

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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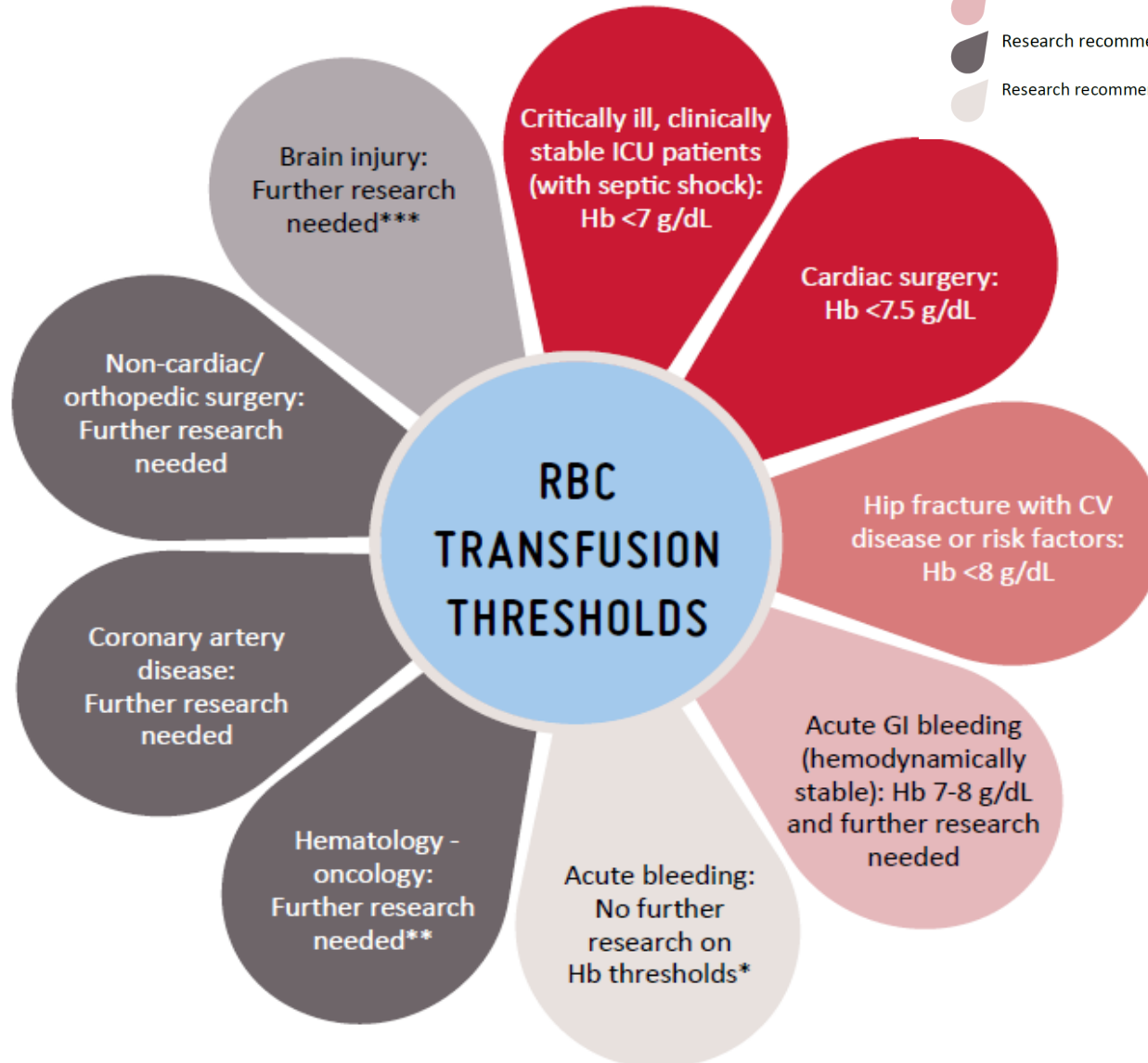
Preguntas PICO (Población, Intervención, Comparador, Resultado)

