Restriktivní transfuzní strategie

- i u akutního infarktu myokardu?

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no conflict of interest

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přehled

1. anémie

2. anémie na ICU

3. transfúzní trigger

4. studie

5. *guidelines*
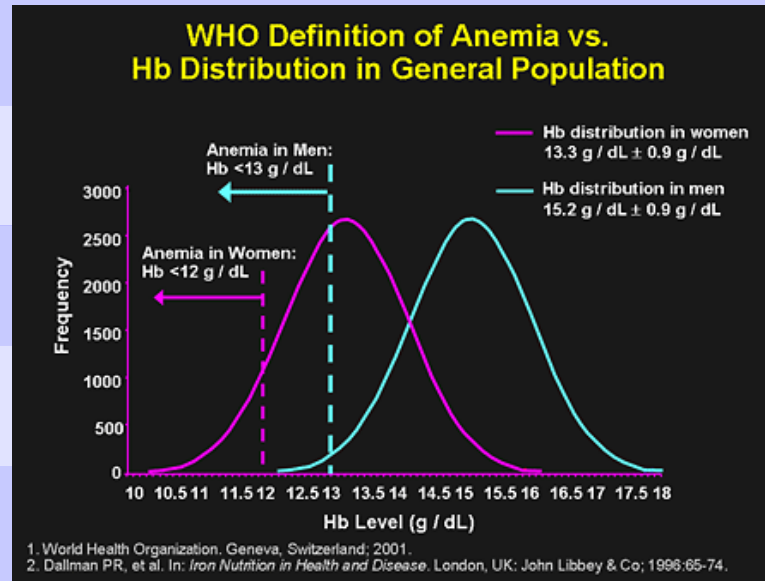
anémie

Anemia *(WHO)*

Hb level <13,0 g/dL in men

Hb level <12,0 g/dL in women

derived in the 1960s from

very small and low-quality studies

NUTRITIONAL ANAEMIAS

Report of a
WHO Scientific Group

GENEVA

1968

3. CRITERIA FOR THE DIAGNOSIS OF ANAEMIA

In detecting and evaluating an anaemia problem in a community, reference standards are necessary, even though they may be somewhat arbitrary. The report [2] of the 1958 WHO Study Group recommended haemoglobin values below which anaemia could be considered to exist. These figures were chosen arbitrarily and it is still not possible to define normality precisely.[3] However, more recent data [4] indicate that the values given previously should be modified. It is recommended that, in future studies, anaemia should be considered to exist in those whose haemoglobin levels are lower than the figures given below (the values given are in g/100 ml of venous blood of persons residing at sea level) :

children aged 6 months to 6 years :	11
children aged 6–14 years :	12
adult males :	13
adult females, nonpregnant :	12
adult females, pregnant :	11

anémie
na ICU

✪ Anemia Frequency

>60% of ICU patients upon admission
90% of ICU patients by day 3 in ICU
97% of ICU patients by day 8

Thomas J, Jensen L, Nahirniak S, Gibney RT. Anemia and blood transfusion practices in the critically ill: a prospective cohort review. Heart Lung. 2010;39(3):217-225.

