U.S. Department of Health and Human Services

National Institutes of Health

Department of Transfusion Medicine

Blood Transfusion:
Precision vs Imprecision Medicine

Harvey G. Klein, MD
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Clinical Center
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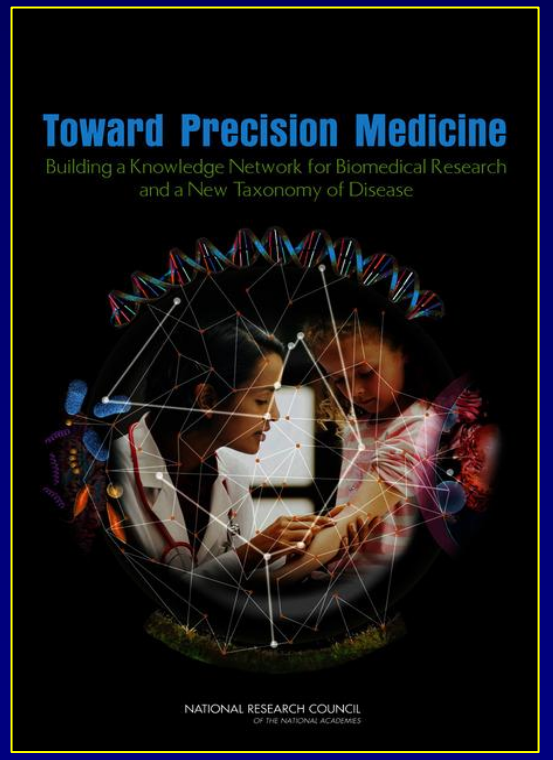
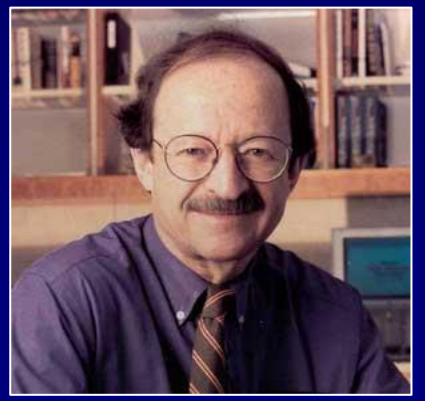
“Tonight, I'm launching a new Precision Medicine Initiative to bring us closer to curing diseases like cancer and diabetes — and to give all of us access to the personalized information we need to keep ourselves and our families healthier.”

— President Barack Obama, State of the Union Address, January 20, 2015

“refers to the tailoring of medical treatment to the individual characteristics of each patient.”



"The concept of precision medicine — prevention and treatment strategies that take individual variability into account — is not new; blood typing, for instance, has been used to guide blood transfusions for more than a century. But the prospect of applying this concept broadly has been dramatically improved by the recent development of large-scale biologic databases (such as the human genome sequence), powerful methods for characterizing patients (such as proteomics, metabolomics, genomics, diverse cellular assays, and even mobile health technology), and computational tools for analyzing large sets of data."



Collins FS, Varmus, N Engl J Med 2015; 372:793-795

JAMA

VIEWPOINT

Red Blood Cell Transfusion
Precision vs Imprecision Medicine

Harvey G. Klein, MD
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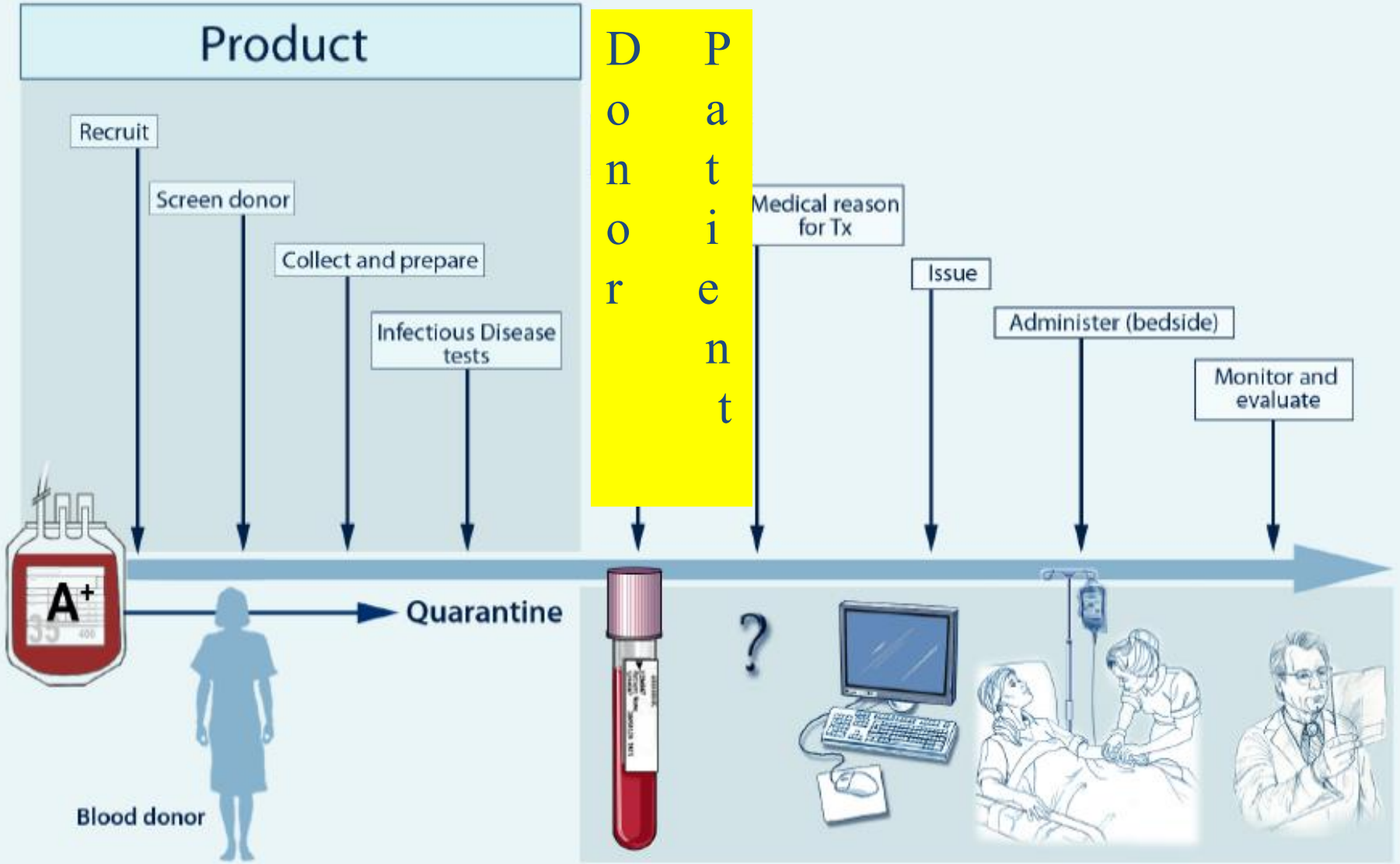
In the early 20th century discovery of blood groups led to the first example of "precision medicine." By matching blood donors with their recipients, personalized therapy improved transfusion safety.[1] In the 1960s, the National Institutes of Health (NIH) established a partitioned data set on a mainframe computer with 2700 blood donors phenotyped by serology for 20 red blood cell antigens. Combining mid-20th century genetic typing technology with the emerging field of informatics served to enhance donor-recipient compatibility and red blood cell inventory management. "Extended typing" simplified transfusion for patients with red blood cell antibodies, reduced the risk of future red blood cell alloimmunization, and became standard management for patients with sickle cell disease. However most hospitals faced with transfusion compatibility problems still tried to identify antigen-negative red blood cell units by screening local inventories with inefficient, labor-intensive serologic assays.

In a pilot program, a regional blood center in Wisconsin genotyped 43 066 donors for 42 clinically relevant antigens in a 4-year period.[2] More than 99% of patient orders for red blood cell units were filled. Now in routine use, this program has successfully filled approximately 14 000 requests by using genotype data. A web-based interface allows community hospitals to search local inventories for the most suitable units via an antigen query portal. This example of precision medicine, largely invisible to the practicing physician, could transform the way compatible blood is supplied and provide better, more efficient care. Start-up costs, legacy information systems, and the need for US Food and Drug Administration–licensed molecular assays have delayed widespread adoption of this approach in the United States. However, blood services in several European countries are introducing comparable systems.

In contrast to the precision of genotyping and personalized red blood cell matching, the decision to transfuse red blood cell units has become less precise. Cur-

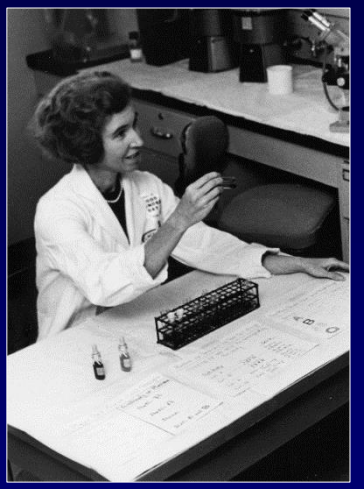
Klein HG et al. JAMA. 2015;314(15):1557-1558

Transfusion Process



NIH Precision Technology -1960's

- Partitioned data set on mainframe computer
- 2700 donors phenotyped for 20 RBC Ag
- Weekly Printouts of Available Donors
- Donors recruited by phenotype
  - antibody compatibility
  - Extended typing
  - Reduced alloimmunization



21st Century Technology

- Significant blood group genes cloned
- New generation automated DNA analyzers
- Rapid screening for nucleotide polymorphisms
- DNA sequence differences have been correlated with RBC antigen expression
- Web-based data storage and analytics

Precision Transfusion 21st Century

TRANSFUSION BLOOD GROUP GENOMICS

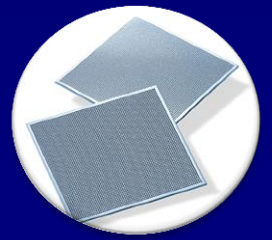
CME/SAM

Implementing mass-scale red cell genotyping at a blood center

Willy A. Flegel,[1] Jerome L. Gottschall,[2,3] and Gregory A. Denomme[3]

BACKGROUND: When problems with compatibility beyond ABO and D arise, currently transfusion services search their inventories and perform time-consuming serologic testing to locate antigen-negative blood. These

Alloimmunized transfusion recipients require antigen-negative blood for safe transfusion. Blood centers are best suited to provide antigen-negative blood because they have the entire regional blood inventory at their disposal. Current prac-



Donor Selection

Data Management

Donor Genotyping

Red Cell Genotyping:
What problem(s) are we trying to solve?

Genotyping has the potential to change provision and logistics of antigen-negative blood and improve safety

- -Support alloimmunized patients
- -Prevent alloimmunization
- - Improve RBC storage

Provide better matches, rare units, reduce costs

- - “Dry matching”
- - Web-based local/national inventories
- - Reduced shipping and transportation

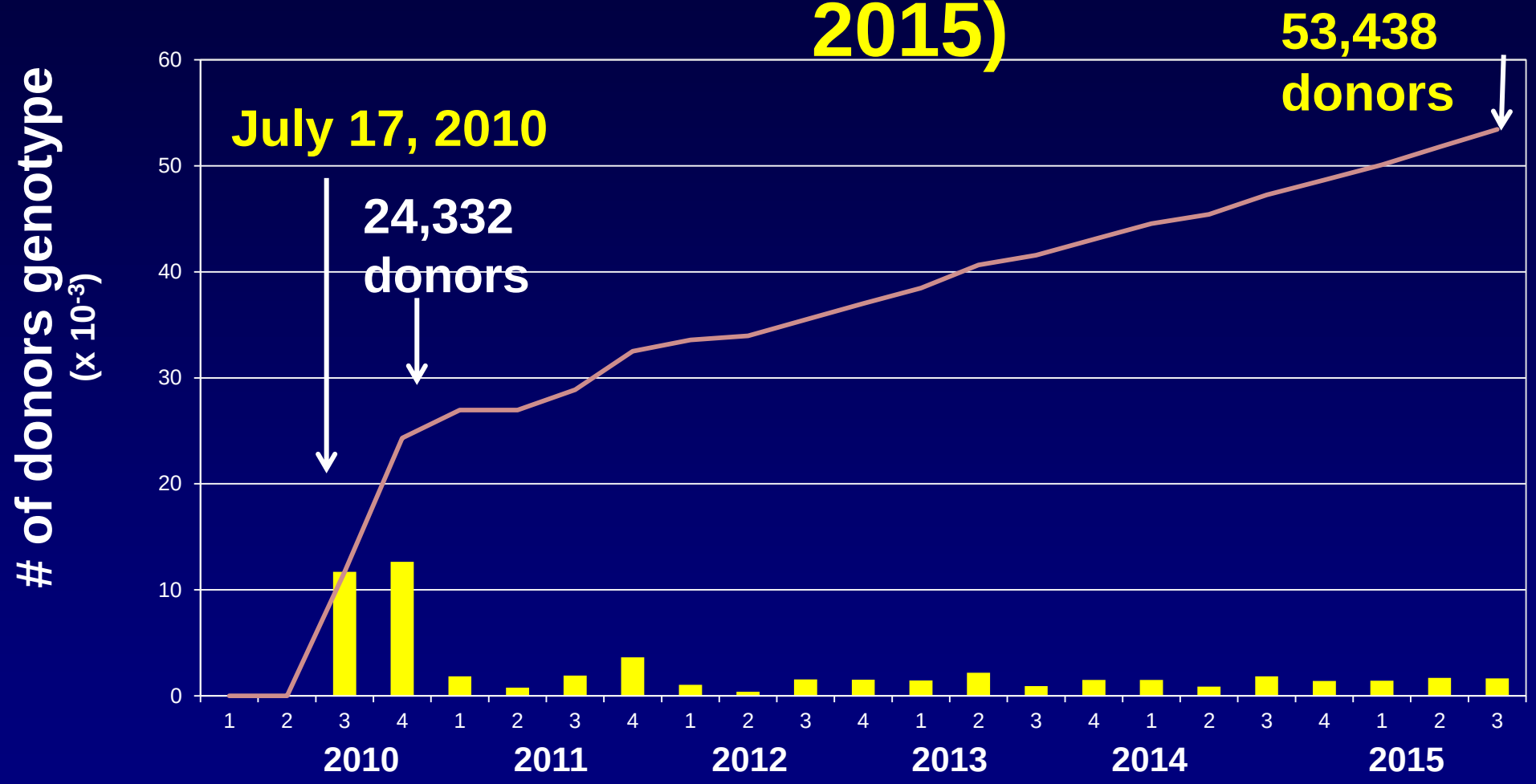
Integrating RBC Genotyping into the Blood Supply Chain*

- ~25,000 genotype database implemented in 6 months
  - 53,438 blood donors genotyped for ~42 blood group antigens over 5 years
  - Database maintained by genotyping 4,000 repeat donors/yr
  - Africans Americans, Native Americans, ABO 3:3:1:1

- Screening donor units for rare antigen-negative types using antisera has not occurred in nearly 6 years

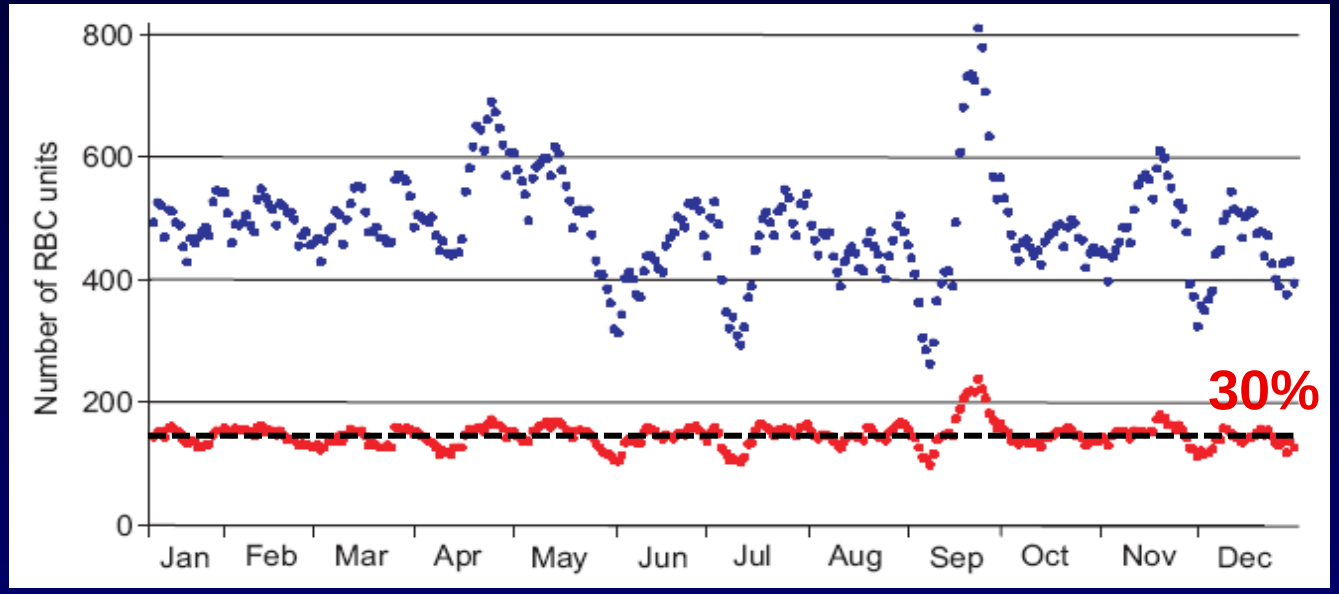
*Lancet Haematol. 2015 Jul;2(7):e282-9.PMID: 26207259

Donor Red Cell Genotyping (2010 – 2015)

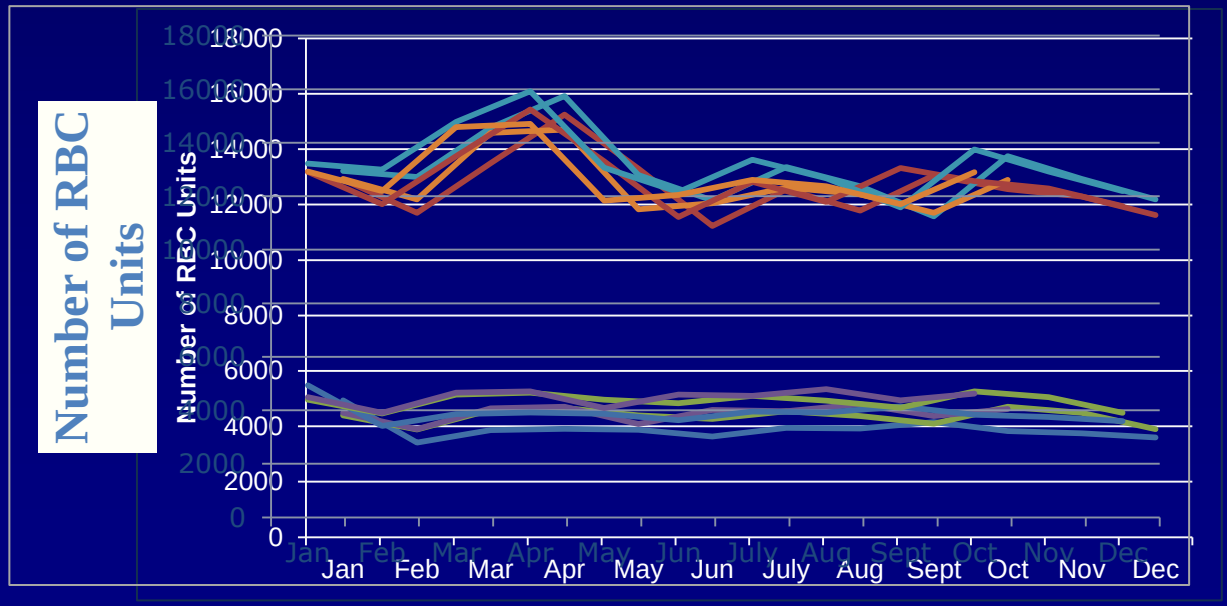


Transfusion: 2015; 55: 2610-2615

Number of units with a genotype



Daily 7-day



Monthly 3-year
2013 = 30%
2014 = 33%
2015 = 35%

Genotyping and Blood Supply

- The impact of extended typing

	Serology	Genotyping
Time	30 years	4 years
Donors (n)	72,272	43,066

Flegel WA, Gottschall, JL, Denomme GA. Lancet Haematology 2015 Jul;2(7):e282- **Integration of red cell genotyping into the blood supply chain: a population-based study.**

Genotyping and blood supply

- The impact of extended typing

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Time	30 years	4 years
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Minimum	1 antigen	
Maximum	28 antigens	

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Genotyping and blood supply

- The impact of extended typing

	Serology	Genotyping
Time	30 years	4 years
Donors (n)	72,272	43,066
Minimum	1 antigen	26 antigen
Maximum	28 antigens	42 antigens

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Genotyping and blood supply

- The impact of extended typing

	Serology	Genotyping
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Antigens (n)	322,264	1,667,026

Flegel WA, Gottschall, JL, Denomme GA. Lancet Haematology 2015 Jul;2(7):e282- **Integration of red cell genotyping into the blood supply chain: a population-based study.**

Genotyping and Blood Supply

The real impact»

- Genotyped RBC units supplied 95% of all clinical requests.