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

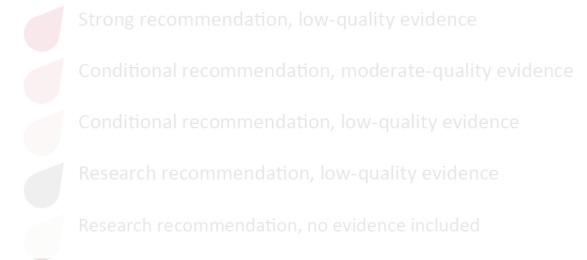
- Pacientes graves ingresados en UCI (PICO 4)
- Pacientes con riesgo CV sometidos a cirugía no CV (PICO 5)
- Peroperatorio de cirugía cardíaca (PICO 6)
- Hemorragia aguda digestiva (PICO 6) o de otro origen (PICO 14)
- Enfermedad coronaria (PICO 7)
- Pacientes onco-hematológicos (PICO 10 y 11)
- Afección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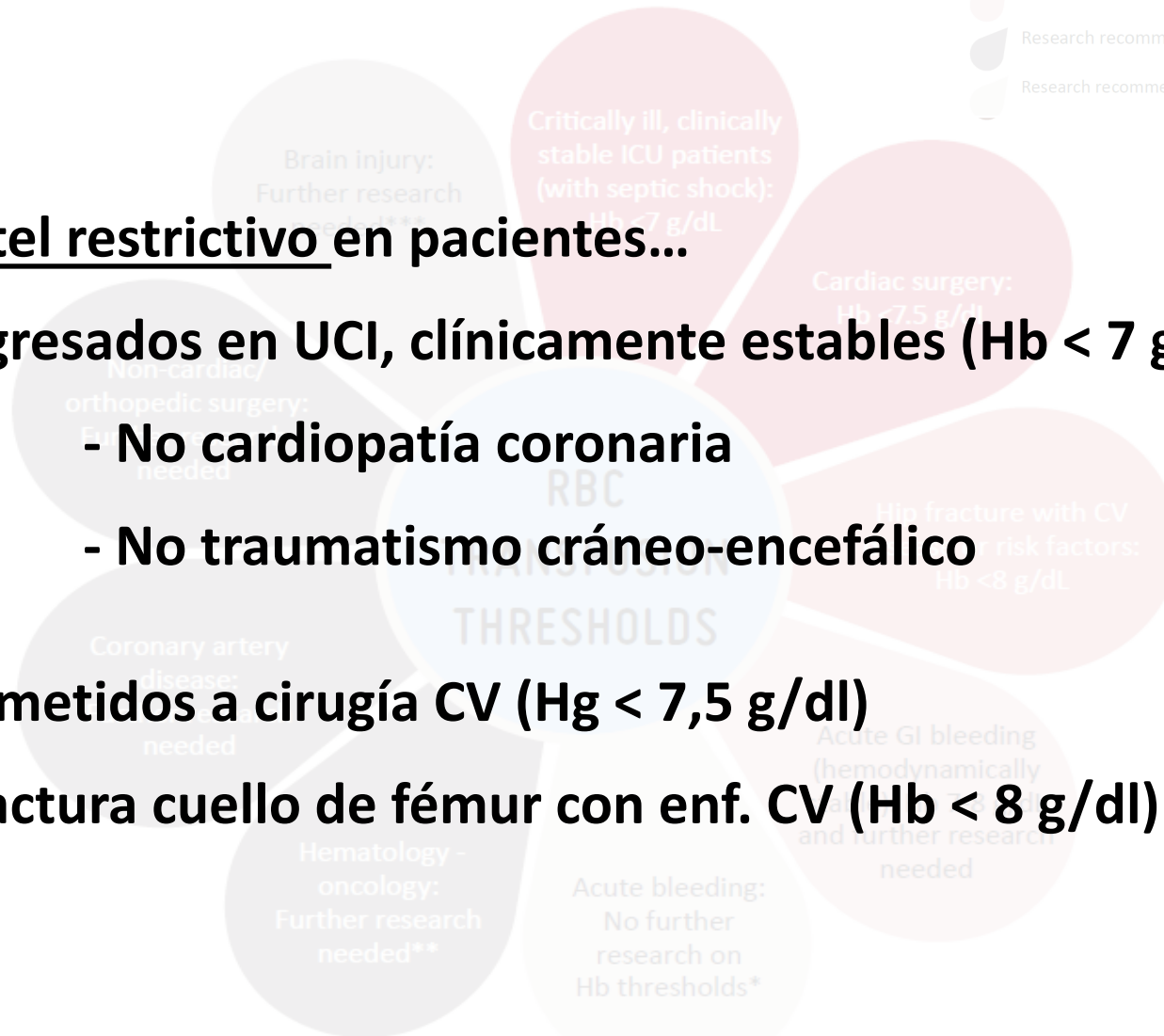


Recomendaciones



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)



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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

