



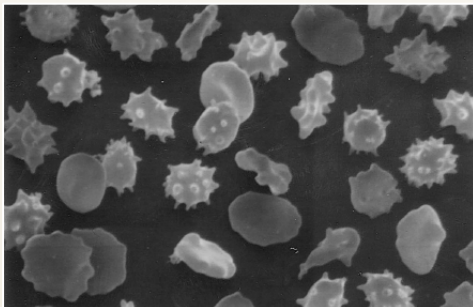
Red Cells – Is Fresh Best?

Nancy M Heddle MSc., FCSMLS(D)
Professor, Department of Medicine
McMaster University
Hamilton, Canada

Changes During Red Cell Storage

- Structural

- Clumping of RBCs
- Lose membrane phospholipid
- Biconcave → spherocyte / shistocyte

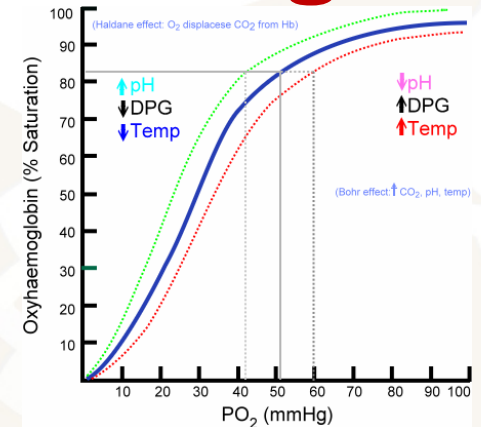


- Biochemical

- ATP depletion
- 2,3-DPG depletion
- NO depletion

- Inflammatory

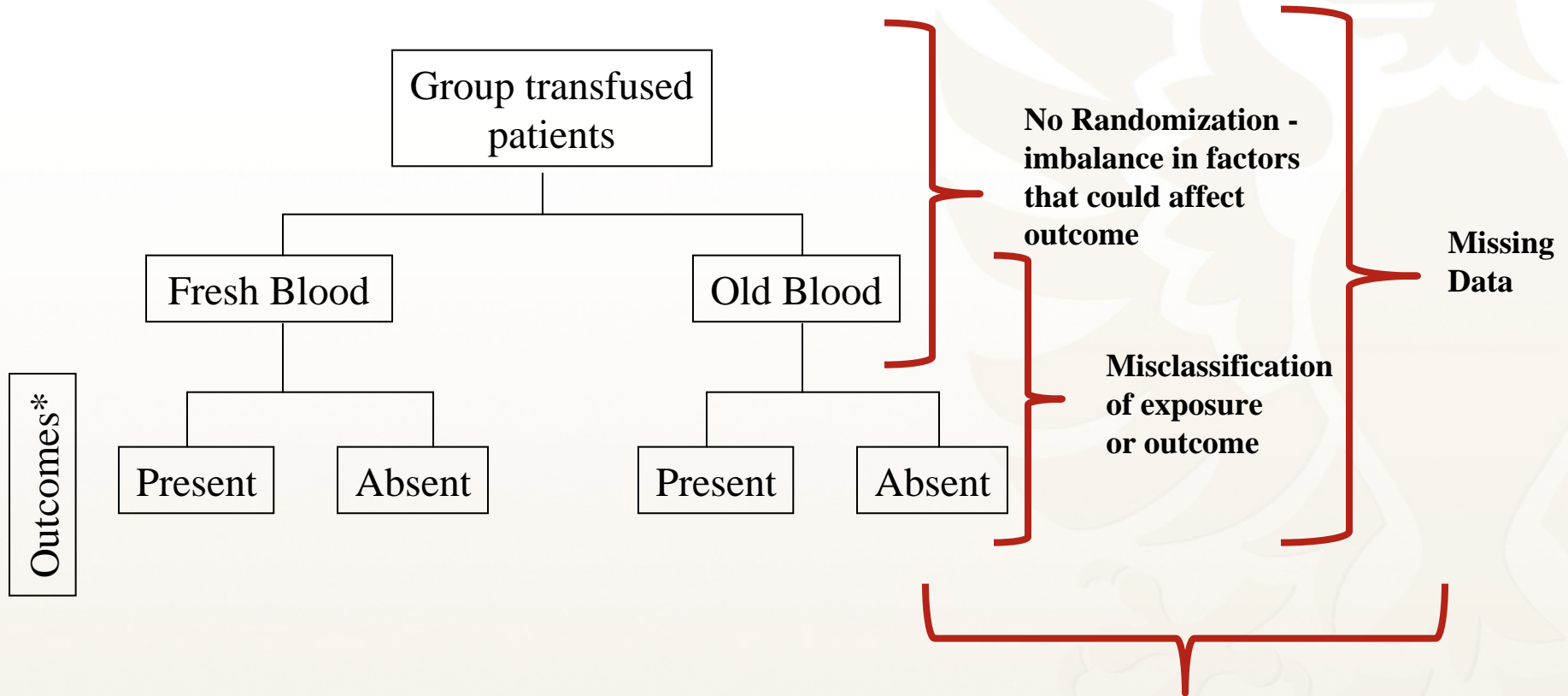
- ↑ Inflammatory mediators



Objectives

- Focus on clinical data
 - “*old blood is bad for you*” debate
- Retrospective data published
 - Pitfalls/limitations
 - MTRP – Australia Connection
 - Meta-analysis
- RCTs
 - Update on efficacy studies
 - Pragmatic RCT (June 2010)
 - Modeling
 - Waived Consent

Retrospective Cohort Studies



- *Outcomes:
- Morbidity
 - Mortality

BIAS

Studies Investigating Age of Blood

Study	# Pts	Outcome(s) Significant	Outcome(s) Not Significant
Basran 06	321	IN-HOS-Mortality, ICU-LOS, H-LOS	
Dessertaine 08	534		Mortality, Infection
Edna 98	336		Mortality
Gagic 04	181		ALI
Keller 02	86	H-LOS	ICU-LOS, Intubation
Kneyber 08	67		Mortality, ICU-LOS, Intubation
Koch 08	6002	Mortality, MODS, Infect, Intubation	
Leal-Noval 08	66		Mortality H-LOS, ICU-LOS
Leal-Noval 03	897		ICU-LOS, Intubation, MI, <i>Infection??</i>
Murrell 05	275	ICU-LOS	Mortality, % ICU-Stay,
Mynster 00	303	Infections	
Mynster 01	740		Mortality, Cancer recurrence
Offner 02	61	Infection	
Taylor 06	428		Mortality, HOS-LOS, ICU-LOS, Infect
Purdy 97	31	Mortality	
Spinella 09	202	Mortality, DVT	
Vamvakas 00	268		H-LOS, ICU-LOS, Intubation
Vamvakas 99	416	Pneumonia	Wound Infection,
Van de Watering 06	2732		Mortality, HOS-ICU, ICU-LOS
Vandromme 09	1615	Pneumonia	
Weinberg 08	1813	Mortality	
Weinberg 08	1624	Mortality, MOF, Infection	ARDS,
Yap 08	670		Mortality, ICU-LOS, Intub, Infect, Vent-Hrs
Zallen 99	63	MODS	
Martin 94	698	ICU-LOS	
NUMBER		14 Studies	15 Studies

 North America
 Europe & Australia

ORIGINAL ARTICLE

Duration of Red-Cell Storage and Complications after Cardiac Surgery

Colleen Gorman Koch, M.D., Liang Li, Ph.D., Daniel I. Sessler, M.D.,
Priscilla Figueroa, M.D., Gerald A. Hoeltge, M.D., Tomislav Mihaljevic, M.D.,
and Eugene H. Blackstone, M.D.

RESULTS

The median duration of storage was 11 days for newer blood and 20 days for older blood. Patients who were given older units had higher rates of in-hospital mortality (2.8% vs. 1.7%, $P=0.004$), intubation beyond 72 hours (9.7% vs. 5.6%, $P<0.001$), renal failure (2.7% vs. 1.6%, $P=0.003$), and sepsis or septicemia (4.0% vs. 2.8%, $P=0.01$). A composite of complications was more common in patients given older blood (25.9% vs. 22.4%, $P=0.001$). Similarly, older blood was associated with an increase in the risk-adjusted rate of the composite outcome ($P=0.03$). At 1 year, mortality was significantly less in patients given newer blood (7.4% vs. 11.0%, $P<0.001$).

