

# Actualización en Anemia y Medicina Transfusional

Ciudad Real

22-23 de Noviembre 2019



XXI JORNADAS ANUALES GIEMSA  
XIV JORNADAS ANUALES AWGE



## El Consenso de Frankfurt – JAMA 2019

Dr. Arturo Pereira

Clinical Review & Education

JAMA | Special Communication

## Patient Blood Management Recommendations From the 2018 Frankfurt Consensus Conference

Markus M. Mueller, MD; Hans Van Remoortel, PhD; Patrick Meybohm, MD, PhD; Kari Aranko, MD, PhD; Cécile Aubron, MD, PhD; Reinhard Burger, PhD; Jeffrey L. Carson, MD, PhD; Klaus Cichutek, PhD; Emmy De Buck, PhD; Dana Devine, PhD; Dean Fergusson, PhD; Gilles Folléa, MD, PhD; Craig French, MB, BS; Kathrine P. Frey, MD; Richard Gammon, MD; Jerrold H. Levy, MD; Michael F. Murphy, MD, MBBS; Yves Ozier, MD; Katerina Pavenski, MD; Cynthia So-Osman, MD, PhD; Pierre Tiberghien, MD, PhD; Jimmy Volmink, DPhil; Jonathan H. Waters, MD; Erica M. Wood, MB, BS; Erhard Seifried, MD, PhD; for the ICC PBM Frankfurt 2018 Group

JAMA. 2019;321(10):983-997. doi:[10.1001/jama.2019.0554](https://doi.org/10.1001/jama.2019.0554)

Recomendaciones basadas en la evidencia sobre tres temas:

- Anemia preoperatoria 3 cuestiones
- **Dintel transfusional 11 cuestiones**
- Programas PBM 3 cuestiones

# Consenso de Frankfurt:

## Comentarios del Prof. Manuel Muñoz

### Generales

- Faltan organizaciones con mucha solera en PBM como la NATA, IFPBM o SABM
- No se mencionan las fuentes de financiación
- El concepto de PBM está orientado más al producto que al paciente

# Consenso de Frankfurt:

## Comentarios del Prof. Manuel Muñoz

### Anemia preoperatoria

- Definición: Hb < 13 g/dl para ambos sexos.
- El uso de hierro en la anemia ferropénica debe ser una recomendación fuerte, no solo moderada
- La recomendación sobre uso de Epo debe ser fuerte

# Consenso de Frankfurt:

## Comentarios del Prof. Manuel Muñoz

### Dinteles transfusionales

- Los médicos transfundimos a pacientes, no a datos analíticos

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Recomendaciones basadas en la evidencia sobre tres temas:

- Anemia preoperatoria                      3 cuestiones
- **Dintel transfusional**                      **11 cuestiones**
- Programas PBM                              3 cuestiones

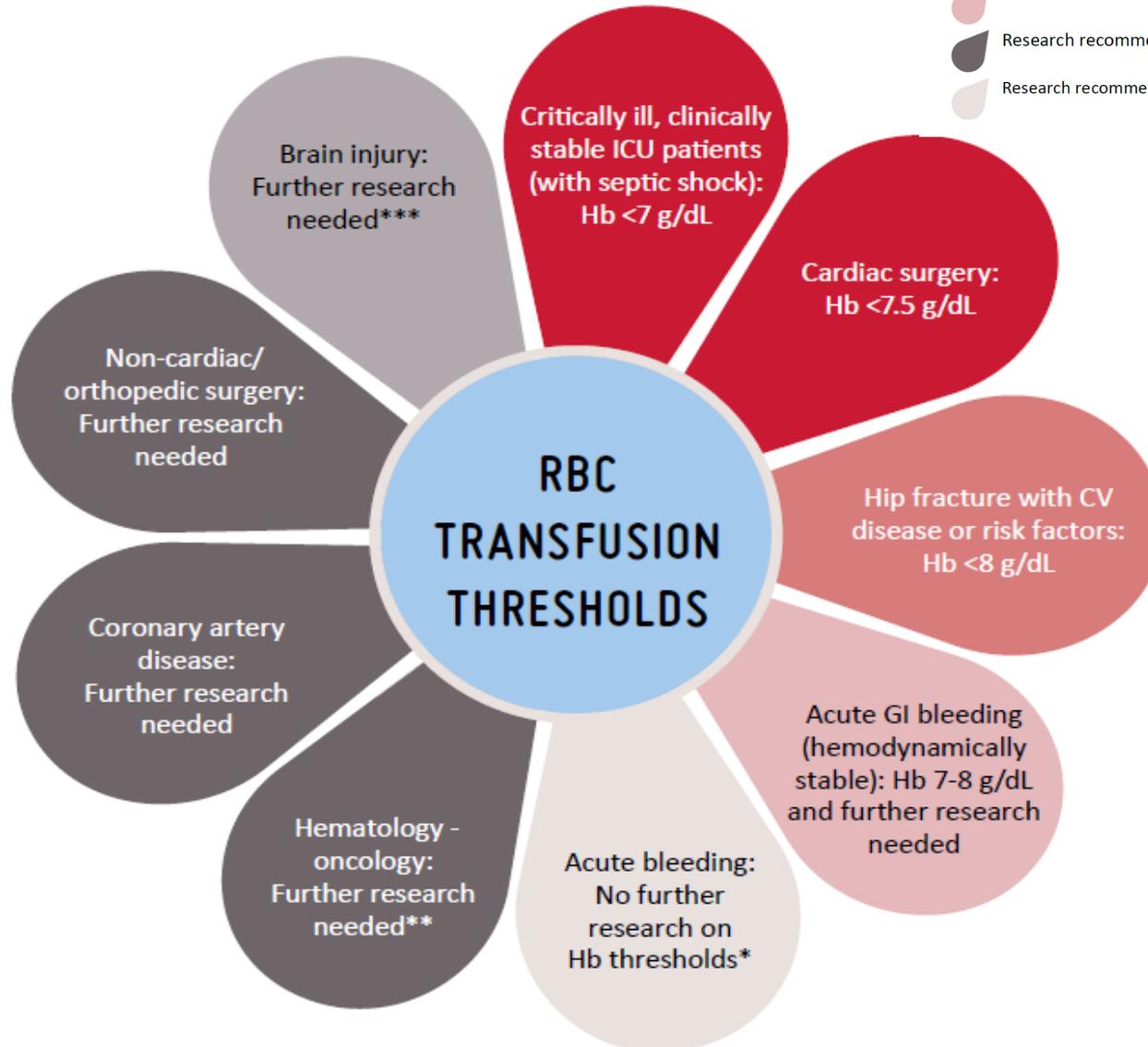
## Preguntas PICO (Población, Intervención, Comparador, Resultado)

Un dintel restrictivo disminuye la mortalidad y mejora otros resultados en comparación con un dintel liberal en ...

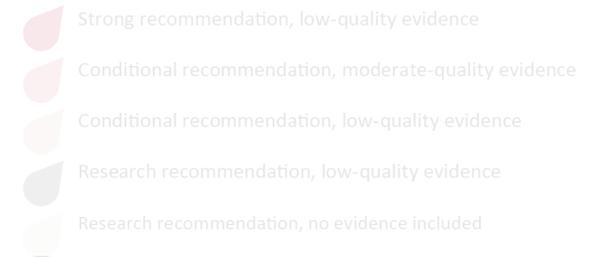
- Pacientes graves ingresados en UCI (PICO 4)
- Pacientes con riesgo CV sometidos a cirugía no CV (PICO 5)
- Peroperatorio de cirugía cardíaca (PICO 6)
- Hemorragia aguda digestiva (PICO 6) o de otro origen (PICO 14)
- Enfermedad coronaria (PICO 7)
- Pacientes onco-hematológicos (PICO 10 y 11)
- Afección aguda del SNC, traumática o isquémica (PICO 12 y 13)

# Recomendaciones

-  Strong recommendation, low-quality evidence
-  Conditional recommendation, moderate-quality evidence
-  Conditional recommendation, low-quality evidence
-  Research recommendation, low-quality evidence
-  Research recommendation, no evidence included