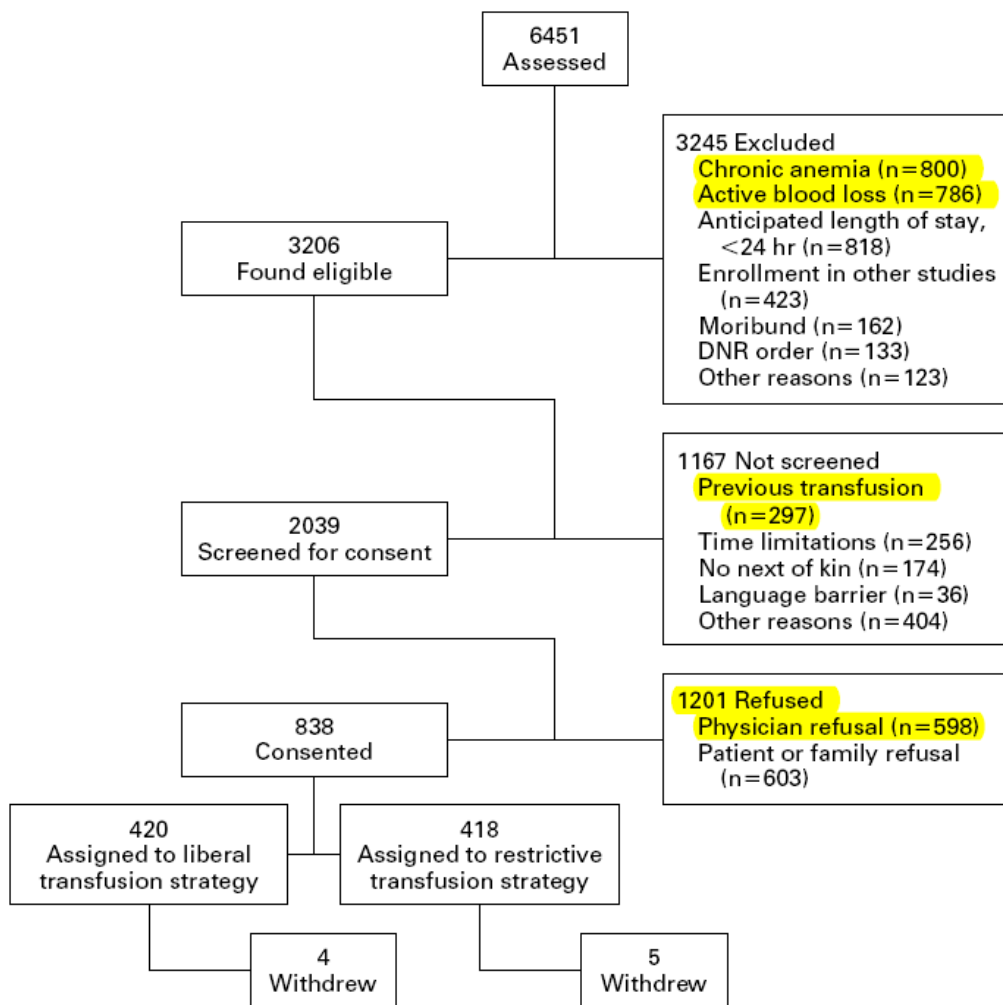


Dintel transfusional: crítica a los ensayos clínicos

- 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

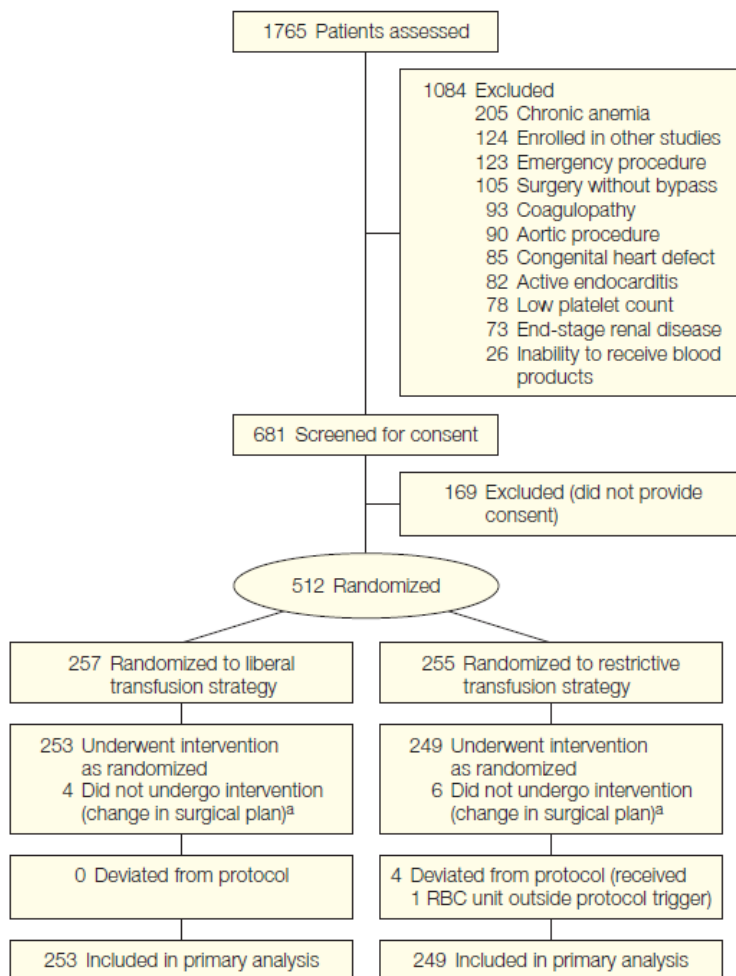


Admitidos 838 (13%)

* 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.