	Serology	Genotyping
Time	30 years	4 years
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Antigen Query Portal

- Portal transmits blood group antigen information with a red cell unit by use of the ISBT 128 number without personal information
- Antigens available to query: **C, E, c, e, M, N, S, s, K, Fya, Fyb, Jka, Jkb** (those antigen-negative types most likely encountered based on inventory and frequency in Wisconsin)
- In the initial rollout, 7 hospitals found 71 units in 52 queries (May - Dec 2013).
- 14 hospital blood banks use antigen query, with most centers 30 – 200+ miles away from the blood center

2015: Genotyping + Antigen query

Blood Center

Red Cell
Genotyping

Rare/Screened Blood

<1:50
1:5000

53,000 donors
42 antigens

DNA

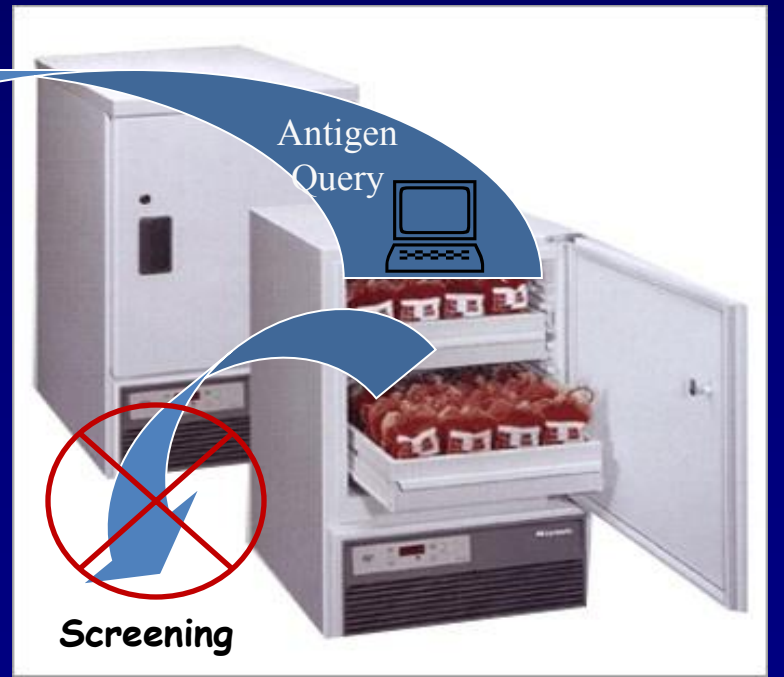
Hospital
Request

Ship

Hospital
Transfusion Service

BCW

= 2.26 x 10^6
(Genotypes)



- Requests were filled for 5661 (99.8%) of 5672 patient encounters in which antigen-negative red cell units needed
- Red cell genotyping met the demand for antigen-negative blood in 5339 (94.1%) of 5672 patient encounters [333 (5.9%)] filled using serological data
- RBC (blood cell) genotyping transformed the way antigen-negative units are provided
- Antigen query portal could reduce the need for transportation of blood and serological screening

What Prevents Adoption ?

- Generations of Serological Experience
- Absence of Licensed Genomics Technology
- Legacy IT Systems
- Organizational Will
- Startup $$$

Summary

- A “high throughput” mass scale genotyping process to create an inventory database of 42-blood group antigen profiles
- Genotype results were electronically transferred to a database where a computer algorithm translated the genotype data into alleles with predicted blood group phenotypes
- Hospitals given online access to a web-based antigen query portal to find antigen-negative units in their inventories
- Availability of a database of genotyped Ag-neg donors (units) improved speed and reliability of providing Ag-neg units

Future

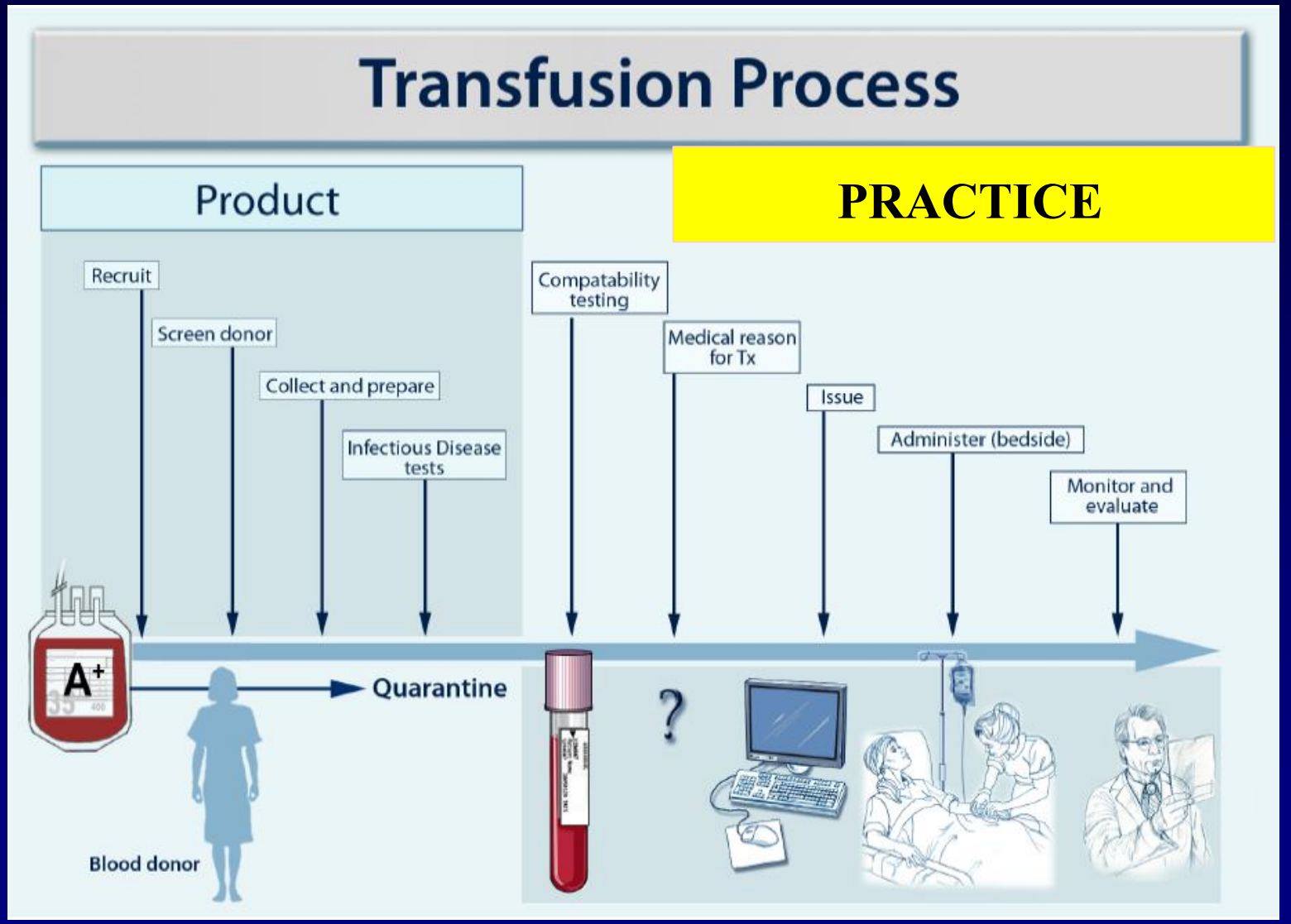
- Extending the network of genotyped blood to other blood centers for rapid access to compatible blood and safer transfusions beyond a single catchment area

- Genotyping of “high risk patients (SCD) and eventually all patients will have genome on EMR

- NextGen Sequencing of donor base

- Virtual networks of RBC genotyped donor databases, web-based ‘in the cloud’ to complement centralized recipient databases for “precision transfusion medicine”

“Imprecision Medicine”



“Variability is the law of life, and as no two faces are the same, so no two bodies are alike, and no two individuals react alike and behave alike under the abnormal conditions which we know as disease”

Sir William Osler, Boston Med Surg J 1903;148:275-279

Transfusion "Rules"

- **The 10/30 rule: Adams and Lundy, 1942***

  -Derived empirically for poor-risk anesthesia patients.

- **Czer and Shoemaker, 1978**– Hct ~ 33%**
  - **In 94 critically ill postop pts, mortality lowest if Hct 27-33**
  - **O_2 availability and Vo_2 increased with transfusion for Hct < 32%**

**Adams RC , Lundy JS. Anesthesia in cases of poor risk. Some suggestions for decreasing the risk. Surg Gynecol Obstet 1942; 74:1011-19.*

*** Czer LS, Shoemaker WC. Optimal hematocrit value in critically ill postoperative patients Surg Gynecol Obstet. 1978 Sep;147(3):363*

The “Trigger”

- Friedman et al. (1980)* described the “factors that motivate physicians to order blood”

- In a study of 535,031 male and female surgical patients, PCV was an important and arbitrary component of this decision

- They recommended a lower trigger for women

** Friedman BA et al. An analysis of blood transfusion of surgical patients by sex: a question for the transfusion trigger. Transfusion 1980 20:179*

The NEW ENGLAND JOURNAL of MEDICINE

MEDICINE AND SOCIETY

Debra Malina, Ph.D., *Editor*

Assessing the Gold Standard — Lessons from the History of RCTs

Laura E. Bothwell, Ph.D., Jeremy A. Greene, M.D., Ph.D., Scott H. Podolsky, M.D., and David S. Jones, M.D., Ph.D.

Over the past 70 years, randomized, controlled trials (RCTs) have reshaped medical knowledge and practice. Popularized by mid-20th-century

Trialists countered that RCTs could determine whether new interventions were superior to the standard of care given to control groups.[4] Others

"Even as RCTs have become standard in pharmaceutical research, clinical researchers have struggled to apply them to other areas of medicine".

"Critics have become increasingly adept at ferreting out flaws in RCTs, forcing trialists to be more vigilant in their designs".

Problems With Clinical Trials

- Asking the right question
- Inadequate controls or no controls
- Misalignment problem
- Non-reproducible data
- Inadequately powered
- Publication bias

Critical Care Medicine

2007 - VOLUME 35, NUMBER 6

Randomization in clinical trials of titrated therapies: Unintended consequences of using fixed treatment protocols*

Katherine J. Deans, MD, MHSc; Peter C. Minneci, MD, MHSc; Anthony F. Suffredini, MD; Robert L. Danner, MD; William D. Hoffman, MD; Xizhong Ciu; Harvey G. Klein, MD; Alan N. Schechter, MD; Steven M. Banks, PhD; Peter Q. Eichacker, MD; Charles Natanson, MD

Routine Care Control

Routine Care Control

- Critical illnesses vary in severity

Routine Care Control

- Critical illnesses vary in severity
- Treatment is frequently adjusted based on severity (“titrated”)

Routine Care Control

- Illness varies in severity
- Treatment is frequently adjusted based on severity (“titrated”)
- Severity of illness and treatment level are often linked

Therapeutic Misalignment:

The International Journal of Transfusion Medicine
Vox Sanguinis

Vox Sanguinis (2010) **99**, 16

REVIEW

DOI: 10.1111/j.1423-0410.2010.013

The relevance of practice misalignments to trials in transfusion medicine

K. J. Deans,[1,2] P. C. Minneci,[1,2] H. G. Klein[3] & C. Natanson[4]

[1] *Department of Surgery, The Children's Institute for Surgical Science, The Children's Hospital of Philadelphia, Philadelphia, PA, USA*
[2] *Department of Surgery, University of Pennsylvania School of Medicine, Philadelphia, PA, USA*
[3] *Department of Transfusion Medicine, Warren G. Magnuson Clinical Center, National Institutes of Health, Bethesda, MD, USA*
[4] *Critical Care Medicine Department, National Institutes of Health, Bethesda, MD, USA*

Vox Sanguinis

Practice misalignments can occur in any clinical trial investigating a pre-existi
therapy that is typically adjusted based on clinical characteristics outside of the tr
setting. To eliminate the heterogeneity in clinical practice, recent trials investig
ing titrated therapies have randomized patients to fixed-dose regimens witho
including a routine care control group receiving titrated therapy. In these trials, t

Background: Therapeutic Misalignment in Transfusion Trials

Transfusion Trials at High Risk for Therapeutic Misalignment

- Transfusions usually adjusted for severity of disease

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- Testing two ends of routine care

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- Care administered independent of need

Transfusion Trials at High Risk for Therapeutic Misalignment

- Transfusions usually adjusted for severity of disease
- Testing two ends of routine care
- Care administered independent of need
- No routine practice (care) control

Severity of Illness and Level of Treatment

Severity of Illness	Treatment Level
Mild	Low
Moderate	Mid-range
Severe	High

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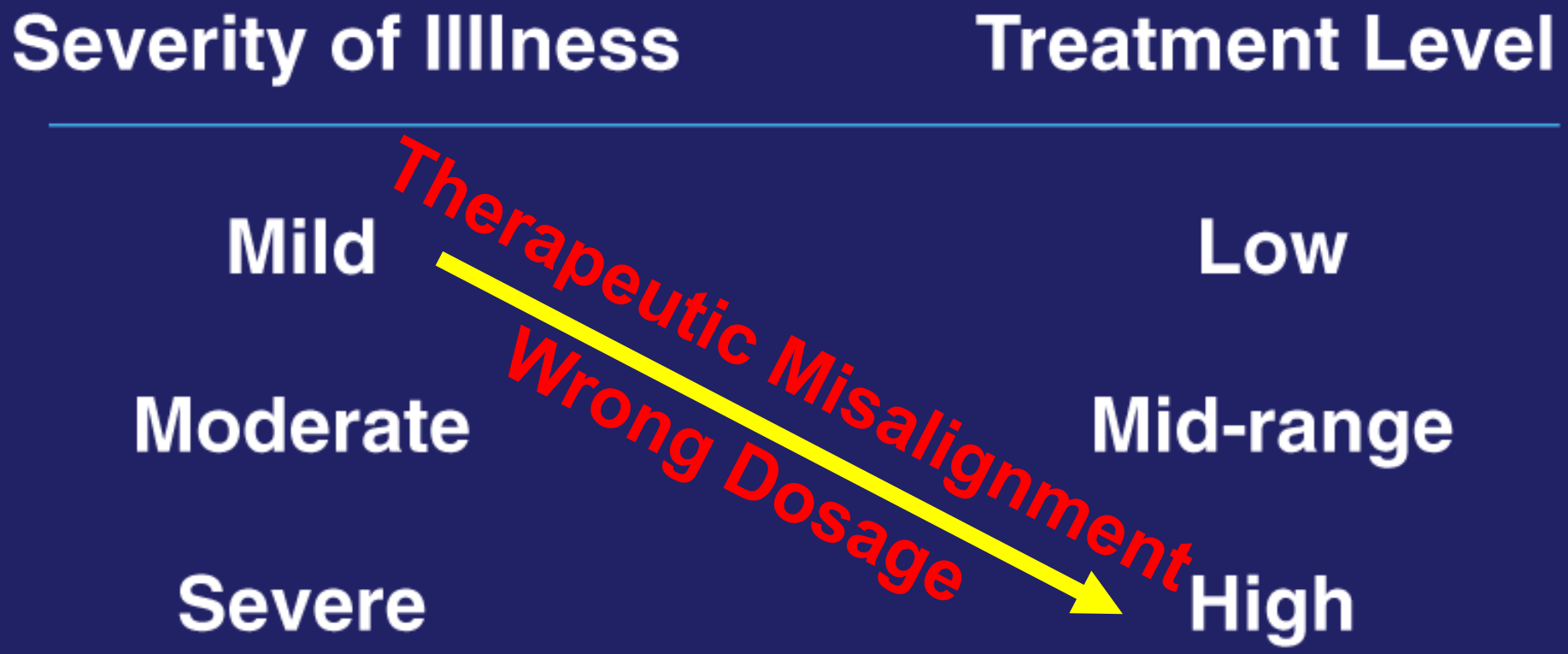
Severity of Illness and Level of Treatment



Severity of Illness and Level of Treatment

Transfusion Trigger Study

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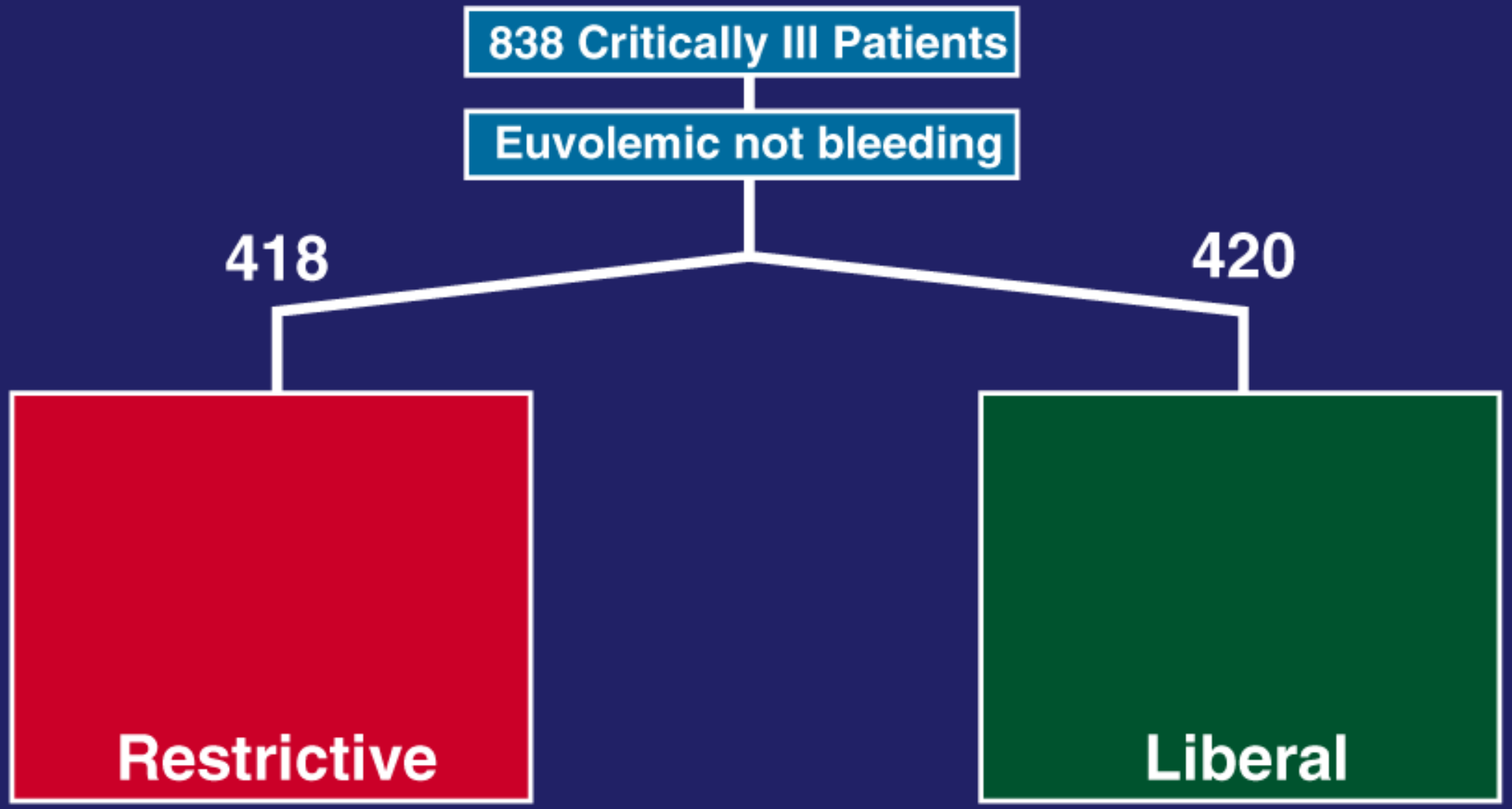
838 Critically Ill Patients