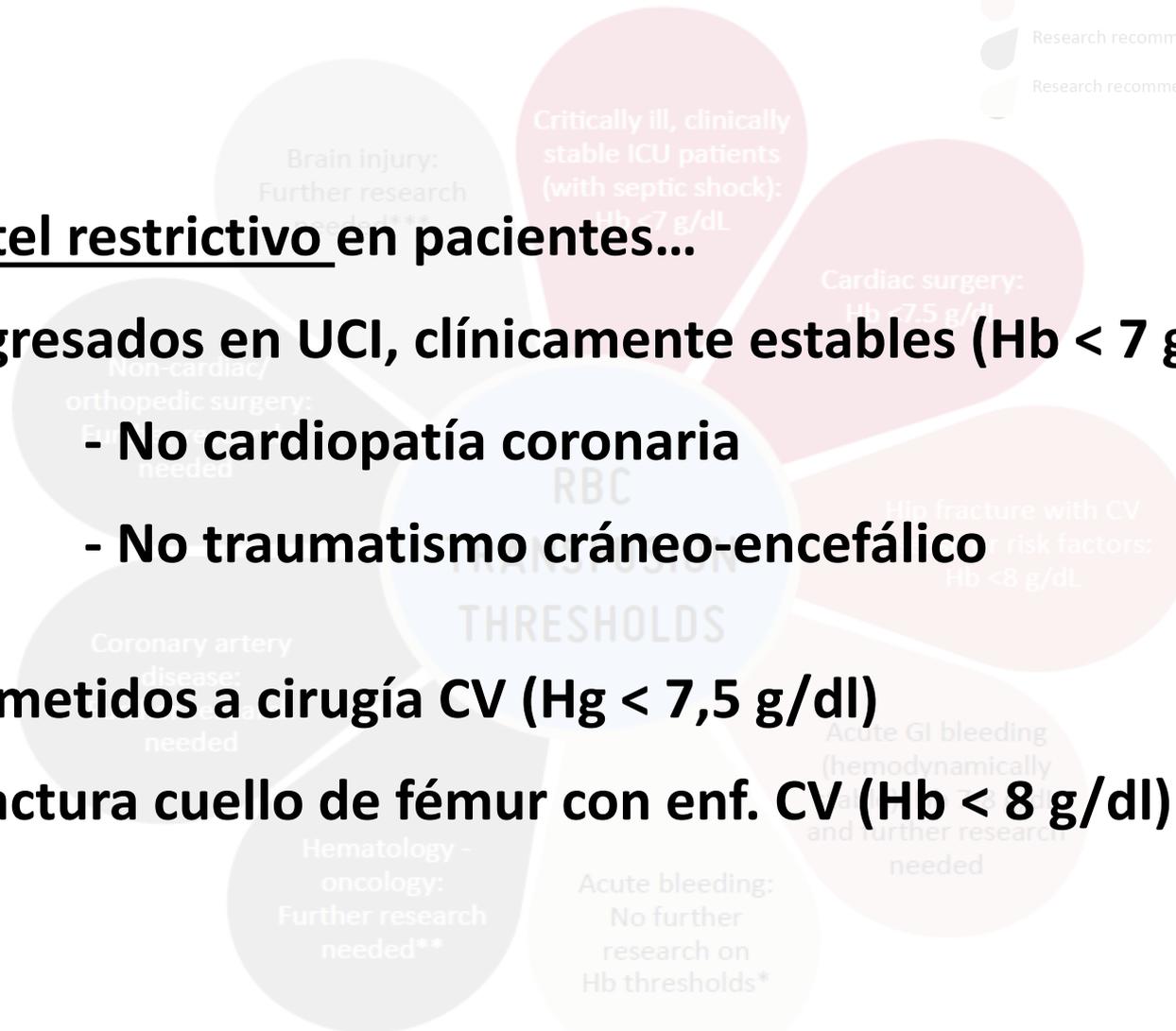


# Recomendaciones



## Dintel restrictivo en pacientes...

- Ingresados en UCI, clínicamente estables (Hb < 7 g/dl)
  - No cardiopatía coronaria
  - No traumatismo craneo-encefálico
- Sometidos a cirugía CV (Hb < 7,5 g/dl)
- Fractura cuello de fémur con enf. CV (Hb < 8 g/dl)



## Clinical Review & Education

JAMA | Special Communication

### Patient Blood Management Recommendations From the 2018 Frankfurt Consensus Conference

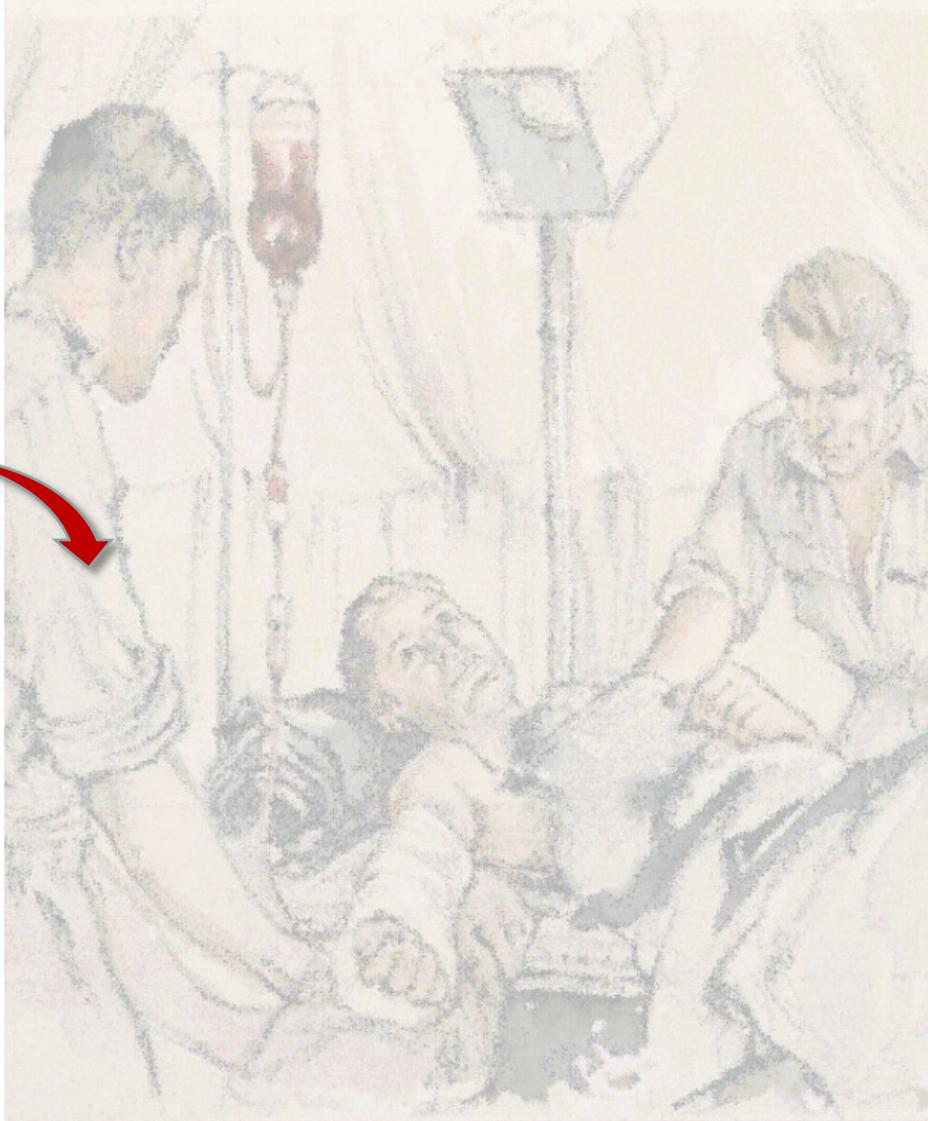
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**IMPORTANCE** Blood transfusion is one of the most frequently used therapies worldwide and is associated with benefits, risks, and costs.

