HOPE

HOPE Improving cerebral perfusion after stroke

A randomized trial on **H**emodynamic **O**ptimization of cerebral **P**erfusion after **E**ndovascular therapy in patients with acute ischemic stroke (**HOPE** study)

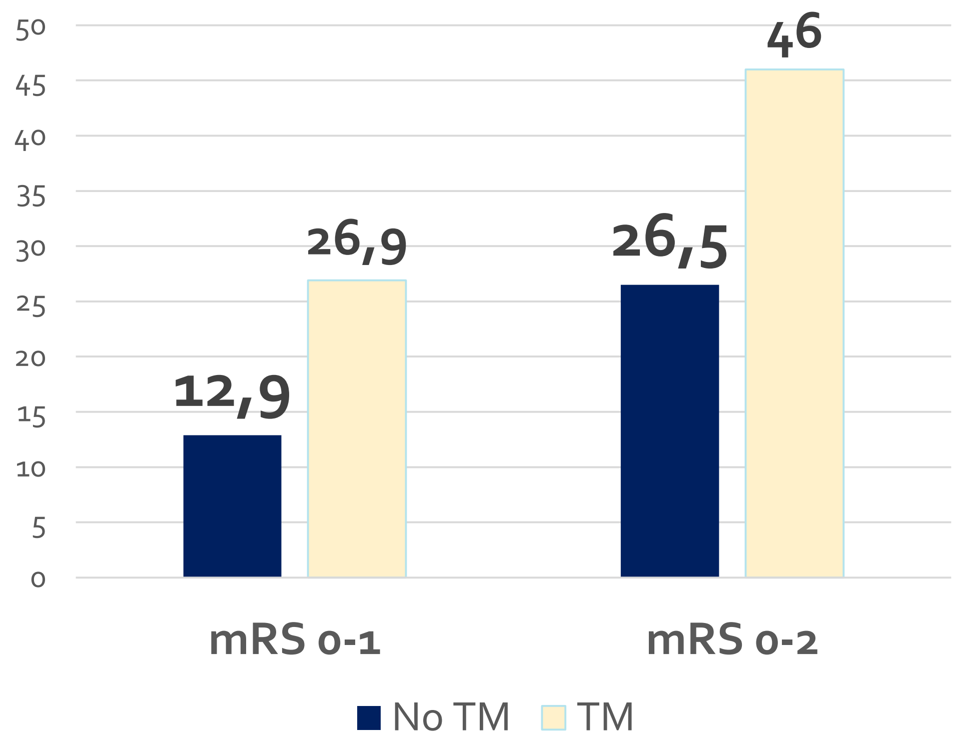
Recanalización

≠

Reperfusión

≠

Mejoría clínica



Más de la mitad van mal!!

Futile thrombectomy (20-50%)

Preprocedural

- Large core
- Older age + higher NIHSS score
- Rankin >2
- Collateral failure

Intraprocedural

- Challenge for timely vascular access to the occlusion site
- Tandem ICA occlusion
- Procedural duration (groin to recan. >60')
- >3 passes
- Distal embolization
- Early re-occlusion
- Collateral failure

Postprocedural

- Detrimental in-hospital complications (comorbidities)
- **Reperfusion injury** (hemorrhagic conversion, edema)
- **Collateral failure**
- **No reflow** phenomenon
- Early **re-occlusion**

La respuesta fisiológica del organismo a una oclusión persistente es subir la presión arterial

American Journal of Emergency Medicine (2007) **25**, 32–38

ELSEVIER

The American Journal of Emergency Medicine

www.elsevier.com/locate/ajem

Original Contribution

Prevalence of elevated blood pressure in 563 704 adult patients with stroke presenting to the ED in the United States

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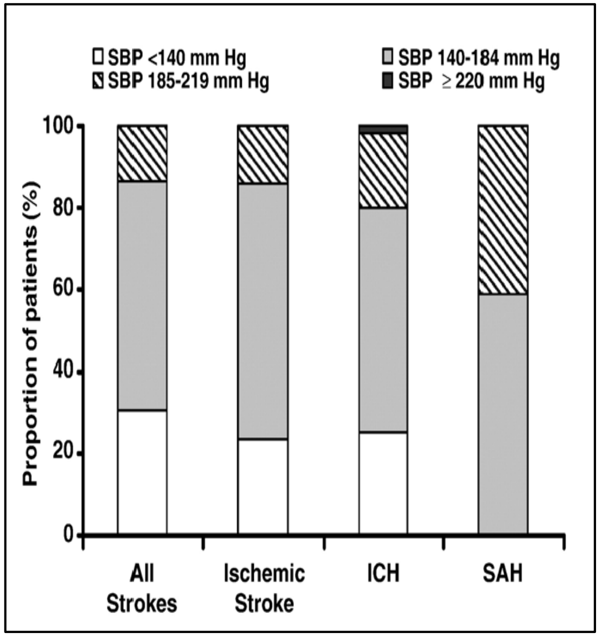

Blood Pressure After Endovascular Thrombectomy and Outcomes in Patients With Acute Ischemic Stroke

An Individual Patient Data Meta-analysis

Aristeidis H. Katsanos, MD, Konark Malhotra, MD, Niaz Ahmed, MD, Georgios Seitidis, MSc, Eva A. Mistry, MD, Dimitris Mavridis, PhD, Joon-Tae Kim, MD, Areti Angeliki Veroniki, PhD, Ilko Maier, MD, Marius Matusevicius, MD, Pooja Khatri, MD, Mohammad Anadani, MD, Nitin Goyal, MD, Adam S. Arthur, MD, Amrou Sarraj, MD, Shadi Yaghi, MD, Ashkan Shoamanesh, MD, Luciana Catanese, MD, Maria Kantzanou, MD, Theodora Psaltopoulou, MD, Alexandros Rentzos, MD, Marios Psychogios, MD, Brian Van Adel, MD, Alejandro M. Spiotta, MD, Else Charlotte Sandset, MD, Adam de Havenon, MD, Andrei V. Alexandrov, MD, Nils H. Petersen, MD, and Georgios Tsivgoulis, MD