Comparison of very different patient groups gives different results !

apples

oranges

Data un-adjusted for differences in patient groups!

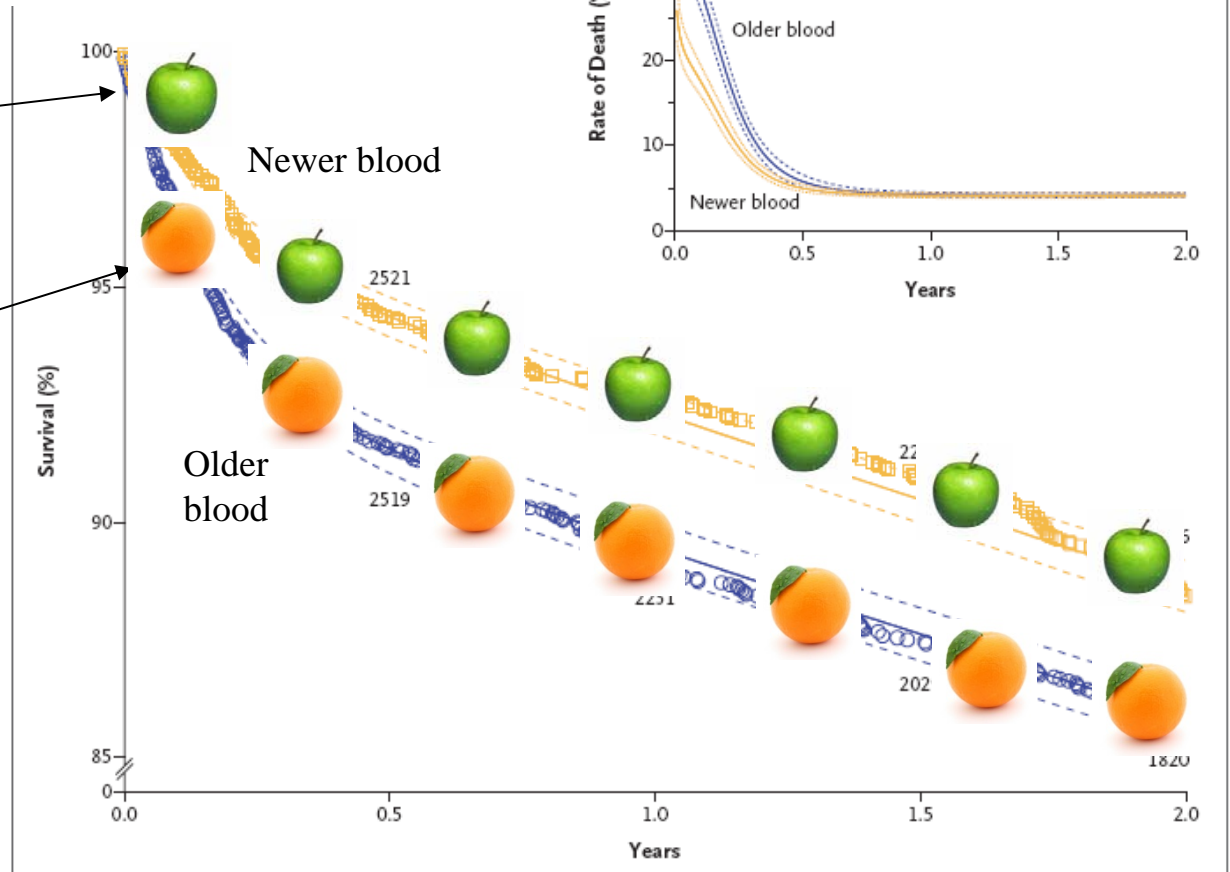


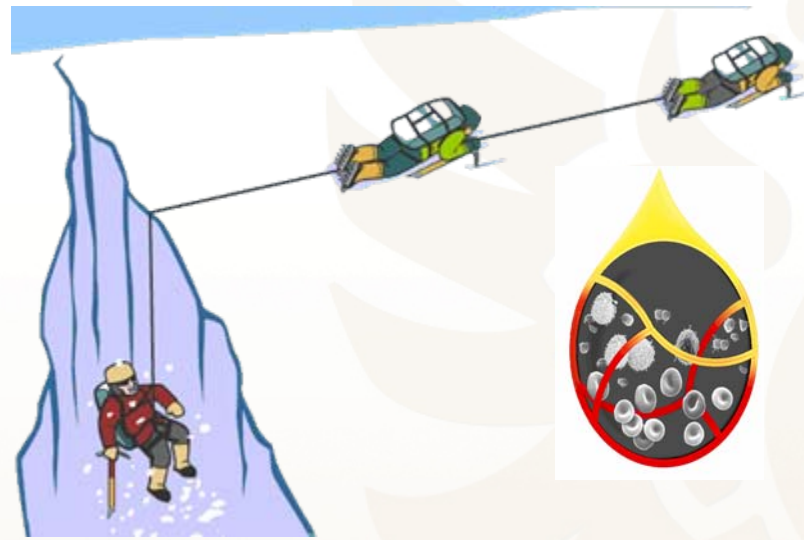
Figure 3. Kaplan–Meier Estimates of Survival and Death.

The curves show data from 2872 patients who were given exclusively newer blood (stored for 14 days or less) and

In this un-adjusted comparison,

determined by the Kaplan–Meier method, is superimposed on the parametric survival function estimator. In this un-adjusted comparison, the percentage of patients receiving older blood who survived was lower than the percentage of those receiving newer blood who survived, especially during the initial follow-up period.

Pitfalls in RBC Storage Research that Lead to Bias



Pitfall #1: Total # of red cell units differ between comparison groups

- Non transfused controls
- Oldest RBC used to define storage age cohort
- Number of RBC transfused stored > “x” days
- Comparisons based on all RBC transfused during hospitalisation

Pitfall # 2: Failure to control for ABO blood groups

Pitfall # 3: Storage time dichotomised for analyses

Pitfall # 4: RBC issue policy

Adjustments to Minimize Bias

Pitfall	Bias	Effect on Conclusion	Correction
Multivariate analyses: Colinearity error	“Effect” is based on exclusion of known risk factor	Overestimate adverse outcome	Keep known risk factor in model
Stratification: #RBC-strata defined too broad	Bias by number of RBCs remains within strata	Overestimate adverse outcome	Create more smaller strata
Matched controls: Missing data	Excluding individual patients disrupts created balance	Biased outcome in unknown direction	Exclude patient/control combinations
Long running studies	Shift in transfusion triggers, and progress in medicine	Overestimate adverse outcome (more RBC in early era)	Adjust for year of transfusion

MTRPs Contribution: The Australia Connection!

Eikelboom J et al., AHJ, May, 2010



- Retrospective cohort study
- REB approval
- Data collection from the TRUST database
 - Demographic and medical data on all hospitalized patients (45 variables)
 - Transfusion data on transfused patients (80 variables)
 - Selected laboratory test results
 - Data from April 2002 to Sept 2006

Inclusion Criteria

- Admitted to and discharged from one of the acute care hospitals in Hamilton (April 2002 – Sept 2006)
- Most responsible diagnosis – Cardiovascular disease (ICD10 codes: I-20 to I-25; I-63 to I-67; I-70-I-74)
- Tx at least 1 RCC
- Pts with multiple admissions – only the 1st included

Primary Outcome

- In-hospital mortality

Summary of Cumulative Exposure to Old Blood

Running average
of age of blood
transfused

Running maximum age
of blood transfused

Each was analysed:

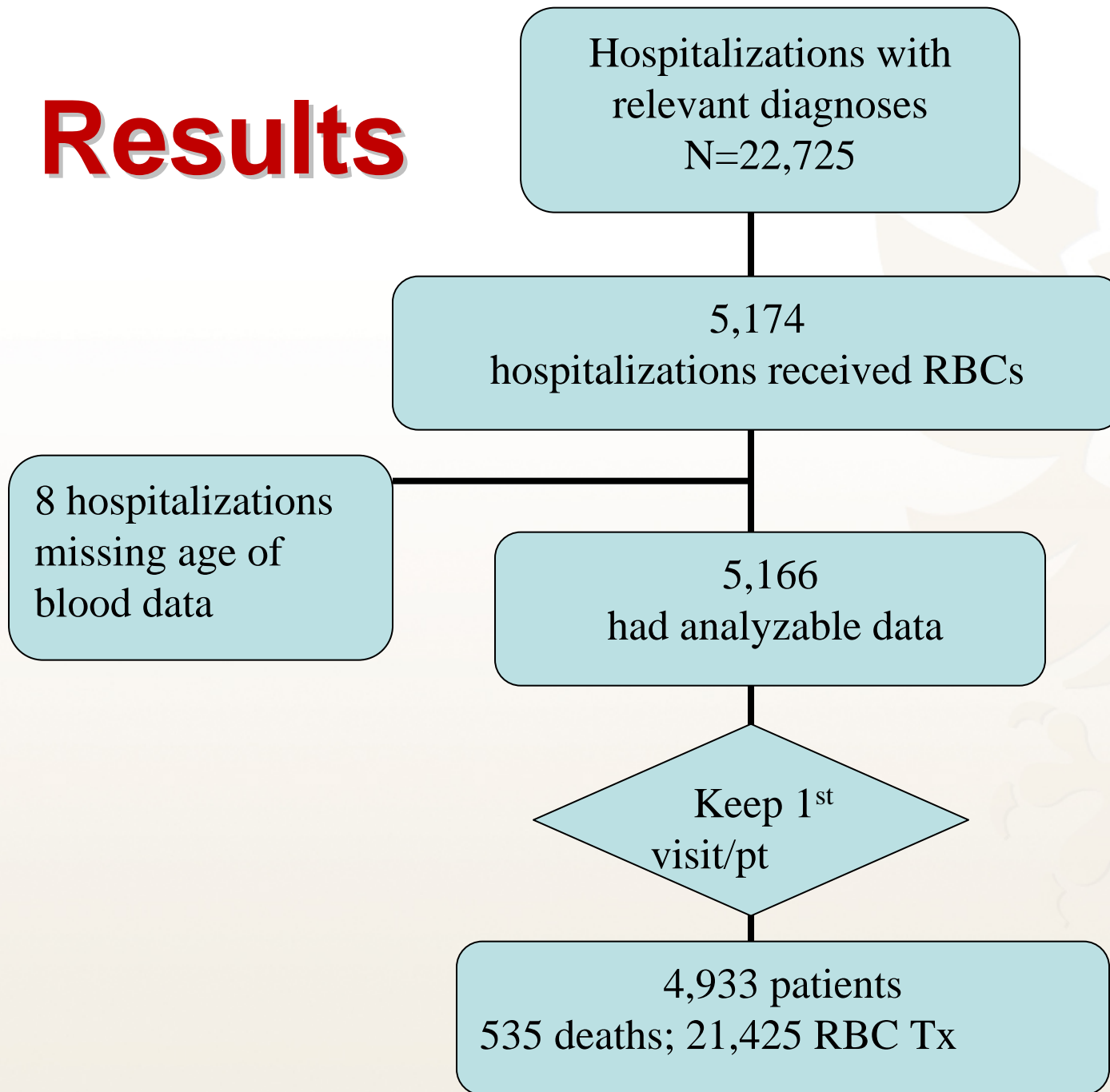
- As a continuous variable
- Categorized using quartiles as cut points
- Categorized age in 10 day intervals
- Categorized by weeks (≤ 2 weeks; 2-3 weeks; 3-4 weeks; 4-5 weeks and 5-6 weeks)

Possible to investigate dose response relationship

Statistical Analysis

- Cox regression analysis
- Time dependent stratification (controlled for confounders)
 - Defined by the cumulative number of transfusions over time
 - Mortality rate for 1 transfusions
 - Mortality rate for 2 transfusion ...etc
 - Followed till death or discharge
- Baseline explanatory variables
 - Demographic covariates (age, sex)
 - Clinical covariates (cardiovascular diagnosis, in hospital procedures & transfusion related data)

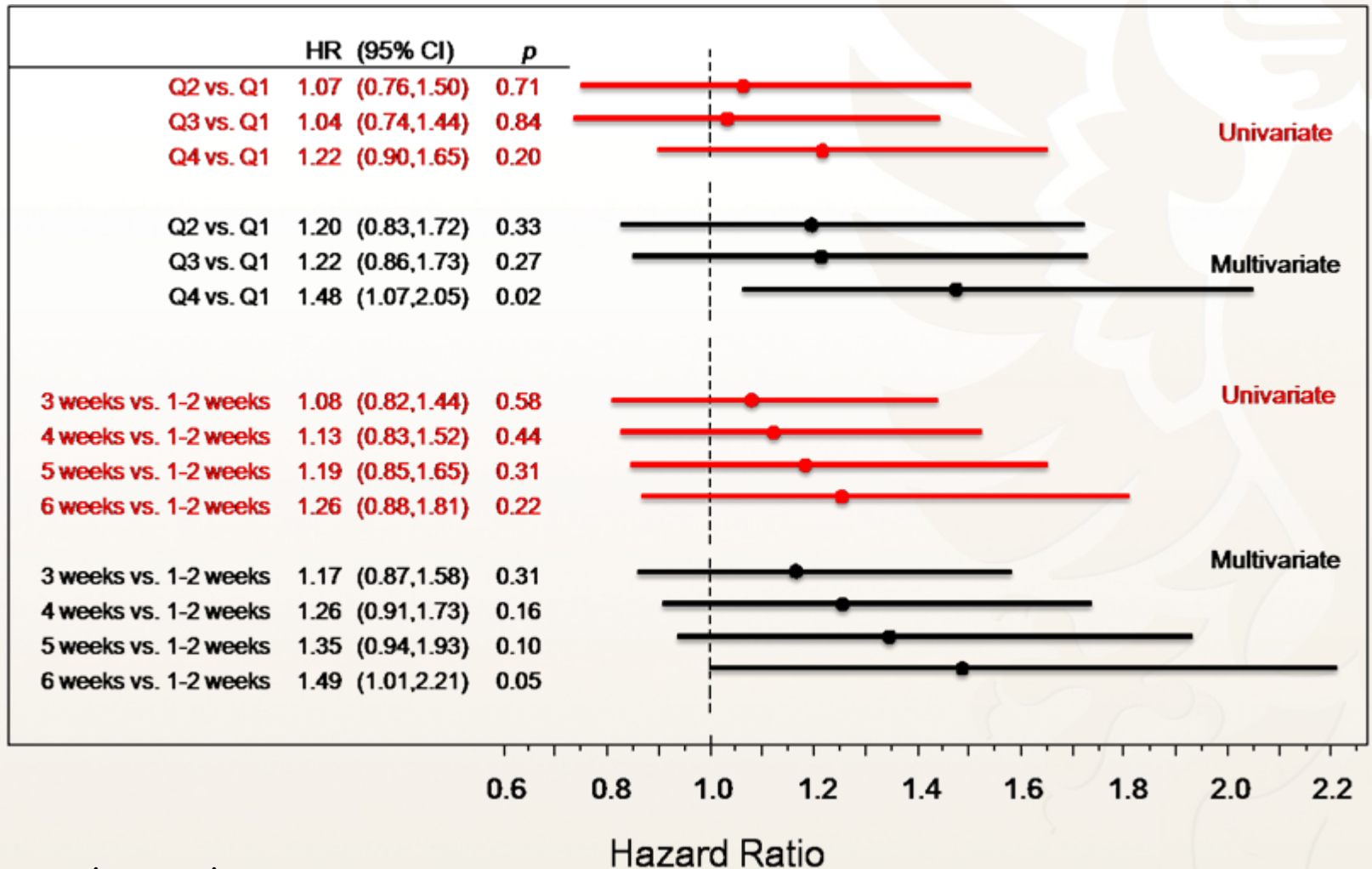
Results



Baseline Characteristics

Characteristic	Number (%) or Median (IQR)
Female, n (%)	1,942 (39.4)
Age, Days; median IQR)	72 (63, 78)
Diabetes n (%)	1,358 (27.5)
Heart Failure or Cardiomyopathy n (%)	835 (16.9)
Major Cardiovascular Diagnosis	
Ischemic heart disease	4,188 (84.9)
Cerebrovascular disease	378 (7.7)
Peripheral artery disease	1,079 (21.9)
Other vascular disease	21 (0.4)
Cancer n (%)	275 (5.6)
Intervention n (%)	4,160 (84.3)
Baseline hemoglobin, g/L; median (IQR)	115 (100, 130)
Baseline creatinine, μ mol/L; median (IQR)	91 (72, 119)
Duration of hospital stay, days; median (IQR)	11 (8, 19)
Median age Tx blood (IQR) [days]	17 (13, 22)