**OBJECTIVE** To develop a set of evidence-based recommendations for patient blood management (PBM) and for research.

**EVIDENCE REVIEW** The scientific committee developed 17 Population/Intervention/Comparison/Outcome (PICO) questions for red blood cell (RBC) transfusion in adult patients in 3 areas: preoperative anemia (3 questions), RBC transfusion thresholds (11 questions), and implementation of PBM programs (3 questions). These questions guided the literature search in 4 biomedical databases (MEDLINE, EMBASE, Cochrane Library, Transfusion Evidence Library), searched from inception to January 2018. Meta-analyses were conducted with the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) methodology and the Evidence-to-Decision framework by 3 panels including clinical and scientific experts, nurses, patient representatives, and methodologists, to develop clinical recommendations during a consensus conference in Frankfurt/Main, Germany, in April 2018.

**FINDINGS** From 17 607 literature citations associated with the 17 PICO questions, 145 studies, including 63 randomized clinical trials with 23 143 patients and 82 observational studies with more than 4 million patients, were analyzed. For preoperative anemia, 4 clinical and 3 research recommendations were developed, including the strong recommendation to detect and manage anemia sufficiently early before major elective surgery. For RBC transfusion thresholds, 4 clinical and 6 research recommendations were developed, including 2 strong clinical recommendations for critically ill but clinically stable intensive care patients with or without septic shock (recommended threshold for RBC transfusion, hemoglobin concentration <7 g/dL) as well as for patients undergoing cardiac surgery (recommended threshold for RBC transfusion, hemoglobin concentration <7.5 g/dL). For implementation of PBM programs, 3 clinical and 3 research recommendations were

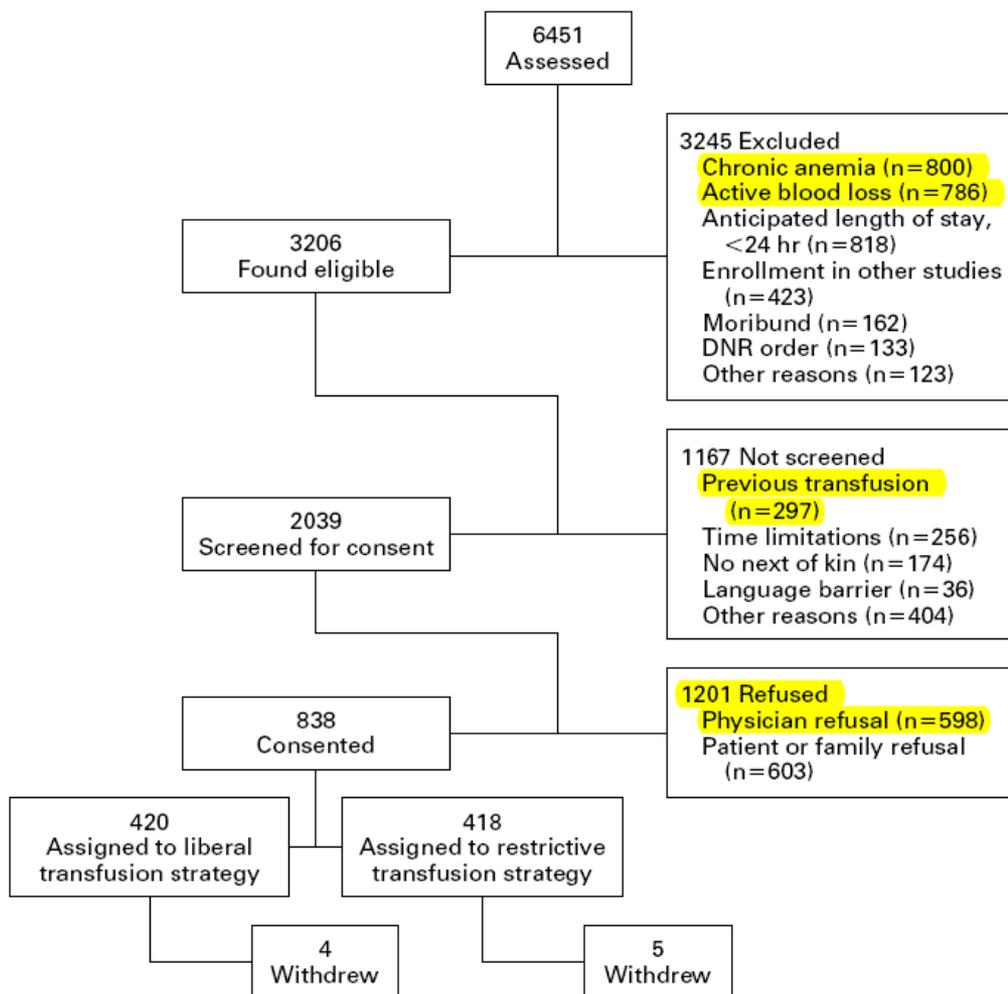


## **Dintel transfusional: crítica a los ensayos clínicos**

- Falta de validez externa
- Disonancia entre el propósito y la realidad
- Disonancia entre PICOs y recomendaciones  
(influencia ideológica o de valores externos al estudio)
- Escasa potencia para eventos raros pero graves
- Fenómenos *LIT* y *MIA* (distorsiones en la información)
- Factores de confusión y de enredo
- Visión restringida de la realidad clínica (cifras de Hb)

