TRANSFUSIÓ EN L'HEMORRÀGIA DIGESTIVA

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Hemorràgia Digestiva & Transfusió

L'hemorràgia digestiva es causa d'un 13.8% de totes les transfusions
Wallis, Transfusion Med 2006

44% a 55% dels pacients amb hemorràgia digestiva reben alguna transfusió de UCH
Hearnshaw, AP&T 2010
Restellini, AP&T 2013

Escassa evidencia, regim tranfusional

BENEFICI
* Millora l'anèmia

PERJUDICI
* Expansió de volèmia
* Complicacions potencials

INCONVENIENTS POTENCIALS DE LA TRANSFUSIÓ EN L'HEMORRÀGICA DIGESTIVA

- Disrupció del coàgul: *(per increments de flux/pressió)*
- Alteracions en la cascada de la coagulació
- Complicacions relacionades amb la transfusió

→ Recidiva hemorràgica

* Edat dels hematies: alteracions per l'emmagatzematge

rigidesa de la membrana cel·lular
modificacions de la membrana
→ Hemolisis → Alliberació d'Hb i Fe

Alteració de l'oxigenació tissular

Depleció d'O.N.

Risc infeccions

canvis metabólics
depleció de 2,3-DPG:
↑ afinitat d'Hb per l'O_2

→ Disfunció endotelial
Fracàs Orgànic

* Efecte immunosupressor de la Tf

Duggan J.M. Aliment Pharmacol Ther 2001;15:1109

VOLUME RESTITUTION

ANIMAL DATA

Adverse effect of rapid or excessive fluid replacement

↓

Restoring blood pressure by transfusion, expansion of circulating volume or vasoconstrictors, difficults hemostasis

early clot is fragile and capable of dislodgement if the compensatory reduction of vessel pressure/flow is not allowed

* Shaftan et al. Surgery 1965;58:851-6.
* Bickell et al. Surgery 1991;110:529-36.
* Bickell et al. Circulatory Shock 1989;28:321-32.
* Milles et al. Surgery 1966;60:434-42.
* Shaftan et al. J Cardiovasc Surg (Torino) 1964;5:251-6.
* Stern et al. Ann Emerg Med 1993;22:155-63.

VOLUME RESTITUTION & BLEEDING

Fluid restitution may worsen bleeding due to different mechanisms:

- Mechanical disruption of formed clots

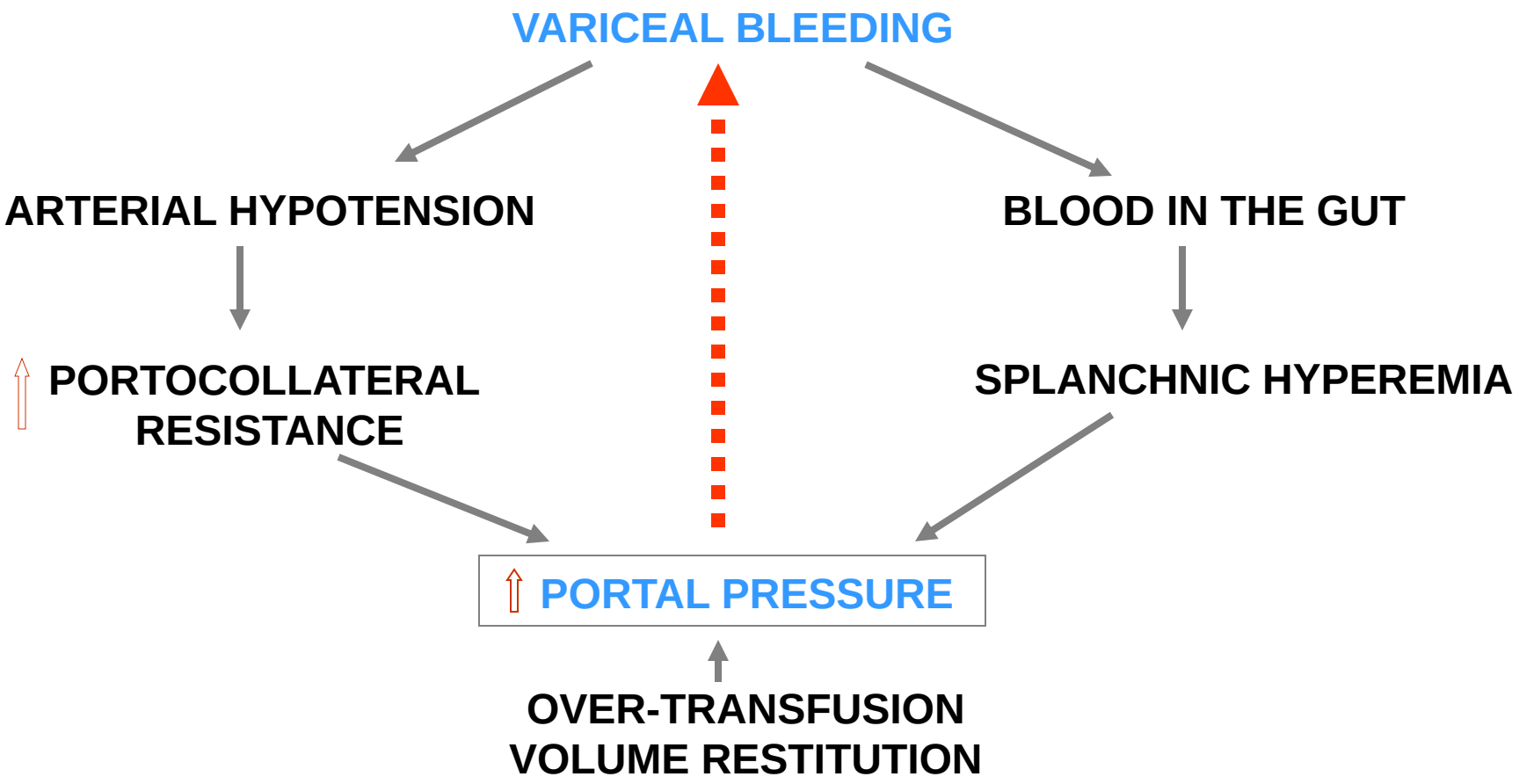
- Altering coagulation cascade

    * Diluting clotting factors

    * Disturbing platelet aggregation

* Jorgensen et al. Throm Res 1980:17:13
* Stibbe & Kirby. BMJ 10975;2:750
* Evans PA et al. Br J Anaesth 1998;81:198
* Treib J et al. Haemostasis 1996;26:210
* Stump DC et al. Trasnfusion 1985;25:349
* Mardel SN et al. Lancet 1996;347:825
* Roberts I et al. Lancet 2001;357:385

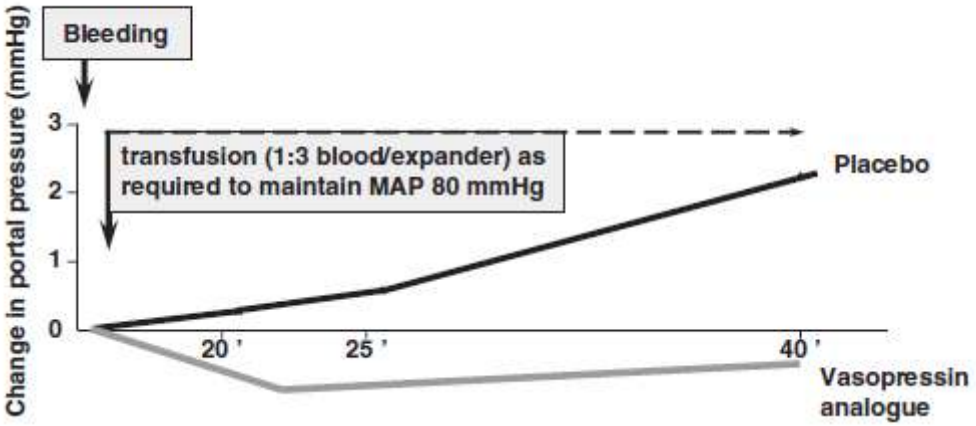
FACTORS INFLUENCING PORTAL PRESSURE DURING ACUTE BLEEDING



* McCormick et al. Gut 1995;36:100.
* Kravetz eta al. Gastroenterology 1986;90:1232 & Hepatology 1989;9:808
* Castañeda et al. Hepatology 2000;31:581 & Hepatology 2001;33:821
* Chen L & Groszmann R. Gastroenterology 1996;111:1103

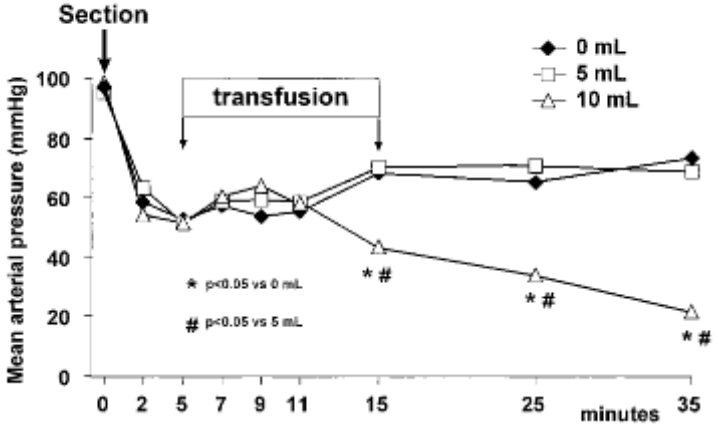
Effects of Blood Volume Restitution Following Bleeding in Portal Hyertension

EFFEC ON PORTAL PRESSURE

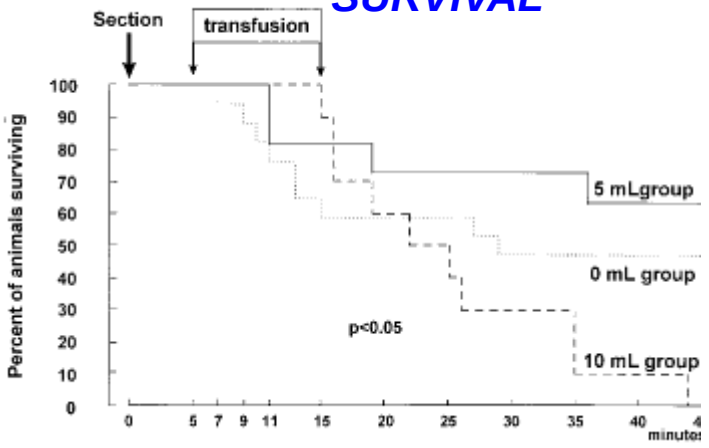


Even using a conservative target (MAP= 80 mmHg) volume replacement induced a rebound increase in portal pressure

UNCONTROLLED BLEEDING



SURVIVAL



Boyer Jlet al. N Eng J Med 1966;275:750-4/ Kravetz D et al. Gastroenterology 1986;90:1232-40/ Kravetz D et al. HEPATOLOGY 1989;9:808-14/ Koshy A et al. Clin Sci 1990;78:193-7/ Castañeda B et al. HEPATOLOGY 2000;31:581-6/ Castañeda B et al. HEPATOLOGY 2001;33:821-5.