transfúzní
trigger

Transfúzní trigger

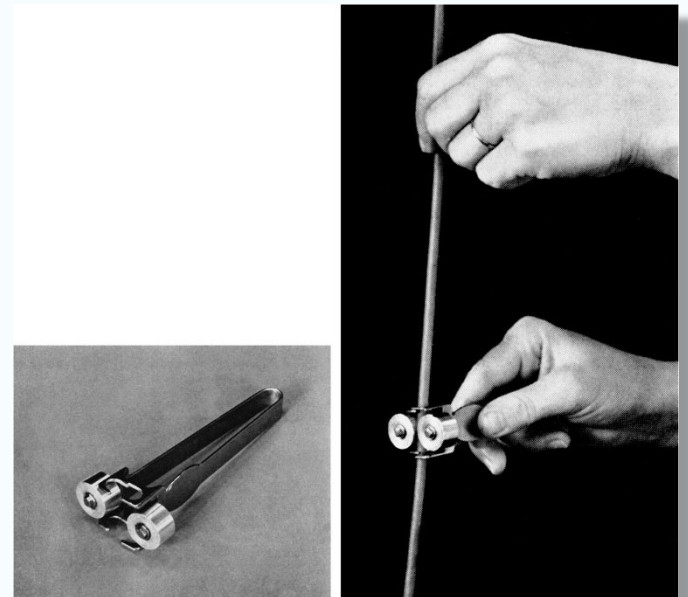- *Adams, Lundy* **1942**

- *Allen* **1982**

- *Hébert* **1999**

Adams RC, Lundy JS

Adams RC, Lundy JS: Anesthesia in cases of poor surgical risk. Some suggestions for decreasing the risk.
Surg Gynecol Obstet *1942;64:1011-1019*

Dr. John Silas Lundy, 1934

Lundy's rapid-infusing hand roller

Allenové pravidlo

Allen JB, Allen FB. The minimum acceptable level of hemoglobin.

Int Anesthiol Clin *1982; 20: 1 –22*

.... recommended that patients should be transfused when hemoglobin levels decreased below 10 g/dl or hematocrit values decreased below 30% (10/30 rule).

These recommendations were not based on randomized controlled trials, but rather on tradition….

Thus, this 10/30 rule, first proposed in the early 1940s and made even more popular in 1982 as a transfusion trigger, is not supported by good clinical evidence in the critically ill patient.

studie

The New England Journal of Medicine

## A MULTICENTER, RANDOMIZED, CONTROLLED CLINICAL TRIAL OF TRANSFUSION REQUIREMENTS IN CRITICAL CARE

PAUL C. HÉBERT, M.D., GEORGE WELLS, PH.D., MORRIS A. BLAJCHMAN, M.D., JOHN MARSHALL, M.D., CLAUDIO MARTIN, M.D., GIUSEPPE PAGLIARELLO, M.D., MARTIN TWEEDDALE, M.D., PH.D., IRWIN SCHWEITZER, M.SC., ELIZABETH YETISIR, M.SC., AND THE TRANSFUSION REQUIREMENTS IN CRITICAL CARE INVESTIGATORS FOR THE CANADIAN CRITICAL CARE TRIALS GROUP*

TRICC study

- **838** pacientů na kanadských ICU

- XI/1994 – XI/1997

- **liberální** strategie (Hb **10-12 g/dl**)
  vs. **restriktivní** strategie (Hb **7-9 g/dl**)

- **30-ti** denní **mortalita** se nelišila

- určité **subpopulace** (< 55 let, APACHE < 20)
  měly signifikantně **nižší** 30-ti denní mortalitu
  u **restriktivní** strategie

Hébert. N Engl J Med 1999;340:409-17.