# Escasa generabilidad o validez externa

## Árbol de exclusiones del estudio TRICC: \*



**Evaluados: 6451**

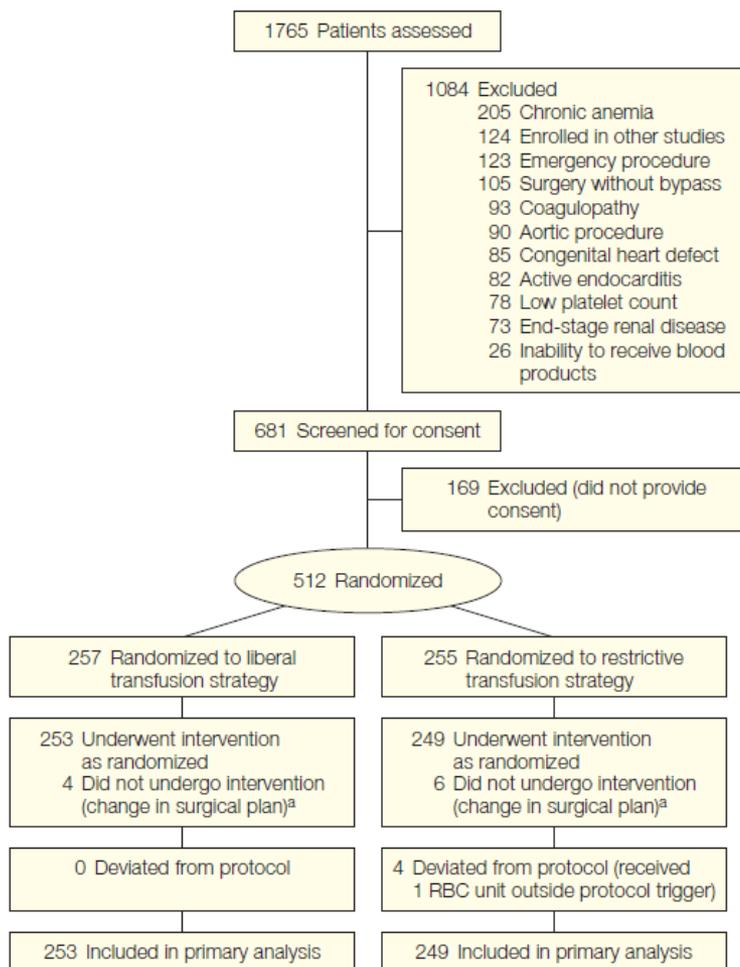


**Admitidos 838 (13%)**

\* Hébert *et al.* N Engl J Med 1999;340;409-17

# Escasa generabilidad o validez externa

## Árbol de exclusiones del estudio TRACS: \*



**Evaluados: 1756**



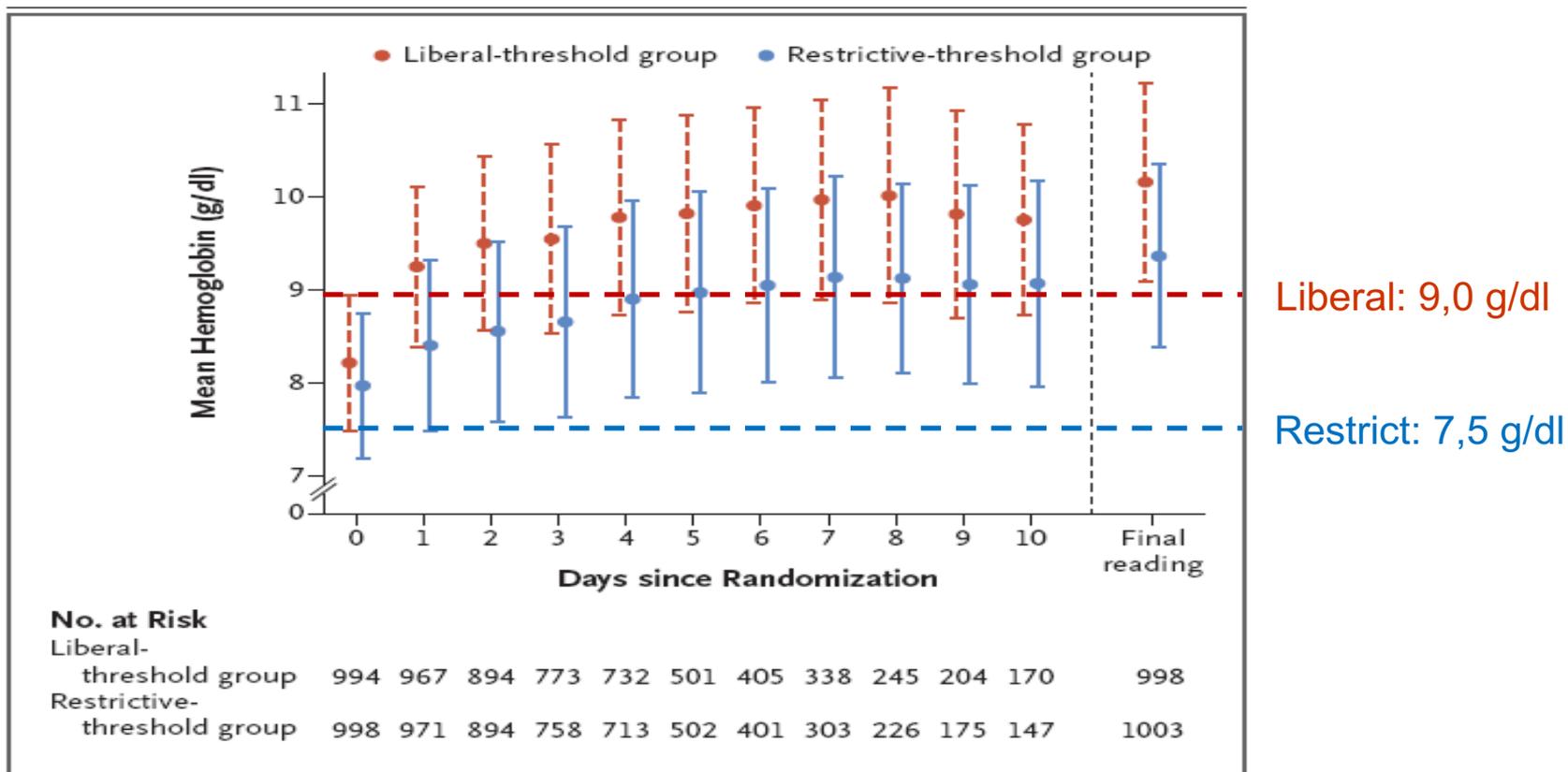
**Analizados: 502 (28%)**

\* Hajjar *et al.* JAMA 2010;304:1559-1567

# Disonancia entre propósito y realidad

Liberal vs. restrictive transfusion after cardiac surgery.

Murphy GL et al. **TITRe2** investigators. *NEJM* 2015; 372: 997-1008.



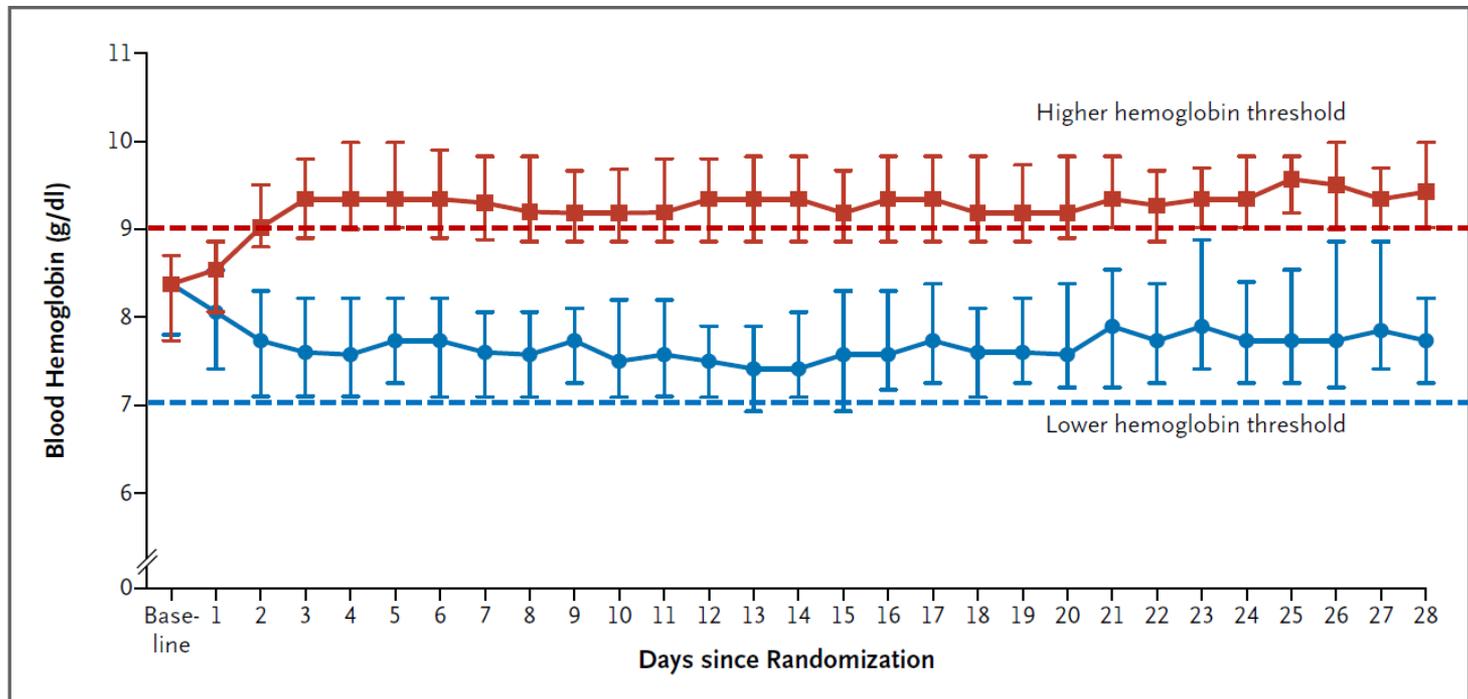
**Figure 1. Mean Daily Nadir in Hemoglobin Level.**

I bars indicate standard deviations, which were calculated independently at each time point.

# Disonancia entre propósito y realidad

## Transfusion Threshold in Septic Shock.

Holst et al. **TRISS** Investigators. *NEJM* 2014; 371:1381-1399.