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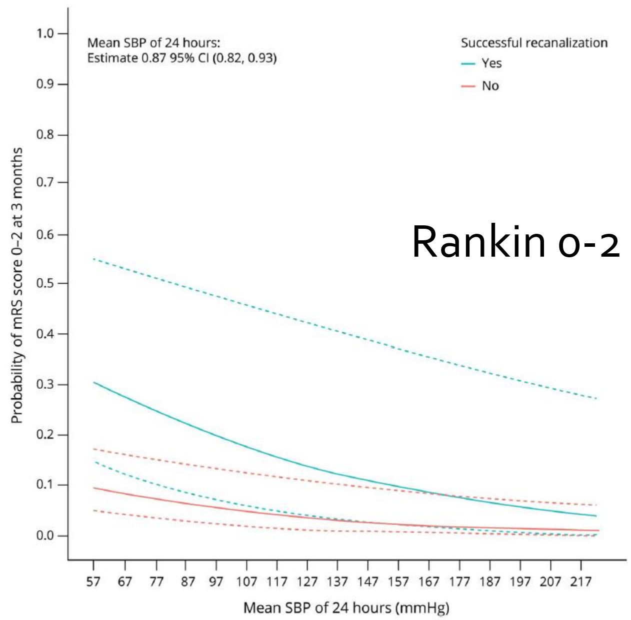
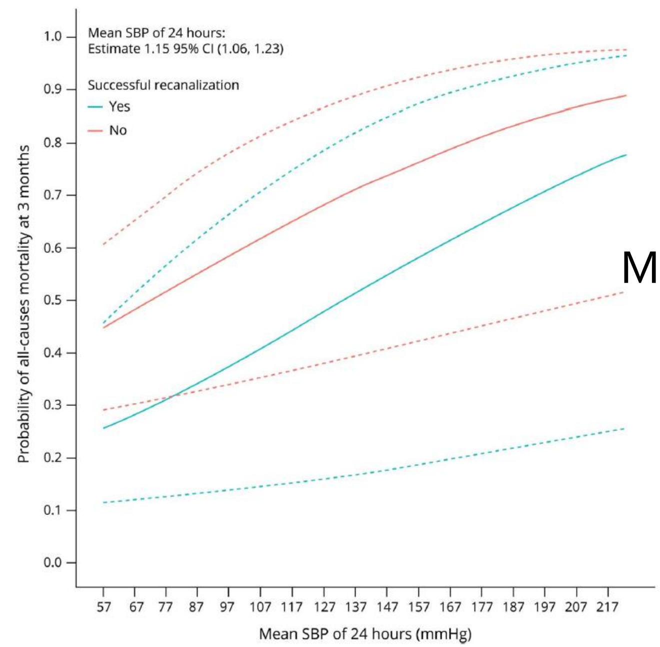
Neurology® 2022;98:e291-e301. doi:10.1212/WNL.0000000000013049

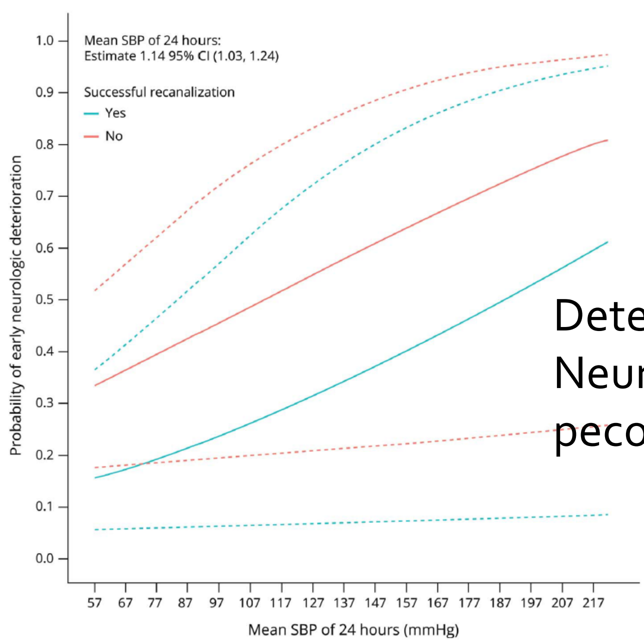
Meta-análisis con datos individuales de 5874 pacientes de 7 estudios publicados (pacientes con LVO y mediciones de TA durante las 24 hores post-trombectomia)