liberal
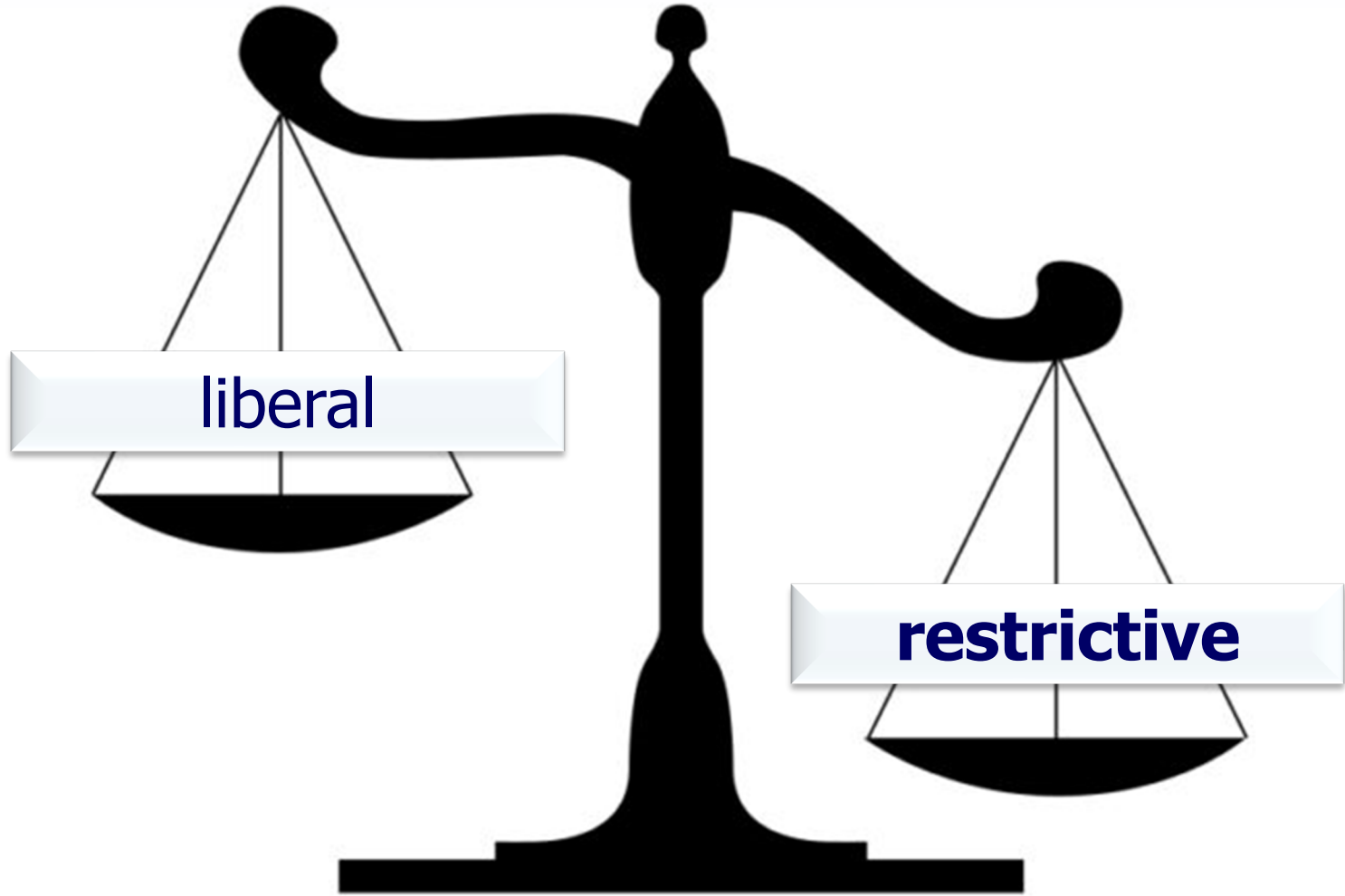
restrictive ✓

restrictive vs liberal:

Mazer. N Engl J Med 2017;377:2133

Estcourt. Cochrane Database Syst Rev 2017;CD011305

Holst. N Engl J Med 2014;371:1381

Murphy. N Engl J Med 2015;372:997

Carson. Cochrane Database Syst Rev 2016;CD002042

- …..

reduction of allogenic transfusion 43-50% (!)

☑ Laborübersicht
30.12.2022 18:19 − 06.01.2023 18:19

Variablen	Zeit	06.01.23 06:18	05.01.23 05:30	04.01.23 05:43	03.01.23 05:40	02.01.23 06:27	01.01.23 06:16	31.12.22 05:37
Blutbild visite								
Hämoglobin 13.5-15.4[g/dl]		8.4	8.7	9.5	8.6	8.4	9.1	10.5
Hämoglobin 13.5-15.4[g/dl]		9.9	9.8	9.4	9.2	9.8	10.0	
Hämoglobin 13.5-15.4[g/dl]		6.5	6.5	6.8	6.9	7.1	7.2	6.7
Hämoglobin 13.5-15.4[g/dl]		7.6	7.8	7.9	8.1	8.6	8.7	8.8
Hämoglobin 13.5-15.4[g/dl]		9.9	12.4	13.0	14.0	13.9		
Hämoglobin 13.5-15.4[g/dl]		7.5	8.3	9.5	8.4			
Hämoglobin 13.5-15.4[g/dl]		8.8	9.1	8.7	8.9	9.6	10.8	11.6
Hämoglobin 13.5-15.4[g/dl]		6.2	6.4	7.4	7.3	8.7	8.3	6.7
Hämoglobin 13.5-15.4[g/dl]		10.4	10.4	10.6	10.8	10.4	11.5	11.5
Hämoglobin 13.5-15.4[g/dl]		6.9	6.9	7.7	8.2	9.3		

TRICC

The New England Journal of Medicine

A MULTICENTER, RANDOMIZED, CONTROLLED CLINICAL TRIAL OF TRANSFUSION REQUIREMENTS IN CRITICAL CARE

Conclusions A restrictive strategy of red-cell transfusion is at least as effective as and possibly superior to a liberal transfusion strategy in critically ill patients, with the possible exception of patients with acute myocardial infarction and unstable angina. (N Engl J Med 1999;340:409-17.)