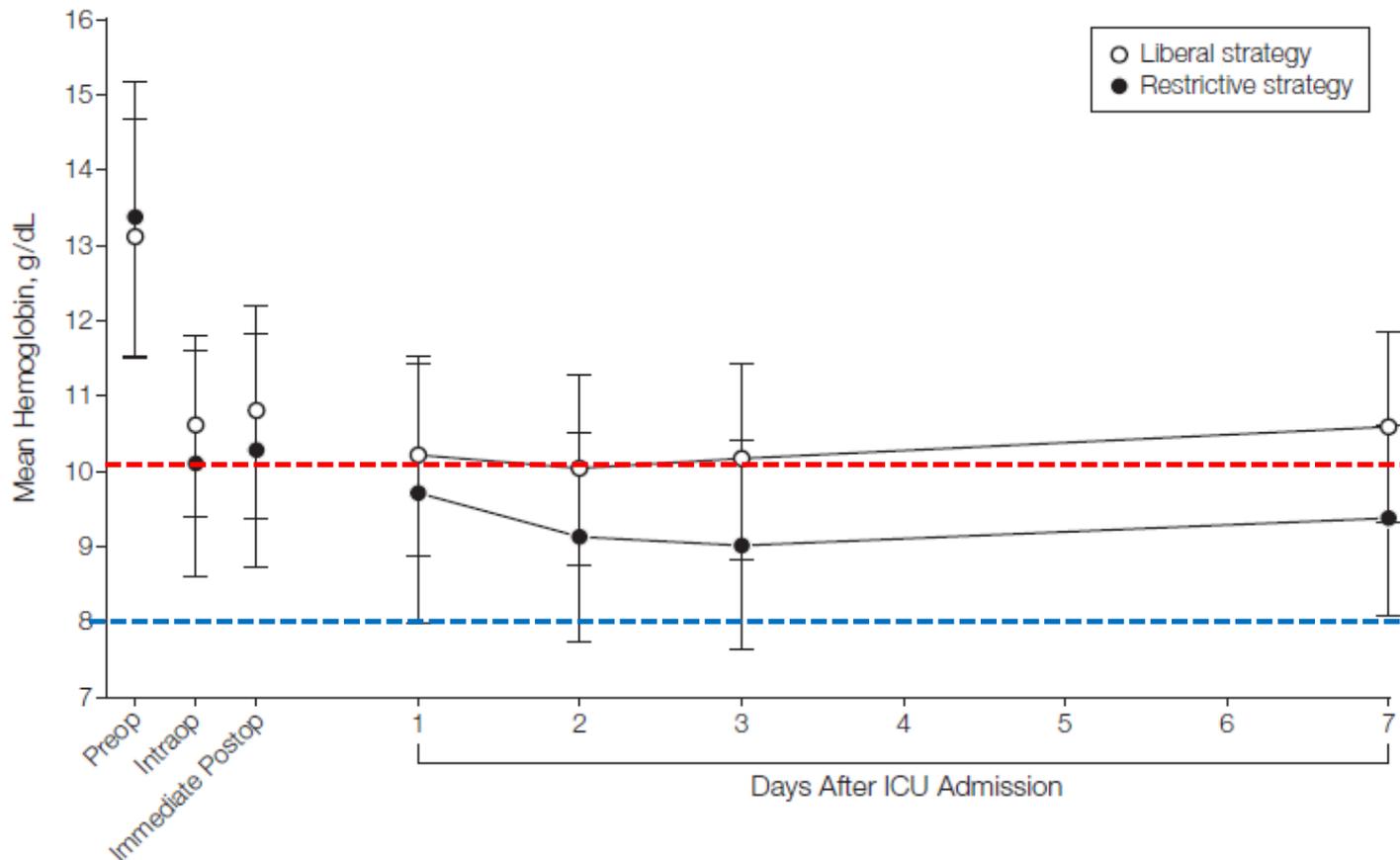
**Figure 2. Blood Hemoglobin Levels in Patients in the ICU at Baseline and after Randomization.**

The graphs show the median daily lowest levels of blood hemoglobin in the lower-threshold group and the higher-threshold group. Baseline values were the lowest blood hemoglobin level measured in the 24 hours before randomization. Day 1 was defined as the time of randomization to the end of that day and lasted a median of 15 hours in the lower-threshold group and 14 hours in the higher-threshold group. The I bars indicate the 25th and 75th percentiles.

# Disonancia entre propósito y realidad

## Transfusion Requirements After Cardiac Surgery (TRACS Trial).

Hajjar et al. *JAMA* 2010; 304:1559-1567.



## **Disonancia entre propósito y realidad**

Transfusion Threshold in Septic Shock.

Hébert et al. **TRICC** Investigators. *NEJM* 1999; 340:409-417.

### **Success of Treatment**

The average daily hemoglobin concentrations were  $8.5 \pm 0.7$  g per deciliter in the restrictive-strategy group and  $10.7 \pm 0.7$  g per deciliter in the liberal-strategy group ( $P < 0.01$ ). The average hemoglobin concentrations also differed significantly between

## **Disonancia entre preguntas y conclusiones**

### **PICOs:**

“Un dintel restrictivo disminuye la mortalidad y mejora...”

### **Conclusión de los ensayos clínicos:**

“Un dintel restrictivo NO EMPEORA la mortalidad...”

### **Valoración externa a los ensayos clínicos:**

“*Per se* la transfusión aumenta la mortalidad;  
*ergo*, si no transfundimos mejoraremos la supervivencia.”

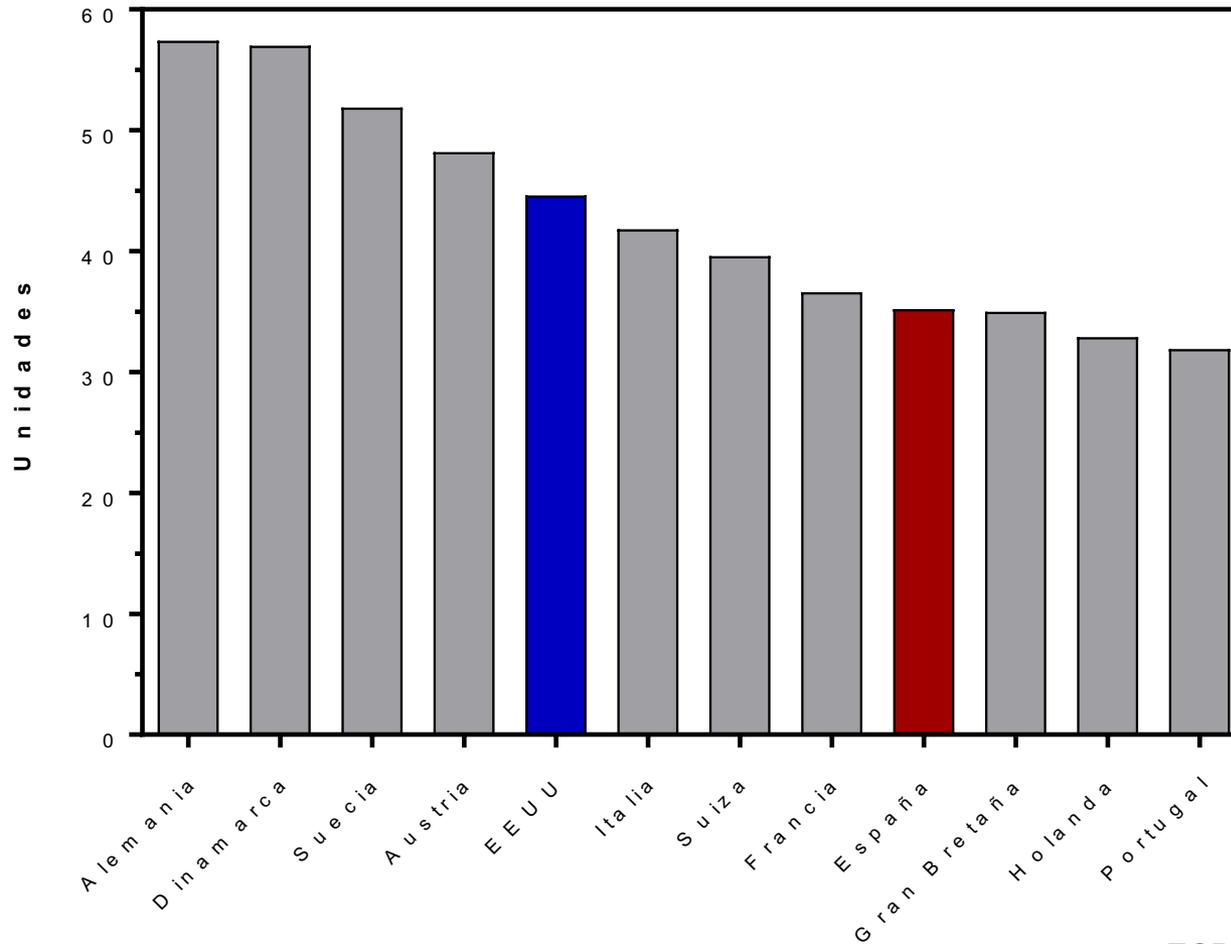
## **Disonancia entre preguntas y conclusiones**