Results- Regression Models



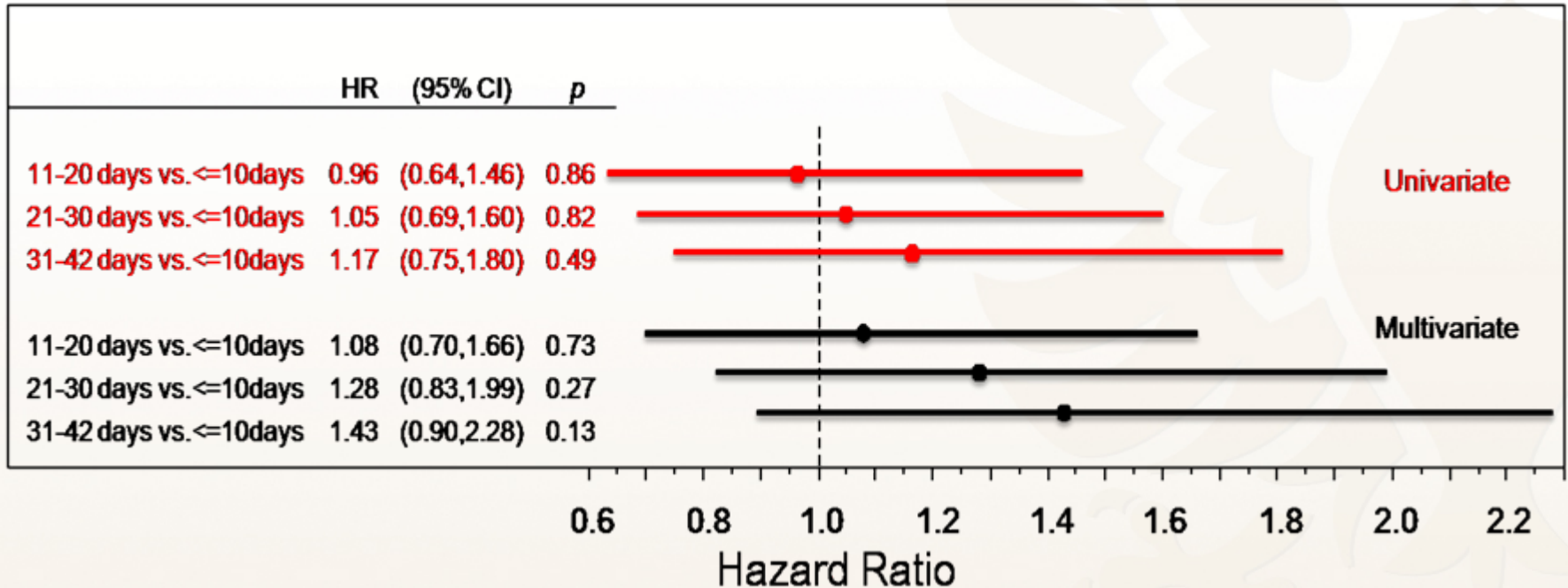
Age: running maximum

Stratified by: number of unit transfused;

Adjusted for: demographics, clinical characteristics, interventions, ABO group/compatibility

Results – Regression Model

10 day intervals



Age: running maximum age

Stratified by: number of unit transfused;

Adjusted for: demographics, clinical characteristics, interventions, ABO group/compatibility

Conclusions

- The results suggest a continuous and graded association between increasing duration of red cell storage and risk of in-hospital mortality in patients with cardiovascular disease.
- Limitations of an observational study design are acknowledged; however, attempts were made to minimize bias from confounders by:
 - Stratification on cumulative # of RBC transfusions
 - Adjustment for fixed and time variant confounders
 - Sensitivity analyses (different models)

**EMPHASIZES THE NEED FOR
PROSPECTIVE RCTS TO
RESOLVE THE AGE OF
BLOOD ISSUE**

Meta-analysis – Clinical Studies (age of blood & harm)

Vamvakas, Transfusion 2010

Inclusion Criteria:

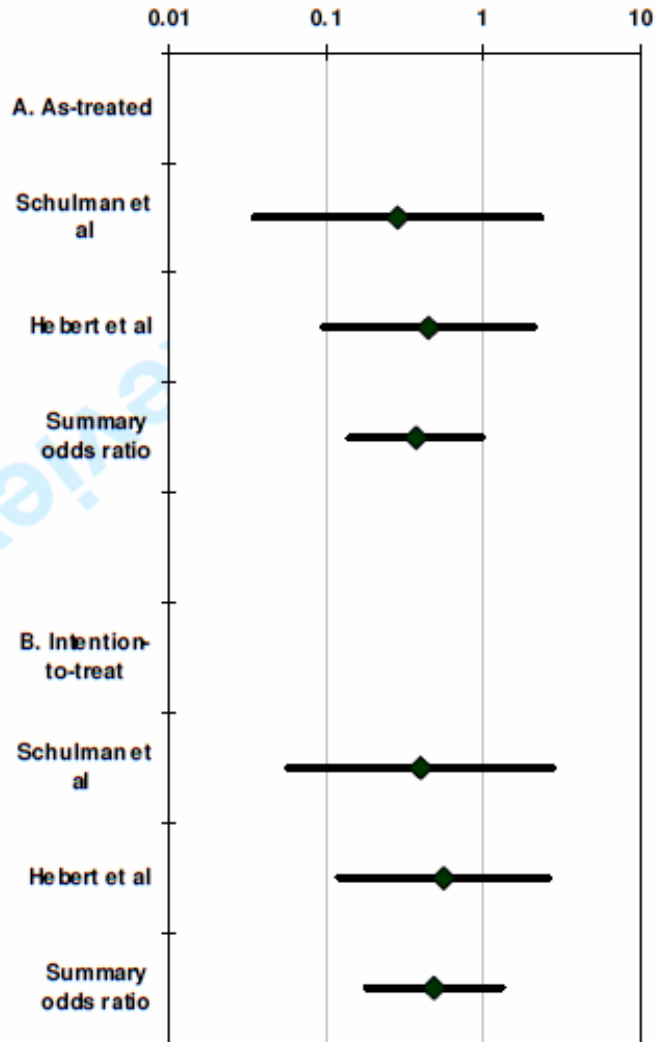
- Reported on 1 of the following clinical outcomes
 - mortality, organ failure, infection, length of mechanical ventilation, and/or LOS
- Defined the exposure (RBC storage) as:
 - mean + SD storage of all transfused RBCs,
 - oldest (or oldest and second oldest) transfused RBC unit(s),
 - RBCs stored for more than a specified number of days.

Observational studies:

- reported *adjusted* findings on at least one of the outcomes and adequacy of adjustment could be assessed.

Results - RCTs

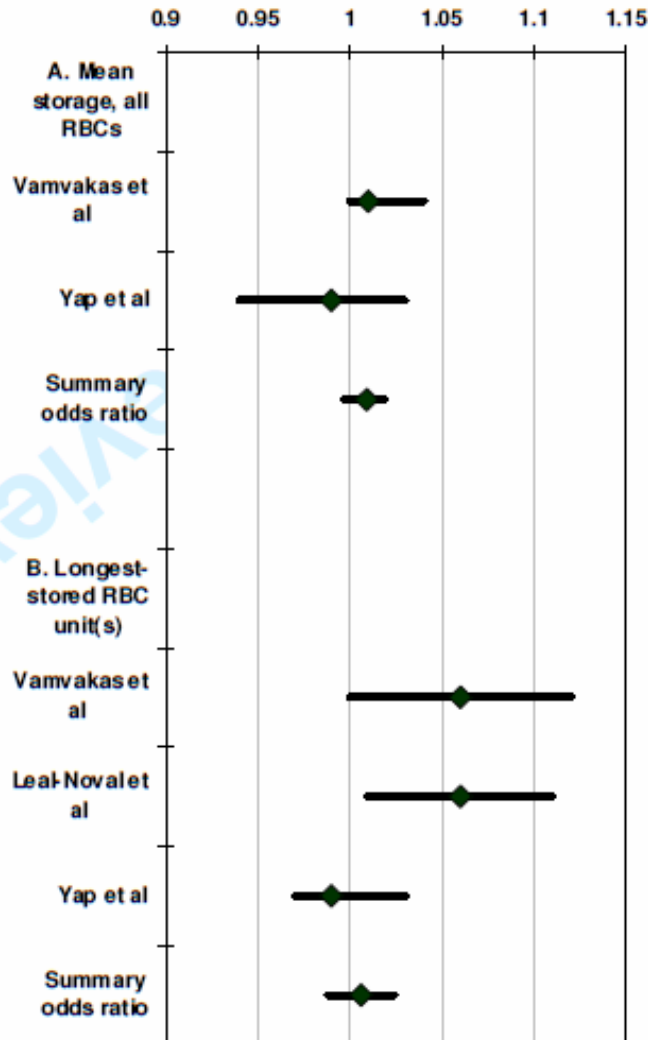
In-hospital mortality



- 6 RCTS identified – 2 eligible
- As treated: reported by authors
- ITT: calculated by author
- Summary OR:
 - As treated: Showed a significant reduction in mortality with old blood
 - OR 0.38; 95% CI, 0.14-0.99; $p < 0.05$)
 - ITT – not significant