Hébert. N Engl J Med 1999;340:409-17.

ORIGINAL ARTICLE

Restrictive or Liberal Red-Cell Transfusion for Cardiac Surgery

METHODS

In this multicenter, open-label, noninferiority trial, we randomly assigned 5243 adults undergoing cardiac surgery who had a European System for Cardiac Operative Risk Evaluation (EuroSCORE) I of 6 or more (on a scale from 0 to 47, with higher scores indicating a higher risk of death after cardiac surgery) to a restrictive red-cell transfusion threshold (transfuse if hemoglobin level was <7.5 g per deciliter, starting from induction of anesthesia) or a liberal red-cell transfusion threshold (transfuse if hemoglobin level was <9.5 g per deciliter in the operating room or intensive care unit [ICU] or was <8.5 g per deciliter in the non-ICU ward). The primary composite outcome was death from any cause, myocardial infarction, stroke, or new-onset renal failure with dialysis by hospital discharge or by day 28, whichever came first. Secondary outcomes included red-cell transfusion and other clinical outcomes.

ORIGINAL ARTICLE

RESULTS

The primary outcome occurred in 11.4% of the patients in the restrictive-threshold group, as compared with 12.5% of those in the liberal-threshold group (absolute risk difference, −1.11 percentage points; 95% confidence interval [CI], −2.93 to 0.72; odds ratio, 0.90; 95% CI, 0.76 to 1.07; P<0.001 for noninferiority). Mortality was 3.0% in the restrictive-threshold group and 3.6% in the liberal-threshold group (odds ratio, 0.85; 95% CI, 0.62 to 1.16). Red-cell transfusion occurred in 52.3% of the patients in the restrictive-threshold group, as compared with 72.6% of those in the liberal-threshold group (odds ratio, 0.41; 95% CI, 0.37 to 0.47). There were no significant between-group differences with regard to the other secondary outcomes.

CONCLUSIONS

In patients undergoing cardiac surgery who were at moderate-to-high risk for death, a restrictive strategy regarding red-cell transfusion was noninferior to a liberal strategy with respect to the composite outcome of death from any cause, myocardial infarction, stroke, or new-onset renal failure with dialysis, with less blood transfused. (Funded by the Canadian Institutes of Health Research and others; TRICS III ClinicalTrials.gov number, NCT02042898.)

Blood transfusion and ischaemic outcomes according to anemia and bleeding in patients with non-ST-segment elevation acute coronary syndromes: Insights from the TAO randomized clinical trial

P. Deharo • G. Ducrocq • C. Bode • ... T. Moccetti • Y. Elbez • P.G. Steg ⌨ ✉ • Show all authors

- **post-hoc** analysis TAO trial

- **TAO trial**: RCT in 12.547 patients with NSTEMI

- patients who received transfusion had a ↑ rate of **death** or **MI** *(29.9% vs. 8.1%, p<0.01)*

- patients who received transfusion had a ↑ **LoS** *(5.4 vs. 9.2 days, p<0.001)*

Blood transfusion and ischaemic outcomes according to anemia and bleeding in patients with non-ST-segment elevation acute coronary syndromes: Insights from the TAO randomized clinical trial

P. Deharo • G. Ducrocq • C. Bode • ... T. Moccetti • Y. Elbez • P.G. Steg   ⦿ ✉ • Show all authors

- **Conclusion:** in patients with NSTEMI, blood transfusion was associated with an overall **increased risk** of **death** or **MI** at 180 days

- it was mainly driven by patients without overt **bleeding** and those **hemoglobin > 9.0g/dl**

- this suggests possible **harm of transfusion** in those groups

REALITY
trial

JAMA | Original Investigation

Effect of a Restrictive vs Liberal Blood Transfusion Strategy on Major Cardiovascular Events Among Patients With Acute Myocardial Infarction and Anemia
The REALITY Randomized Clinical Trial

IMPORTANCE The optimal transfusion strategy in patients with acute myocardial infarction and anemia is unclear.