En el pensamiento dominante existe una valoración moral contraria a la transfusión que sesga muchos estudios



# ¿Se transfunde en exceso?

Hematíes: unidades x 1000 habitantes/año



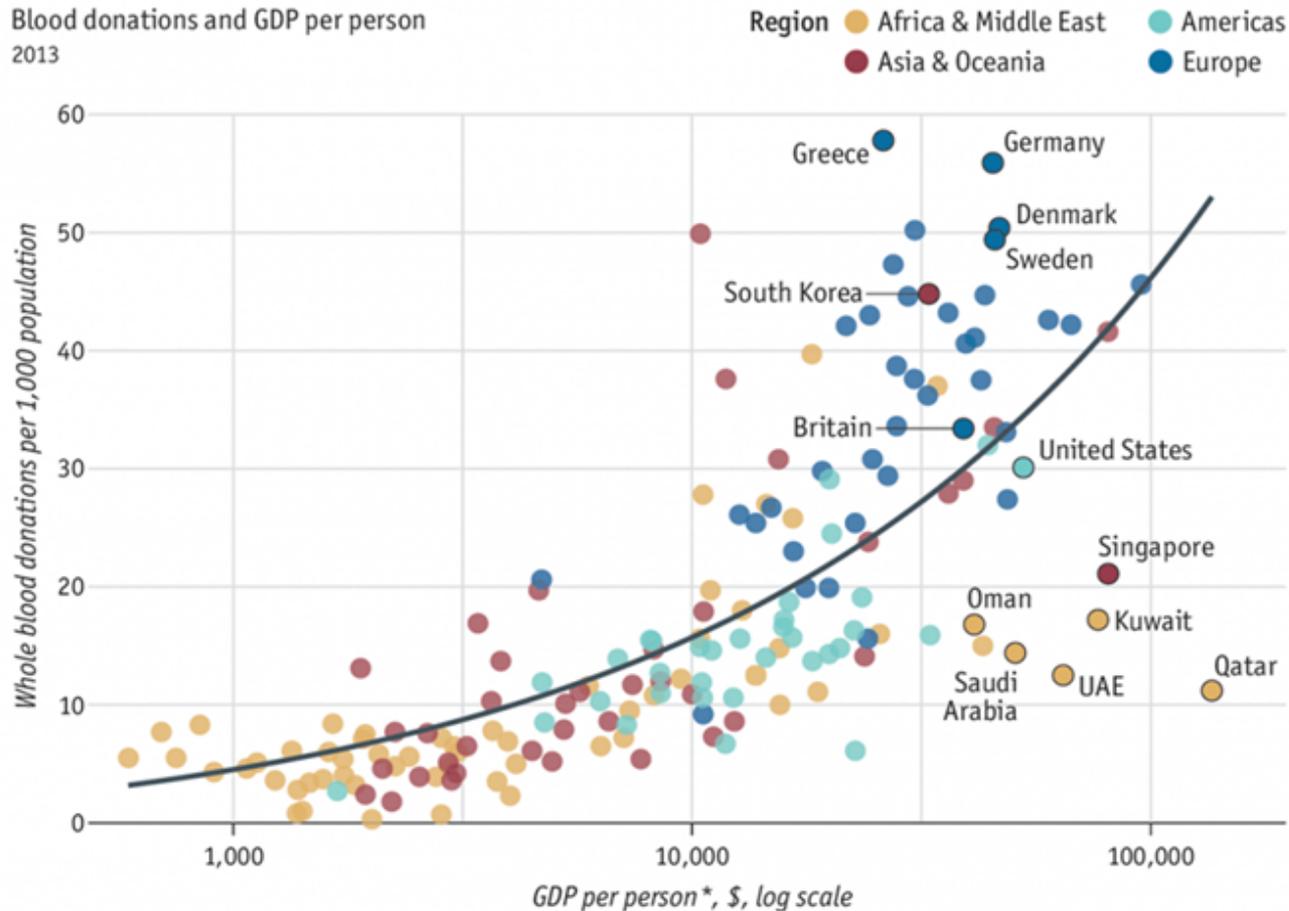
País

- ECBT 2010 Report..  
- 2011 NBCU Survey Report

# ¿Lujo de países ricos?

## There will be blood

Blood donations and GDP per person  
2013



Sources: Global Status Report on Blood Safety and Availability 2016, WHO; World Bank; *The Economist* \*At purchasing-power parity

# ¿Indicación inadecuada?

## Evidencias. Uso adecuado de los componentes sanguíneos

Episodios evaluados: 1.535 en 9 hospitales de Catalunya, 2012

	Episodio	Adecuación (%)
Hematíes	1.059	86
Plaquetas	279	83
Plasma	197	85

Uso adecuado de los hematíes según guía de la SETS 2010

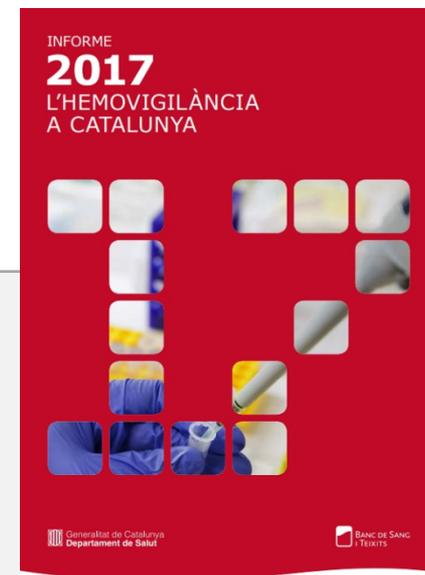
- Hb < 7 g/dl , transfusión justificada
- Hb entre 7 i 8 g/dl, transfusión si riesgo de hipoxia
- Hb entre 8 y 10 g/dl , transfusión si clínica isquémica
- Hb > 10a/dl. transfusión no iustificada

# ¿Es tan peligrosa la transfusión de hematíes?

## Mortalidad atribuible:

### Registro de Hemovigilancia de Cataluña

Periodo:	2003-2017.
Transfusión hematíes:	> 3 millones unidades.
Muertes atribuidas:	3
Incidencia:	<b>&lt; 1 por millón de u.</b>



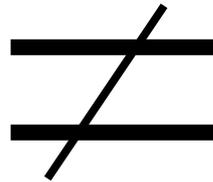
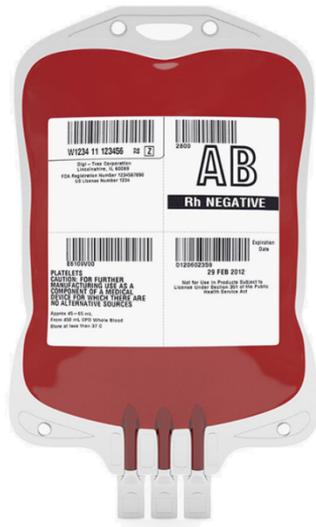
## Escasa potencia para eventos raros pero graves

Tamaño muestral necesario para detectar  $\uparrow$  mortalidad con error  $\alpha = 5\%$  y potencia = 80%

Aumento mortalidad	UCI (mort. 30%)	CCV (mort. 15%)
1 %	33.200	20.500
3 %	22.200	2.400
5 %	20.000	900
10 %	18.000	250

# Escasa potencia para eventos raros pero graves

Fuentes de variabilidad insospechadas



## **Fenómenos *Lost in Translation* y *Missed in Action***

**La información se desvirtúa en el tránsito desde el ensayo clínico al artículo editorial, la revisión, la guía clínica, la opinión de los “expertos”, etc (*LIT*).**

**... o incluso entre los resultados y la conclusión dentro del mismo estudio (*MIA*).**

## “Lost in translation”

The NEW ENGLAND  
JOURNAL of MEDICINE

ESTABLISHED IN 1812

JANUARY 3, 2013

VOL. 368 NO. 1

### Transfusion Strategies for Acute Upper Gastrointestinal Bleeding

Càndid Villanueva, M.D., Alan Colomo, M.D., Alba Bosch, M.D., Mar Concepción, M.D., Virginia Hernandez-Gea, M.D., Carles Aracil, M.D., Isabel Graupera, M.D., María Poca, M.D., Cristina Alvarez-Urturi, M.D., Jordi Gordillo, M.D., Carlos Guarner-Argente, M.D., Miquel Santaló, M.D., Eduardo Muñoz, M.D., and Carlos Guarner, M.D.