Results – Observational Studies

In-hospital mortality



- Cardiac surgery studies
- Summary odds ratio not significant
- CONCLUSION
 - Insufficient evidence to support the hypothesis?
 - Questions whether it is even ethical to do a RCT

4 RCTs – Age of Blood

Type of Study	Country	Acronym	Title
Efficacy	Canada	ARIPI	Age of Red Blood Cells in Premature Infants (Recruiting)
Efficacy	Canada	ABLE	Age of Blood Evaluation (Recruiting)
Efficacy	US	RECESS	Red Cell Storage Duration Study (Temporarily Suspended)
Pragmatic	Canada	INFORM	Informing Fresh versus Old Red Cell Management (Starting June 2010)

ABLE, ARIPI and RECESS

Characteristics	ABLE	ARIPI (Premature Infants)	RECESS
Status	Recruiting	Recruiting	Suspended
Hypothesis	Superiority N=2510	Superiority N=450	Superiority N=1434
Population	Critical Care	Neonates (up to 37 weeks)	Cardiac Surgery
Intervention	Fresh: Blood < 8 days Standard: As per hospital policy	Fresh: Blood < 7 days Standard: As per hospital policy	Fresh: ≤ 10 days Standard: ≥21 days
Outcome	90 day all cause mortality	Composite: NEC; Intraventricular hemorrhage; Bronchopulmonary dysplasia; ROP (30 & 90 days); Mortality	Change in composite multiple organ dysfunction score [MODS] (post-op day 7, discharge, death)

Why was RECESS Suspended?

- Concerns by Alliance for Human Research Protection
 - Ethics & Safety
- Ethical
 - Design fails to compare best current clinical practice
 - Hospitals requesting *oldest blood* from supplier
 - Consent document fails to inform subjects of the endpoint - death

RECESS Update

- OHRP* (Director of Compliance and Oversight)
- Changes:
 - Sites not allowed to maintain a special inventory of old blood or specifically order older blood
 - More frequent monitoring and analysis of adverse events
 - Consent documents revised to disclose risks
 - Increase in sample size
 - Change to inclusion criteria

*Office for Human Research Protections

What will we learn from these studies?

We “will” learn:

- If risk of old blood is increased in selective high risk patients

We will not learn:

- If findings are generalizable to other patients
- The age threshold where risk (lack of product availability) versus benefit (less morbidity/mortality) is acceptable

Will a Pragmatic Study fill this Gap?



Efficacy	Pragmatic
<p data-bbox="146 878 488 939">Explanatory</p> <p data-bbox="146 968 948 1100">Is the intervention beneficial in an ideal situation?</p>	<p data-bbox="991 878 1373 939">Effectiveness</p> <p data-bbox="991 968 1750 1100">Measure degree of benefit in real clinical practice</p> <p data-bbox="991 1133 1676 1195">Does it work in <i>real life</i>?</p>

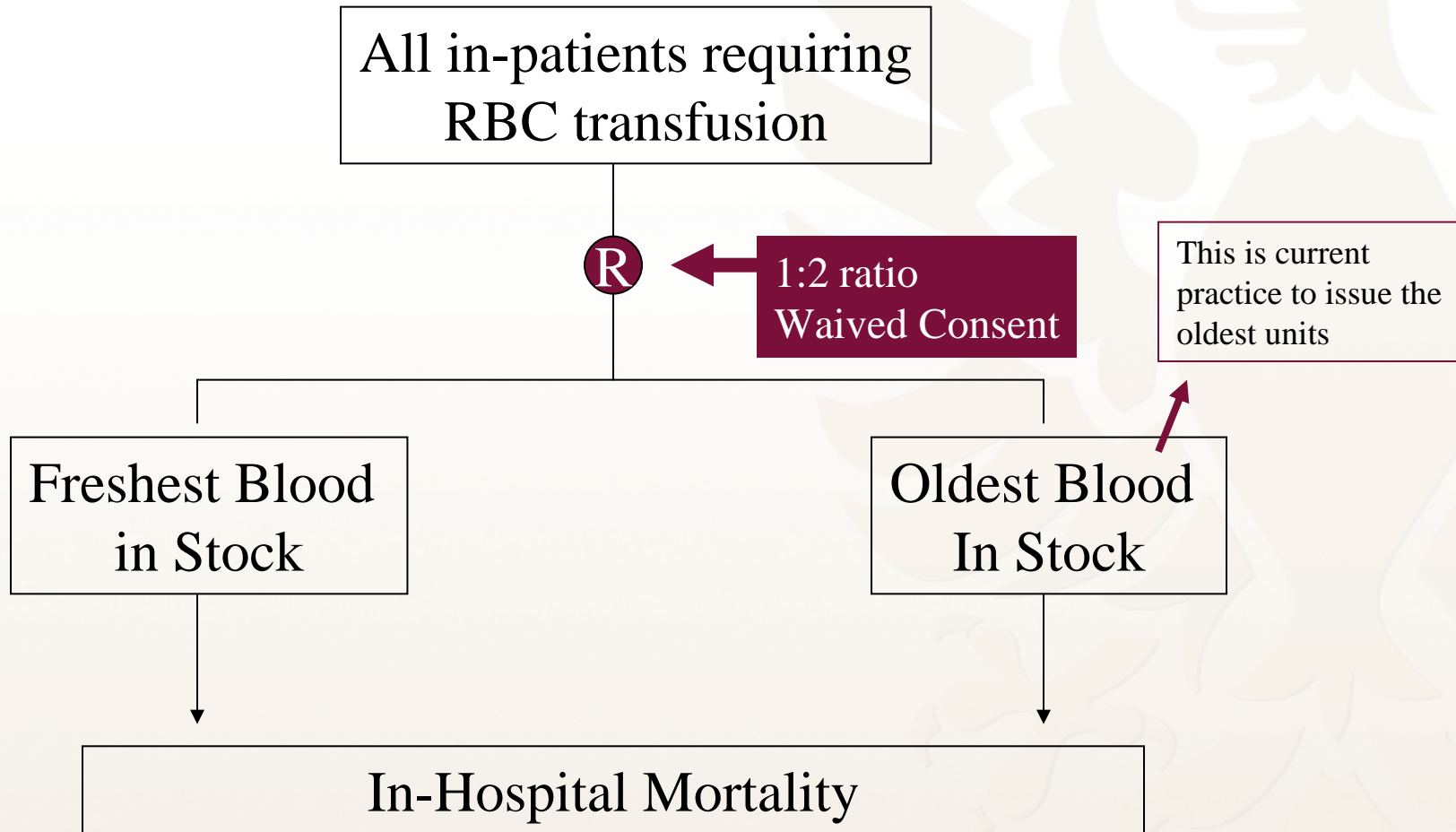
Pragmatic Research Question

PICOT

The word 'PICOT' is written in red, bold, uppercase letters. Four red arrows originate from the letters: one from 'P' points to 'patients', one from 'I' points to 'in-hospital mortality', one from 'C' points to 'compared to patients', and one from 'O' points to 'oldest available blood in stock'.