OBJECTIVE To determine whether a restrictive transfusion strategy would be clinically noninferior to a liberal strategy.

DESIGN, SETTING, AND PARTICIPANTS Open-label, noninferiority, randomized trial conducted in 35 hospitals in France and Spain including 668 patients with myocardial infarction and hemoglobin level between 7 and 10 g/dL. Enrollment could be considered at any time during the index admission for myocardial infarction. The first participant was enrolled in March 2016 and the last was enrolled in September 2019. The final 30-day follow-up was accrued in November 2019.

REALITY study

- open-label, **non-inferiority** RCT

- **35** hospitals in **France** and **Spain**

- **668** patients with **MI** and **Hb 7 – 10** g/dl

- III/2016 – IX/2019

- **restrictive** (transfusion by **Hb ≤ 8**; n = 342)

- **liberal** (transfusion by **Hb ≤ 10**; n = 324)

- primary outcome: **MACE**

  (Major Adverse Cardiovascular Events: all-cause death, stroke, recurrent myocardial infarction, emergency revascularisation)

Research

JAMA | Original Investigation

RESULTS Among 668 patients who were randomized, 666 patients (median [interquartile range] age, 77 [69-84] years; 281 [42.2%] women) completed the 30-day follow-up, including 342 in the restrictive transfusion group (122 [35.7%] received transfusion; 342 total units of packed red blood cells transfused) and 324 in the liberal transfusion group (323 [99.7%] received transfusion; 758 total units transfused). At 30 days, MACE occurred in 36 patients (11.0% [95% CI, 7.5%-14.6%]) in the restrictive group and in 45 patients (14.0% [95% CI, 10.0%-17.9%]) in the liberal group (difference, −3.0% [95% CI, −8.4% to 2.4%]). The relative risk of the primary outcome was 0.79 (1-sided 97.5% CI, 0.00-1.19), meeting the prespecified noninferiority criterion. In the restrictive vs liberal group, all-cause death occurred in 5.6% vs 7.7% of patients, recurrent myocardial infarction occurred in 2.1% vs 3.1%, emergency revascularization prompted by ischemia occurred in 1.5% vs 1.9%, and nonfatal ischemic stroke occurred in 0.6% of patients in both groups.

CONCLUSIONS AND RELEVANCE Among patients with acute myocardial infarction and anemia, a restrictive compared with a liberal transfusion strategy resulted in a noninferior rate of MACE after 30 days. However, the CI included what may be a clinically important harm.

Ducrocq. JAMA 2021;325:552-60.

QUESTION Is a restrictive strategy of blood transfusion noninferior to a liberal strategy among patients with acute myocardial infarction (MI) and anemia?

CONCLUSION This trial found that a restrictive transfusion strategy vs a liberal one resulted in a noninferior rate of MACE among patients with acute MI and anemia, but the confidence interval included what may be a clinically important harm.

© AMA

POPULATION

385 Men
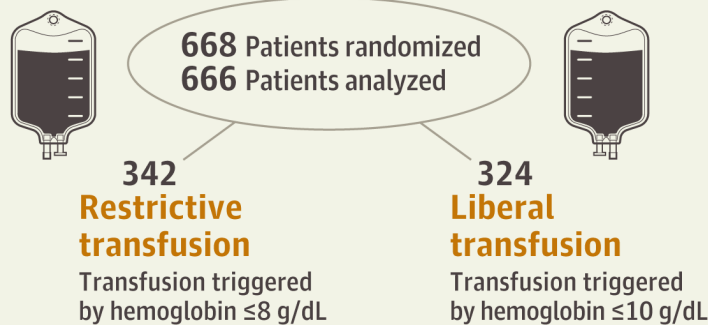281 Women

Adults with MI and anemia
(hemoglobin, 7-10 g/dL)