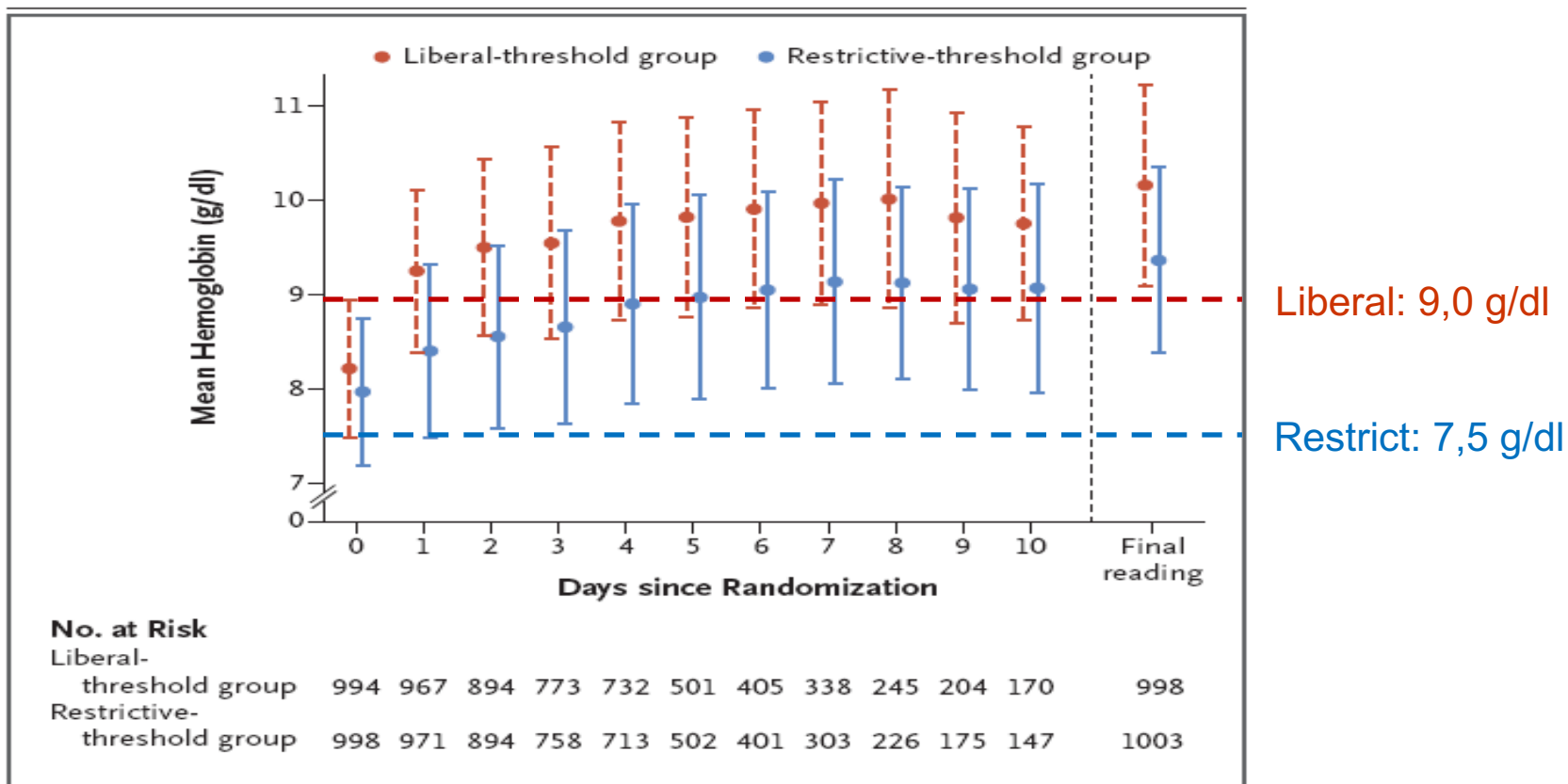


Figure 1. Mean Daily Nadir in Hemoglobin Level.

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.