Fluid resuscitation in critically ill patients

Fundamental in critically ill patients

Potential adverse effects of resuscitation

-interruption of catecholamine-mediated host defense responses by the rapid increase in plasma volume,which might result in a ***reperfusion injury***

- transient hypervolemia or hyperosmolality might exacerbate capillary leak in patients susceptible to *intracranial hypertension* or ***pulmonary edema***

<u>NO conclusive evidence to guide the best resuscitation fluid</u>

- **Type**: *similar survival with albumin & saline in ICU patients*

N Engl J Med 2004;350:2247-56

hydoxyethyl starch (voluven): similar survival (& more renal replacement) than saline in ICU patients

N Engl J Med 2012;367:1901-11

worse survival (& more renal replacement) than Ringer acetate in severe sepsispatients

N Engl J Med 2012;367:124-34

- **Timing**
- **Volume**
- **Rate of fluid administration**
- **Optimal way to monitor** efficacy and safety of fluid resuscitation in various clinical conditions

HEMORRÀGIA DIGEST.:TRACTAMENT

RESUCITACIÓ & SUPORT HEMODINÀMIC

Reposició cautelosa de la volèmia

Evitar hipovolemia
Per a previndre complicacions (Fracàs renal, infeccions, d'altres)

Evitar reposició excessiva
Per a previndre recidiva H.D.A.

Monitorització hemodinàmica estreta

* **Accés venós bo: 2 vies curtes i de calibre gruixut (17-12ga)**
  Via central per a PVC
* **Reposició amb cristal·loides / col·loides**
* **Mantenir pressió venosa central de 4-6 mmHg**
  Diüresi horària > 30cc
  Tensió arterial sistòlica: 90-110 mmHg
* **Transfondre Unitats Concentrats Hematies: Hb sobre 8 g/dl**

Anemia may lead to complications derived to impaired transport of oxygen to tissues, then…

Why should be restricted?

*** Socioeconomic costs**
*** Capacity to adapt**
*** Potential complications**

Reduced use of blood could improve patient outcomes in other critic situations
Hebert PC, N Engl J Med. 1999

Transfusion in cirrhosis may lead to a rebound increase of portal hypertension
Castaneda B, Hepatology 2000

Physiopathology of RBC Transfusion

The aim of RBC transfusion is the need to increase arterial oxygen transport (TaO_2) to the tissues.

TaO_2 depends on arterial oxygen concentration (CaO_2) and cardiac output (Q).

CaO_2 = 1.39 x [Hb] x SaO_2

TaO_2 = CaO_2x Q = 1.39 x [Hb] x SaO_2 x Q

⇓ Hb

Consider *transfusion UPRC*

⇓ Q

- non-compensated *volemic loss*
- reduced *ejection fraction*

(due to myocardial hypoxia..)

⇓ SaO_2

changes in ventilatory function and gas exchange.

VO2 (global oxygen consumption)= TaO2 x ERO2

⇓ **Hb**

Bleeding

(or other causes of anemia)

⇓ **Q**

- non-compensated *volemic loss*
- reduced *ejection fraction*

(due to myocardial hypoxia..)

⇓ **SaO_2**

changes in ventilatory function and gas exchange.

⇓ TaO_2

compensated by increased **ERO_2** (peripheral O_2 extraction: CaO_2 - CvO_2)

Critical TaO_2 (4 to 5 mlO_2/Kg/min)

value at which VO_2 becomes directly dependent on TaO_2

Normal TaO_2 (14 to 16 mlO_2/Kg/min)

compensatory mechanisms in response to anemia

⇓ TaO_2 ⟺ **CaO2** = 1.39 x [Hb] x SaO2

TaO2 = CaO2x Q

- increased **ERO_2** (O_2 extraction)
- increased **Q**

Increase Q

Due to an increase in systolic ejection volume.
This results from an increased venous return (enhanced venous tonus)
from an increase in ventricular performance (neuro-adrenergic stimulation)
from a reduction in left ventricular afterload (by reduction of blood viscosity)
Influx of extravascular fluid to intravascular compartment
(with impaired cardiac function, increase in Q is due to heart rate)

Reposition of volemia is essential in order to increase Q and tolerate acute anaemia
(the heart is the primary mediator of this tolerance)

The decision to perform transfusion should therefore depend on the body's capacity to increase cardiac output