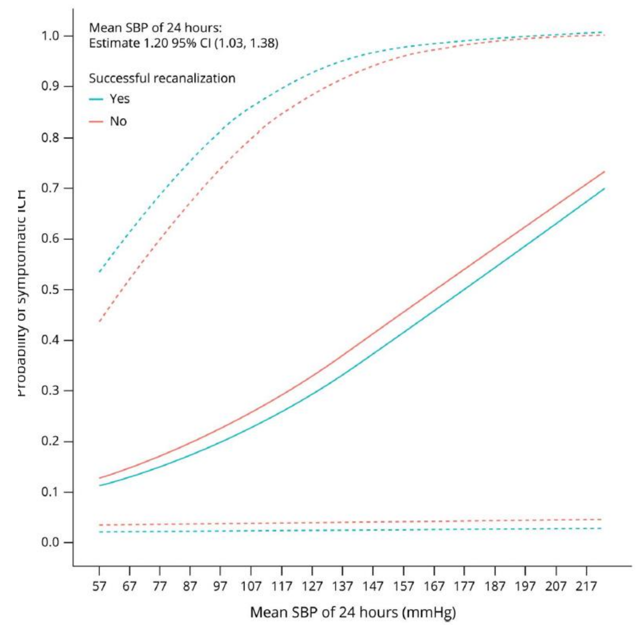
Rankin 0-2



Mortalidad



Deterioro Neurológico pecoz



Hemorragia Cerebral sintomática

Katsanos Neurology 2022

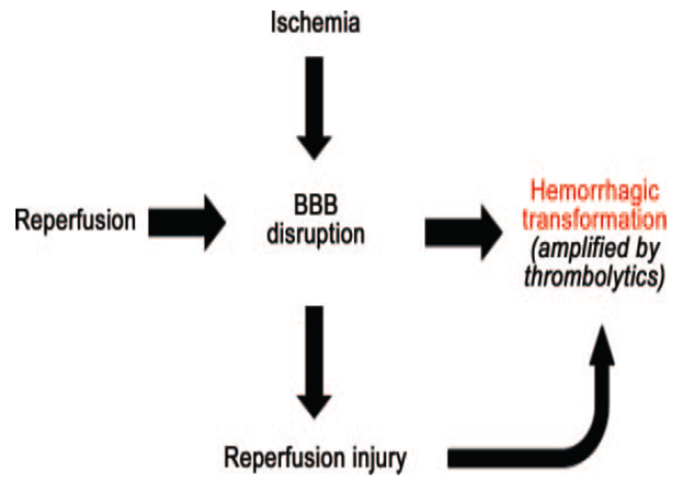
HOPE Improving cerebral perfusion after stroke

Reperfusion injury

Blood–brain barrier, reperfusion injury, and hemorrhagic transformation in acute ischemic stroke

Rakesh Khatri, MD
Alexander M. McKinney, MD
Barbara Swenson, MD
Vallabh Janardhan, MD

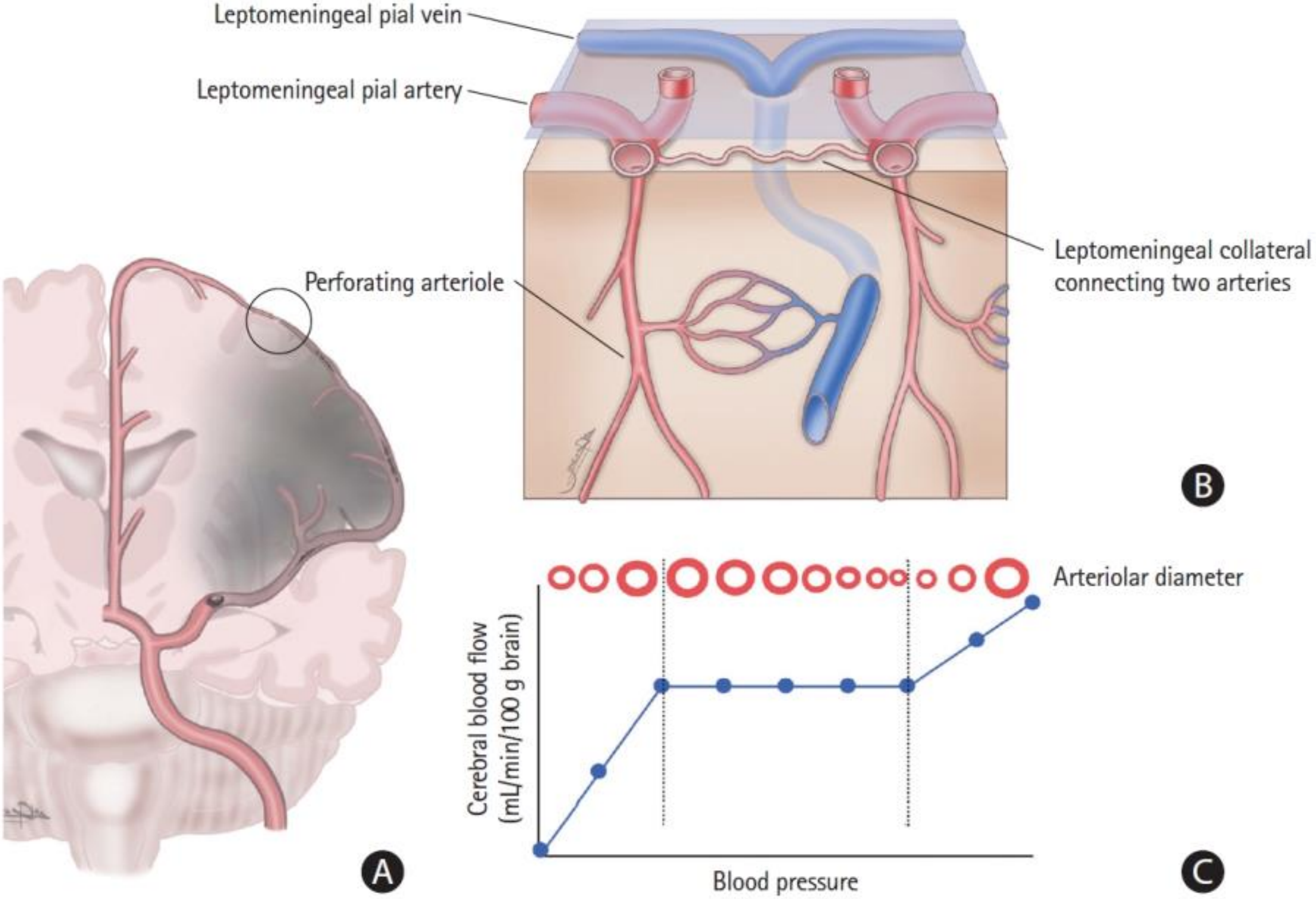
Figure 1 Schematic representation of blood-brain barrier (BBB) changes in acute ischemic stroke



Thrombolytics (IV as well as intra-arterial) can amplify the risk of hemorrhagic transformation secondary to reperfusion injury.

Impact of reperfusion. Reperfusion is essential for brain tissue survival; it also contributes to additional tissue damage and has the potential for HT.[12] Reperfusion injury has been defined in numerous ways, including activation of endothelium, excess production of oxygen free radicals, inflammatory responses and leukocyte recruitment, increase in cytokine production, and edema formation. Common among these mechanisms is BBB disruption.[13]

Circulación colateral



Blood Pressure Drop and Penumbral Tissue Loss in Nonrecanalized Emergent Large Vessel Occlusion

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La PA baja es perjudicial

Background and Purpose—For patients with emergent large vessel occlusion who may not benefit from timely recanalization treatment, maintaining adequate cerebral perfusion to prevent penumbral tissue loss is a key therapeutic strategy. Cerebral perfusion should be proportional to systemic blood pressure (BP) due to the loss of autoregulation properties in ischemic brain tissue. We hypothesized that acute fluctuations in BP would lead to aggravated penumbral tissue loss in persistent large vessel occlusion.