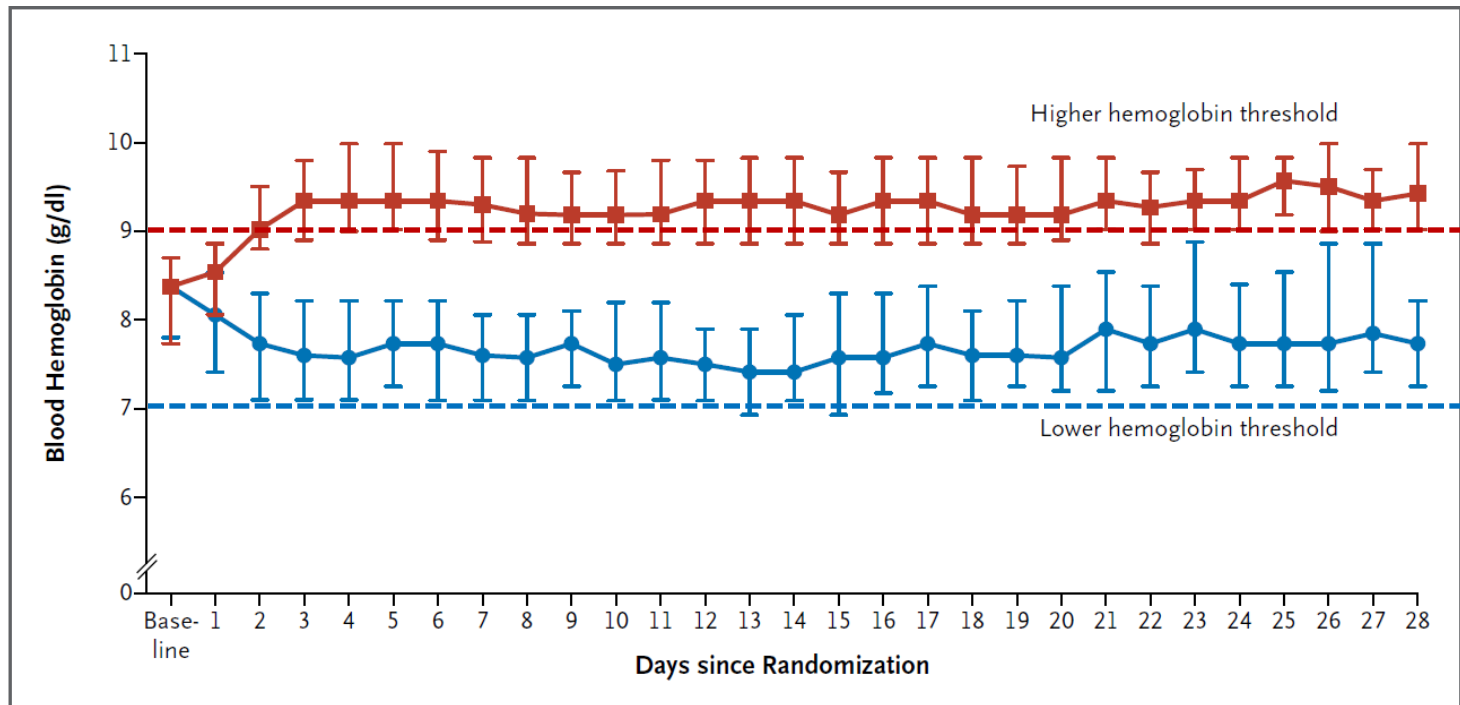


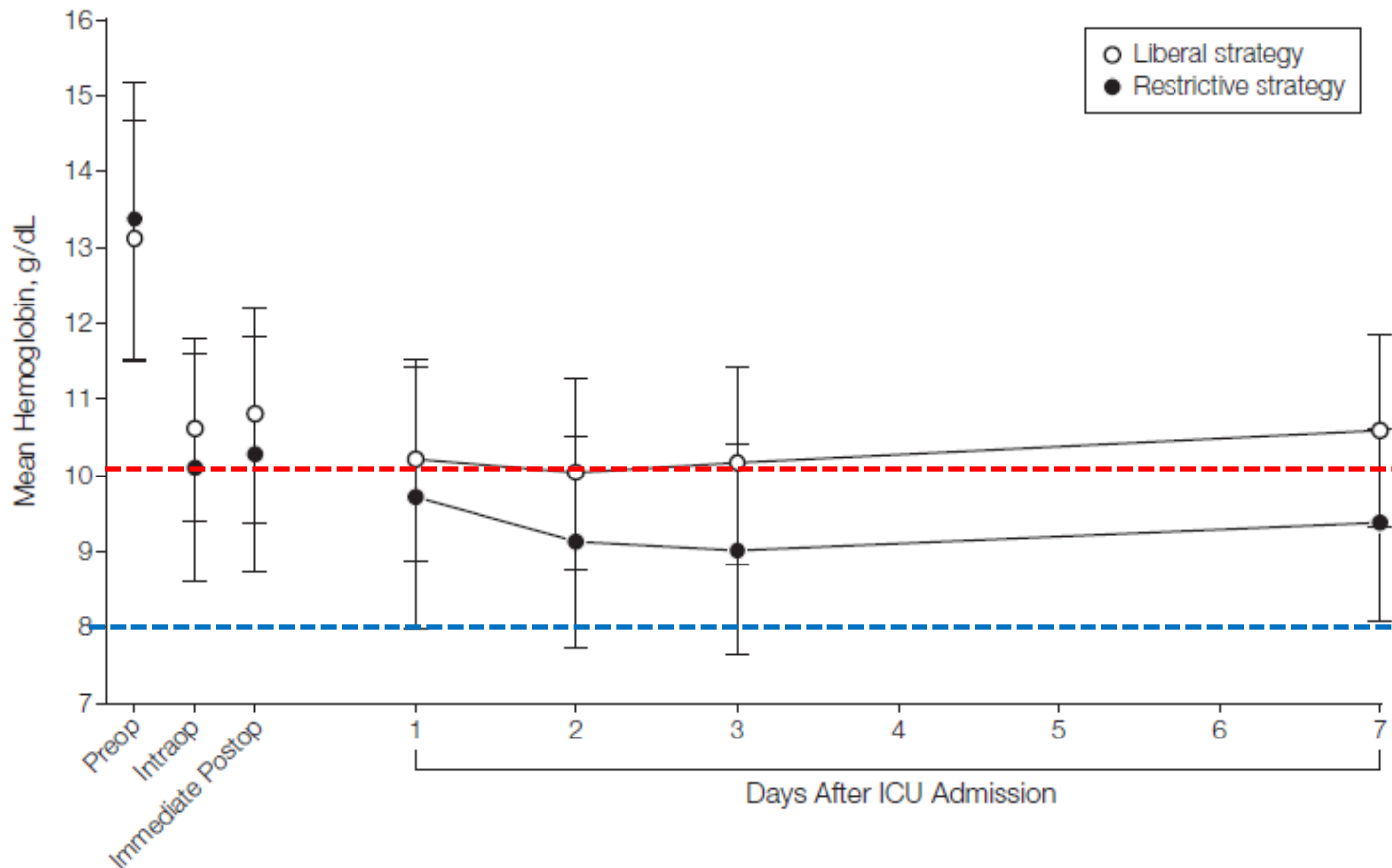
Figure 2. Blood Hemoglobin Levels in Patients in the ICU at Baseline and after Randomization.

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 ± 0.7 g per deciliter in the restrictive-strategy group and 10.7 ± 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.”