Median age: **77** years

LOCATIONS

35 Hospitals
in France and Spain

INTERVENTION

668 Patients randomized
666 Patients analyzed

342
Restrictive transfusion
Transfusion triggered by hemoglobin ≤8 g/dL

324
Liberal transfusion
Transfusion triggered by hemoglobin ≤10 g/dL

PRIMARY OUTCOME

MACE (composite of all-cause death, stroke, recurrent MI, or emergency revascularization prompted by ischemia) at 30 days. (Noninferiority = upper CI of <1.25)

FINDINGS

Occurrence of MACE at 30 days

Restrictive transfusion
36 of 342 patients
(95% CI, 7.5% to 14.6%)

Liberal transfusion
45 of 324 patients
(95% CI, 10.0% to 17.9%)

11%

14%

Between-group difference:
-3.0% (95% CI, -8.4% to 2.4%)

Relative risk for the primary outcome:
0.79 (1-sided 97.5% CI, 0 to 1.19),
meeting criteria for noninferiority

Ducrocq G, Gonzalez-Juanatey JR, Puymirat E, et al. Effect of a restrictive vs liberal blood transfusion strategy on major cardiovascular events among patients with acute myocardial infarction and anemia: the REALITY randomized clinical trial. *JAMA*. Published February 9, 2021. doi:10.1001/jama.2021.0135

Figure 2. Rate of Major Adverse Cardiovascular Events in a Study of the Effect of a Restrictive vs Liberal Blood Transfusion Strategy Among Patients With Acute Myocardial Infarction and Anemia

Log-rank $P = .21$

Liberal group

Restrictive group

Rate of major adverse cardiovascular events (y-axis: 0 to 0.2)

Days after randomization (x-axis: 0 to 30)
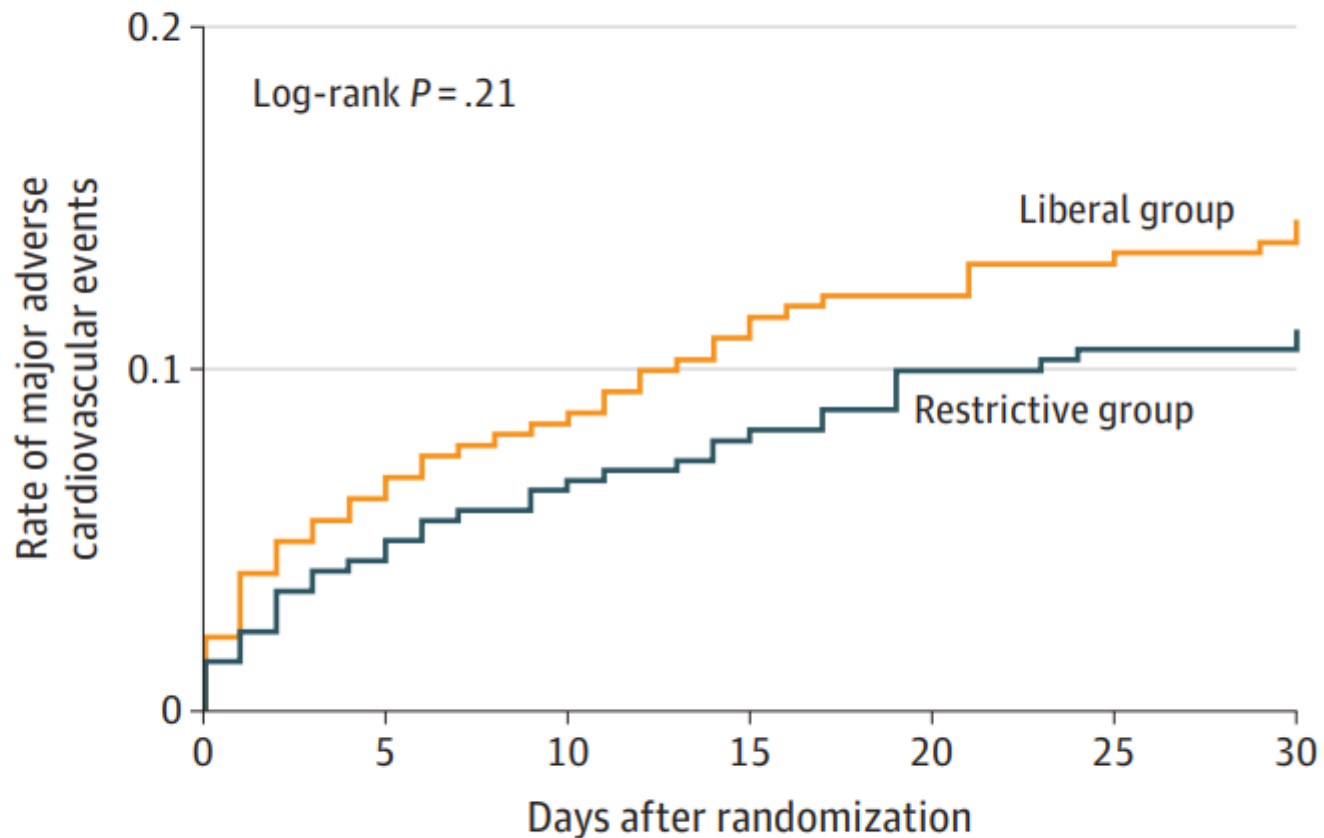
No. of patients at risk