## Conclusión:

En la HDA, la transfusión “restrictiva” (Hb 7g/dl) no es peor y podría ser mejor que la “liberal” (Hb 9 g/dl)

## Características pacientes

- Pacientes estables, con hemorragia controlada
- Endoscopia: bajo riesgo de resangrado
- Sin factores de riesgo CV

## “Missed in action”

Liberal vs. restrictive transfusion after cardiac surgery. Murphy GL et al. **TITRe2** investigators. *NEJM* 2015; 372: 997-1008.

### RESULTS

A total of 2007 patients underwent randomization; 4 participants withdrew, leaving 1000 in the restrictive-threshold group and 1003 in the liberal-threshold group. Transfusion rates after randomization were 53.4% and 92.2% in the two groups, respectively. The primary outcome occurred in 35.1% of the patients in the restrictive-threshold group and 33.0% of the patients in the liberal-threshold group (odds ratio, 1.11; 95% confidence interval [CI], 0.91 to 1.34;  $P=0.30$ ); there was no indication of heterogeneity according to subgroup. There were more deaths in the restrictive-threshold group than in the liberal-threshold group (4.2% vs. 2.6%; hazard ratio, 1.64; 95% CI, 1.00 to 2.67;  $P=0.045$ ). Serious postoperative complications, excluding primary-outcome events, occurred in 35.7% of participants in the restrictive-threshold group and 34.2% of participants in the liberal-threshold group. Total costs did not differ significantly between the groups.

### CONCLUSIONS

A restrictive transfusion threshold after cardiac surgery was not superior to a liberal threshold with respect to morbidity or health care costs. (Funded by the National Institute for Health Research Health Technology Assessment program; Current

## Factores de enredo

Liberal or restrictive transfusion in high-risk patients after hip fracture: the **FOCUS** study. Carson J et al. *NEJM* 2011; 365: 2453-2462.

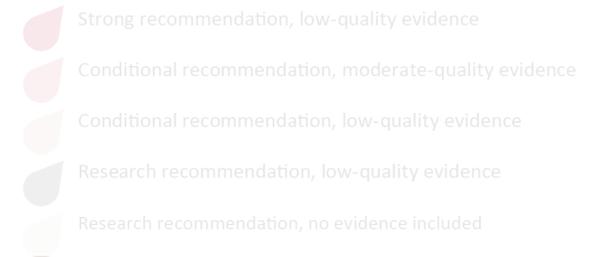
surgery. According to the original protocol, only patients with cardiovascular disease (a history of ischemic heart disease, electrocardiographic evidence of previous myocardial infarction, a history or presence of congestive heart failure or peripheral vascular disease, or a history of stroke or transient ischemic attack) were eligible. In December 2005, eligibility criteria were expanded to enhance recruitment by including patients with any of the following cardiovascular risk factors: a history of or treatment for hypertension, diabetes mellitus, or hypercholesterolemia; a cholesterol more per deciliter; current tobacco use; or a creatinine level of more than 2.0 mg per deciliter.<sup>6</sup>

## Visión restringida de la realidad clínica

Factores que modulan la decisión de transfundir:

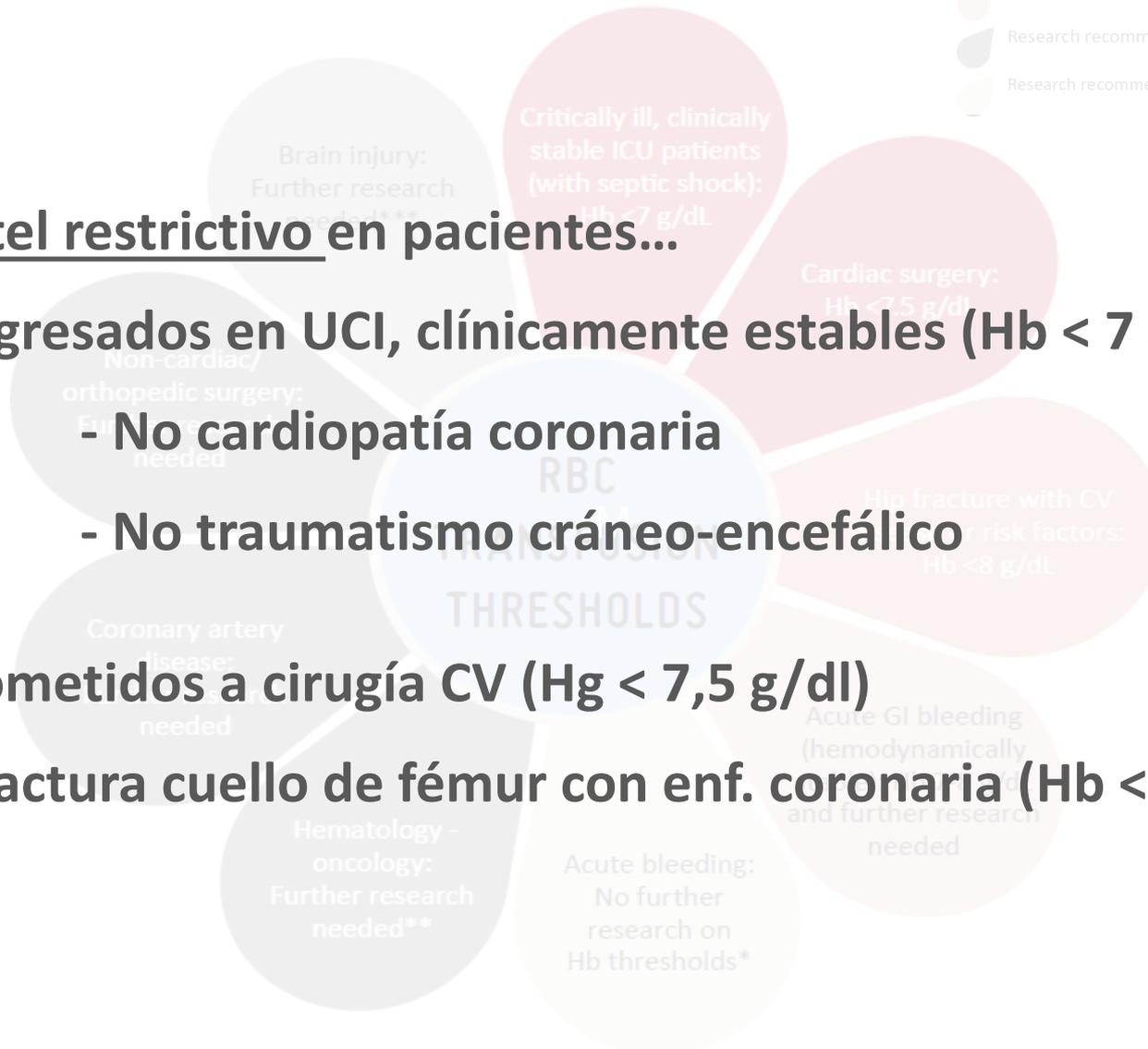


# Recomendaciones



## Dintel restrictivo en pacientes...

- Ingresados en UCI, clínicamente estables (Hb < 7 g/dl)
  - No cardiopatía coronaria
  - No traumatismo craneo-encefálico
- Sometidos a cirugía CV (Hb < 7,5 g/dl)
- Fractura cuello de fémur con enf. coronaria (Hb < 8 g/dl)