Transfusion Trigger Study

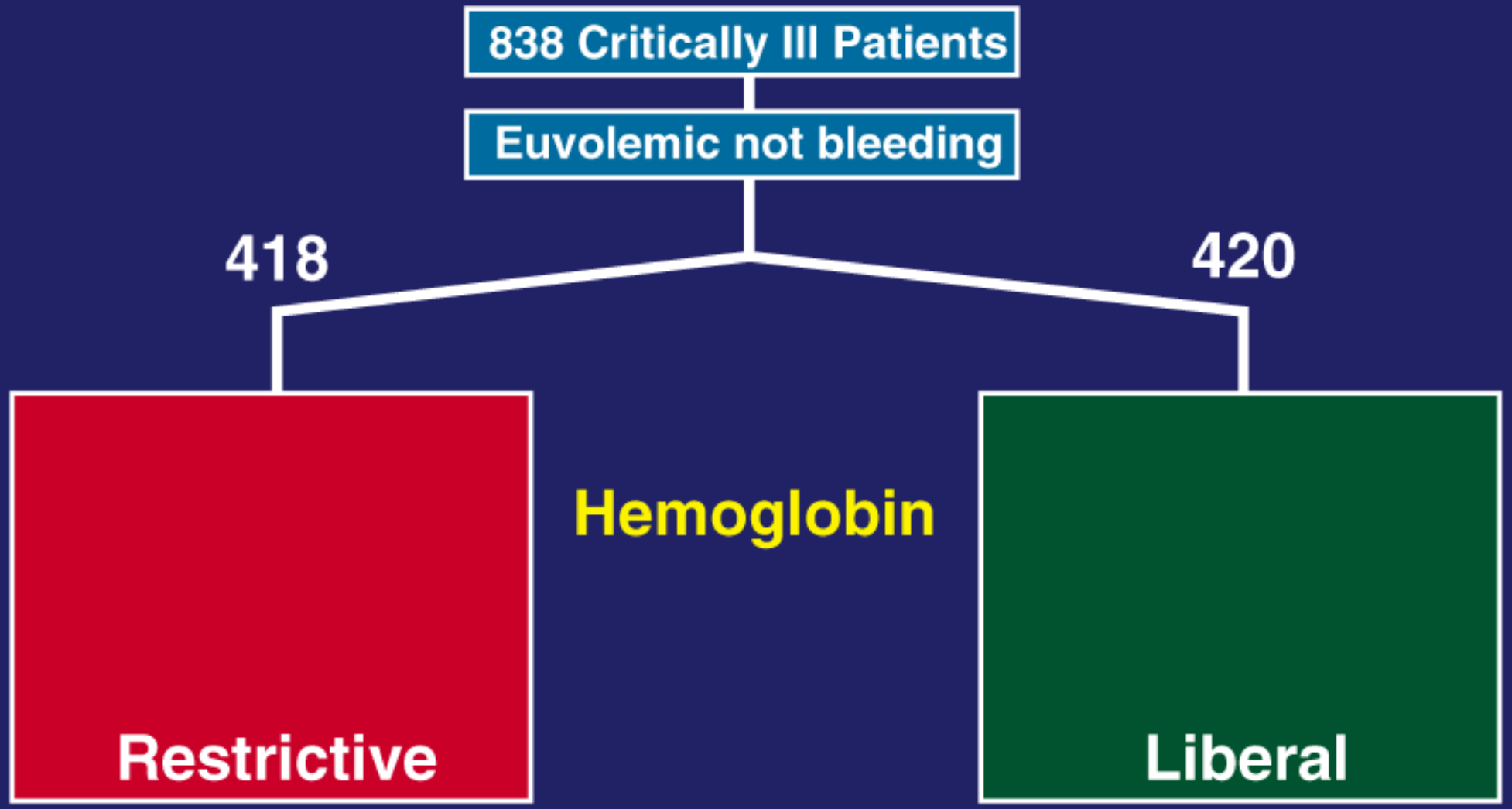
838 Critically Ill Patients

Euvolemic not bleeding

Transfusion Trigger Study



Transfusion Trigger Study



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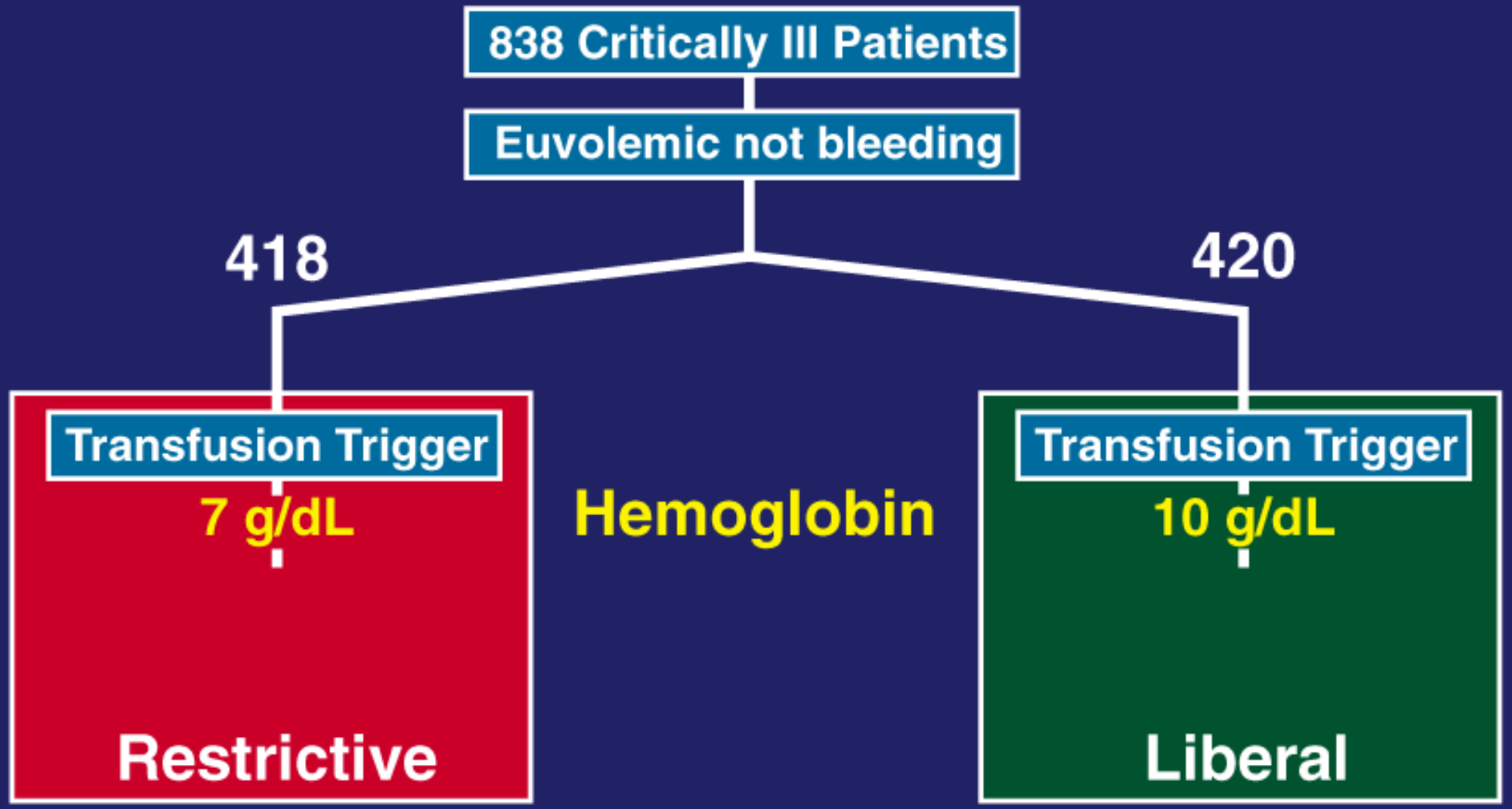

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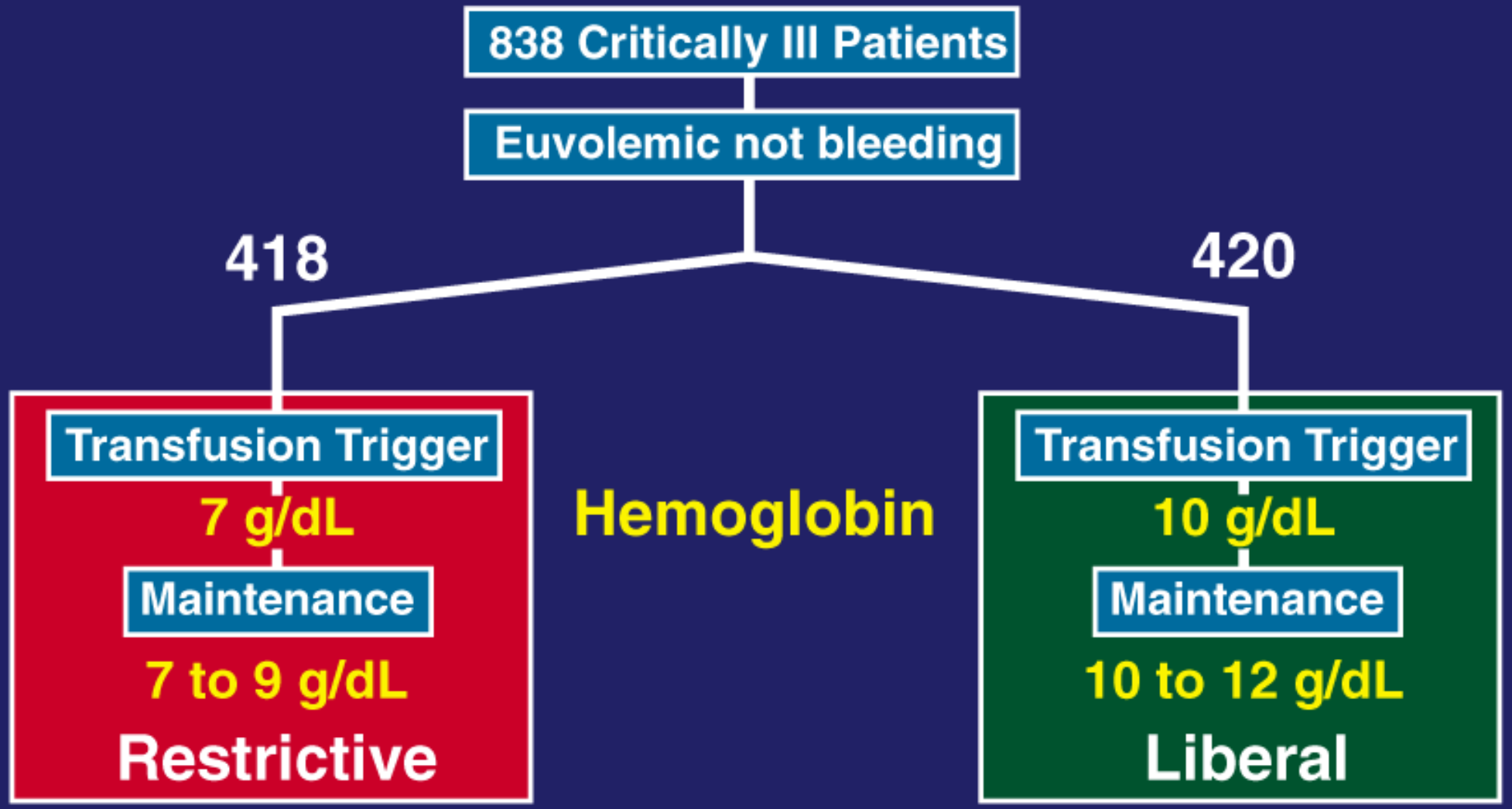
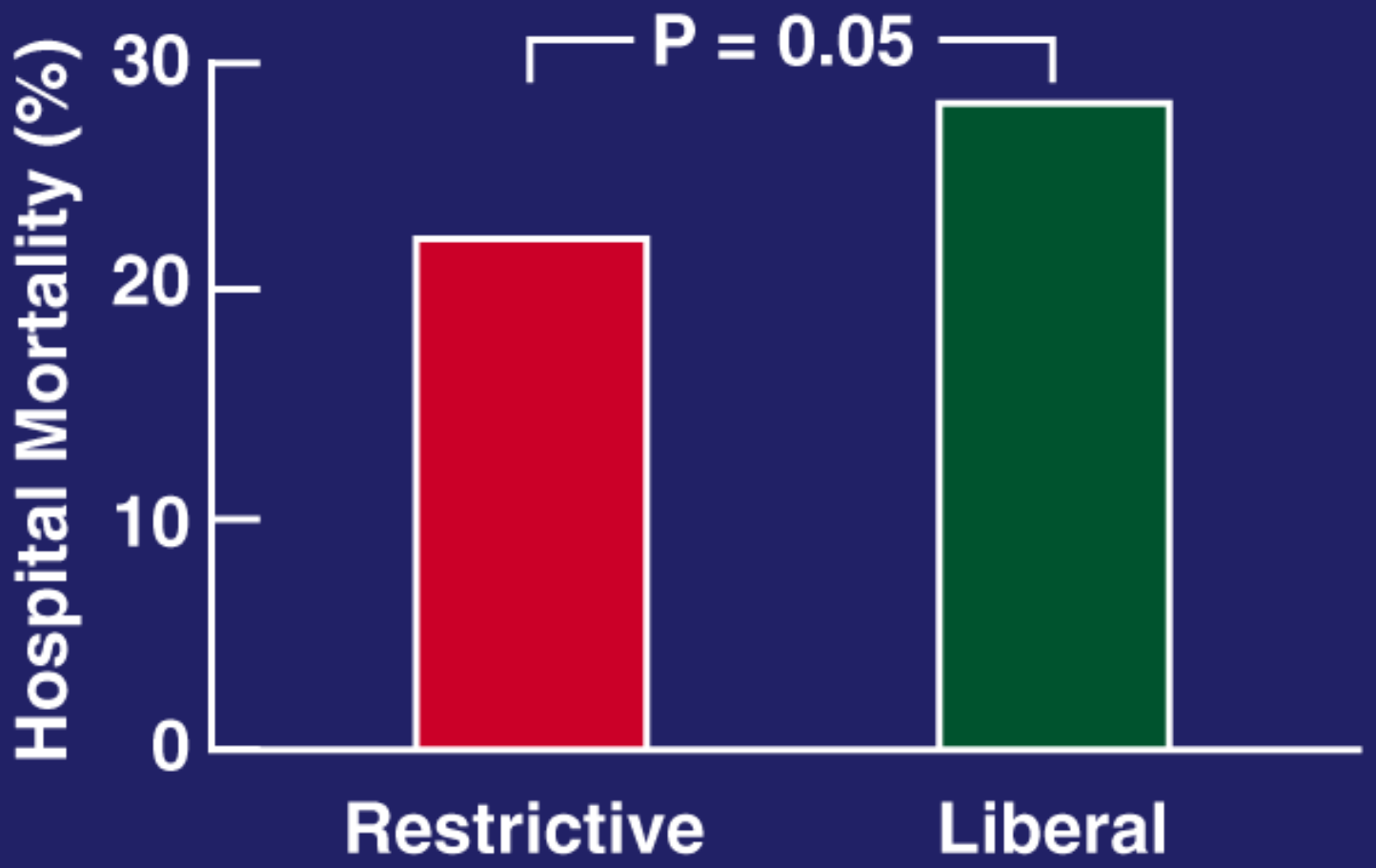


Transfusion Trigger Study: Result



N Engl J Med, 1999; 340:409-17

Transfusion Trigger Study: Conclusion

"We recommend critically ill patients receive red-cell transfusion when hemoglobin concentrations fall below 7.0 g per deciliter"

N Engl J Med, 1999; 340:409-17

Transfusion Trigger Trial: Conclusion

- Is conclusion justified and applicable to all critically ill patients?
- What was routine practice at time of trial?

Survey of Transfusion Practices

Crit Care Med, 1998; 26(3):482-6

Survey of Transfusion Practices

- Hgb transfusion thresholds

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  - APACHE score
  - Shock
  - Lactic acidosis
  - Coronary ischemia

Crit Care Med, 1998; 26(3):482-6

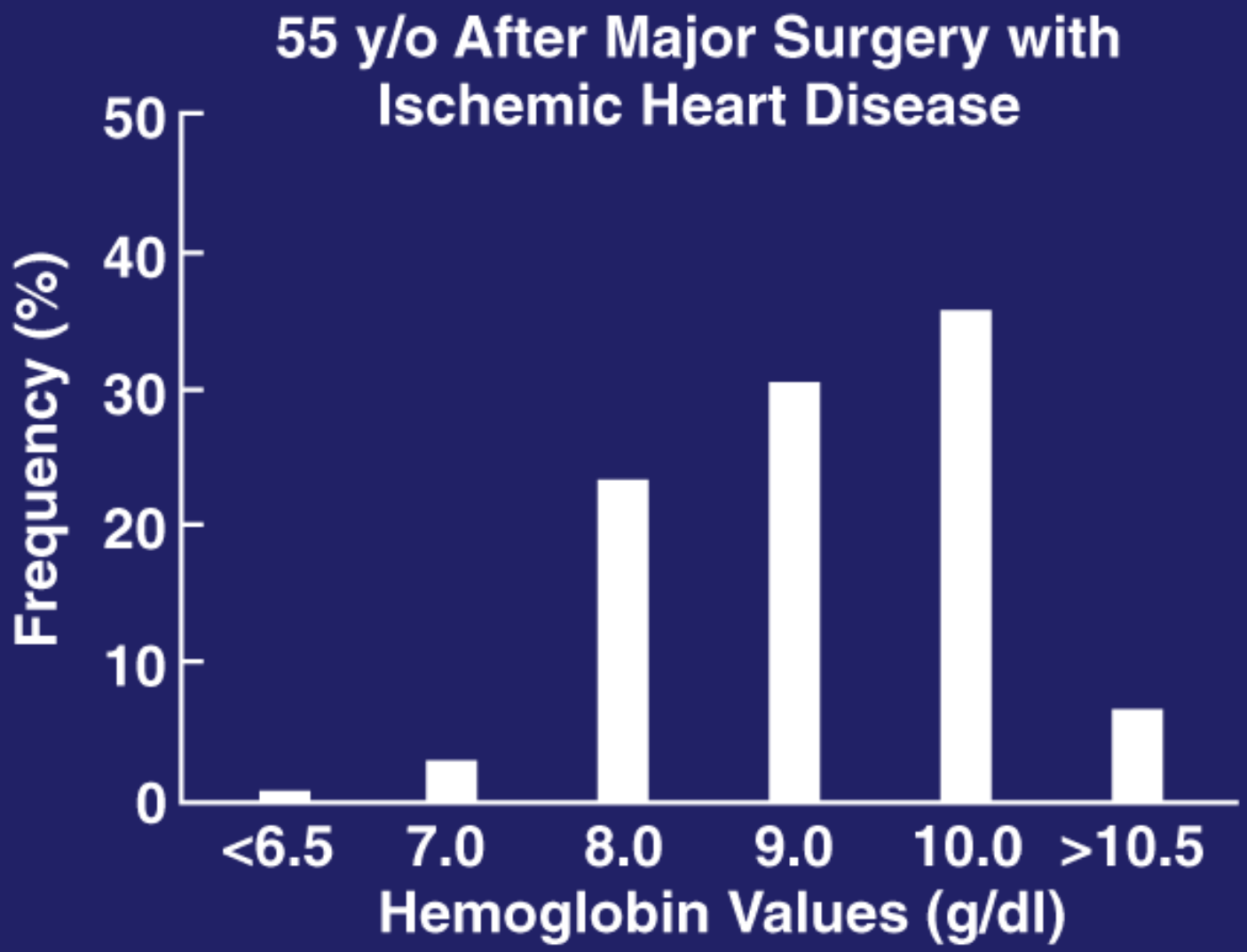
"In this study, we demonstrated that critical care physicians believed that a number of clinical characteristics are important determinants of the transfusion decision"

Crit Care Med, 1998; 26(3): 482-6

"We believe that clinical trials evaluating different transfusion strategies in the critically ill are required before the development and dissemination of practice guidelines in high-risk patient populations".