- Do hospitalized patients who require red cell transfusion have a lower frequency of in-hospital mortality if they are transfused with the freshest available blood in the hospital stock compared to patients transfused with the oldest available blood in stock during their hospital stay?
- Different from current studies:
 - Pragmatic rather than efficacy

Proposed Study (Pragmatic)



Minimal Data Collection: Most data to be collected from LIS and electronic medical record

Challenges/Concerns

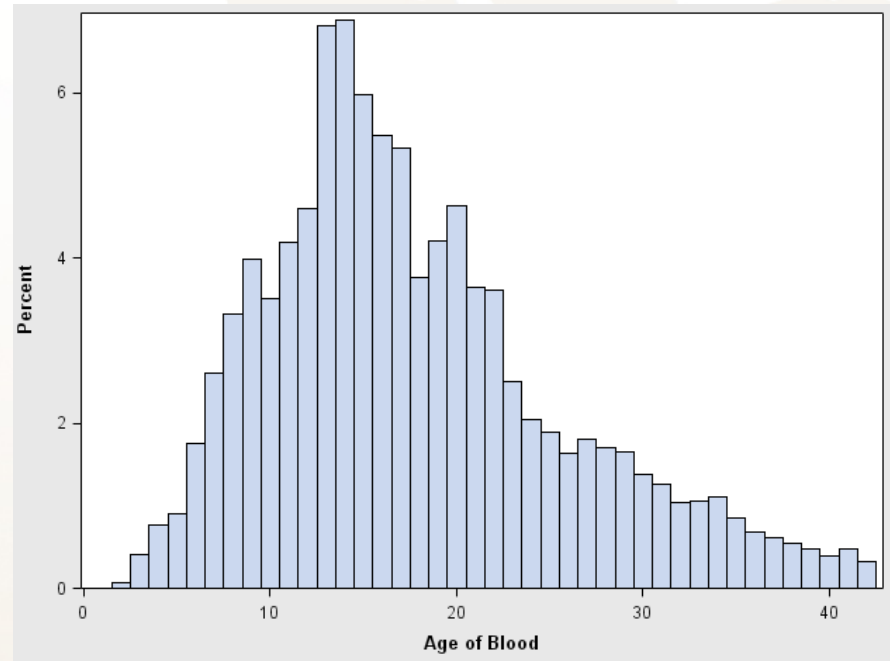
- Will we change the age of stock blood by doing the study?
- Will we achieve good separation of fresh and old blood?
- Will we waste a lot of blood through outdating?
- Waived Consent

Modeling – Age of Blood

- Real inventory information;
- Actual patient and blood demand information: patient ABO/RH, # RBC transfused and date/time of transfusion;
- Simulated randomization (fresh vs. standard=1:2). A patient is randomly assigned to a group before their first transfusion and keeps assignment.
- Ordering stock replacement was also simulated: delivery at 12:00 am every day

Would some patients be deprived of “standard care”?

- Standard care is to issue any blood up to 42 days old
- Typically, the oldest blood is issued first
- Median age of blood stocked is 16 days (range 2 to 42)
IQR 12, 22)

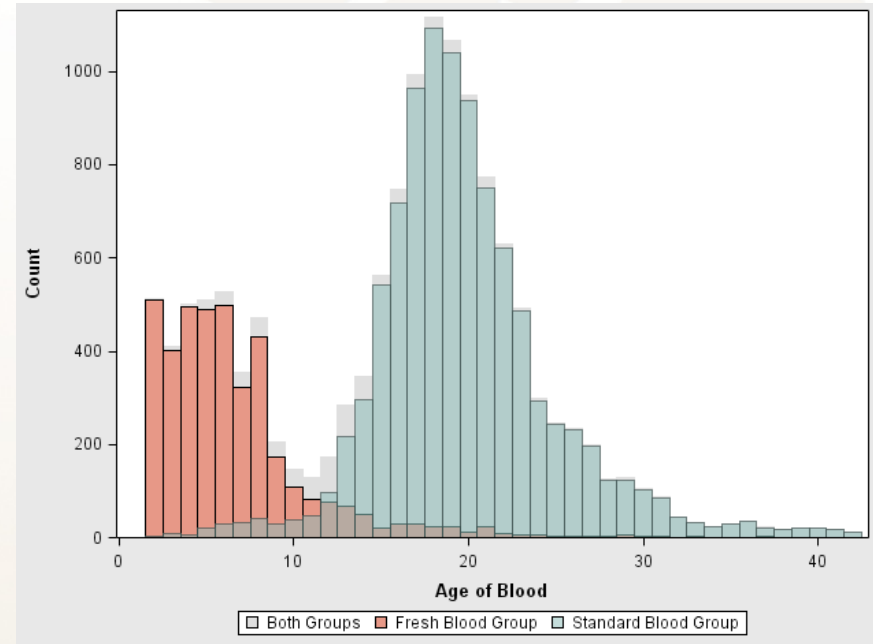


Based on 2 years of HHS data
(McMaster site)

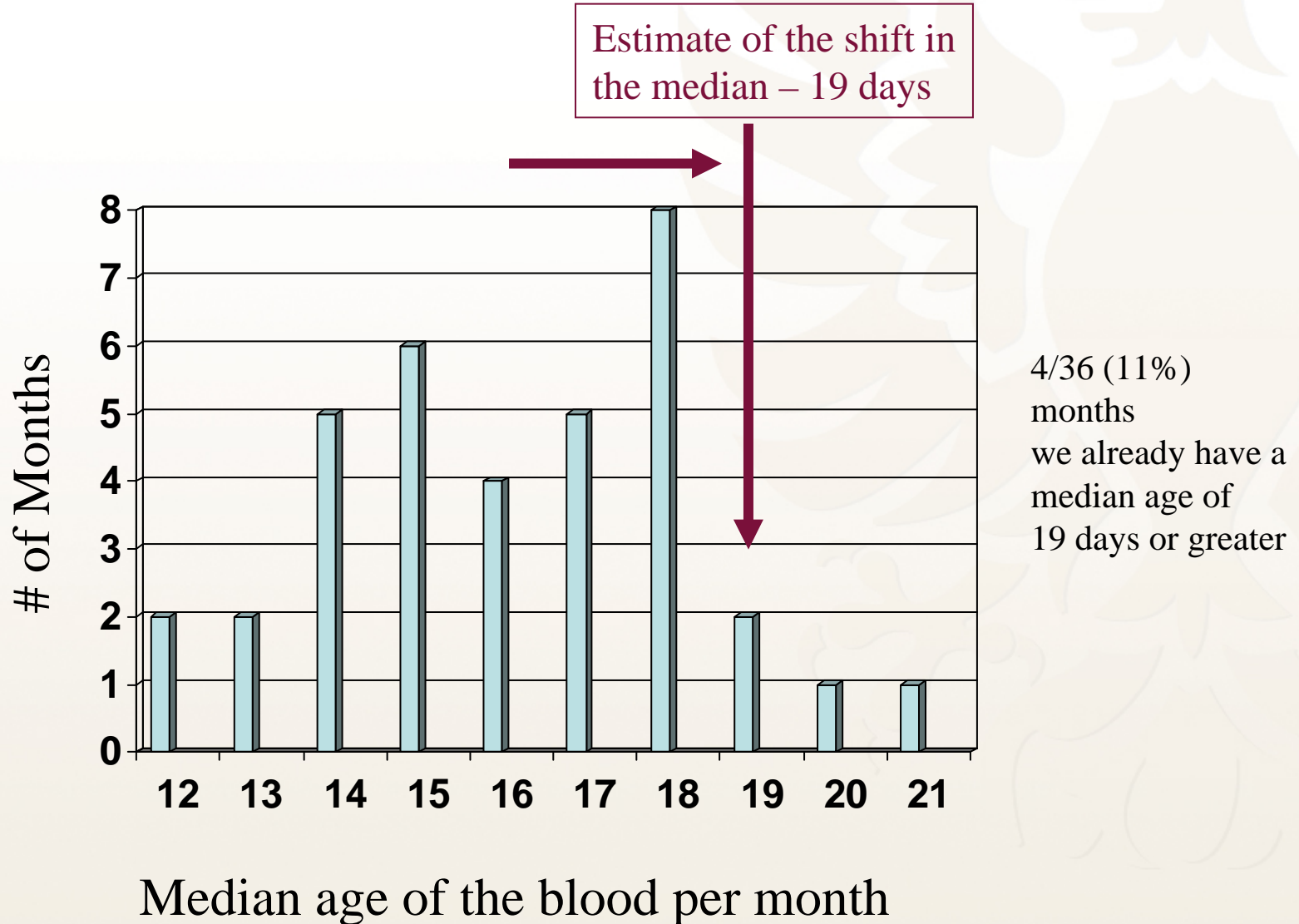
Modeling – Impact of the Study

- What happens if we randomize some patients to the freshest blood and some to the older blood