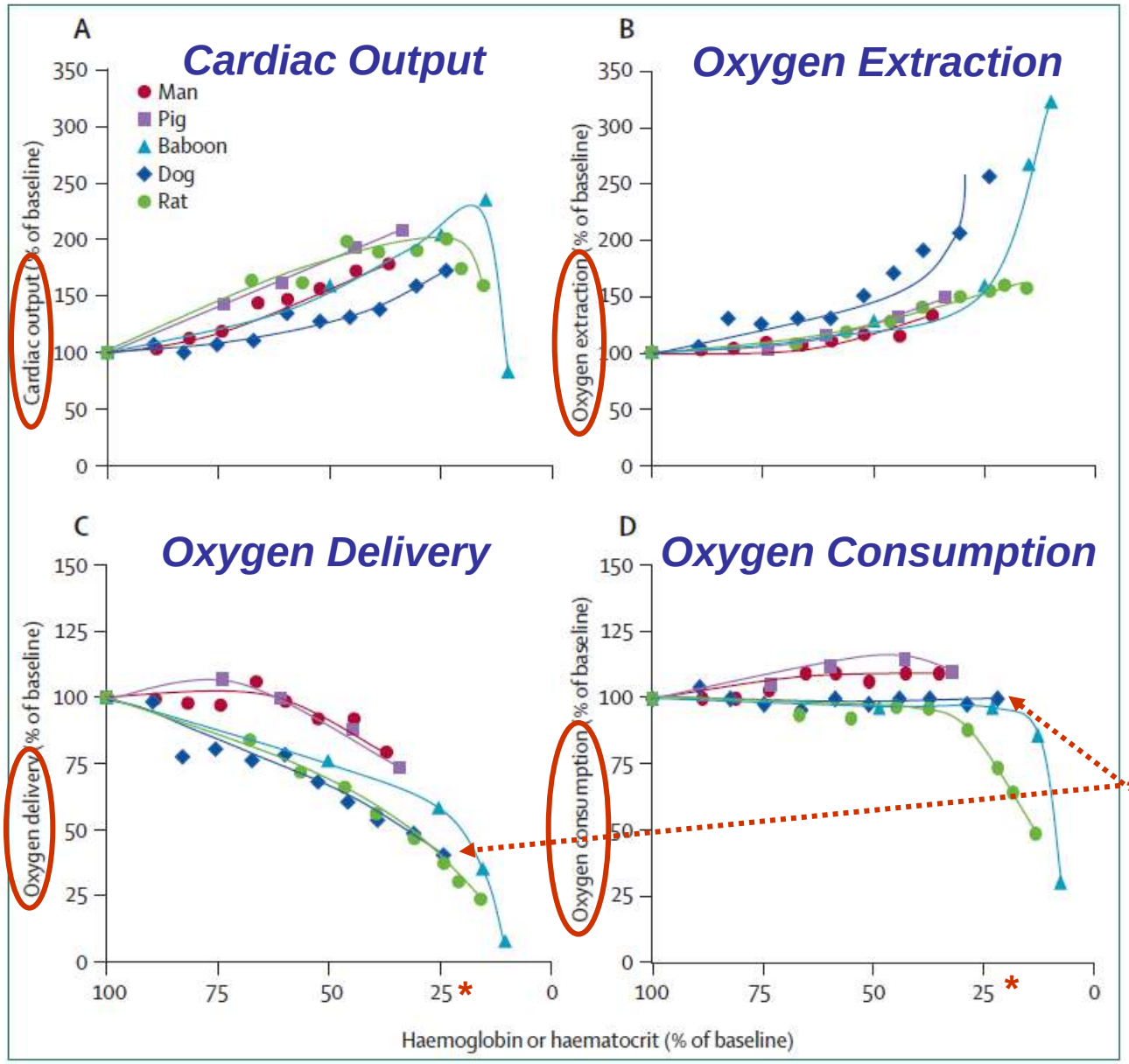
Increase ERO2

(not yet fully understood)

-redistribution of blood flow from organs with a high ERO2 reserve (kidney, liver) to organs with limited ERO2 reserve (heart, brain). Driven by an increase in neuro-adrenergic stimulation

- recruitment of capillaries
- reduction in haemoglobin affinity for oxygen

Changes in cardiac output and oxygen extraction, delivery and consumption with decrease of Hb concentration in humans, pigs, baboons, dogs, and rats



"critical Hb≤ 5 g/dL"

Weiskopf RB et al. jAMA 1998;279:217–21/ van Woerkens EC et al. J Appl Physiol 1992;72:760–69/ Moss GS et al. Surg Gynecol Obstet 1976;142:357–62/ van der Linden P et al. Anesthesiology 2003;99:97–104/ Jamnicki M et al. J Cardiothorac Vasc Anesth 2003;17:747–54.

POTENTIAL COMPLICATIONS OF BLOOD TRANSFUSION

Infections

HIV 1 and HIV2	$1/20^6$–30^6
Hepatitis B	1/100000–200000
Hepatitis C	$1/10^6$–20^6
HTLV I and II	1/641000
Bacterial contamination	$1/50^6$
Malaria	$1/40^6$

OTHER POTENTIAL COMPLICATIONS OF BLOOD TRANSFUSION

Immune-mediated reactions

Febrile reaction	1/300
Urticaria or other cutaneous reaction	1/50–100
RBC alloimmunisation	1/100
Mistransfusion	1/14000–19000
Haemolytic reaction	1/6000
Fatal haemolysis	$1/10^6$
TRALI	1/5000
TRIM	Unknowm (May be high)
Anaphylaxis	1/20000–50000
GvHD	Uncommon
Immunomodulation	Unknown