Crit Care Med, 1998; 26(3): 482-6

Transfusion Thresholds



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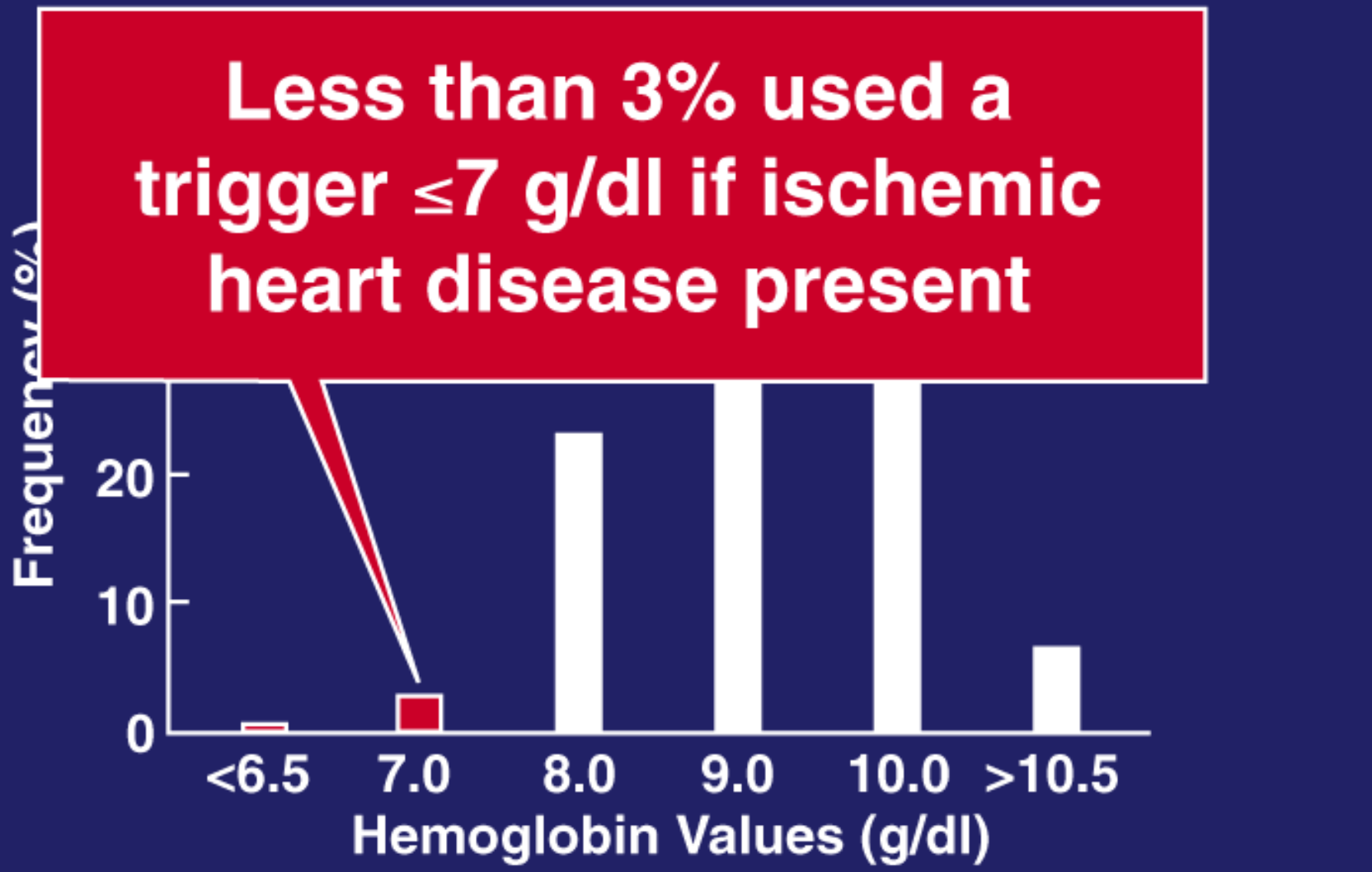
Transfusion Thresholds



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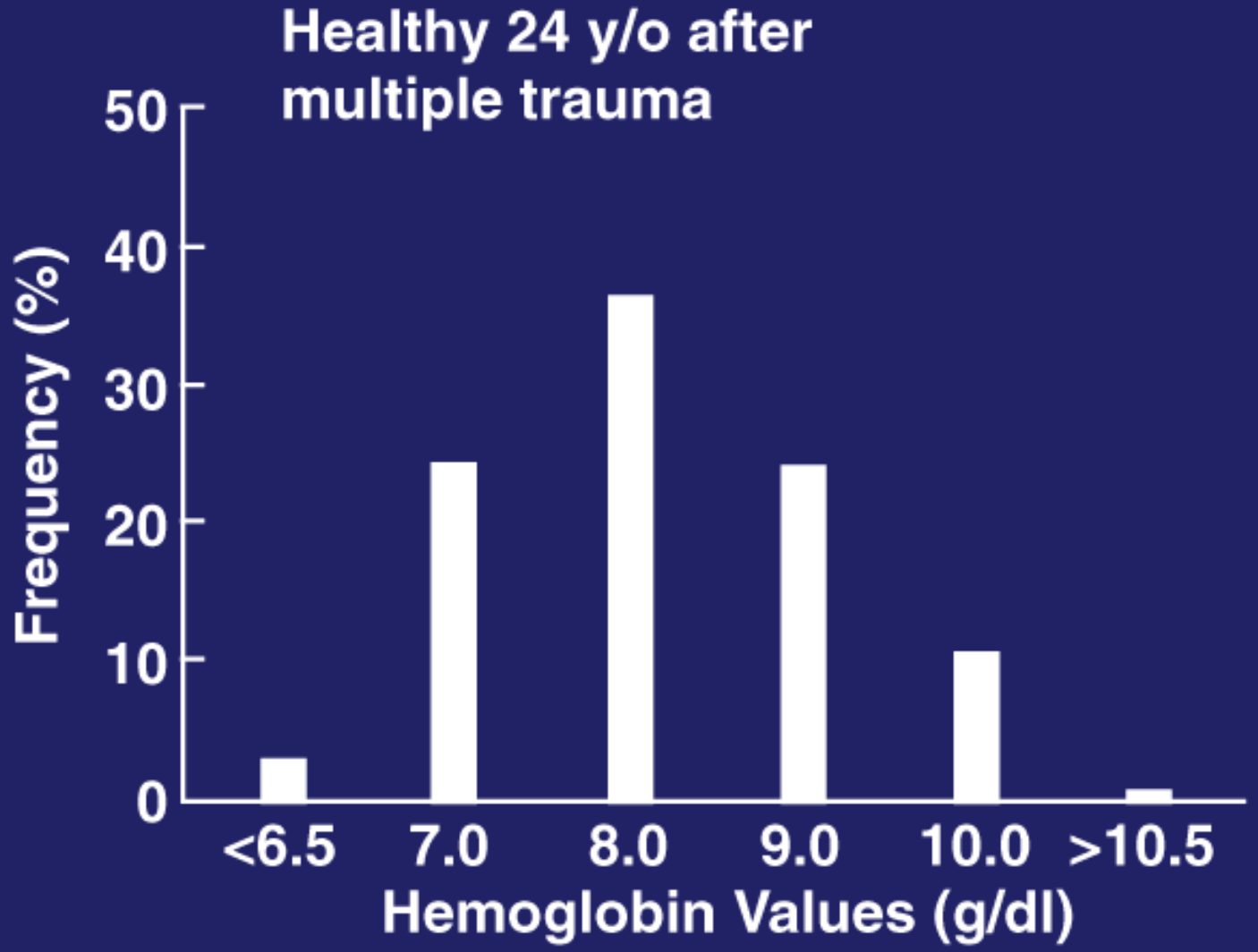
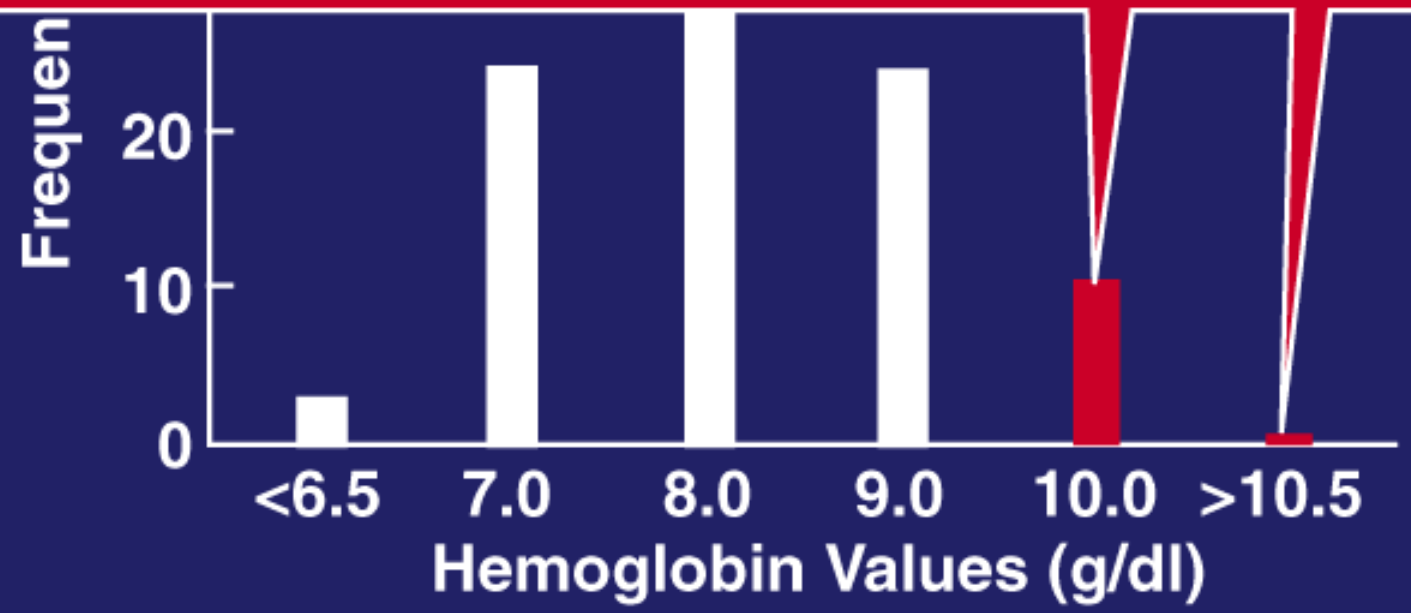
Transfusion Thresholds



Crit Care Med, 1998; 26(3):482-6

Transfusion Thresholds

Only 12% used a trigger ≤10 g/dl in young, healthy patients not actively bleeding



Crit Care Med, 1998; 26(3):482-6

Ischemic Heart Disease and Transfusion Trigger

Crit Care Med, 2001 - N Engl J Med, 1999

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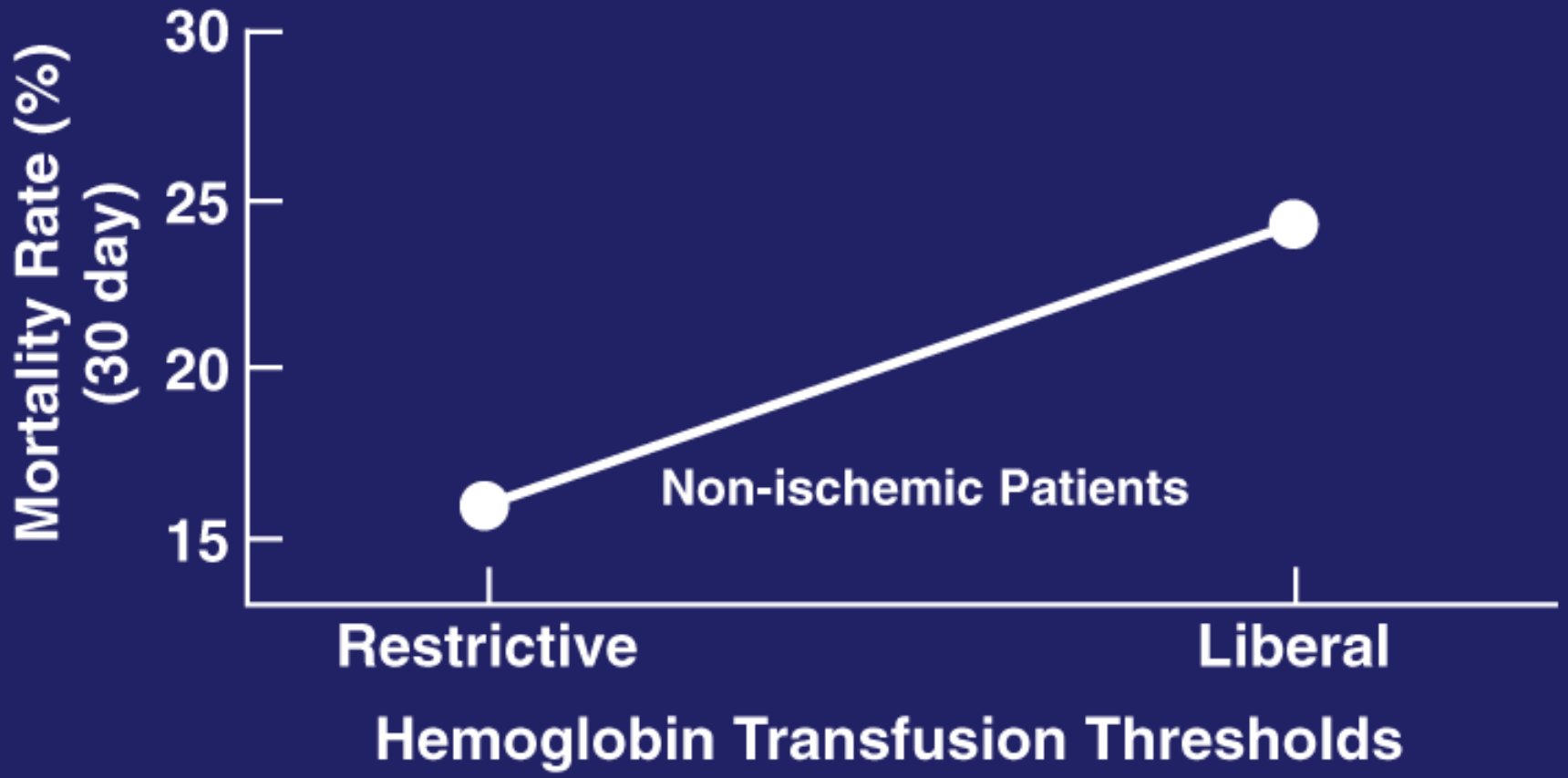

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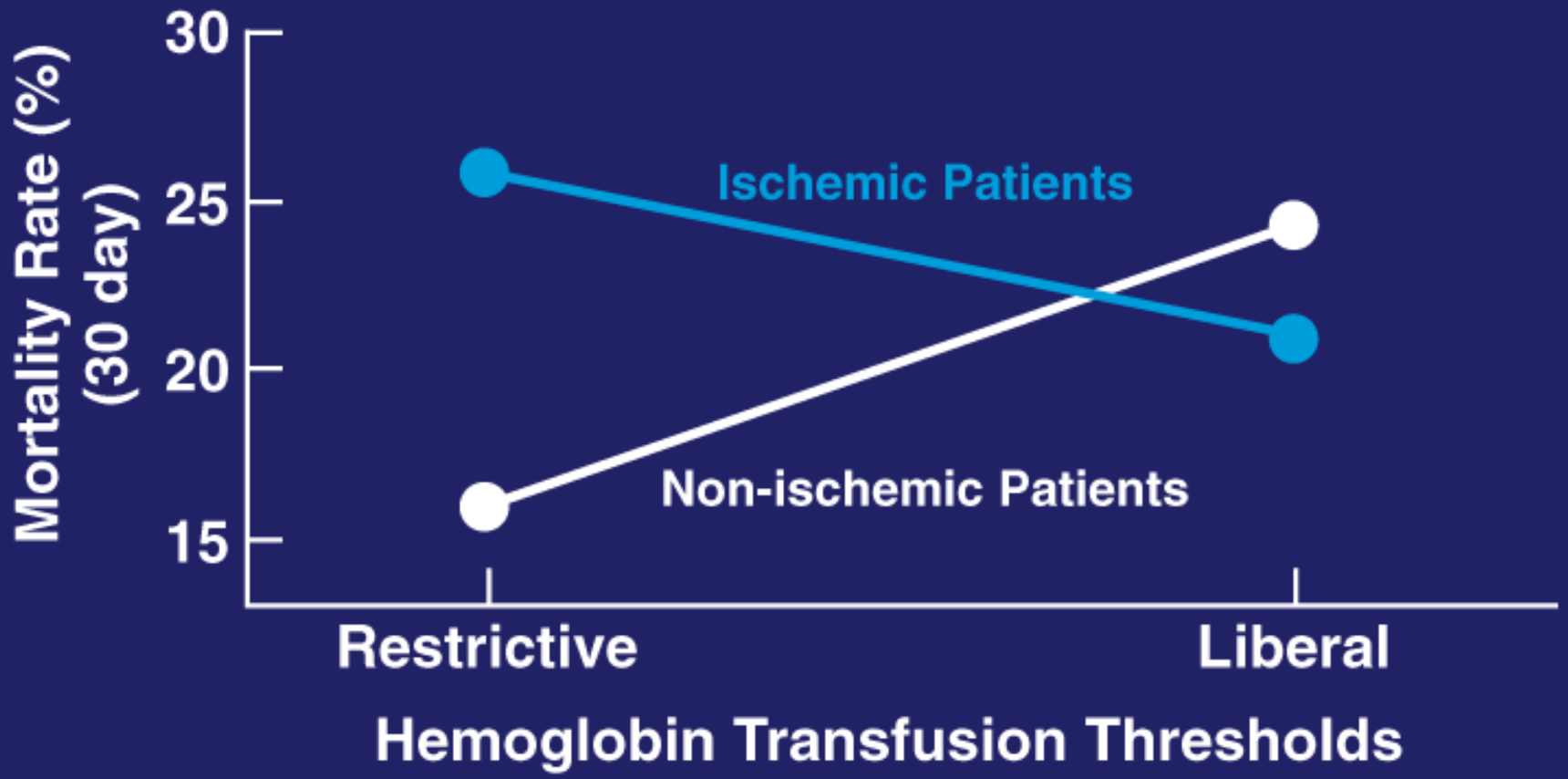

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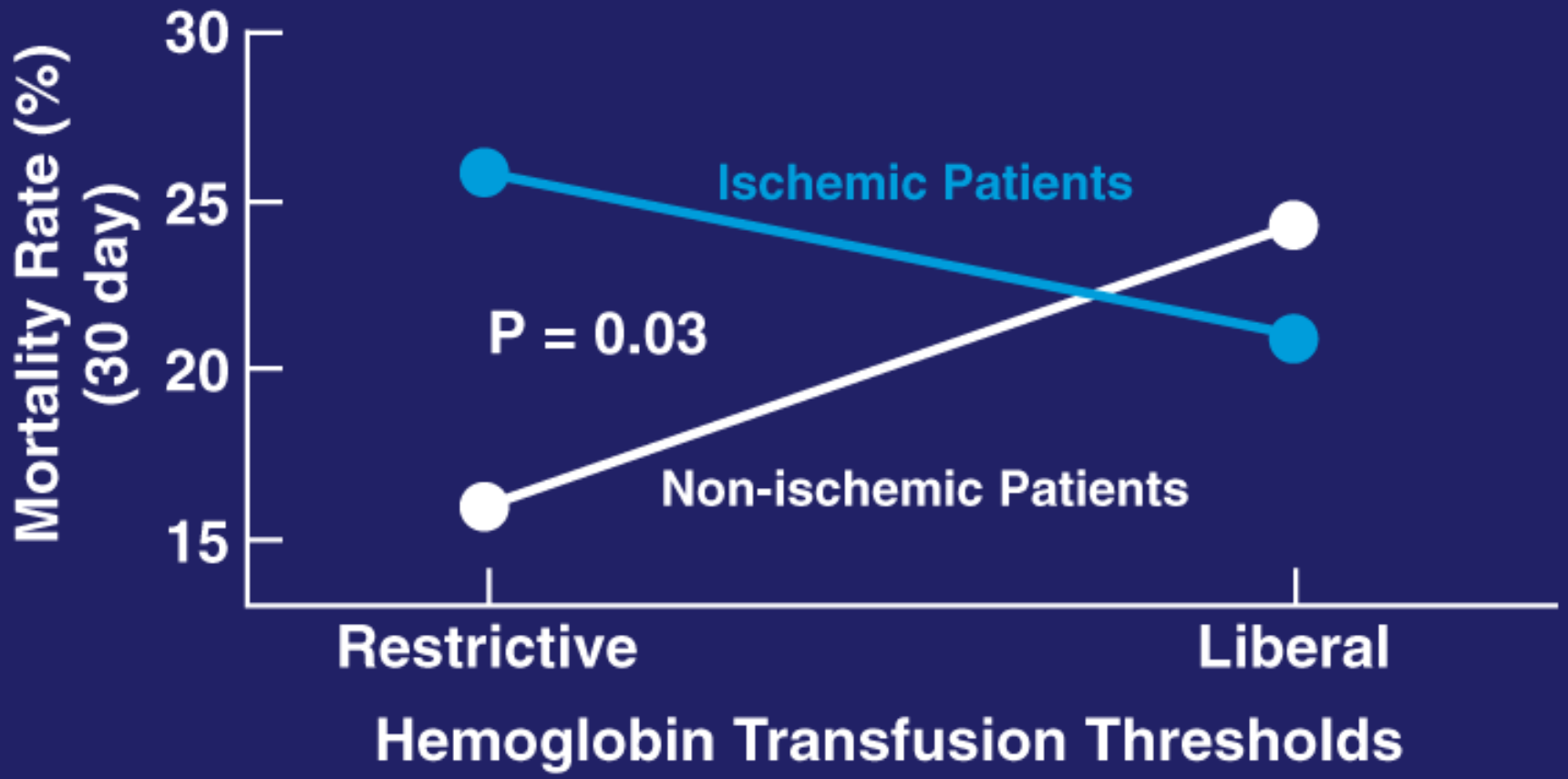

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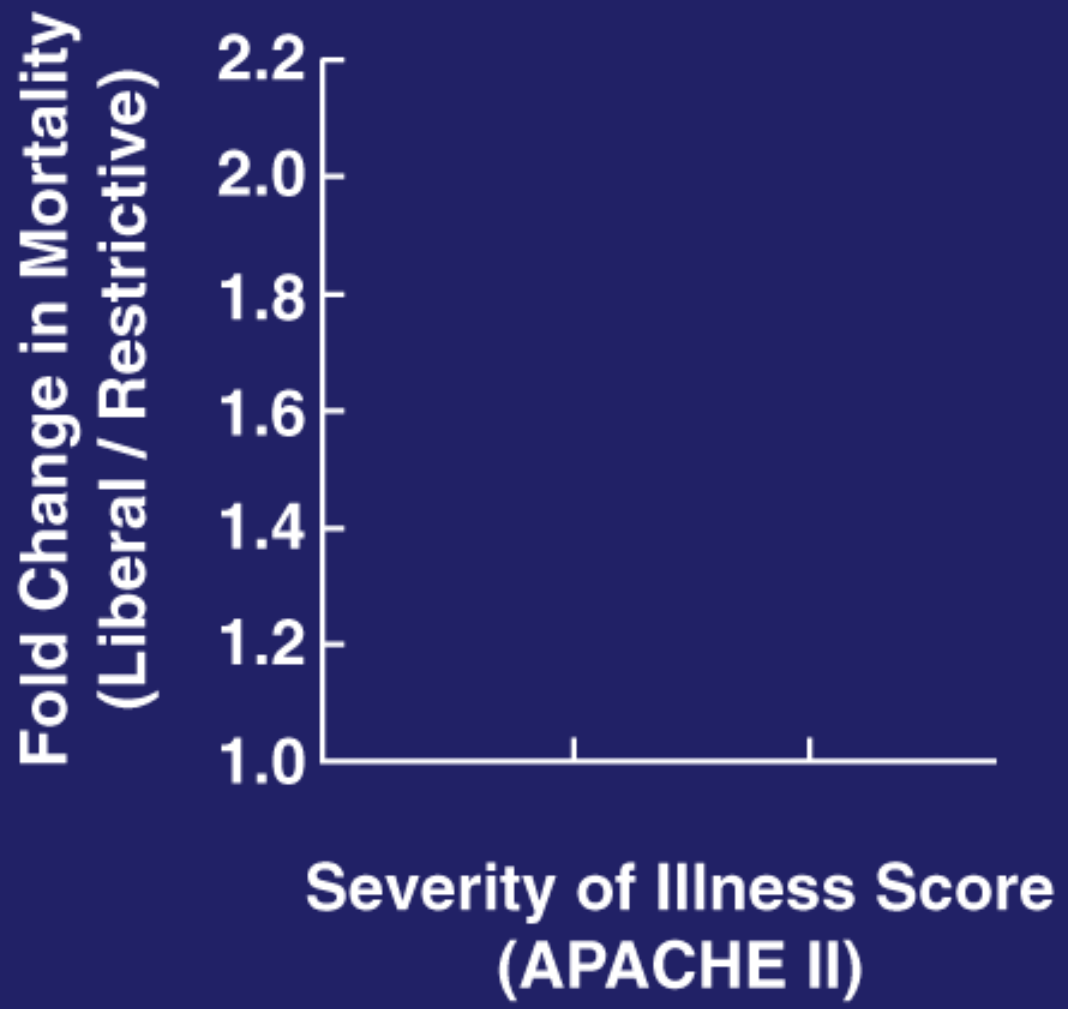