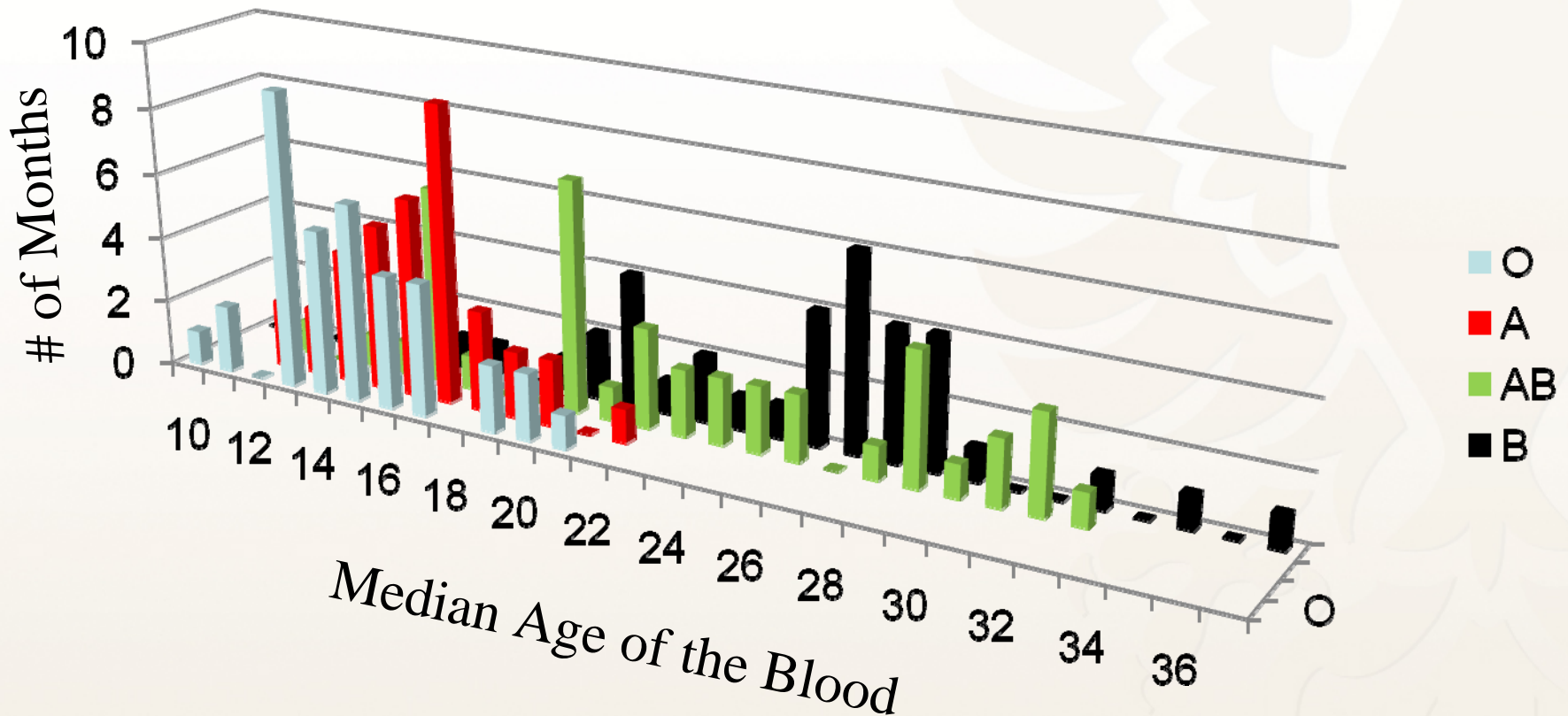
	Fresh Blood	Standard Blood
Median	6 days	19 days
IQR	4 - 8	17 - 22



Estimated Shift vs Current Practice

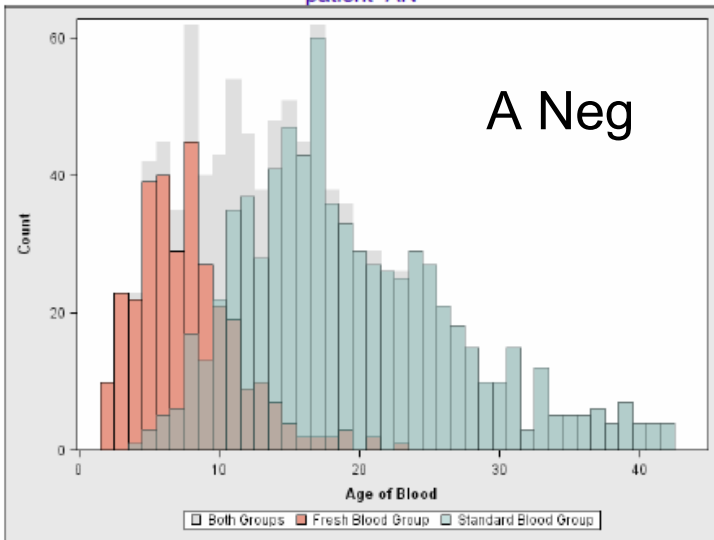


Median Monthly Age Distribution by Blood Group (36 months)

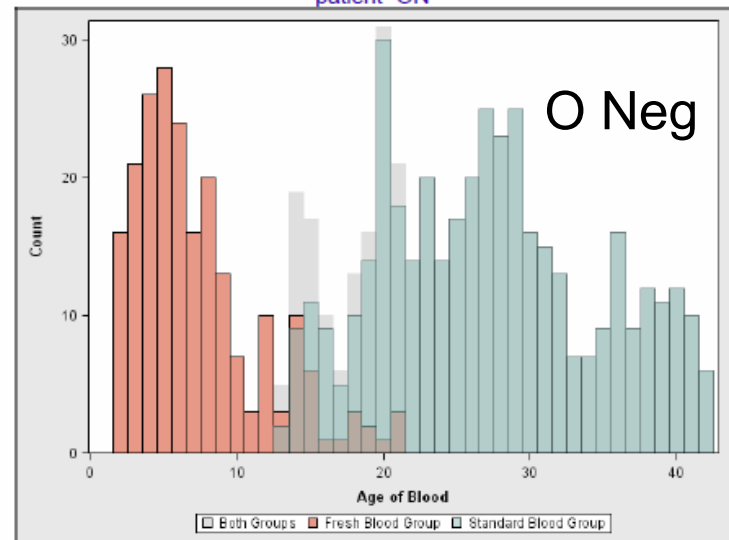


Will we get Good Separation by Randomizing 1:2 Ratio?