	0	5	10	15	20	25	30
Liberal group	324	301	293	285	281	278	275
Restrictive group	342	326	319	314	307	305	305

Outcome	No. (%)		Difference (95% CI), %	Relative risk (1-sided 97.5% CI)
	Restrictive	Liberal		
Primary (major adverse cardiovascular events), No./total No. (%) [95% CI][a]				
As-treated population	36/327 (11.0) [7.5 to 14.6]	45/322 (14.0) [10.0 to 17.9]	−3.0 (−8.4 to 2.4)	0.79 (0.00 to 1.19)
As-randomized population	38/342 (11.1) [7.6 to 14.6]	46/324 (14.2) [10.2 to 18.2]	−3.1 (−8.4 to 2.3)	0.78 (0.00 to 1.17)
Secondary (individual outcomes in the as-randomized population)[b]	n = 342	n = 324		
All-cause death	19 (5.6)	25 (7.7)		
Cardiovascular	13 (68.4)	21 (84.0)		
Noncardiovascular	3 (15.8)	2 (8.0)		
Unknown	3 (15.8)	2 (8.0)		
Nonfatal recurrent myocardial infarction[c]	7 (2.1)	10 (3.1)		
ST-segment elevation recurrent myocardial infarction	0	3 (30.0)		
Non–ST-segment elevation recurrent myocardial infarction	7 (100.0)	7 (70.0)		
Type 1: spontaneous recurrent myocardial infarction	4 (57.1)	4 (40.0)		
Type 2: recurrent myocardial infarction secondary to an ischemic imbalance	2 (28.6)	5 (50.0)		
Type 4b: recurrent myocardial infarction related to stent thrombosis	1 (14.3)	1 (10.0)		
Emergency revascularization	5 (1.5)	6 (1.9)		
Nonfatal ischemic stroke	2 (0.6)	2 (0.6)		

Table 2. Hemoglobin Levels and Transfusions Among the As-Randomized Population in a Study of the Effect of a Restrictive vs Liberal Blood Transfusion Strategy on Patients With Acute Myocardial Infarction and Anemia

| Variable	No. (%)	
	Restrictive (n = 342)	Liberal (n = 324)
Hemoglobin level, mean (SD), g/dL		
At admission	10.0 (1.7)	10.1 (1.6) [n = 322]
Most recent prior to randomization	9.0 (0.8)	9.1 (0.8) [n = 323]
Lowest value during hospital stay	8.3 (0.9)	8.8 (0.9) [n = 323]
At discharge	9.7 (1.0) [n = 337]	11.1 (1.4) [n = 320]
Red blood cell transfusion		
Patients who received ≥1 unit of packed red blood cells	122 (35.7)	323 (99.7)[a]
Units transfused, No.	342	758