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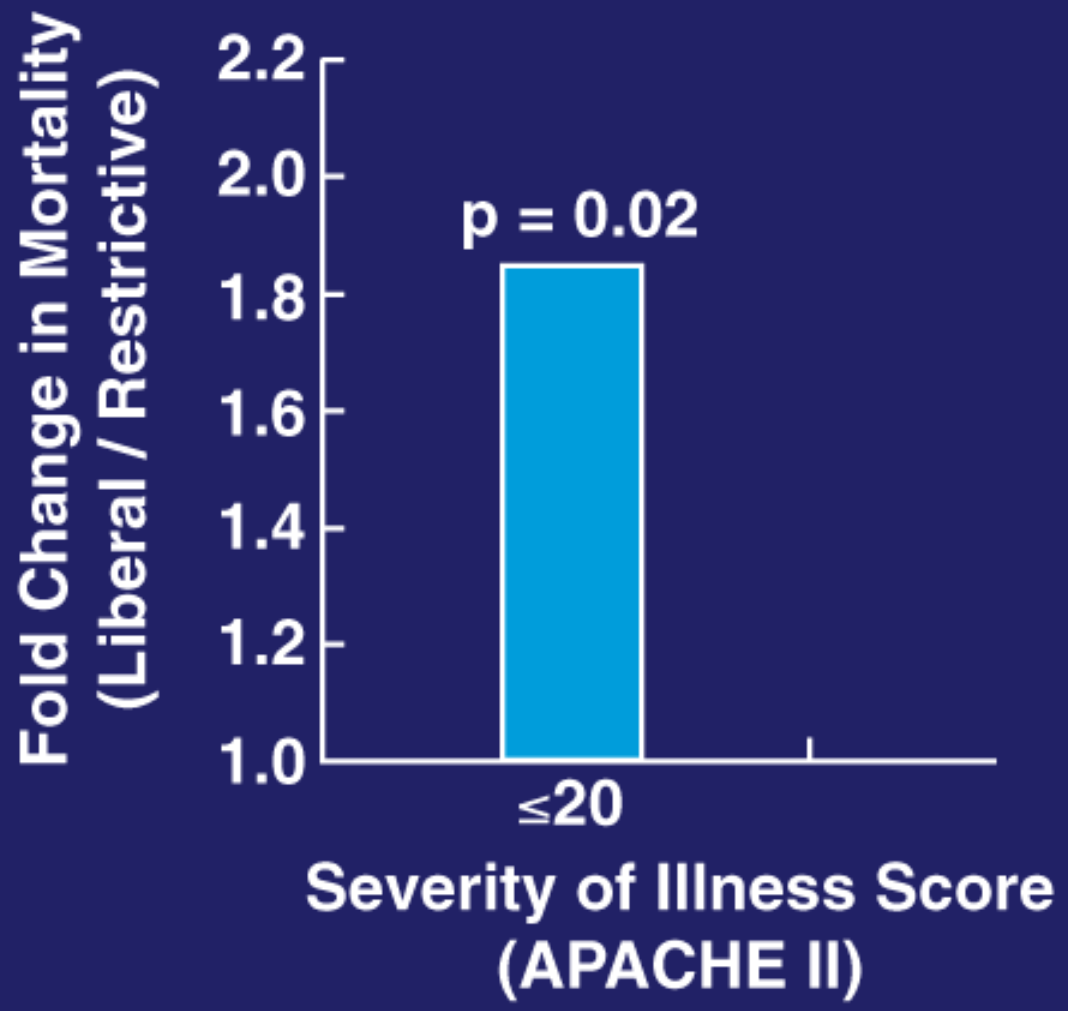

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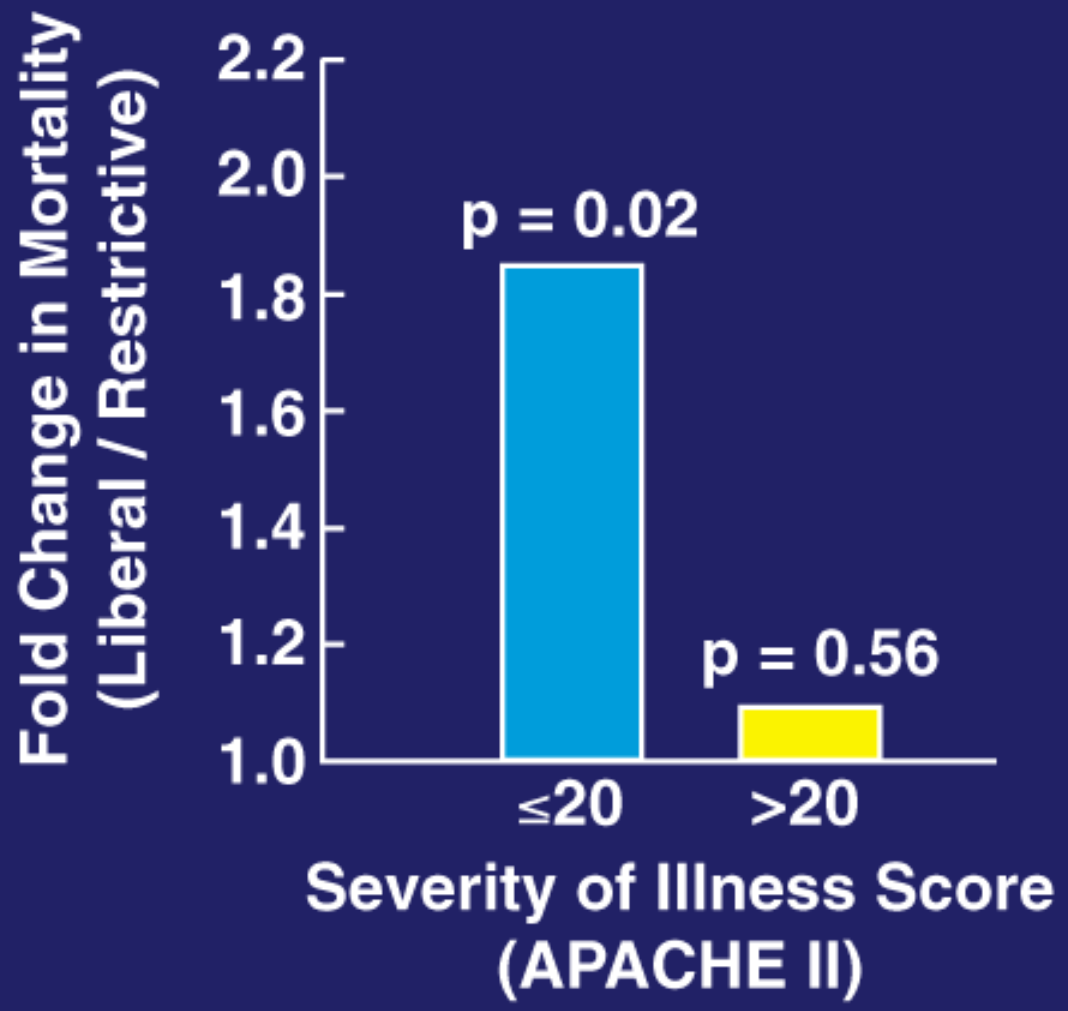

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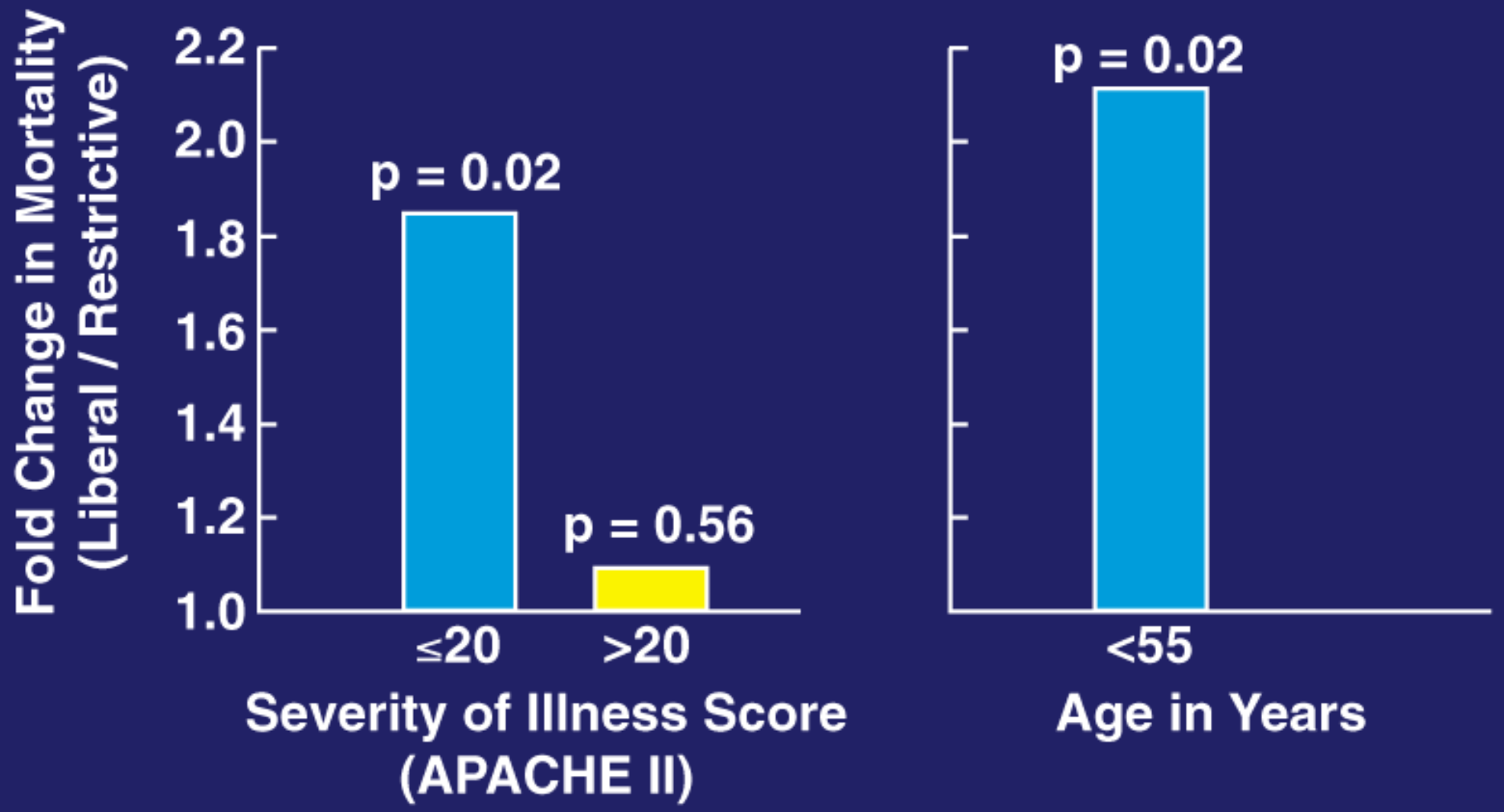

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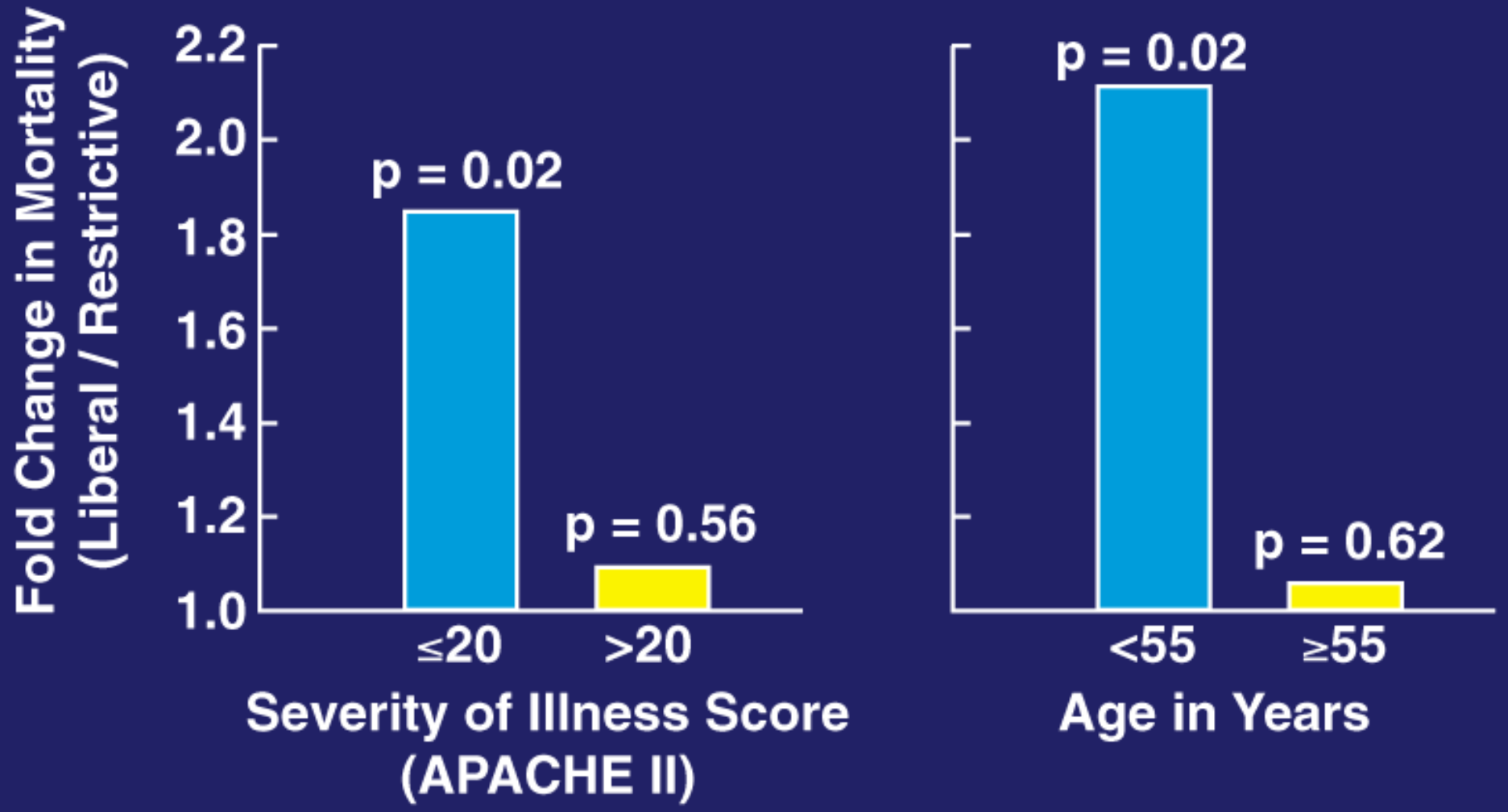

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- Comparison of arms with different therapeutic misalignments is uninformative
- Titrated care representing routine practice was not used to monitor safety or as a basis to change current practice

Transfusion trigger trials enrolling patients with cardiovascular disease 1995 – present

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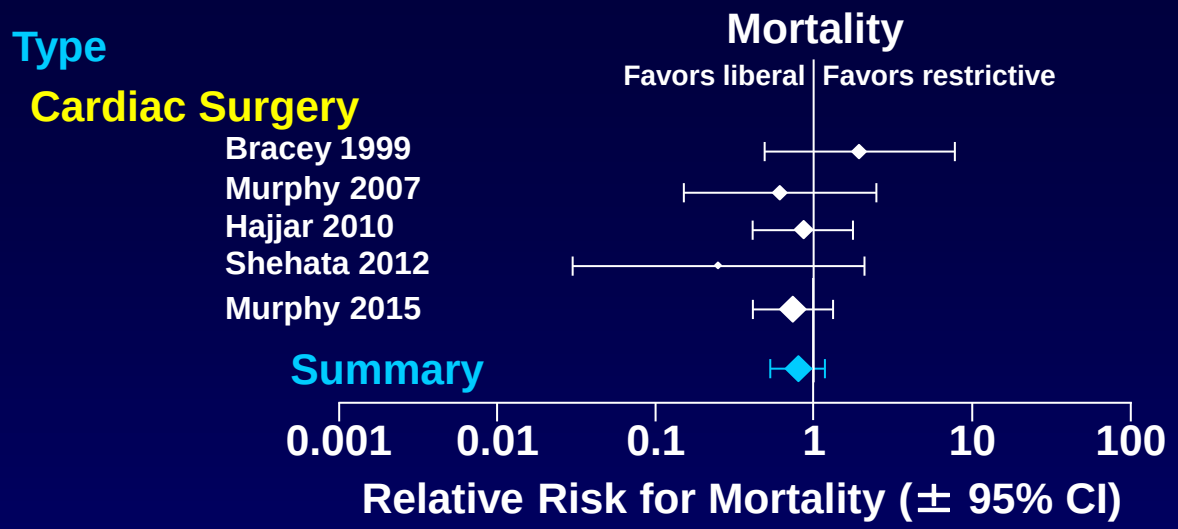
Sixteen Transfusion Trigger Trials Including Patients with Cardiovascular Disease



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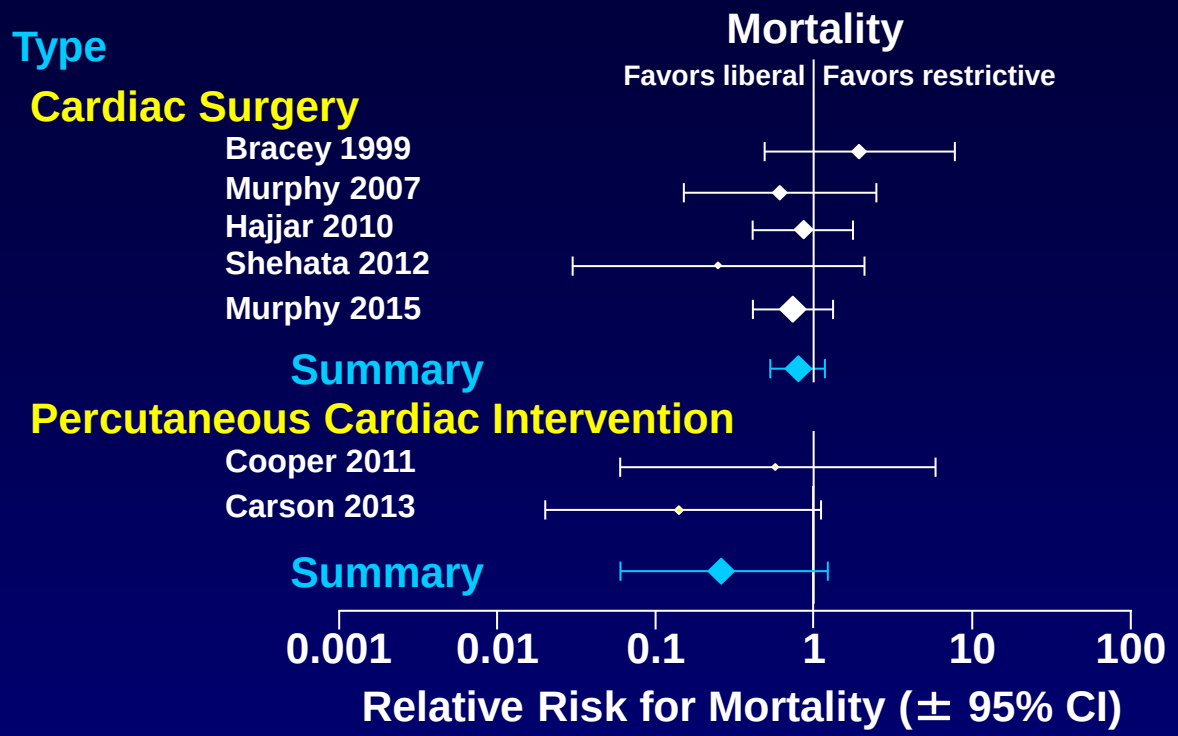