Methods—A total of 80 patients with persistent large vessel occlusion of internal carotid artery or middle cerebral artery admitted within 24 hours after onset, and with a baseline, National Institutes of Health Stroke Scale score ≥4-point were included. Baseline and follow-up (median 88 hours) magnetic resonance images were analyzed, and penumbra was defined as the T_{max}>6 s region excluding baseline infarction. The hypoperfusion intensity ratio (T_{max}>10 s/T_{max}>6 s) was calculated within the penumbra. Penumbral tissue loss (%) was defined as the proportion of follow-up infarct in the penumbra. With serial BP measurements in the first 24 hours (median 29, interquartile range 26–35), BP and BP variability parameters, including $BP_{dropmax}$ (change from local maxima to minima), were calculated and compared. Generalized linear models were applied to examine the association between BP parameters and the penumbral tissue loss.

Results—The median penumbral volume was 79.3 mL (interquartile range, 38.2–129.6) and median penumbral tissue loss was 36.7% (interquartile range, 12.0–56.1). In a multivariable analysis, systolic BP (SBP) $SBP_{dropmax}$ (β±SE of fourth quartile, 17.82±6.58; *P* value, 0.01) and diastolic BP (DBP) $DBP_{dropmax}$ (β±SE of fourth quartile, 14.04±6.38; *P* value, 0.01) were associated with increasing penumbral tissue loss, independently of age, baseline infarction and hypoperfusion intensity ratio. DBP_{incmax}, SBP_{max}, DBP_{max}, $SBP_{max-min}$, $DBP_{max-min}$, and most of the DBP variability indices were associated with penumbral tissue loss.

Conclusions—BP fluctuations, even a brief and drastic BP drop in the first 24 hours, significantly contributed to penumbral tissue loss irrespective of baseline hypoperfusion. (*Stroke*. 2019;50:00-00. DOI: 10.1161/STROKEAHA.119.025426.)

Necesitamos presión para mantener una buena circulación colateral!

HOPE Improving cerebral perfusion after stroke

¿La hipertensión inducida puede ser beneficiosa?

Results

In the modified intention-to-treat analyses, 76 and 77 patients were included in the intervention and control groups, respectively. After adjustment for age and initial stroke severity, induced hypertension increased the occurrence of the primary (odds ratio 2.49, 95% confidence interval [CI] 1.25–4.96, $p = 0.010$) and secondary (odds ratio 2.97, 95% CI 1.32–6.68, $p = 0.009$) efficacy endpoints. Sixty-seven (88.2%) patients of the intervention group exhibited improvements in NIHSS scores of ≥2 points during induced hypertension (mean SBP 179·7 ± 19.1 mm Hg). Safety outcomes did not significantly differ between groups.

Conclusion

Among patients with noncardioembolic stroke who were ineligible for revascularization therapy and those with progressive stroke, phenylephrine-induced hypertension was safe and resulted in early neurologic improvement and long-term functional independence.

Therapeutic-induced hypertension in patients with noncardioembolic acute stroke

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Neurology® 2019;93:e1-e9. doi:10.1212/WNL.0000000000008520

Methods

In this multicenter randomized clinical trial, patients with acute noncardioembolic ischemic stroke within 24 hours of onset who were ineligible for revascularization therapy and those with progressive stroke during hospitalization were randomly assigned (1:1) to the control and intervention groups. In the intervention group, phenylephrine was administered intravenously to increase systolic blood pressure (SBP) up to 200 mm Hg. The primary efficacy endpoint was early neurologic improvement (reduction in NIH Stroke Scale [NIHSS] score of ≥2 points during the first 7 days). The secondary efficacy endpoint was a modified Rankin Scale score of 0 to 2 at 90 days. Safety outcomes included symptomatic intracranial hemorrhage/edema, myocardial infarction, and death.

Figure 5 Systolic blood pressure (SBP) over time in each group

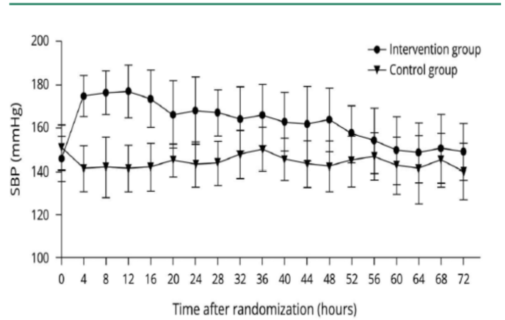
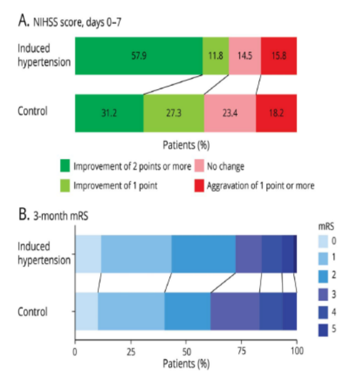


Figure 3 Early neurologic outcomes at day 7 and functional outcomes at day 90



(A) NIH Stroke Scale (NIHSS) score and modified Rankin Scale (mRS) score.

Objetivo de PA en función del grado de recanalización conseguido durante la trombectomía

Blood pressure levels post mechanical thrombectomy and outcomes in large vessel occlusion strokes

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ABSTRACT

Objective: There are limited data evaluating the effect of post mechanical thrombectomy (MT) blood pressure (BP) levels on early outcomes of patients with large vessel occlusions (LVO). We sought to investigate the association of BP course following MT with early outcomes in LVO.