# Recomendaciones

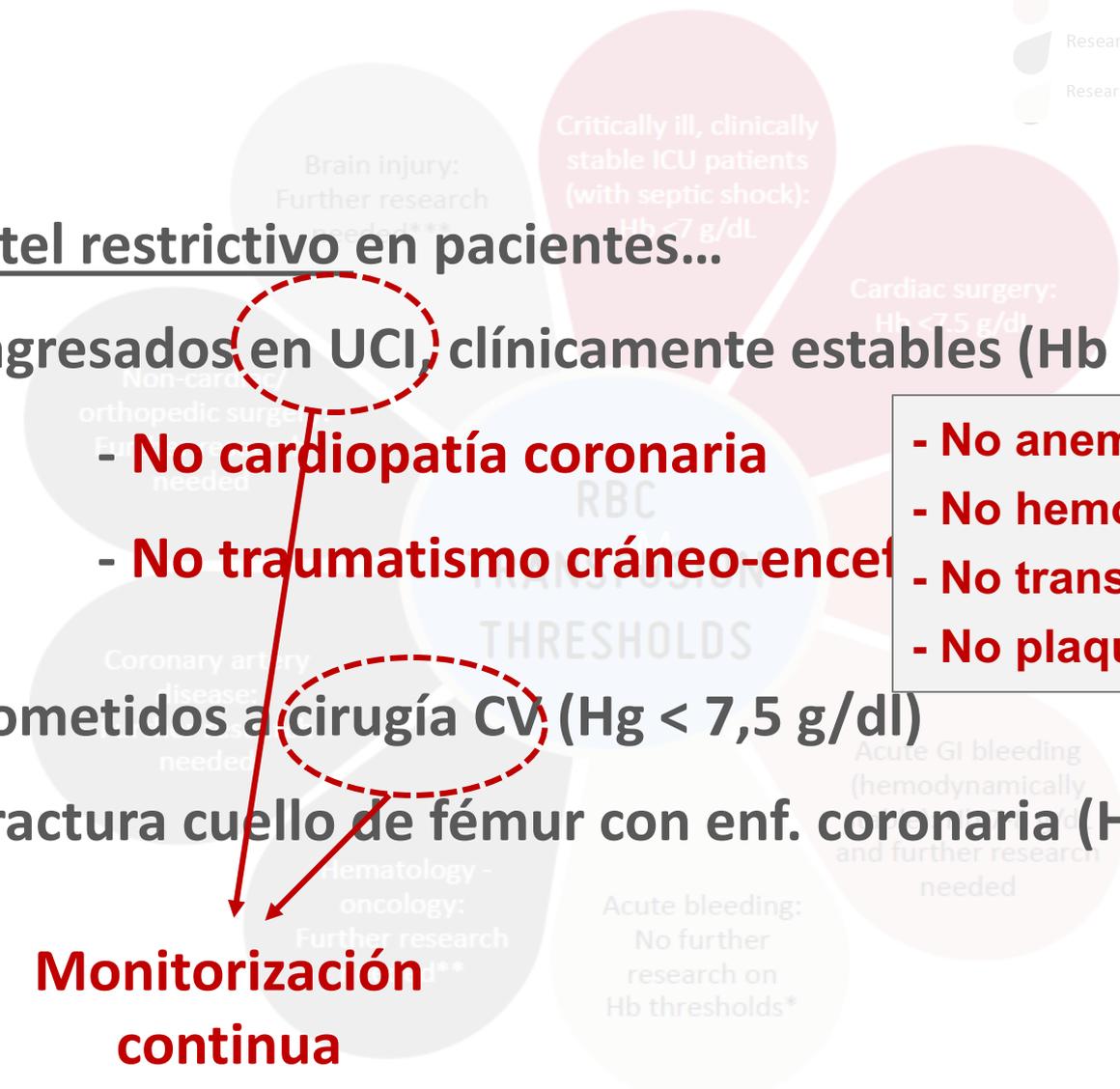
-  Strong recommendation, low-quality evidence
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- Fractura cuello de fémur con enf. coronaria (Hb < 8 g/dl)

- No anemia previa
- No hemorragia
- No transfusión previa
- No plaquetas, plasma, etc.

**Monitorización  
continua**

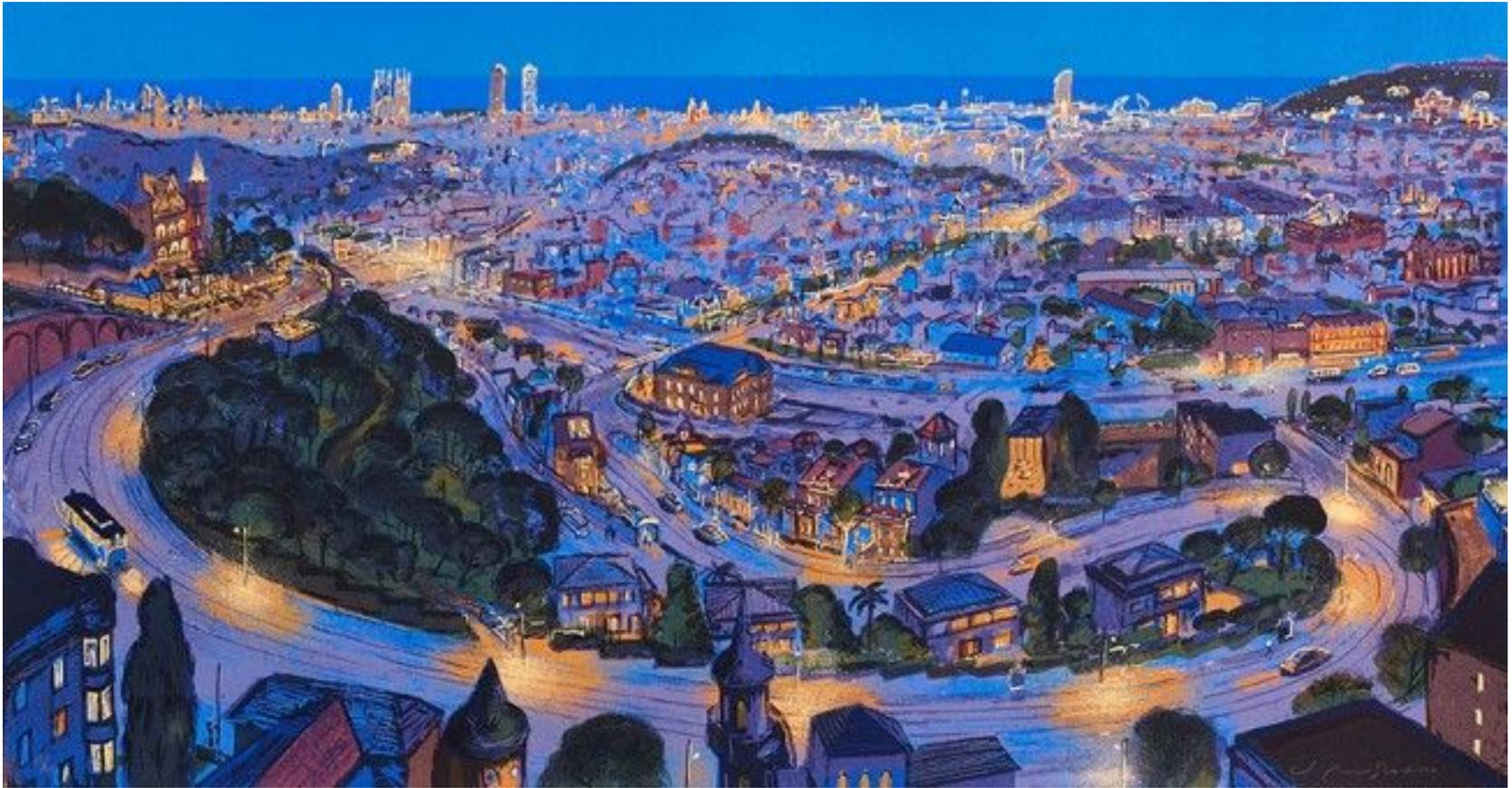


## **Recomendación**

“No existe una cifra de Hb que pueda tomarse como dintel universal para la transfusión de hematíes.”

“La indicación debe fundamentarse en el mejor juicio clínico a la hora de evaluar todos los factores relacionados con el paciente y con su entorno.”

# Gracias por su atención



Barcelona desde la sierra de Collserola

*Josep Moscardó, 2014*