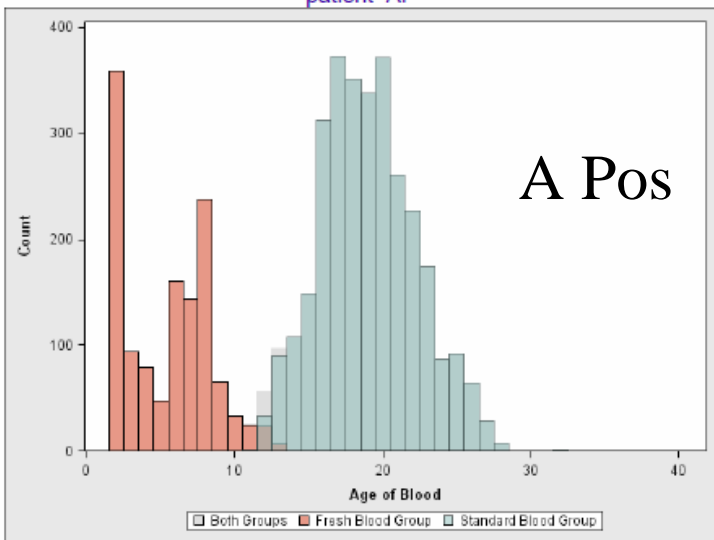
patient=AN



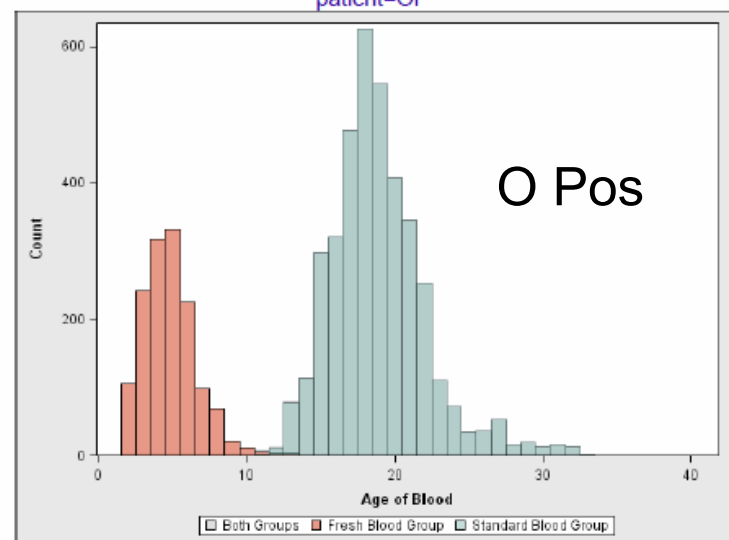
patient=ON



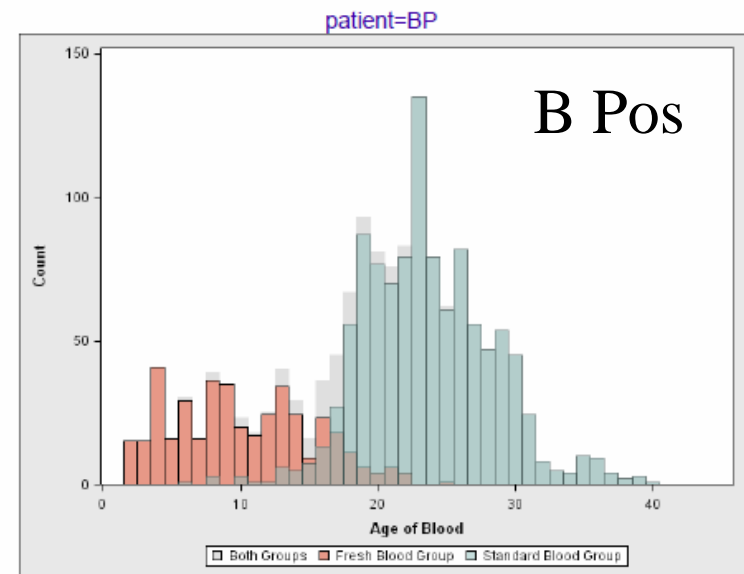
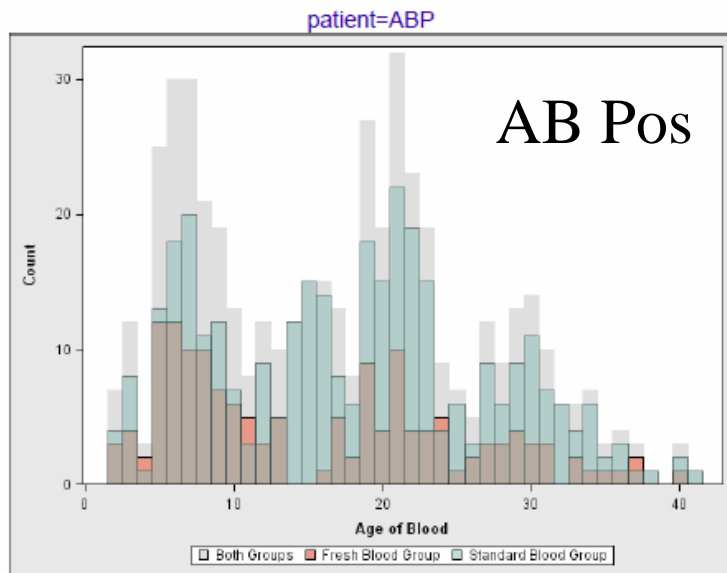
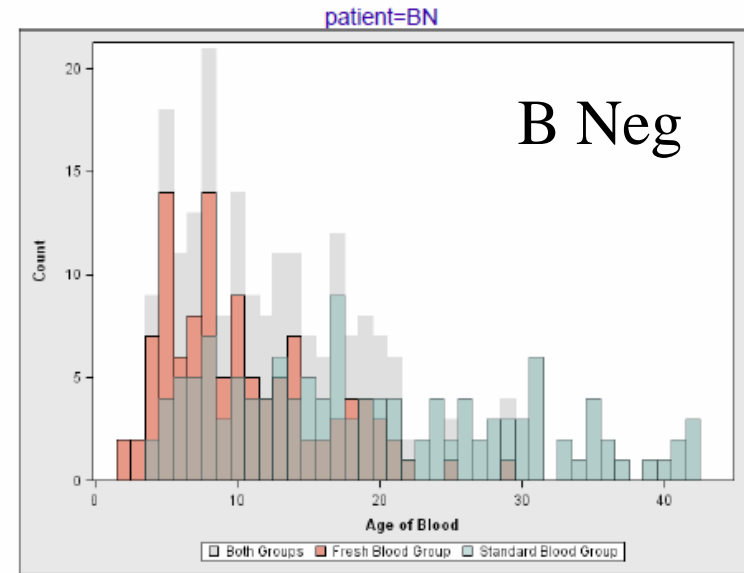
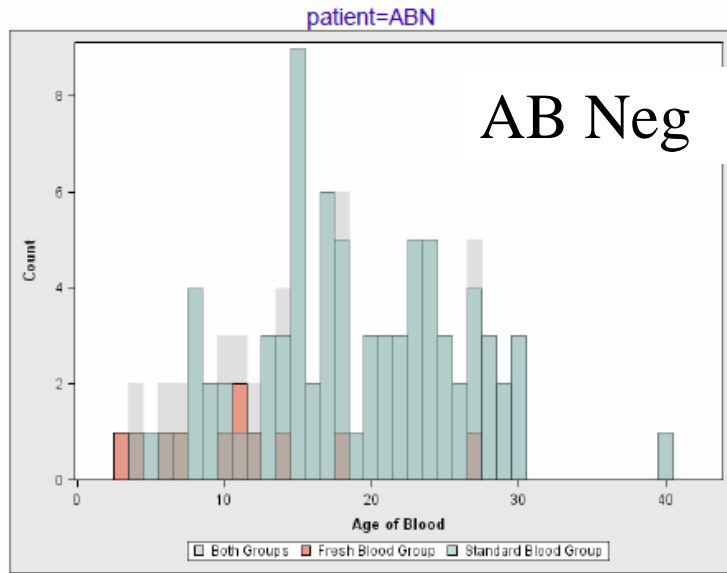
patient=AP



patient=OP



Separation through Randomization



Thoughts Around the Issue of Consent

Why would we not be able to get informed consent on all transfused hospitalized patients?

Too much work?

Not an acceptable answer

Not Feasible

Why?

- many patients transfused within hours
- trial relies totally on the infrastructure within the hospital transfusion service
- keeping track of consenting and non-consenting patients and randomization allocation would jeopardize patient care.

If informed consent was obtained, those who did not consent would also be impacted by the study – simply doing the study would change the age distribution of the supply

Waived Consent

Criteria Specified in the Tri Council Statement for Waiver of Informed Consent

- 1) The research involves no more than minimal risk to the participants.
- 2) The alteration or waiver is unlikely to adversely affect the welfare of the participants.
- 3) It is impossible to carry out the research and to answer the research question properly, given the research design, without the alteration or waiver.
- 4) Whenever possible and appropriate, the participants will be debriefed and provided with additional pertinent information after participation or at a later time during the study.
- 5) The altered or waived consent does not involve a therapeutic intervention, or other clinical or diagnostic interventions.

Current Status

- Grant submitted for Funding (CIHR & CBS)
 - Pilot - feasibility
- May 1, 2010 – REB approval
- June 2010 – planned startup
- Pilot will run for 3 to 6 months
- If feasibility is shown
 - Proceed with a large pragmatic study
 - 30,000 patients

Conclusions/Comments

- Area dominated by retrospective studies
 - Bias is a major problem
- Suggest a continuous and graded association between increasing duration of red cell storage and risk of in-hospital mortality in patients with cardiovascular disease
- 3 RCTS (efficacy) currently underway
 - Efficacy
 - Limitations: Generalizability, & informing the optimal age threshold
- Pragmatic RCT - complementary



Thank you for your attention