Non-immune reactions

TACO	1-10/100
Hypotensive reactions	Unknown
Transfusion-related iron overload	
Michrochimerism	1/5-10000
Posttansfusion purpura	
Metabolic toxicities (hipoCa, hipoK, hipotrermia, coagulopathy)	

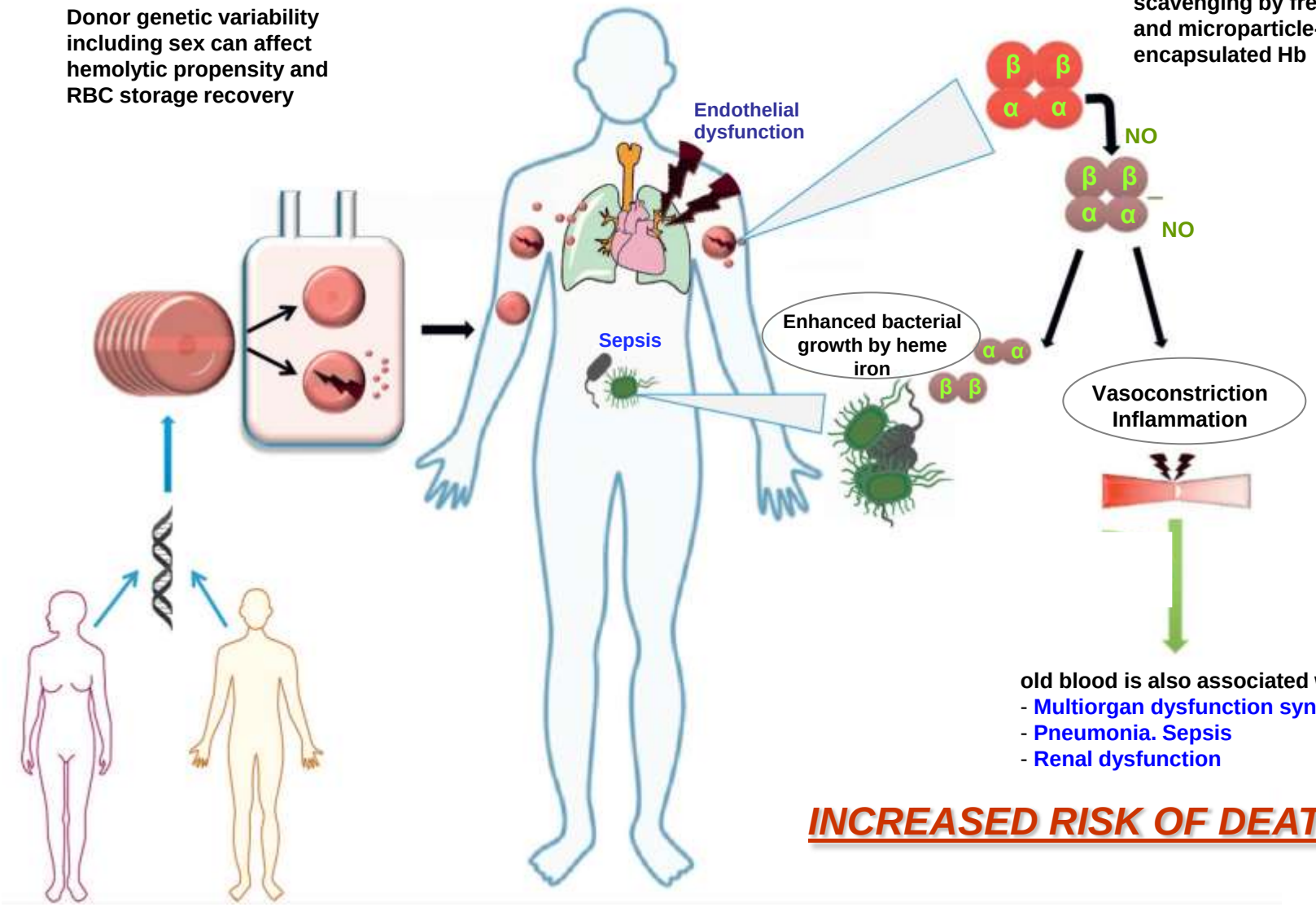
OLD BLOOD STORAGE LESION

Donor hemolytic propensity

Donor genetic variability including sex can affect hemolytic propensity and RBC storage recovery

Susceptible host

Vascular NO scavenging by free and microparticle-encapsulated Hb



old blood is also associated with

- **Multiorgan dysfunction syndrome**
- **Pneumonia. Sepsis**
- **Renal dysfunction**

INCREASED RISK OF DEATH

Wang D et al. Metaanalysis.Transfusion 2012;52:1184 / Yu B et al. Transfusion 2012;52:1410