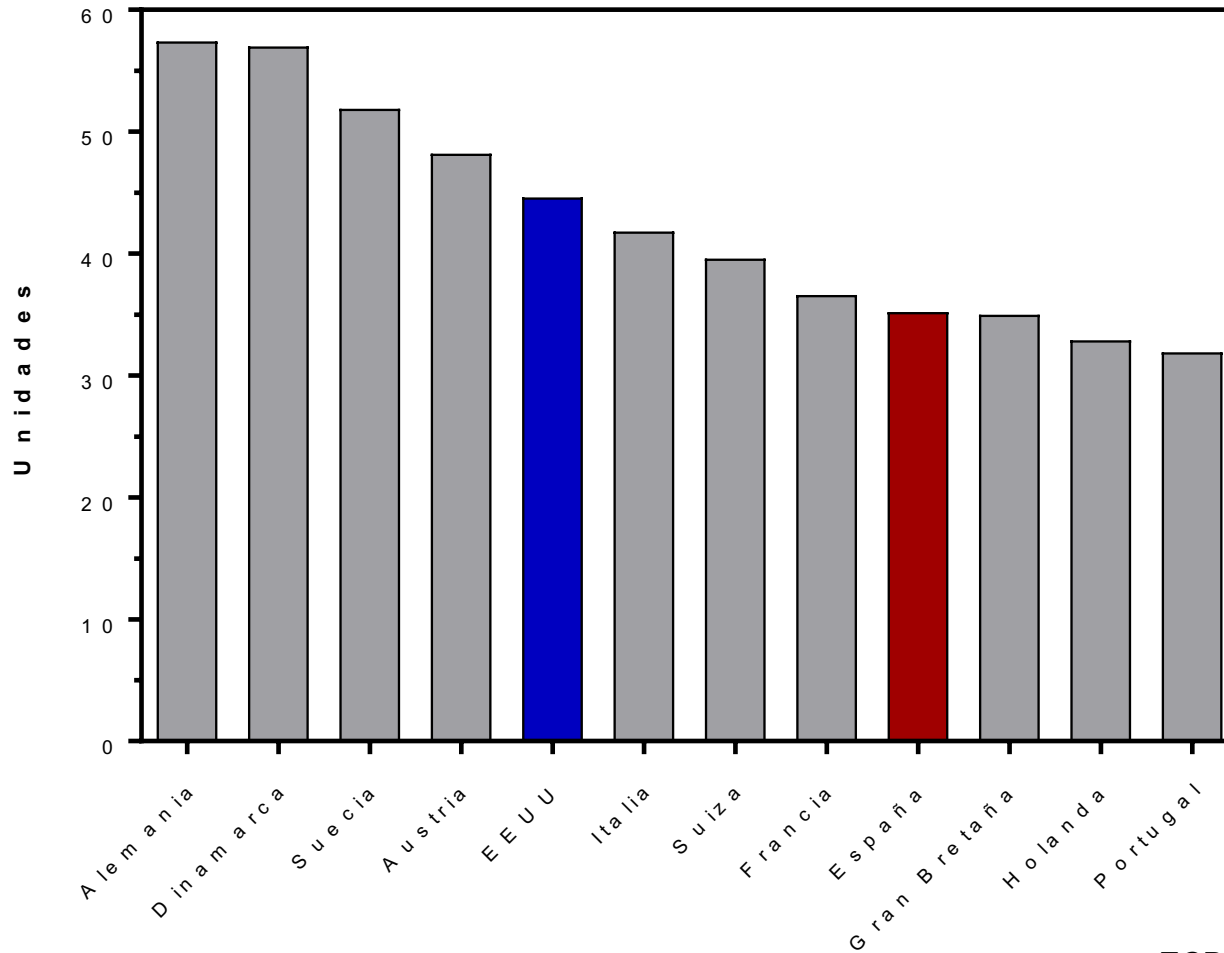
Disonancia entre preguntas y conclusiones