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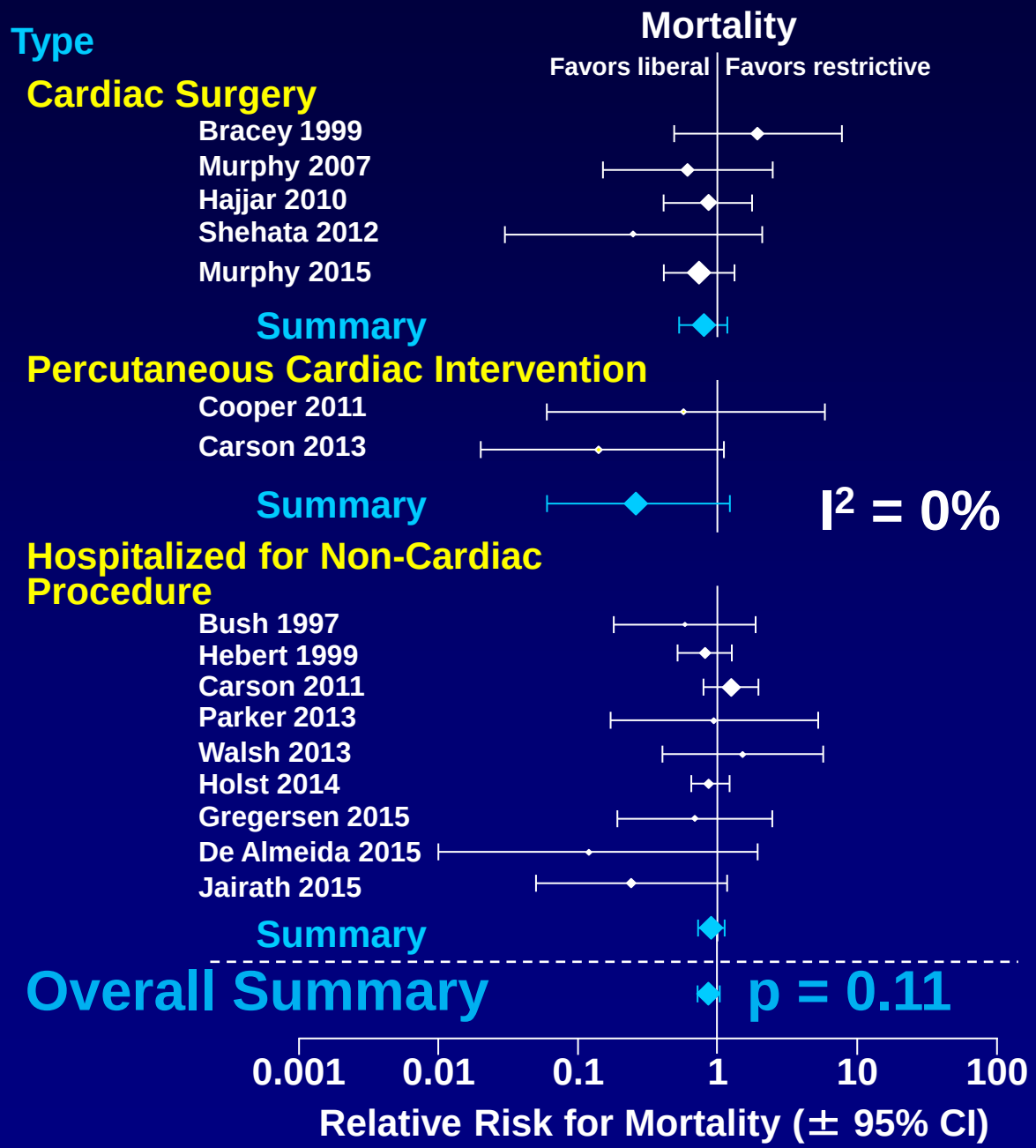

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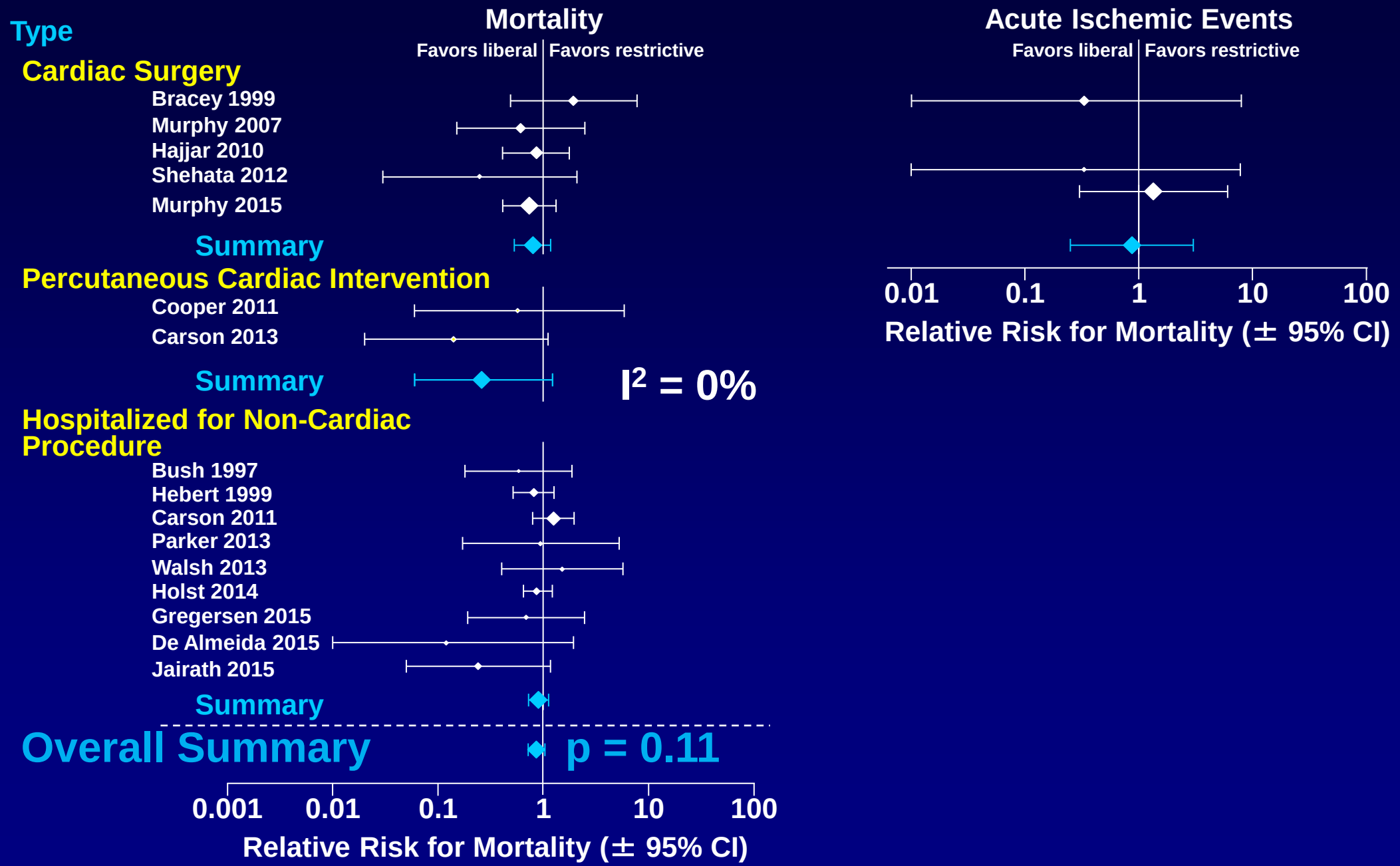

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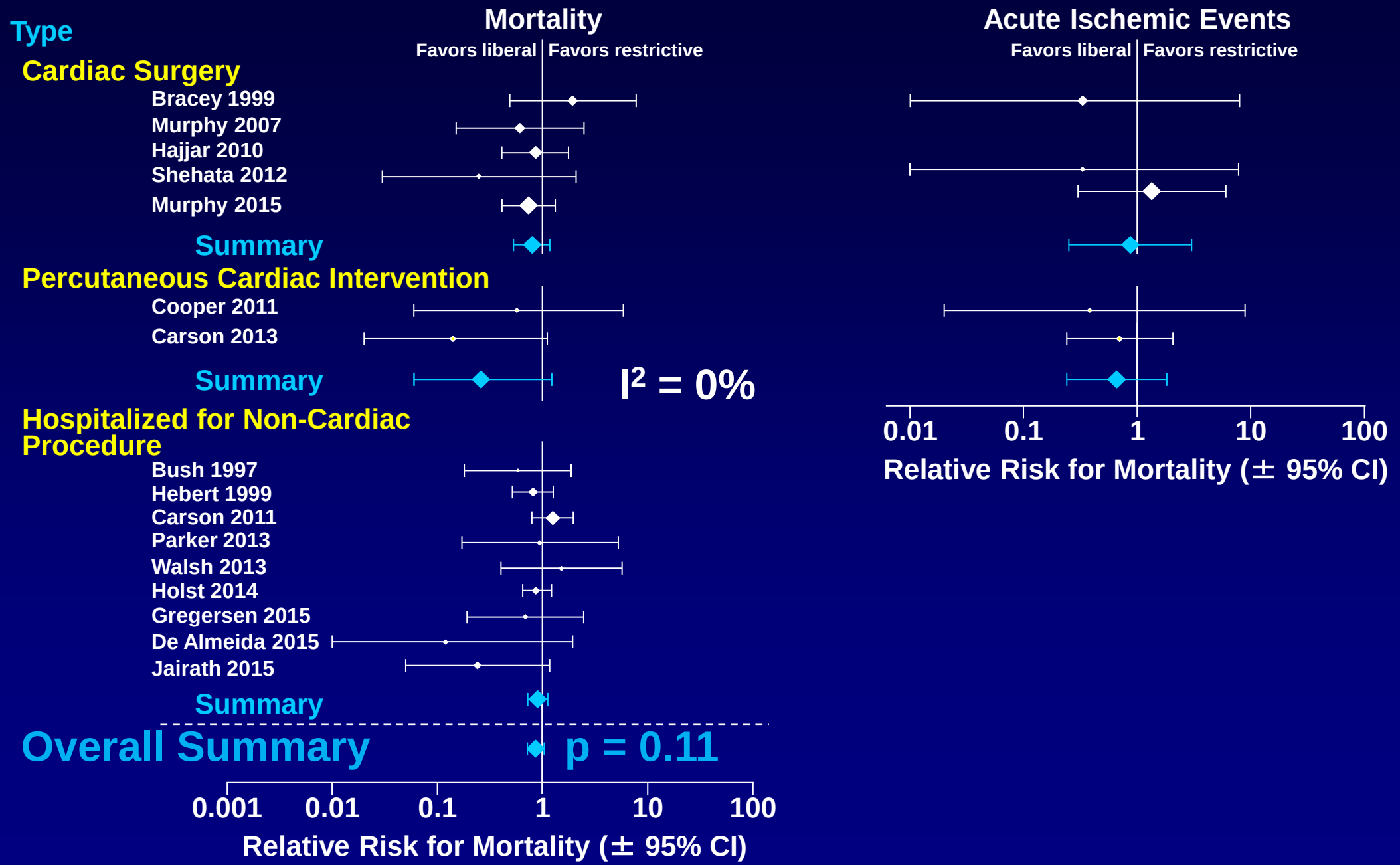

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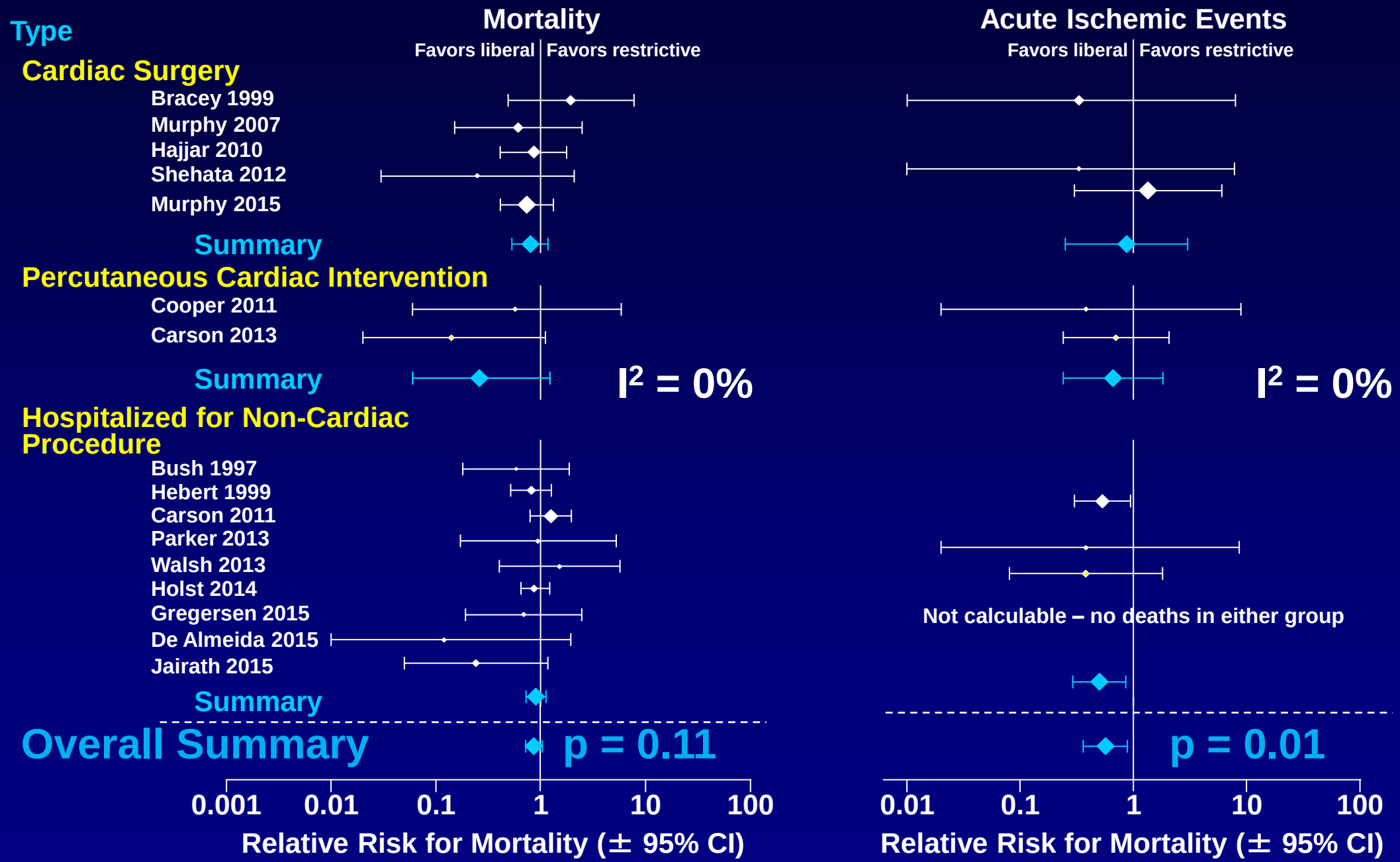

Figure 2.

Nine Transfusion Trigger Trials Including Patients With and Without Cardiovascular Disease

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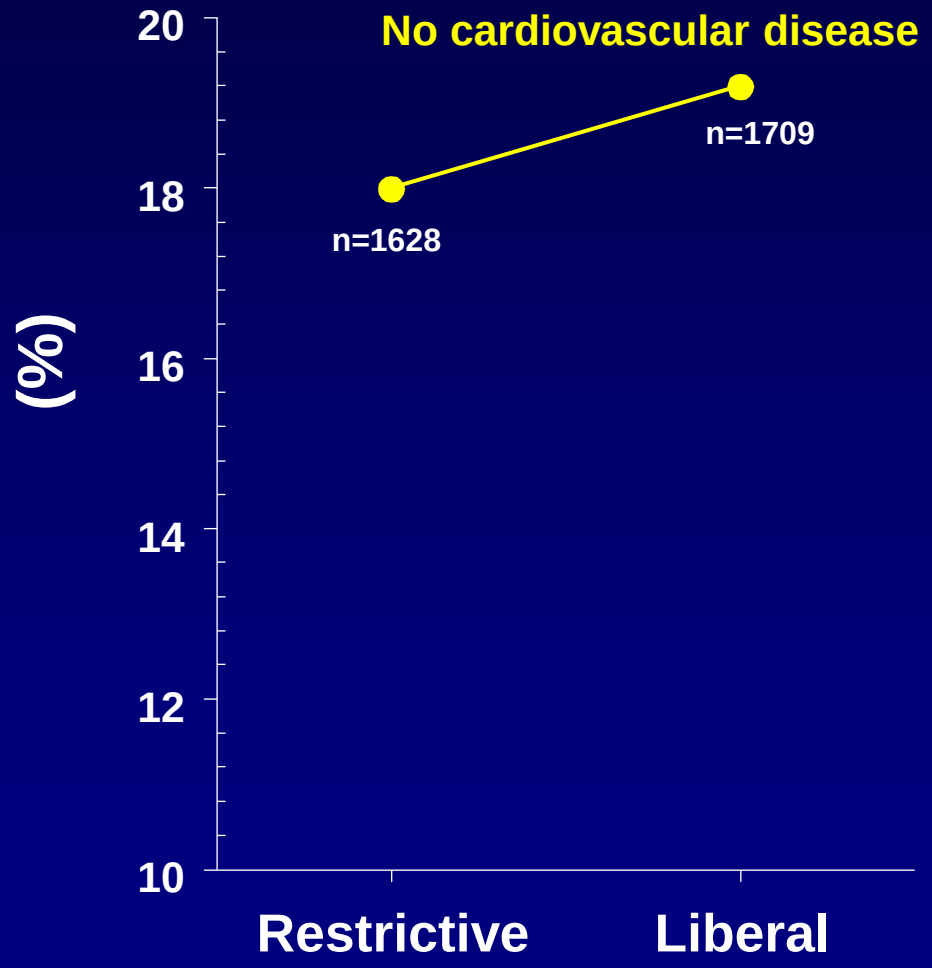

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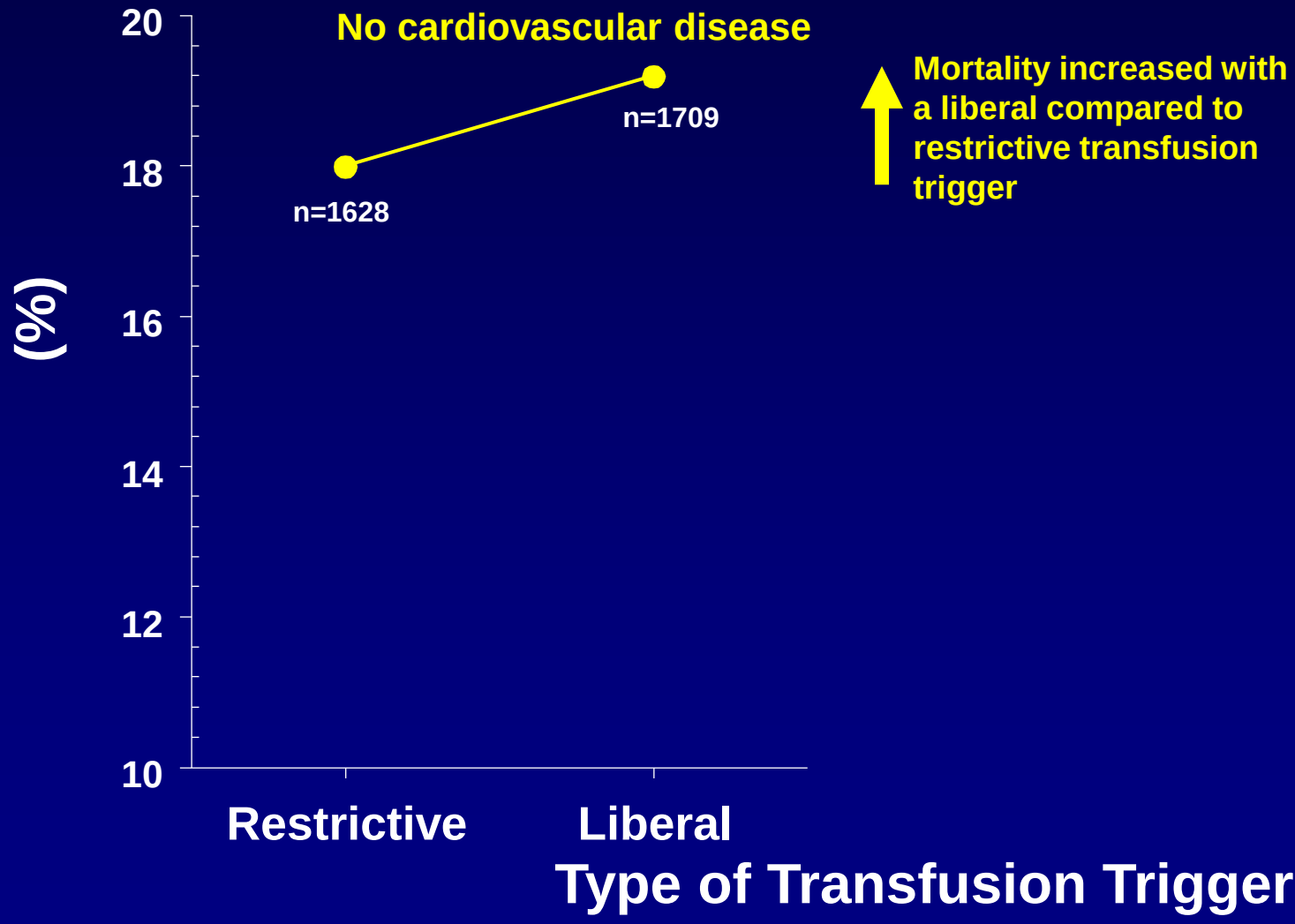