Methods: Consecutive patients with LVO treated with MT during a 3-year period were evaluated. Hourly systolic BP (SBP) and diastolic BP (DBP) values were recorded for 24 hours following MT and maximum SBP and DBP levels were identified. LVO patients with complete reperfusion following MT were stratified in 3 groups based on post-MT achieved BP goals: <140/90 mm Hg (intensive), <160/90 mm Hg (moderate), and <220/110 mm Hg or <180/105 mm Hg when pretreated with IV thrombolysis (permissive hypertension). Three-month functional independence was defined as modified Rankin Scale score of 0-2.

Results: A total of 217 acute ischemic stroke patients with LVO were prospectively evaluated. A 10 mm Hg increment in maximum SBP documented during the first 24 hours post MT was independently ($p = 0.001$) associated with a lower likelihood of 3-month functional independence (odds ratio [OR] 0.70; 95% confidence interval [CI] 0.56-0.87) and a higher odds of 3-month mortality (OR 1.49; 95% CI 1.18-1.88) after adjusting for potential confounders. In addition, achieving a BP goal of <160/90 mm Hg during the first 24 hours following MT was independently associated with a lower likelihood of 3-month mortality (OR 0.08; 95% CI 0.01-0.54; $p = 0.010$) in comparison to permissive hypertension.

Conclusions: High maximum SBP levels following MT are independently associated with increased likelihood of 3-month mortality and functional dependence in LVO patients. Moderate BP control is also related to lower odds of 3-month mortality in comparison to permissive hypertension. Neurology® 2017;89:1-8

<140/90
- intensivo

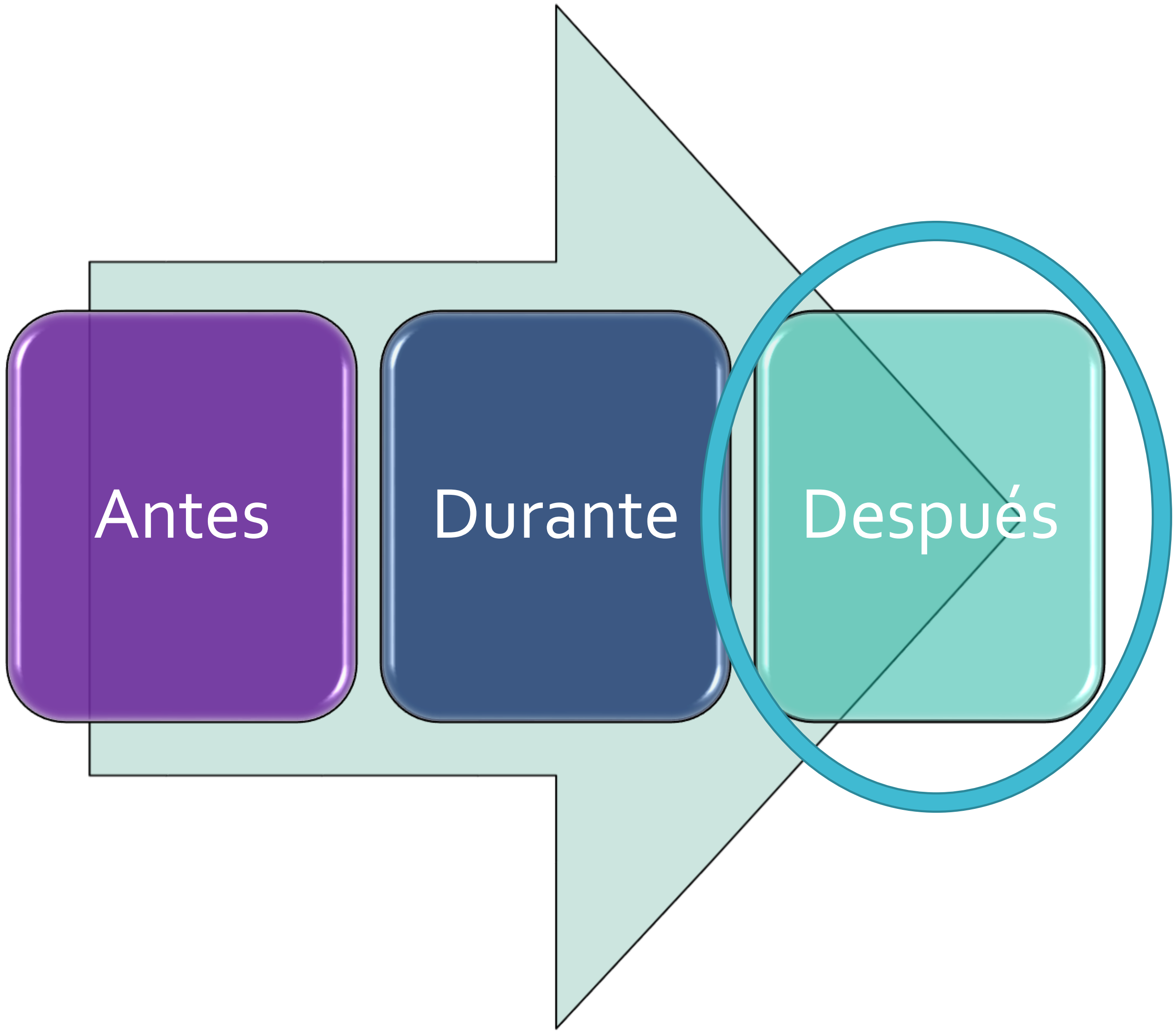
<160/90
- moderado

<220/110 o <180/105 si rt-PA
- permisivo

N=217

TICI 2b-3

Presión arterial y resultado trombectomía mecánica



¿Qué hacemos con la PA **post-trombectomía?**

Subirla
- Mejorará la perfusión
- Mejora circulación colateral

No tratar
- No hay motivo claro

Bajarla
- Menos riesgo hemorragia
- Menos riesgo edema

En resumen...