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



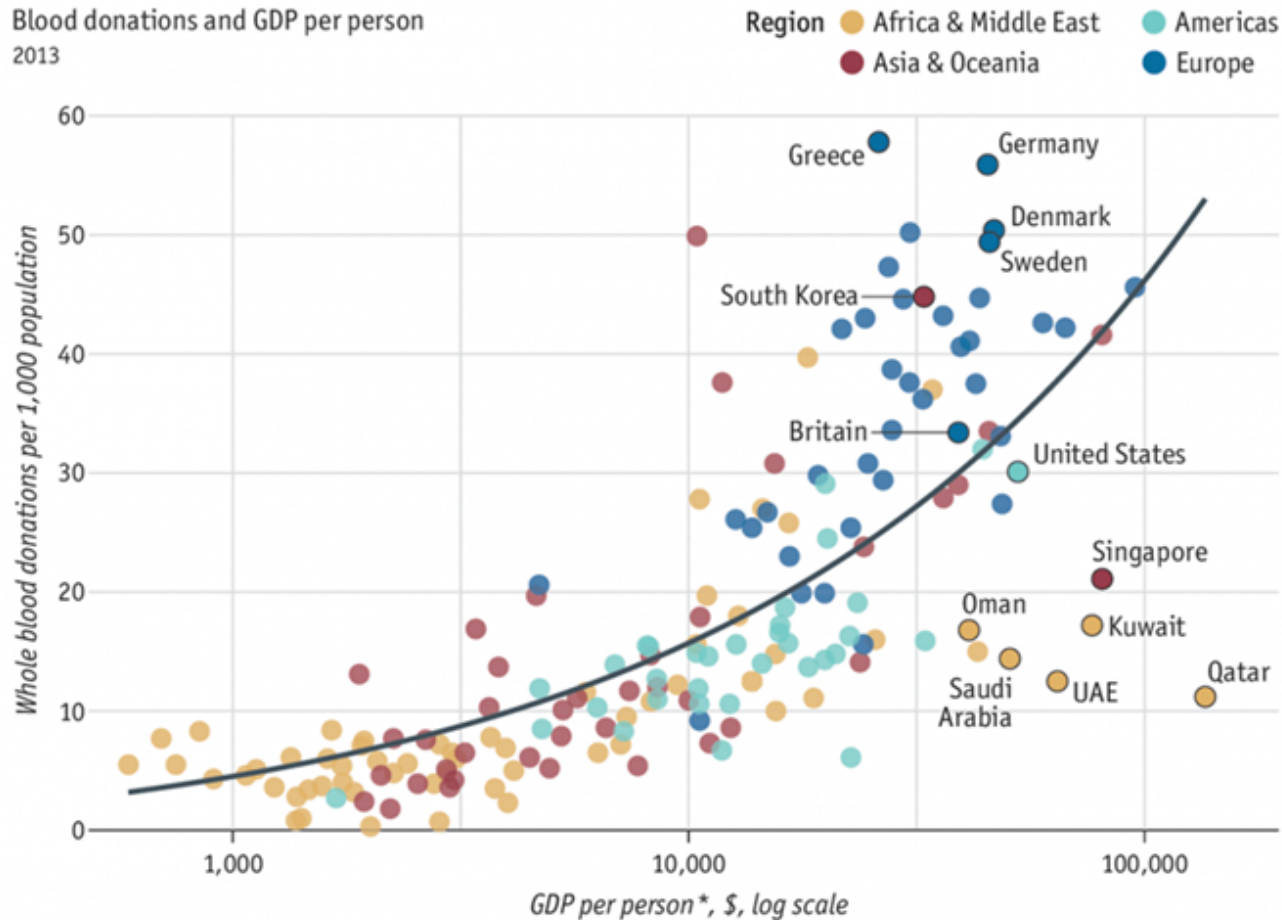
País

- 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:	< 1 por millón de u.



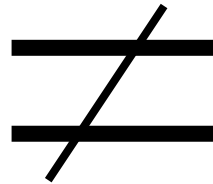
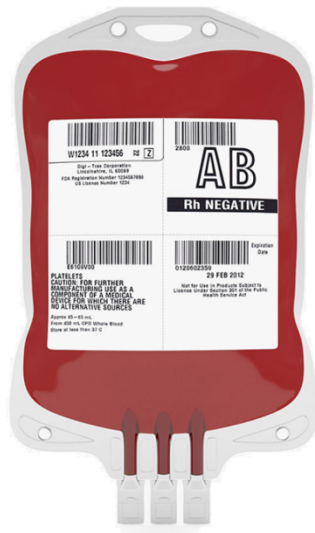
Escasa potencia para eventos raros pero graves

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.⁶

Visión restringida de la realidad clínica

Factores que modulan la decisión de transfundir:

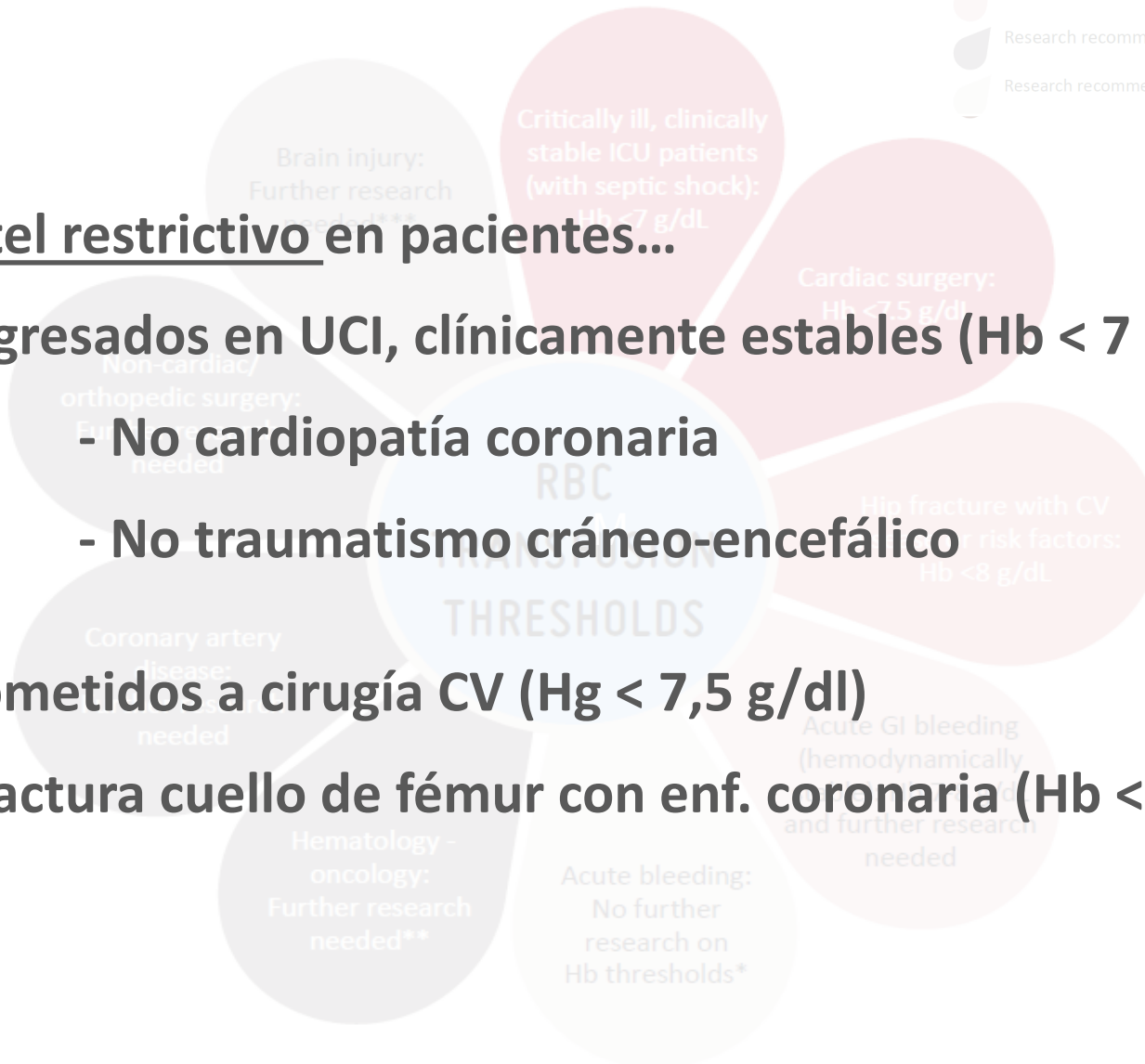


Recomendaciones






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Recomendaciones

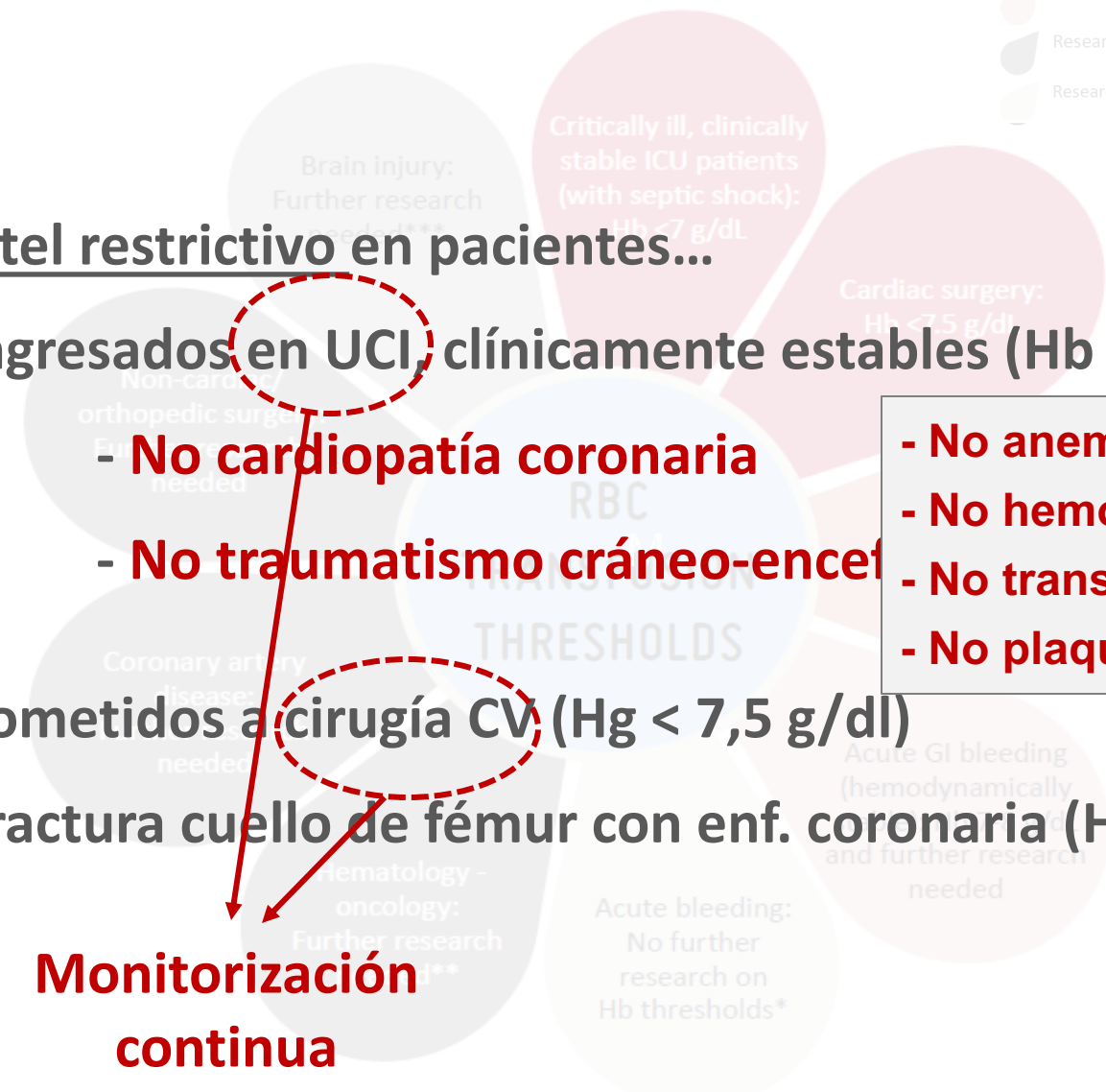
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- No anemia previa
- No hemorragia
- No transfusión previa
- No plaquetas, plasma, etc.

**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