Figure adapted from Kanias T & Gladwin M.T. Transfusion 2012;52:1388

TRANSFUSION REQUIREMENTS
RESTRICTIVE vs LIBERAL

Trial	Comparison	Setting & N	Outcomes
Hébert et al *N Engl J Med*. 1999;340:409	Restrictive Tf: when Hb<70 (to 70-90) Liberal Tf: when Hb<100 (to 100-120)	N=838 (418 vs 420) ICU Patients Exclusion G.I bleeding	30-d MORTALITY Similar (18.7% vs 23.3%) Better with restritive in APACHE ≤20/ Age <55 More Cardiac events (CHF & ACS) with liberal Tf No Tf in 33% vs 0
Lacroix et al *N Engl J Med*. 2007;356:1609	Restrictive Tf: when Hb<70 (to 85-95) Liberal Tf: when Hb<95 (to 110-120)	N=637 (320 vs 317) Pediatric ICU Exclusion G.I bleeding	Similar MODS (Multi-Organ-Dysfunction Synd.) Similar 28-d MORTALITY Similar adverse events No Tf in 54% vs 2%
Carson et al *N Engl J Med*. 2011;365:2453	Restrictive Tf: when Hb<80 (to >80) Liberal Tf: when Hb<100 (to >100)	N=2016 (1009 vs 1007) Hip-fracture surgery & Cardiovasc.dis. (or risk factors) Exclusion G.I bleeding	Similar 60-d DEATH OR INABILITY TO WALK WITHOUT ASSISTANCE Similar 30-d & 60-d MORTALITY Similar acute coronary synd. Similar adverse events

TRANSFUSION REQUIREMENTS In Gastrointestinal Bleeding

Trial	Comparison	Setting & N	Outcomes
Blair et al *Br J Surg*. 1986;73:783-785	Tf ≥ 2 UPRBC vs No Tf during first 24-h unless Hb <80 (or persistent shock)	N=50 (24 vs 26) Acute G.I. bleeding (no-variceal)	REBLEEDING (Tf vs No): 37% vs 4% (p <0.01) Death (Tf vs No): 8% vs 0 Tf reverse the hypercoagulable response to bleeding (shortened cloting times with bleeding corrected with Tf)
Villarejo et al *Acta Gastroenterol Latinoam 1999;29:261*	Tf if HTc <28% vs Tf if HTc <21%	N=60 (30 vs 30) Final N=27 Acute G.I. bleeding (no-variceal)	Similar rate of organ failure Similar hospital stay No mortality
Hearnshaw et al *Aliment Pharmacol & Ther* 2010;32:215	Prospective Observational Study U.K. Multicenter <u>Retrospective Comparasion:</u> Early (<12h.) Tf vs No Early Tf Groups inhomogeneous	N=4441(1974 Tf, 44%) Acute G.I. bleeding (variceal & no-variceal) Endoscopy in all	Higher rebleeding in Early-Tf (24% vs 7%) (23% vs 15%, for group with Hb ≤80) (24% vs 7%, for group with Hb >80) Higher rebleeding with Tf after adjustment by Rockall & Hb (OR= 2.26, 95%CI= 1.76-2.90) Higher Mortality in Early-Tf (12% vs 5%) (13% vs 13%, for group with Hb ≤80) (11% vs 4%, for group with Hb >80) Higher mortality adjusted by Rockall (not by Rockall+Hb)

TRANSFUSION REQUIREMENTS In Gastrointestinal Bleeding

Trial	Comparison	Setting & N	Outcomes
Taha et al *Frontline Gastroenterol* 2011;2:218	Observational Study Scotland.UK. Singlecenter Retrospective Comparasion: Tf (<24h.) vs No Tf Groups inhomogeneous	N=1340 (564 Tf, 42%) Acute G.I. bleeding (no-variceal) Endoscopy in all	Higher 30-d Mortality in Tf (8% vs 3%) (7% vs 1%, for group with Hb <100) (12% vs 4%, for group with Hb ≥100) Higher mortality with Tf after adjustment for age, Rockall, Charlson & Hb (OR= 1.9, 95%CI= 1.0-1.3) Higher 2-yr Mortality in Tf (35% vs 19%) (33% vs 16%, for group with Hb <100) (40% vs 20%, for group with Hb ≥100) Higher mortality adjusted for age, Rockall, Charlson & Hb (OR= 1.7, 95%CI= 1.3-2.3)
Restellini et al *Aliment Pharmacol & Ther* 2013;37:316	Observational Study Canadian Registry (RUGBE). Multicenter Retrospective Comparasion: Early (<24h.) Tf vs No Tf Groups inhomogeneous	N=1677 (900 Tf, 54%) Acute G.I. bleeding (no-variceal) Endoscopy in all	Higher rebleeding in Early-Tf (23% vs 11%) Higher rebleeding with Tf after adjustment for confounders (comorbidty. HDK instability, initial Hb, rectal or NG blood, high-risk stigmata, Tf of plasma, use of PPI): OR= 1.8, 95%CI= 1.2-2.8 Higher Mortality in Early-Tf (7% vs 4%) No significance after adjustment for confounders (ASA score, use of plasma, NG blood & rebleeding): OR= 1.0, 95%CI= 0.6-1.8

DESIGN OF THE STUDY

Severe acute G.I. Bleeding + Age >18ys.
& No-exclusion criteria

↓

Randomization
Immediately after admission
Stratified according to PHT

↙ ↘

Restrictive strategy group
Hb threshold for transfusion of RBC= 7 g/dL
Target: 7-9 g/dL

Liberal strategy group
Hb threshold for transfusion of RBC= 9 g/dL
Target: 9-11 g/dL

UPRBC transfused one at a time. Hb measured after transfusion to decide further Tf.
Transfusion was allowed at any time when:

* symptoms or signs related with anemia
* massive bleeding
* surgical intervention was required.

