%)	0.92 (0.69–1.24)	0.59	− 2 (− 9 to 5)	Low due to risk of bias, imprecision, and inconsistency
	> 6 h	30/55 (55%)					
Supraventricular arrhythmia during the first 5 days of vasopressor therapy[a]	Overall	40/446 (9%)					
Myocardial injury during the first 5 days of vasopressor therapy[a]	Overall	16/446 (4%)					
Digit or limb ischemia during the first 5 days of vasopressor therapy[a]	Overall	11/446 (2%)					
Mesenteric ischemia during first 5 days[a]	Overall	9/446 (2%)					
Major bleeding during first 5 days[a]	Overall	33/446 (7%)					
Outcome	Sub						
Number of days alive and without organ dysfunction up to day 2			8.4 (1				
Outcome	Subgroup	Median [Q1,		(95% CI)			
Total daily norepinephrine equivalent received over the first 5 days of vasopressor therapy	≤ 6 h	101 [43, 230	44 [16, 159]	2.1 (1.7–2.6)		< 0.01	Moderate due to risk of bias
	> 6 h	69 [37, 171]	21 [5, 77]	3.7 (2.2–6.2)		< 0.01	Moderate due to risk of bias
Outcome	Subgroup	Median [Q1, Q3]	Median [Q1, Q3]	Ratio of medians	*p* value	Quality of evidence	
Fluid balance over first 5 days on vasopressors	Overall	1332 [421, 2252]	1455 [679, 2435]	0.92	0.07	Low due to risk of bias and imprecision	

CI confidence interval, *SD* standard deviation, *Q1* first quartile, *Q3* third quartile

[a] Due to small numbers the odds ratios and % absolute difference are unadjusted with exact confidence intervals

Outcome	Subgroup	Median [Q1, Q3]	Median [Q1, Q3]	Ratio of geometric means (95% CI)	*p* value	Quality of evidence
Total daily norepinephrine equivalent received over the first 5 days of vasopressor therapy	≤ 6 h	101 [43, 230	44 [16, 159]	2.1 (1.7–2.6)	< 0.01	Moderate due to risk of bias
	> 6 h	69 [37, 171]	21 [5, 77]	3.7 (2.2–6.2)	< 0.01	Moderate due to risk of bias

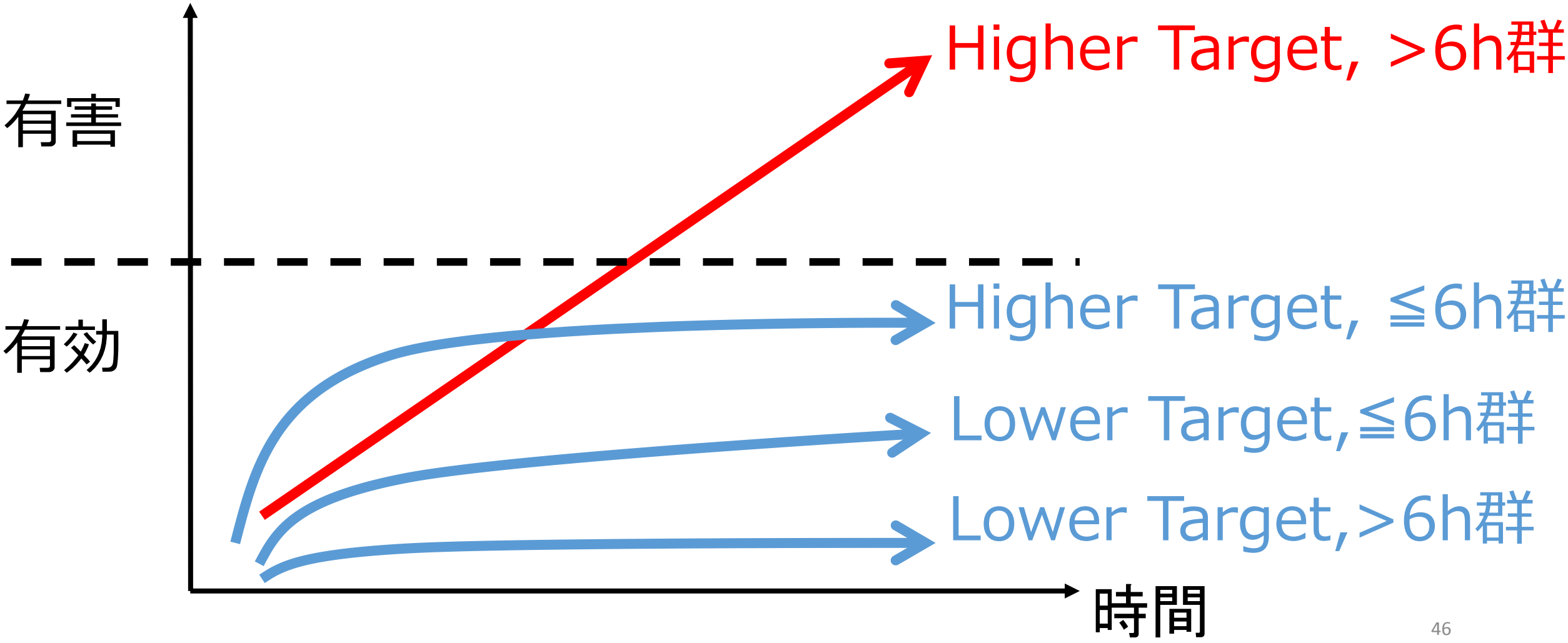
Outcome	Subgroup	Median [Q1, Q3]	Median [Q1, Q3]	Ratio of medians	*p* value	Quality of evidence
Fluid balance over first 5 days on vasopressors	Overall	1332 [421, 2252]	1455 [679, 2435]	0.92	0.07	Low due to risk of bias and imprecision

考察

本研究の結果まとめ

- 平均血圧を高く保つ ≠ 28日生存率の改善
- 高血圧・心不全の既往例でも効果なし
- 6時間以上昇圧薬を継続した群
  - 血圧を高めに設定⇒死亡率↑

累積カテコラミン量


有害
有効
Higher Target, >6h群
Higher Target, ≦6h群
Lower Target,≦6h群
Lower Target,>6h群
時間

本研究の長所

- 適正な基準や解析計画
  - 一般化混合効果モデルを使用
  - 昇圧薬治療の層別化に関連して詳細に解析
  - ４つのサブグループ解析

- 包括的な文献検索
- 適正基準の二重評価

本研究の短所

- 昇圧薬使用時のMAPは想定よりも高い可能性
- 非カテコラミン製剤はノルエピネフリンと異なる
- 高血圧既往はカルテ記載を参照としている
- 少数の有害事象が隠れている

結語

- 昇圧までに6時間以上要した患者において、血圧高値を維持することは死亡率を上げる危険性がある。

- 低血圧での治療群は基礎疾患の有無にかかわらず有害事象とは相関しない。

今回の研究を踏まえて

- SEPSISPAMのサブグループでの結果から、「血圧の目標の個人化」、特に「慢性高血圧患者で血圧目標を高くする」ことが言われてきている。

- 今回はその結果は認められなかったが、普段の血圧を参考に血圧管理を行うことは他のセッティングの結果からも恩恵があることなのかもしれない。

- しかし、それにこだわるばかりにカテコラミンの投与が多くなり、継続されることは害になるだろう。

- 重要なことは、各臓器の酸素供給を維持すること。その目標を維持することができる血圧を各患者で考えるべき。