Considerable información en estudios **observacionales** sobre la importancia de una **individualización** de la presión arterial tras la trombectomía

Pueden ser perjudiciales tanto los episodios hipotensivos como los hipertensivos

ES POSIBLE QUE HAYA QUE TENER DISTINTOS OBJETIVOS DE PRESIÓN ARTERIAL EN FUNCIÓN DEL GRADO DE RECANALIZACIÓN OBTENIDO TRAS LA TROMBECTOMÍA

Sin embargo, sigue siendo **incierta la causalidad** de estas relaciones entre presión arterial y resultados clínicos (beneficio y riesgo) y la duda sólo puede resolverse mediante un **ensayo clínico**

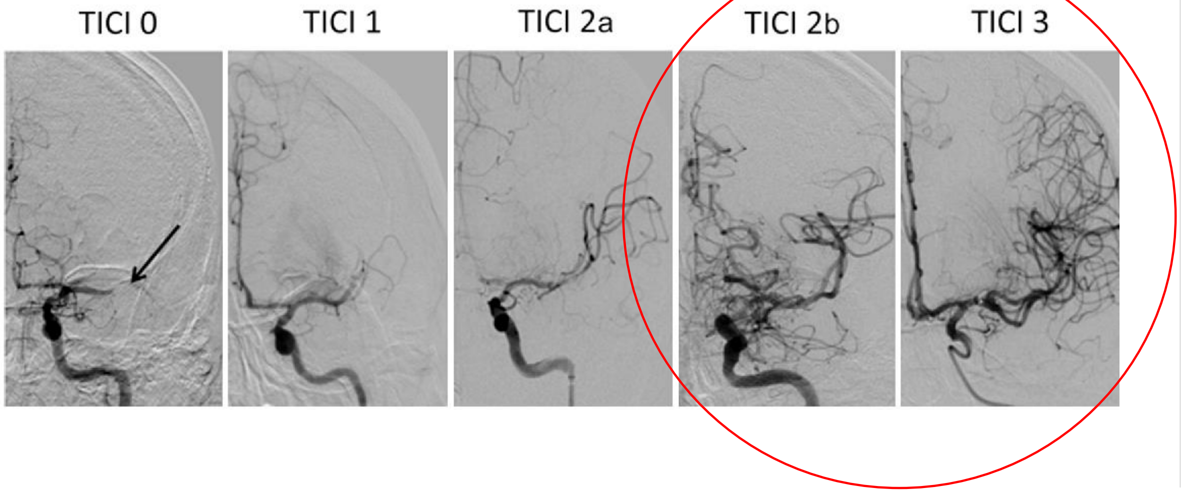
HOPE
Individualizar la presión arterial para optimizar la perfusión

Presión baja
Presión alta → Mal pronóstico

Subir la presión baja si TICI **2b**
Bajar la presión alta si TICI **2c-3** → **Buen pronóstico?**

(Según TICI)

(Menos edema
Menos hemorragia
Mejor perfusión)



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Diseño del estudio

- Ensayo clínico PROBE (Prospective, Randomized, Open, Blinded End-point)
- Promotor: Hospital de la Santa Creu i Sant Pau
- Duración: 4 años
- Muestra estimada: 814 pacientes
- Financiación: Ministerio de Economía y Competitividad (Investigación Clínica Independientes 2020)