EXCLUSION CRITERIA

- Massive exsanguinating bleeding
- Clinical Rockall score of 0 plus Hb >12 g/dl

Other criteria:

- declined blood transfusion

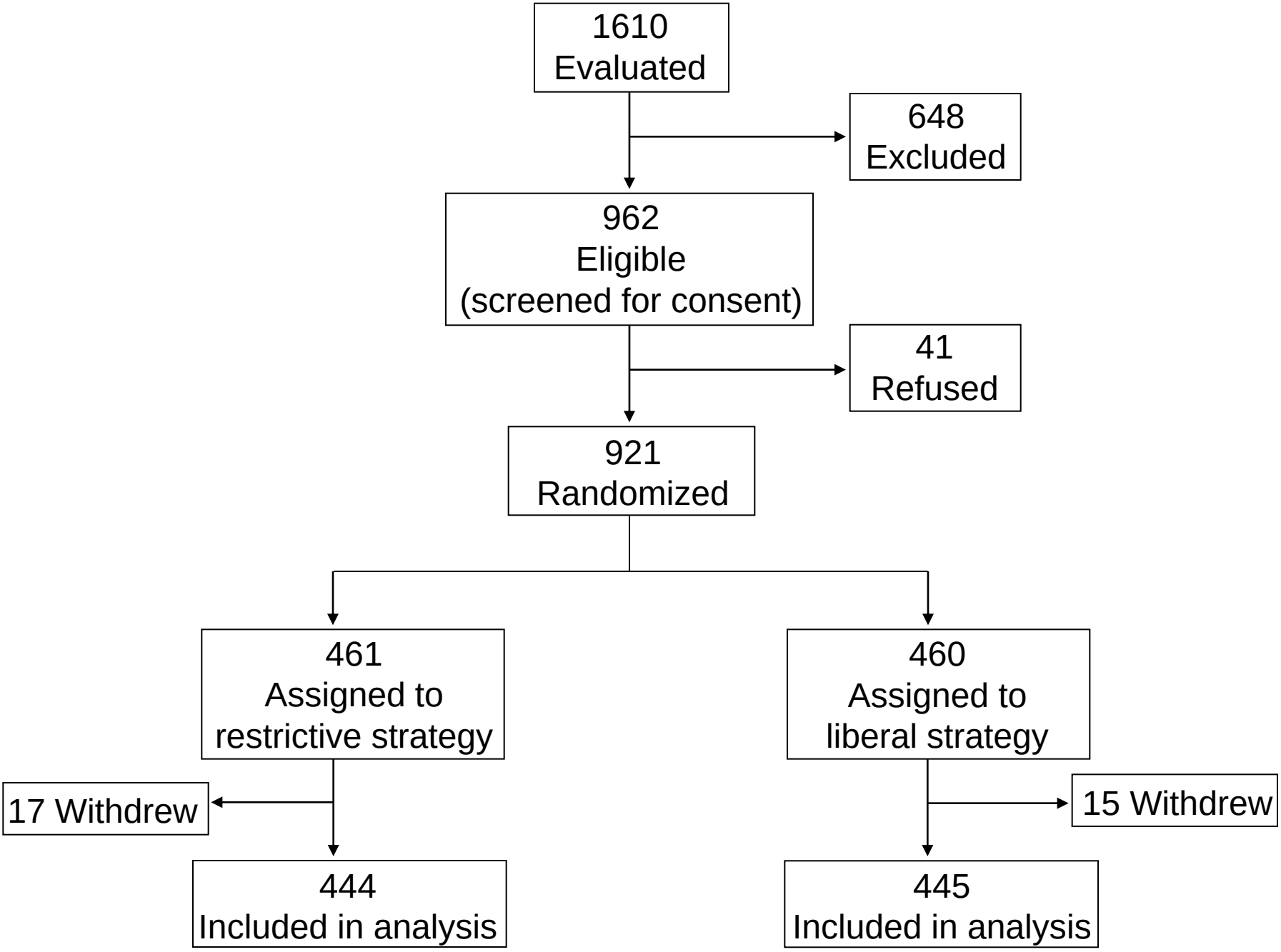
- acute coronary syndrome, symptomatic peripheral vasculopathy, stroke, transient ischemic attack or transfusion within the previous 90 days