current guidelines

Institution	Leitlinientitel	Jahr	Empfehlung
Bundesärztekammer	Querschnittsleitlinie Hämotherapie	2020	Keine, Verweis auf fehlende Daten
American Association of Blood Banks (AABB)	Clinical Practice Guidelines	2016	Keine, Verweis auf fehlende Daten
Verschiedene deutschsprachige Fachgesellschaften	S3-Leitlinie kardiogener Schock	2020	< 65 Jahren bei Hb < 7,0 g/dl mit Ziel Hb 7,0 - 9,0 oder Hkt < 25%;
European Society of Cardiology (ESC)	Akutes Koronarsyndrom	2017	Hb < 8,0 g/dl
American Heart Association (AHA)/American College of Cardiology (ACC)	Guidelines for the Management of Patients with Non-ST-Elevation Acute Coronary Syndrome	2014	Hb > 8 g/dl nicht generell empfohlen bei NSTEMI, sofern Hämodynamik stabil
European Society of Intensive Care Medicine (ESICM)	Transfusion strategies in non-bleeding critically ill adults	2020	Hb 9 – 10 g/dl bei Akutem Koronarsyndrom
American Heart Association (AHA)/American College of Cardiology (ACC)	Guidelines for the Management of Patients with Non-ST-Elevation Acute Coronary Syndrome	2014	Hb > 8 g/dl nicht generell empfohlen bei NSTEMI, sofern Hämodynamik stabil

budoucnost?
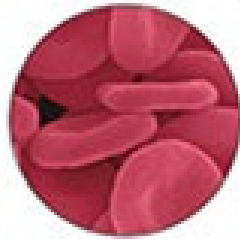
MINT
Myocardial Ischemia and Transfusion

Myocardial Ischemia and Transfusion (MINT)

Liberal Transfusion Strategy

- Patients randomly allocated to the liberal transfusion strategy will receive one unit of packed red cells following randomization and receive enough blood to raise the hemoglobin concentration above 10 g/dL any time the hemoglobin concentration is detected to be below 10g/dL during the hospitalization for up to 30 days. Any transfusion following the initial unit of packed red cells must be preceded by blood test documenting a hemoglobin concentration below 10 g/dL.

Restrictive transfusion strategy

- Receive a transfusion if they develop symptoms related to anemia. Transfusion is also permitted, but not required, in the absence of symptoms only if the hemoglobin concentration falls below 8 g/dL. Blood is administered one unit at a time and the presence of symptoms is reassessed. Only enough blood is given to relieve symptoms. If the transfusion is given because the hemoglobin concentration falls below 8 g/dL, then only enough blood is given to increase the hemoglobin concentration above 8 g/dL.

- Symptoms of anemia that will be indications for transfusion are: 1) Definite angina requiring treatment with sublingual nitroglycerin or equivalent therapy. 2) Unexplained tachycardia or hypotension.

Arm ⓘ

Active Comparator Liberal Transfusion Strategy

Red blood cell transfusion - One unit of packed red cells is transfused following randomization followed by enough red blood cell units to raise the hemoglobin concentration above 10 g/dL any time the hemoglobin concentration is detected to be below 10g/dL during the hospitalization for up to 30 days.

Active Comparator Restrictive Transfusion Strategy

Permitted to receive a red blood cell transfusion if the blood count is below 8 g/dL and the physician believes it is in the patient's best interest. A transfusion will be strongly recommended if the blood count drops to less than 7 g/dL. If the patient has symptoms of angina (e.g., chest discomfort described as pressure or heaviness) that do not go away with medication, a blood transfusion will be ordered regardless of the blood count.

U.S. National Library of Medicine

ClinicalTrials.gov

Study Design

Study Type ⓘ :	Interventional (Clinical Trial)
Estimated Enrollment ⓘ :	3500 participants
Allocation:	Randomized
Intervention Model:	Parallel Assignment
Masking:	Single (Outcomes Assessor)
Primary Purpose:	Treatment
Official Title:	Myocardial Ischemia and Transfusion
Actual Study Start Date ⓘ :	April 25, 2017
Estimated Primary Completion Date ⓘ :	March 2023
Estimated Study Completion Date ⓘ :	October 2023

shrnutí

- restriktivní strategie u ACS je **noninferiorní**

- jsou signály, že může být **superiorní**

- „*singly unit policy*"

- transfuzní trigger u ACS v.s. při **Hb ≤ 7,5 – 8** g/dl

- zohlednění **klinického** stavu

- součást projektu *Patient blood management*

...děkuji Vám za pozornost