GOBIERNO DE ESPAÑA MINISTERIO DE ECONOMÍA Y COMPETITIVIDAD

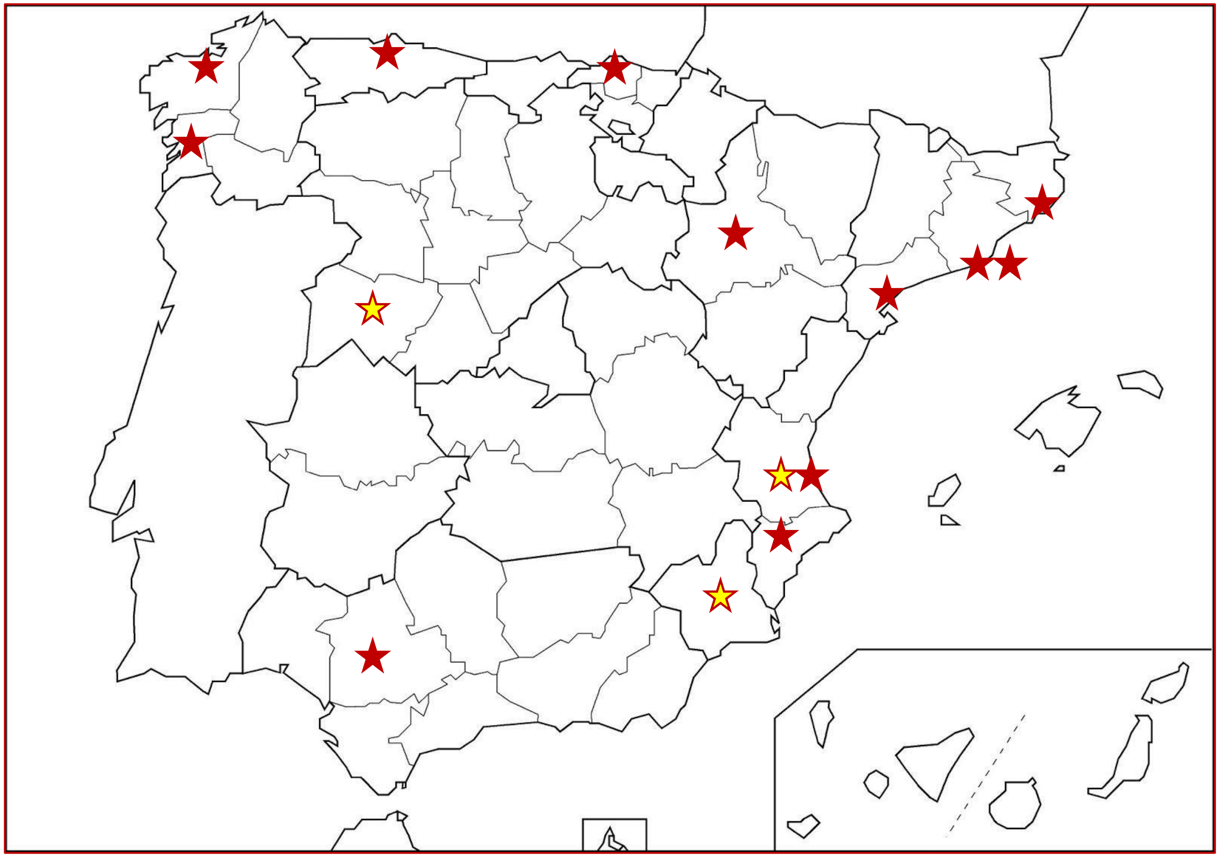
Instituto de Salud Carlos III

Institut santpau Investigació Biomèdica | Barcelona

HOSPITAL DE LA SANTA CREU I SANT PAU

FUNDACIÓ DE GESTIÓ SANITÀRIA

UNIVERSITAT AUTÒNOMA DE BARCELONA



Centros participantes activados: ★

- Hospital de la Santa Creu i Sant Pau (CAT)
- Hospital del Mar (CAT)
- Hospital Josep Trueta (CAT)
- Hospital Universitario Virgen del Rocío (AND)
- Hospital Universitario A Coruña (GAL)
- Hospital Universitario Santiago de Compostela (GAL)
- Hospital Cruces (EUS)
- Hospital La Fe de Valencia (VAL)
- Hospital Central de Asturias (AST)
- Joan XXIII (Tarragona)
- H Universitario Alicante (Alicante)
- H Miguel Servet (Zaragoza)

HOPE Improving cerebral perfusion after stroke

+3 hospitales ☆

Clínico Valencia (Valencia)
Virgen de la Arrixaca (Murcia)
H Universitario Salamanca (Salamanca)

HOPE Improving cerebral perfusion after stroke

Criterios de Inclusión

1. Ictus isquémico <24h
2. Oclusión de gran vaso circulación anterior
3. Tratamiento endovascular
4. Recanalización exitosa (TICI ≥2b)
5. Rankin previo <3
6. Consentimiento informado

Criterios de Exclusión

1. ASPECTS<6
2. Oclusión distal (A2, M3-4)
3. Historia de HIC o HIC en TC basal
4. Insuficiencia cardíaca o angina inestable
5. Disección o aneurisma de aorta
6. Disección TSA, aneurisma o MAV cerebral
7. Historia de arritmias ventriculares
8. Uso de inhibidores de la MAO
9. Riesgo de ictus hemodinámico
10. Inclusión en otro ensayo clínico
11. Embarazo o lactancia

Última serie angiográfica

<60 minutos

Aleatorización

Grupo control

Grupo tratamiento

<60 minutos

PAS <200 mmHg
<180 mmHg (rtPA)

TICI 2b: PAS 140-160 mmHg
TICI 2c/3: PAS 100-140 mmHg

Es importante conseguir el objetivo de PAS lo más rápido posible

HOPE Improving cerebral perfusion after stroke

¿Cómo monitorizamos la Presión Arterial?

Grupo Tratamiento

0-24h	Cada 30’
24-48h	Cada 60’
48-72h	Cada 60’

Fin estudio

Si se administra fármaco, controlar TA a los 5-10’

Grupo Control

Cada 1h	0-24h
Cada 6h	24-48h
Cada 6h	48-72h

Fin estudio

Blinded End-point

Variables de Estudio

Beneficio:
Resultado funcional (Rankin)

Riesgo:
Hemorragia
Edema
Tamaño infarto
Muerte
Deterioro neurológico

Problemas en la vida real

- COVID 19
  - Consentimiento
  - Monitorización remota
- Competencia entre estudios / ensayos
- Centros que no incluyen pacientes
- Nuevas evidencias de la literatura
- Recalcular la n

Ensayo clínico:
ENCHANTED-MT

Intensive blood pressure control after endovascular thrombectomy for acute ischaemic stroke (ENCHANTED2/MT): a multicentre, open-label, blinded-endpoint, randomised controlled trial

Pengfei Yang, Lili Song*, Yongwei Zhang*, Xiaoxi Zhang, Xiaoying Chen, Yunke Li, Lingli Sun, Yingfeng Wan, Laurent Billot, Qiang Li[1], Xinwen Ren, Hongjian Shen, Lei Zhang, Zifu Li, Pengfei Xing, Yongxin Zhang, Ping Zhang, Weilong Hua, Fang Shen, Yihan Zhou, Bing Tian, Wenhuo Chen, Hongxing Han, Liyong Zhang, Chenghua Xu, Tong Li, Ya Peng, Xincan Yue, Shengli Chen, Changming Wen, Shu Wan, Congguo Yin, Ming Wei, Hansheng Shu, Guangxian Nan, Sheng Liu, Wenhua Liu, Yiling Cai, Yi Sui, Maohua Chen, Yu Zhou, Qiao Zuo, Dongwei Dai, Rui Zhao, Qiang Li[2], Qinghai Huang, Yi Xu, Benqiang Deng, Tao Wu, Jianping Lu, Xia Wang, Mark W Parsons, Ken Butcher, Bruce Campbell, Thompson G Robinson, Mayank Goyal, Diederik Dippel, Yvo Roos, Charles Majoie, Longde Wang, Yongjun Wang, Jianmin Liu, Craig S Anderson, for the ENCHANTED2/MT Investigators†*

www.thelancet.com **Published online October 28, 2022**

ENCHANTED-MT

- Hospitales chinos
- Aleatorización a
  - N= 407 Intensivo (<120 mmHg)
  - N= 409 No intensivo (140-180 mmHg)
- En 1 hora
- Durante 72 hores
- Rankin 3 meses
- Estudio detenido prematuramente

-Probabilidad de mal pronóstico mayor en el grupo intensivo
OR 1.37 (1.07-1.76)
-No diferencias en sICH
-No diferencias en mortalidad

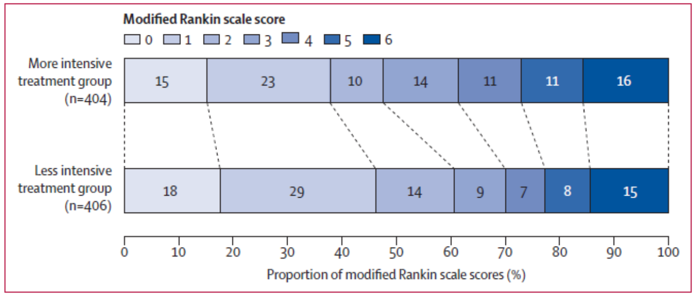


Figure 3: **Distribution of modified Rankin scale scores at 90 days by treatment group**
Raw distribution of scores is shown. Scores on the modified Rankin scale range from 0 to 6: 0=no symptoms, 1=symptoms without clinically significant disability, 2=slight disability, 3=moderate disability, 4=moderately severe disability, 5=severe disability, and 6=death.