- recent trauma or surgery

- lower gastrointestinal bleeding

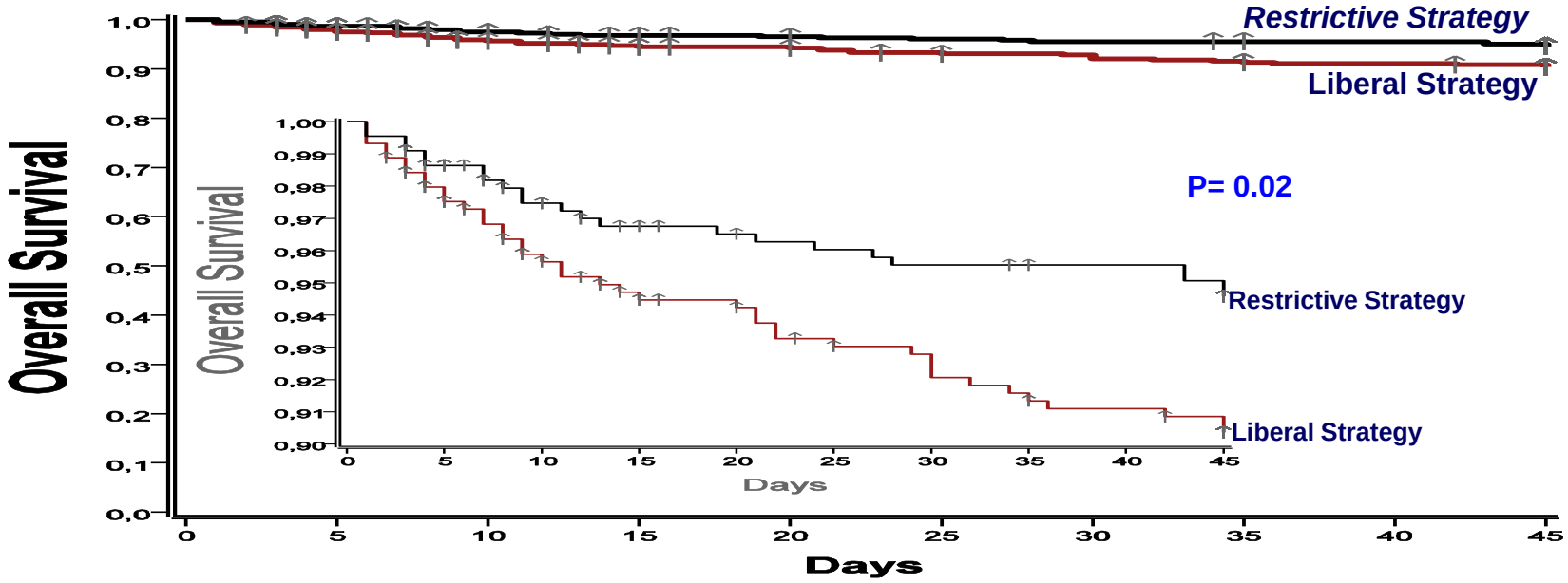
- refusal to participate in the study

- previous decision to avoid specific medical therapy


1610
Evaluated
648
Excluded
962
Eligible
(screened for consent)
41
Refused
921
Randomized
461
Assigned to
restrictive strategy
460
Assigned to
liberal strategy
17 Withdrew
15 Withdrew
444
Included in analysis
445
Included in analysis

RESULTS

SURVIVAL ACCORDING TO TRANSFUSION STRATEGY



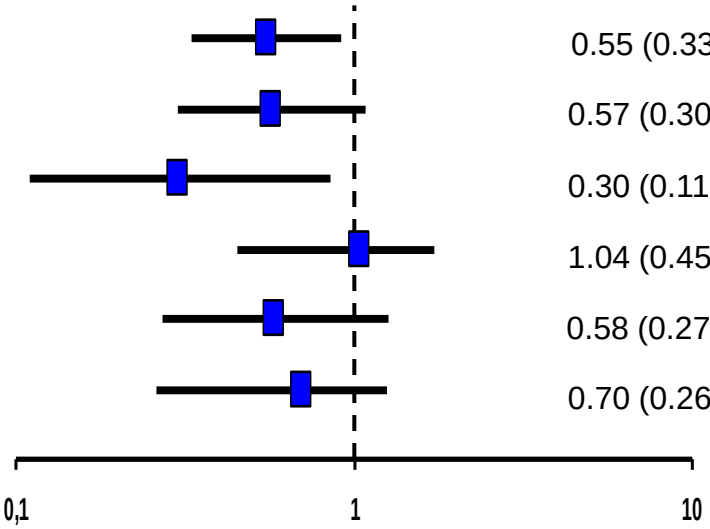
Patients at Risk

Restrictive Strategy	444	429	412	404	401	399	397	395	394	392
Liberal Strategy	445	428	407	397	393	386	383	378	375	372

RESULTS

DEATH BY 6-WEEKS ACCORDING TO SUBGROUP

Subgroup	Restrictive Strategy nº of patients / total nº (%)	Liberal Strategy nº of patients / total nº (%)	Hazard Ratio (95% CI)	P value
Overall	23/444 (5)	41/445 (9)	0.55 (0.33-0.92)	0.02
Patients with cirrhosis	15/139 (11)	25/138 (18)	0.57 (0.30-1.08)	0.08
Child-Pugh class A/B	5/108 (4)	13/109 (12)	0.30 (0.11-0.85)	0.02
Child-Pugh class C	10/26 (38)	12/29 (41)	1.04 (0.45-2.37)	0.91
Bleeding from varices	10/93 (11)	17/97 (17)	0.58 (0.27-1.27)	0.18
Bleeding from peptic ulcer	7/228 (3)	11/209 (5)	0.70 (0.26-1.25)	0.26



TRANSFUSION POLICY IN ACUTE G.I. BLEEDING

Severe acute G.I. Bleeding

↓

HDK & hematologic Assessment
Blood Pressure & Heart Rate
Hemoglobin / Coagulation

↘ ***Hypovolemia***
Cautious Volume Restitution

↓

Anemia

Hb threshold for transfusion of UPRBC

- **General:** ⇢ **trigger: 7 g/dL ⇨ target: 7-9 g/dL**

- **Cardivascular disease**
  Age
  Symptoms
  Ongoing bleeding
  Surgery

⇢ **trigger: 8-9 g/dL ⇨ target: 9-11 g/dL**

transfuse UPRBC one at a time. Measure Hb after transfusion to decide further Tf.

Transfusion can be allowed at any time when:

* symptoms or signs related with anemia
* massive bleeding
* surgical intervention was required