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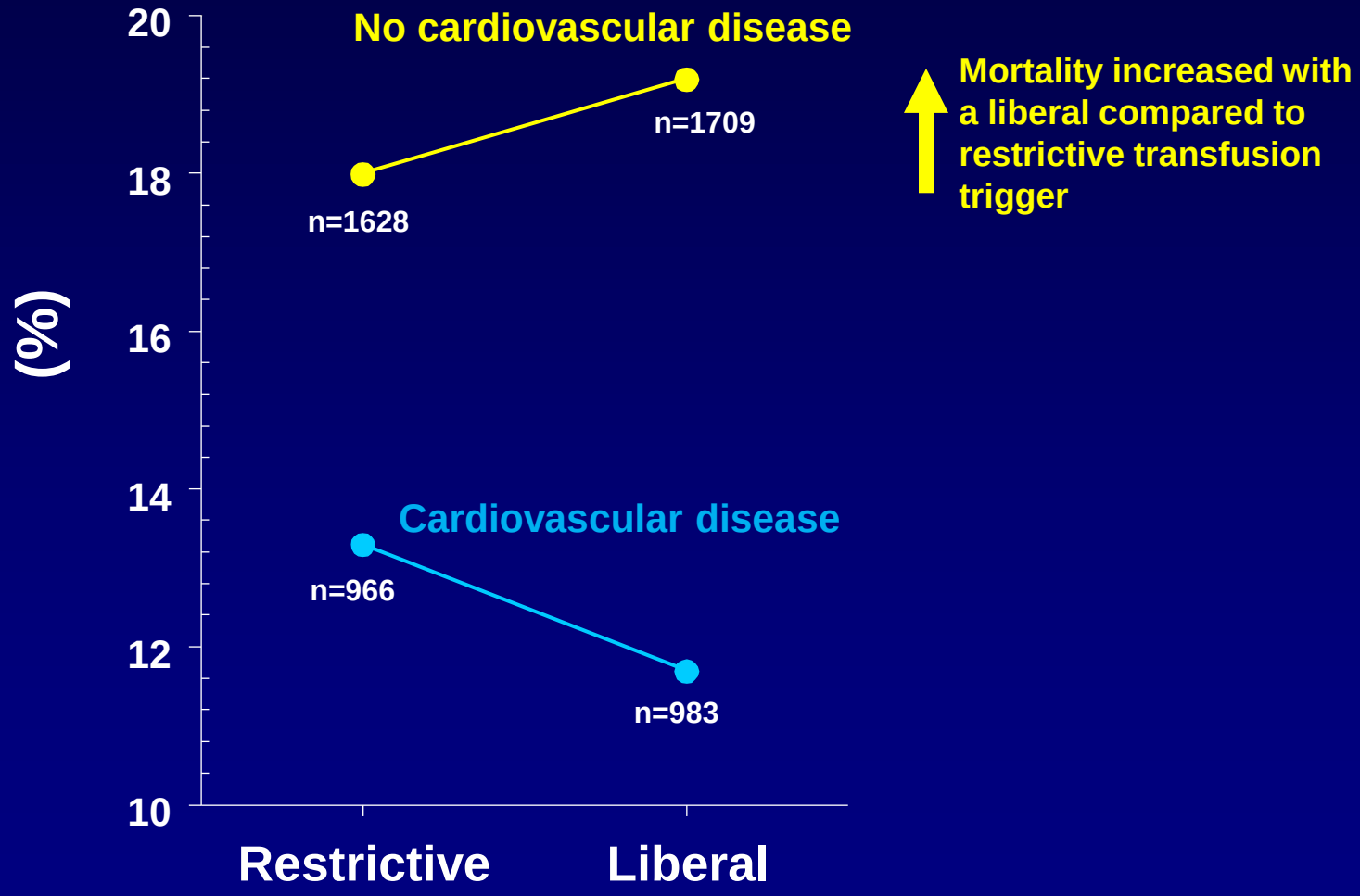

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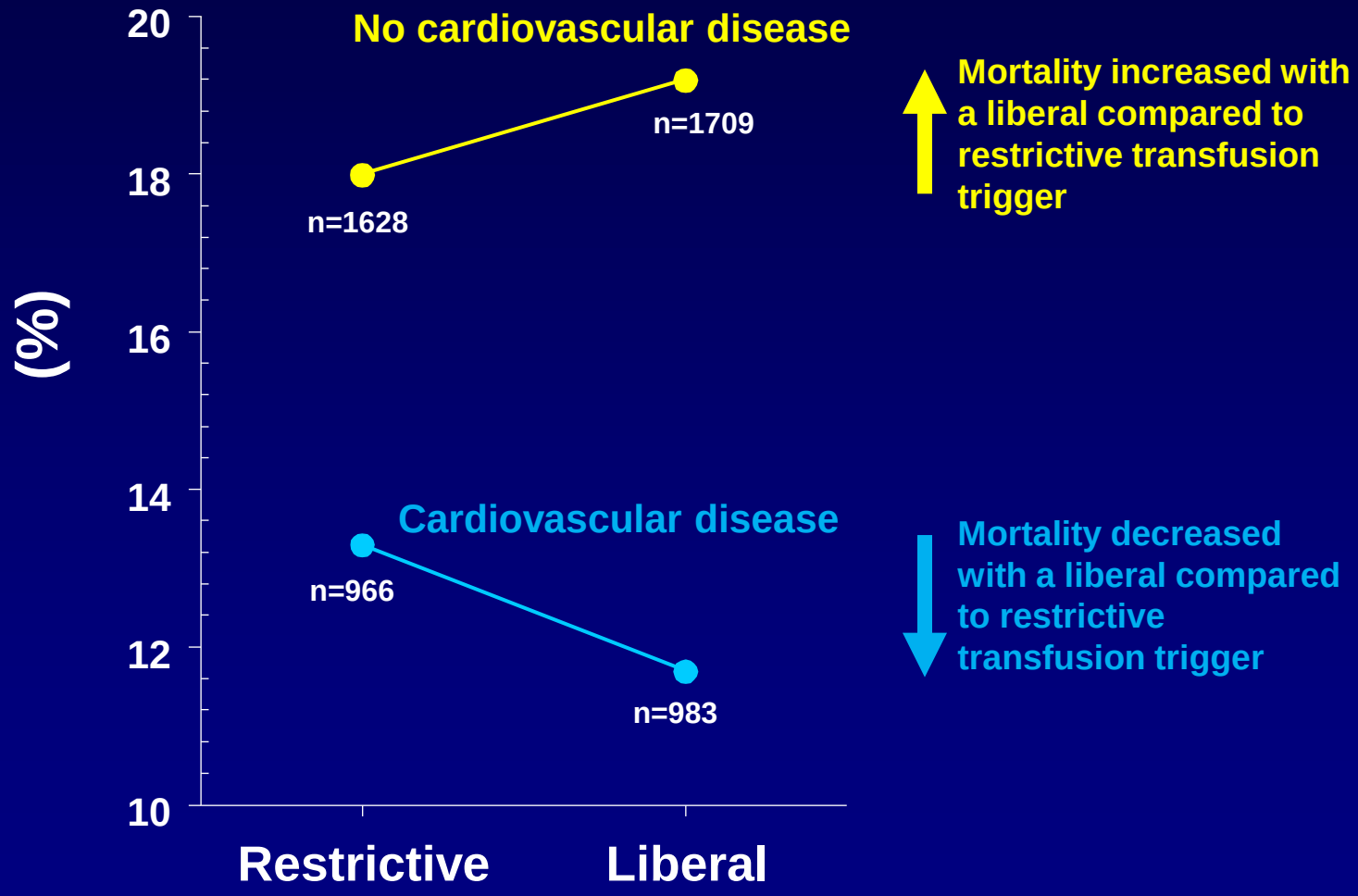

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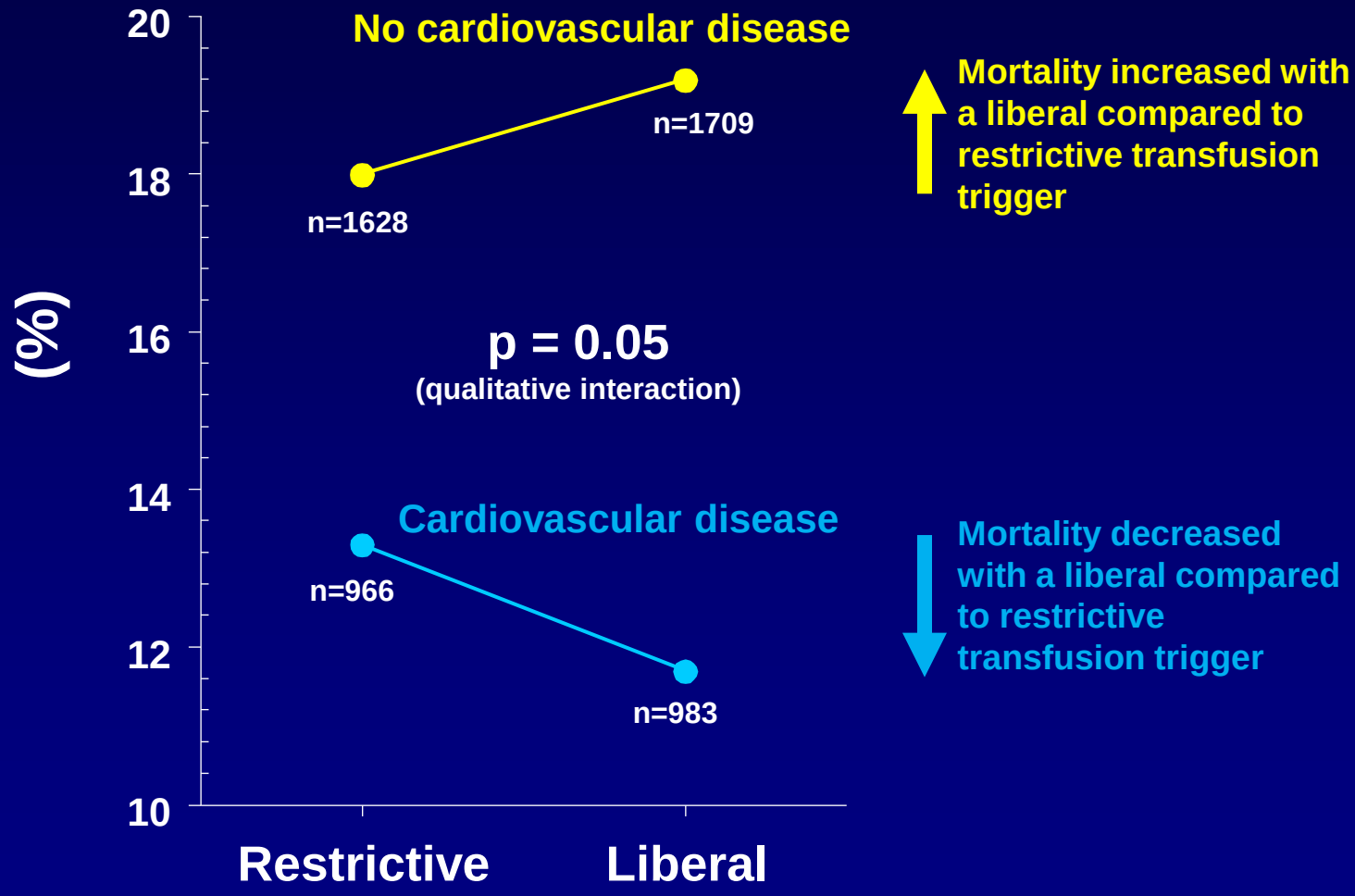

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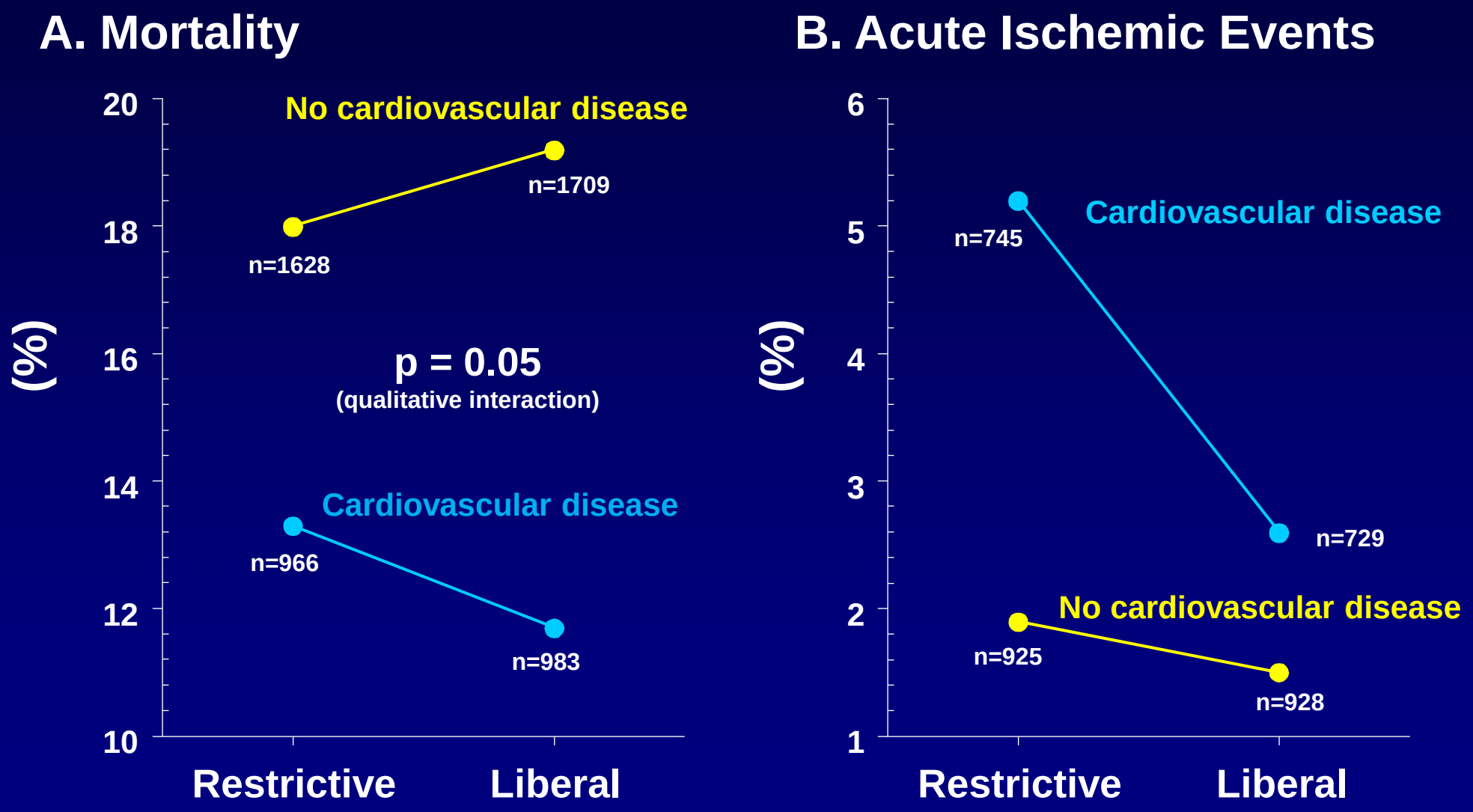

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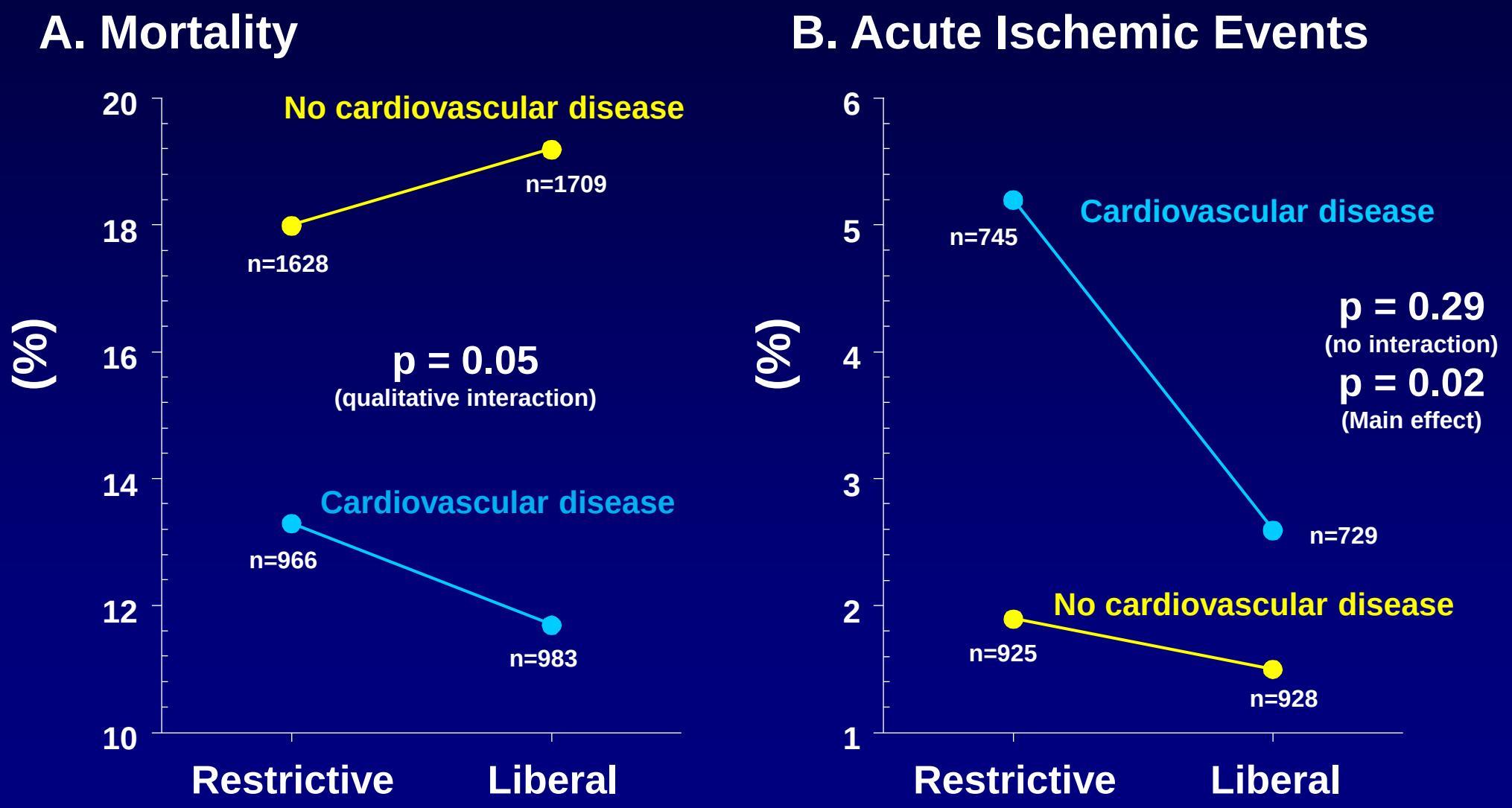

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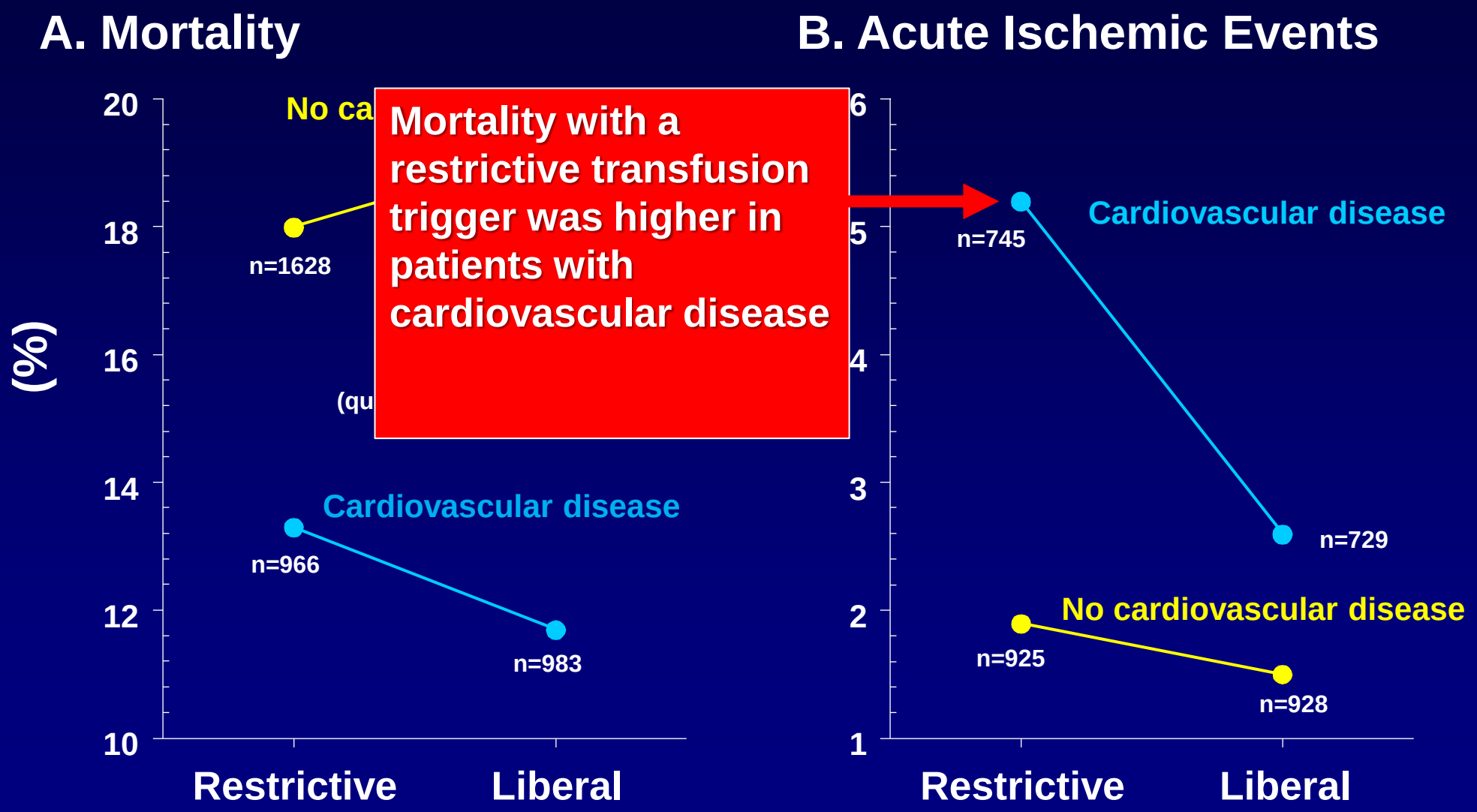