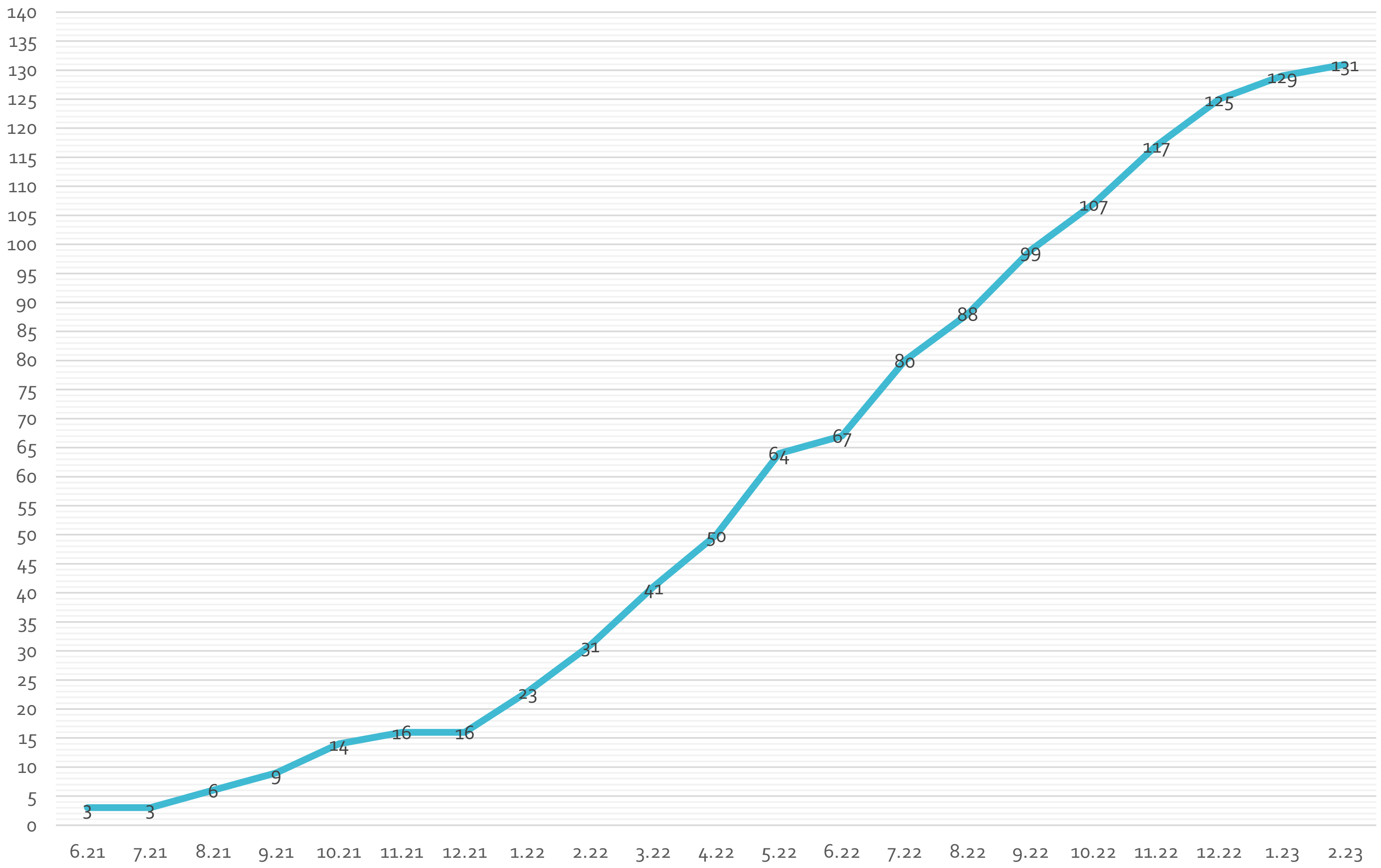
Monitorización del ensayo

- DSMB (*Data Safety Monitoring Board*): 2 clínicos externos al ensayo + 1 epidemiólogo
- *Interim analyses*: 2 análisis intermedios planificados a los 250 y a los 500 pacientes
- Se ha solicitado una valoración preliminar dados los resultados de ENCHANTED-MT

Estudio detenido

En espera resolución DSMB

Hospital	J 21	J 21	A 21	S 21	O 21	N 21	D 21	E 22	F 22	M 22	A 22	M 22	J 22	J 22	A 22	S 22	O 22	N 22	D 22	E 23	F 23	TOTAL
1	4	0	3	3	4	2	0	3	2	3	3	3	1	3	2	2	5	2	4	1	0	51
2					1	0	0	3	1	0	2	2	0	2	2	2	0	1	0	0	1	17
3						0	0	0	2	1	0	0	0	0	0	0	0	0	0	0	0	3
4					0	0	0	0	2	2	0	1	0	1	0	3	1	0	1	0	0	11
5						0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
6						0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7					0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
8									1	4	4	3	2	3	0	2	0	2	0	0	0	21
9												5	0	3	4	2	2	3	3	3	1	26
10																		2	0	0	0	2
11																					0	0
12																						
13																						
14																						
15																						
TOTAL	4	0	3	3	5	2	0	6	8	10	9	15	3	13	8	11	8	10	8	4	2	131



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