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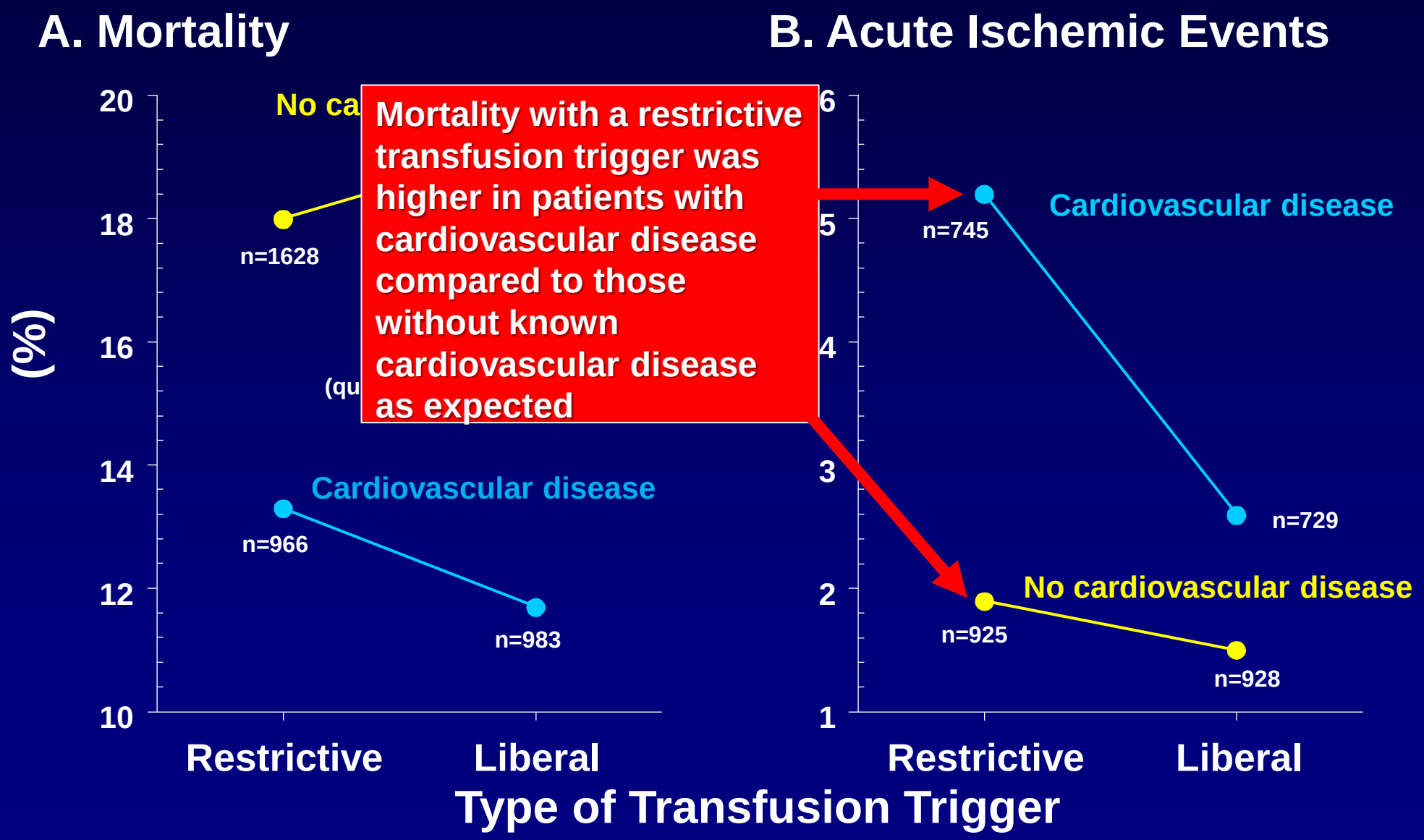

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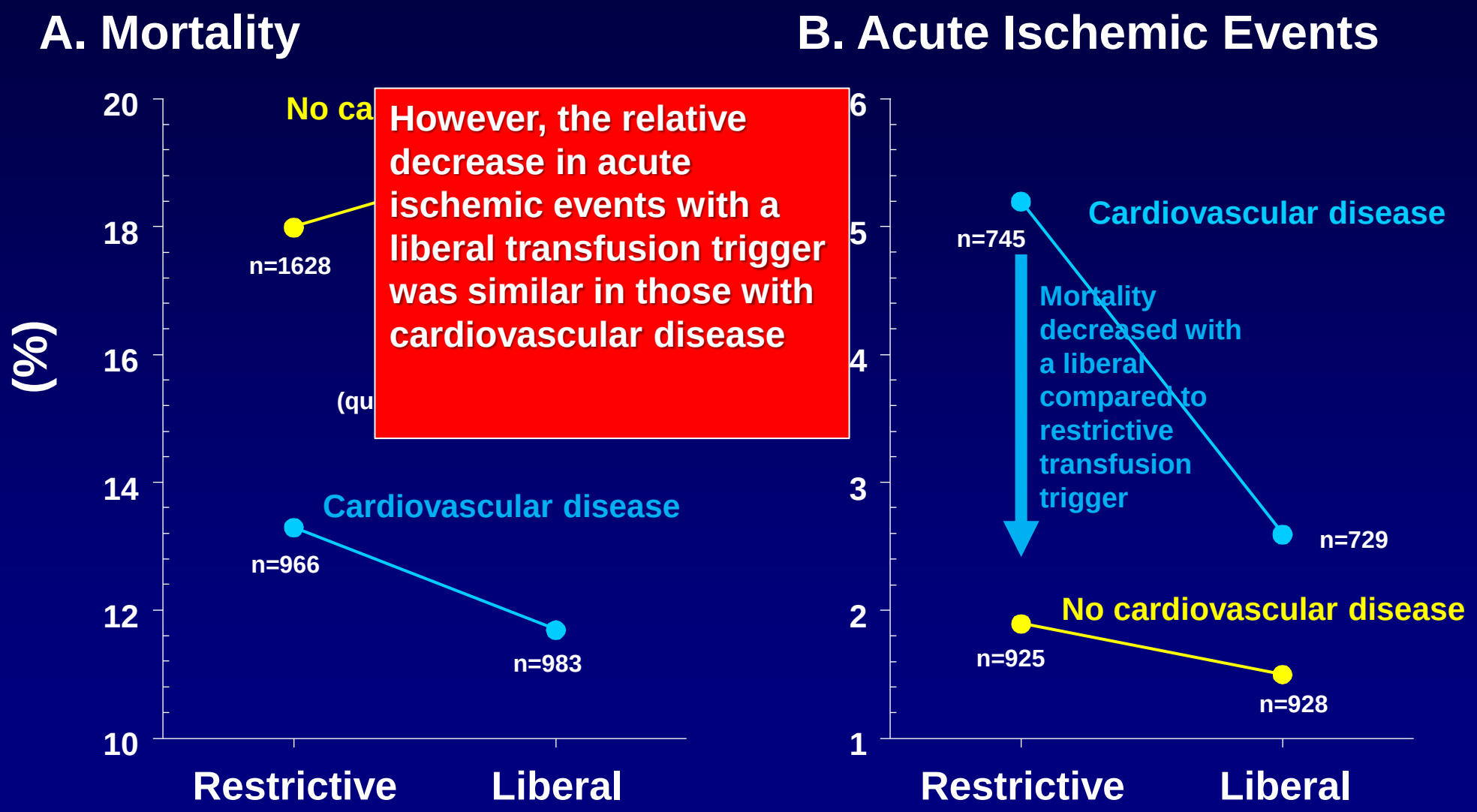

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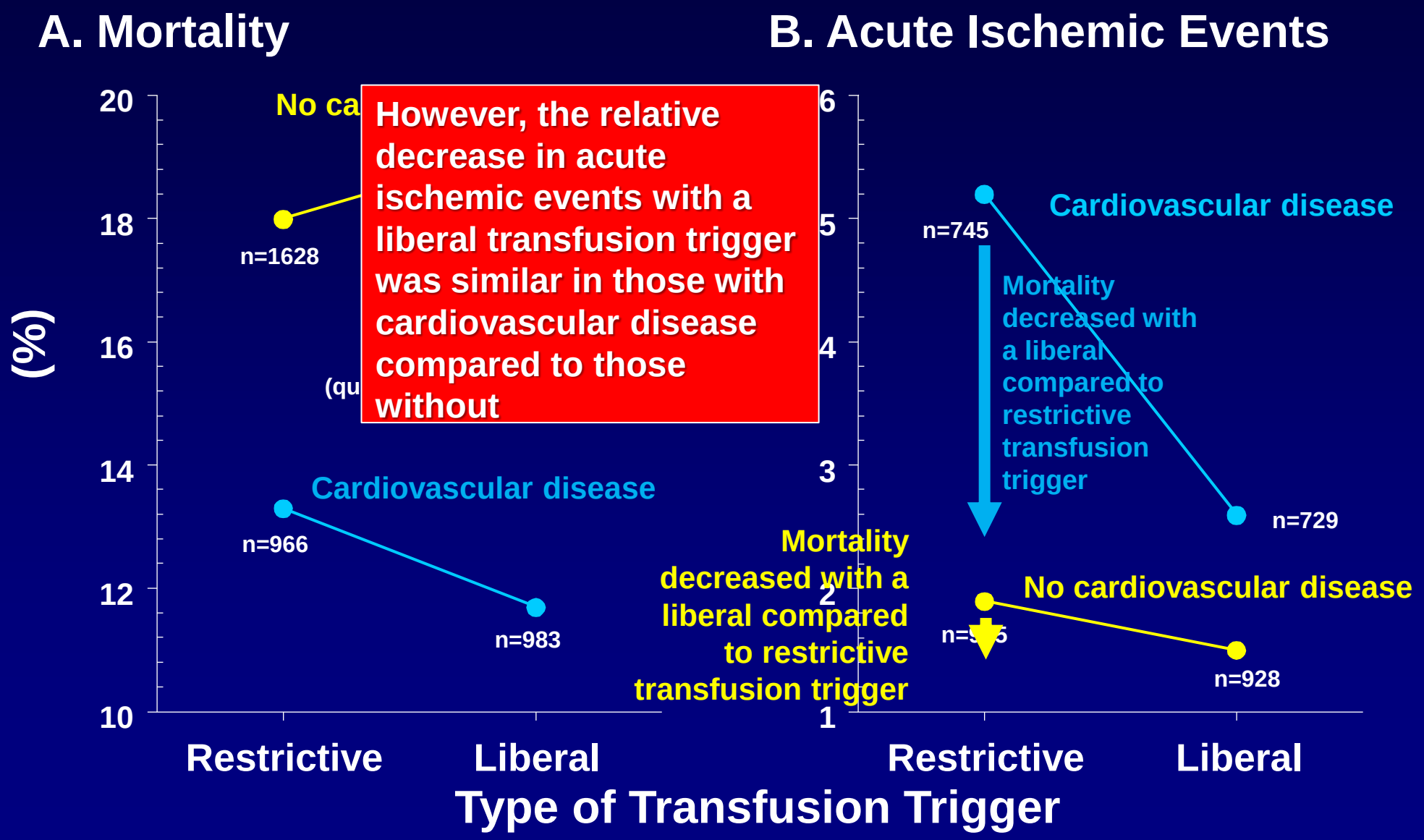

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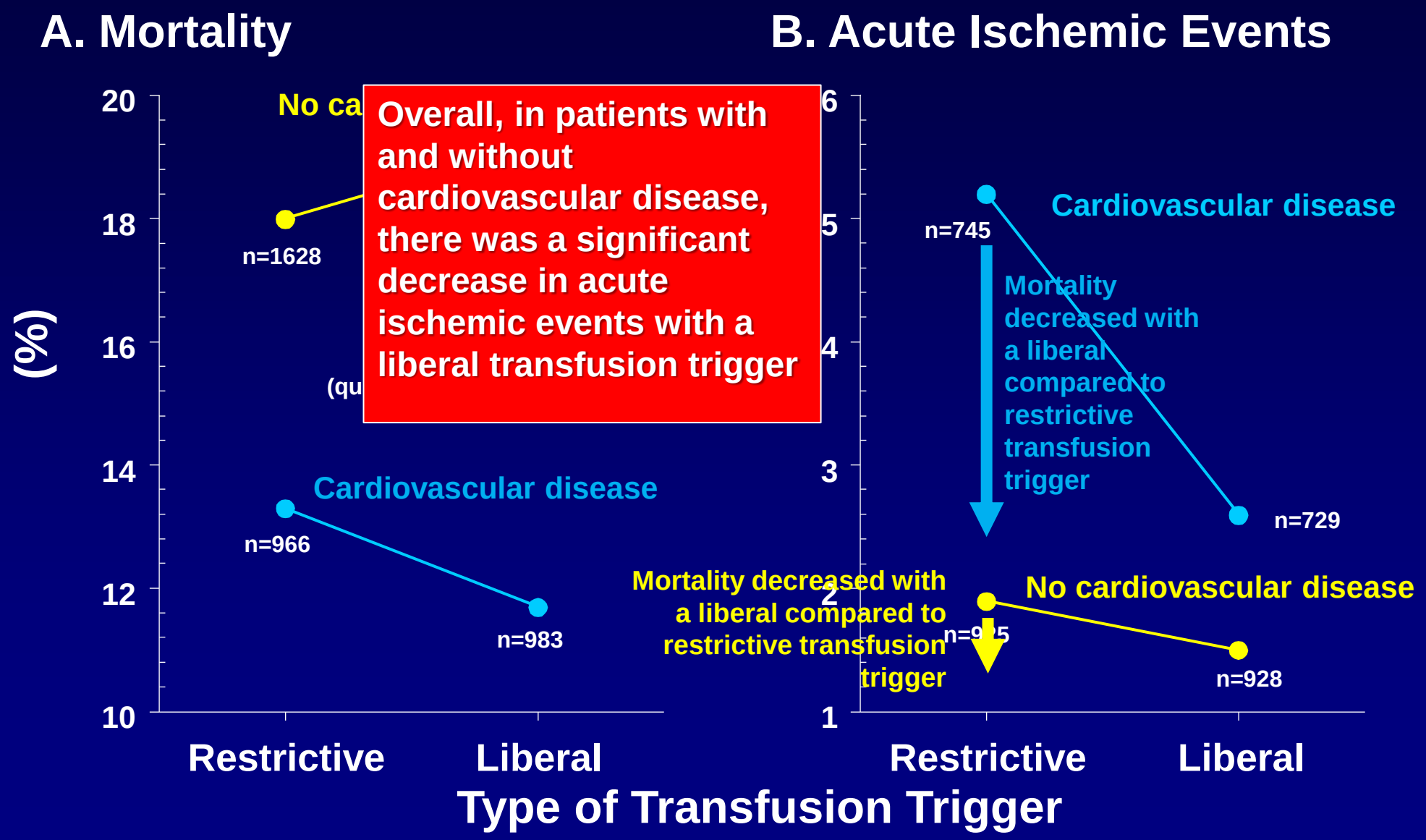

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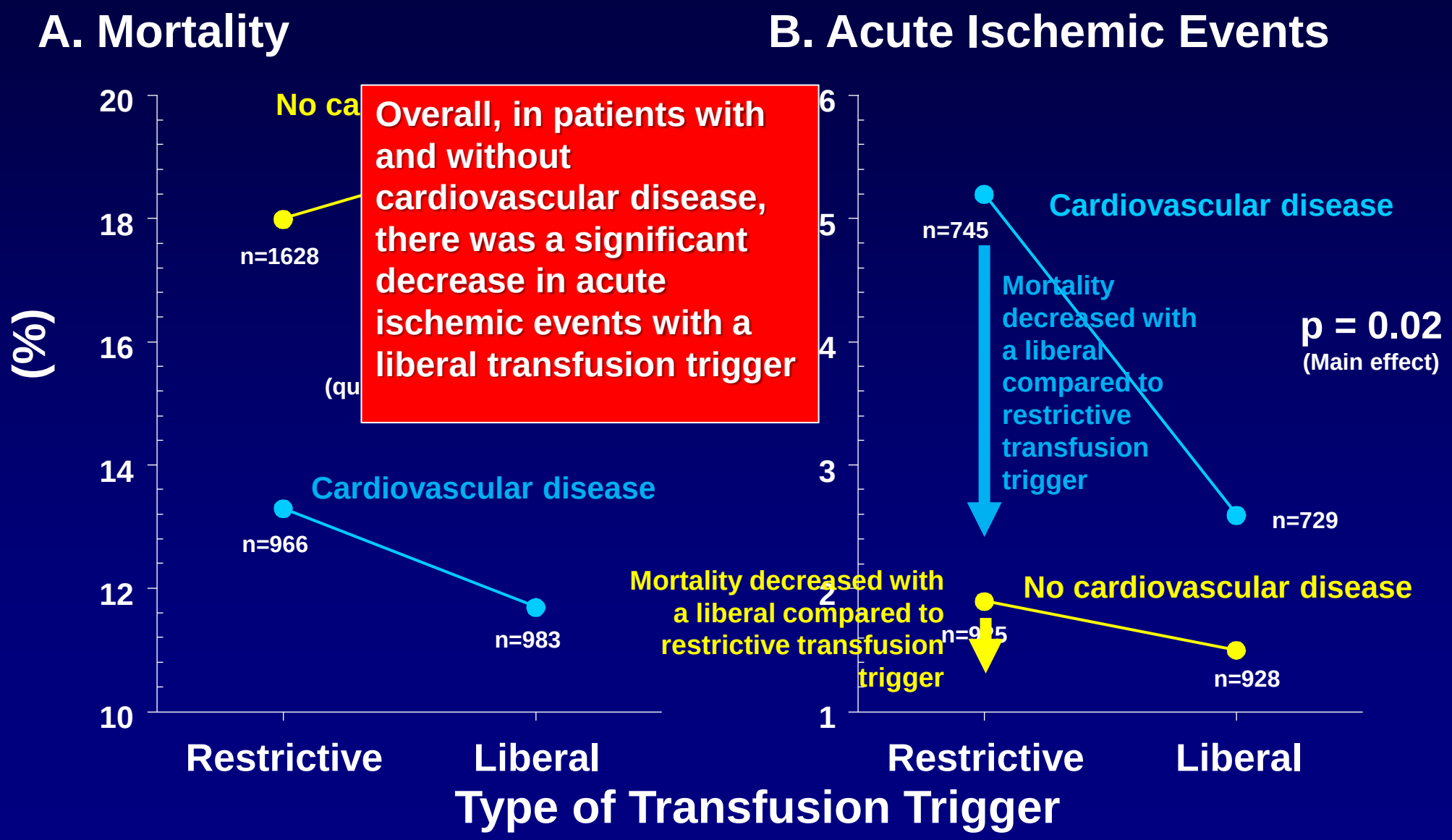

Summary: Transfusion Trials

- Trial design compared two fixed, subjective, extreme hemoglobin “triggers”
- Transfusion trials did not included a control group receiving usual titrated individualized care
- A “restrictive transfusion trigger” in patients with known CVD is associated with increased mortality and acute coronary events.
- Healthcare providers should use caution in applying restrictive transfusion guidelines

Moving Toward Precision Transfusion Trials

- Evidence-based medicine (RCTs) may mislead physicians to use treatments based: the “average patient” vs. “spectrum bias” – design is critical
- Study design should avoid misalignment problems and include appropriate controls
- Future RBC trials for patients with CVD will benefit designs in which fixed triggers and/or alternative titrated strategies are compared to usual, titrated care
- “Precision medicine” trials should take advantages of relevant genetic, physiologic, and clinical measures