



bbts  
**Brighton**  
3-5 oct '18

# How important is avoidance of blood transfusion in renal patients in 2018?

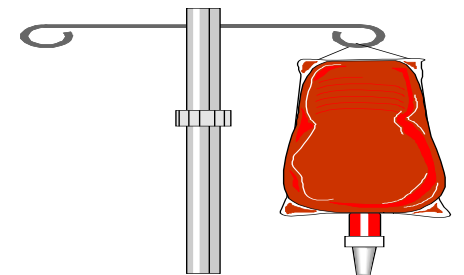
**Iain C. Macdougall**

*Consultant Nephrologist & Professor of Clinical Nephrology*

Renal Unit, King's College Hospital, London



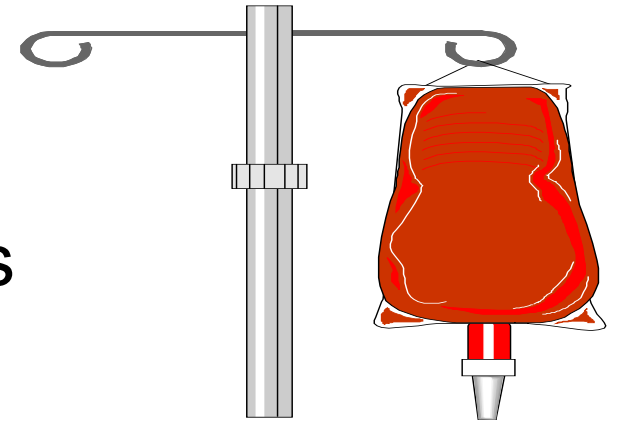
#BBTS2018



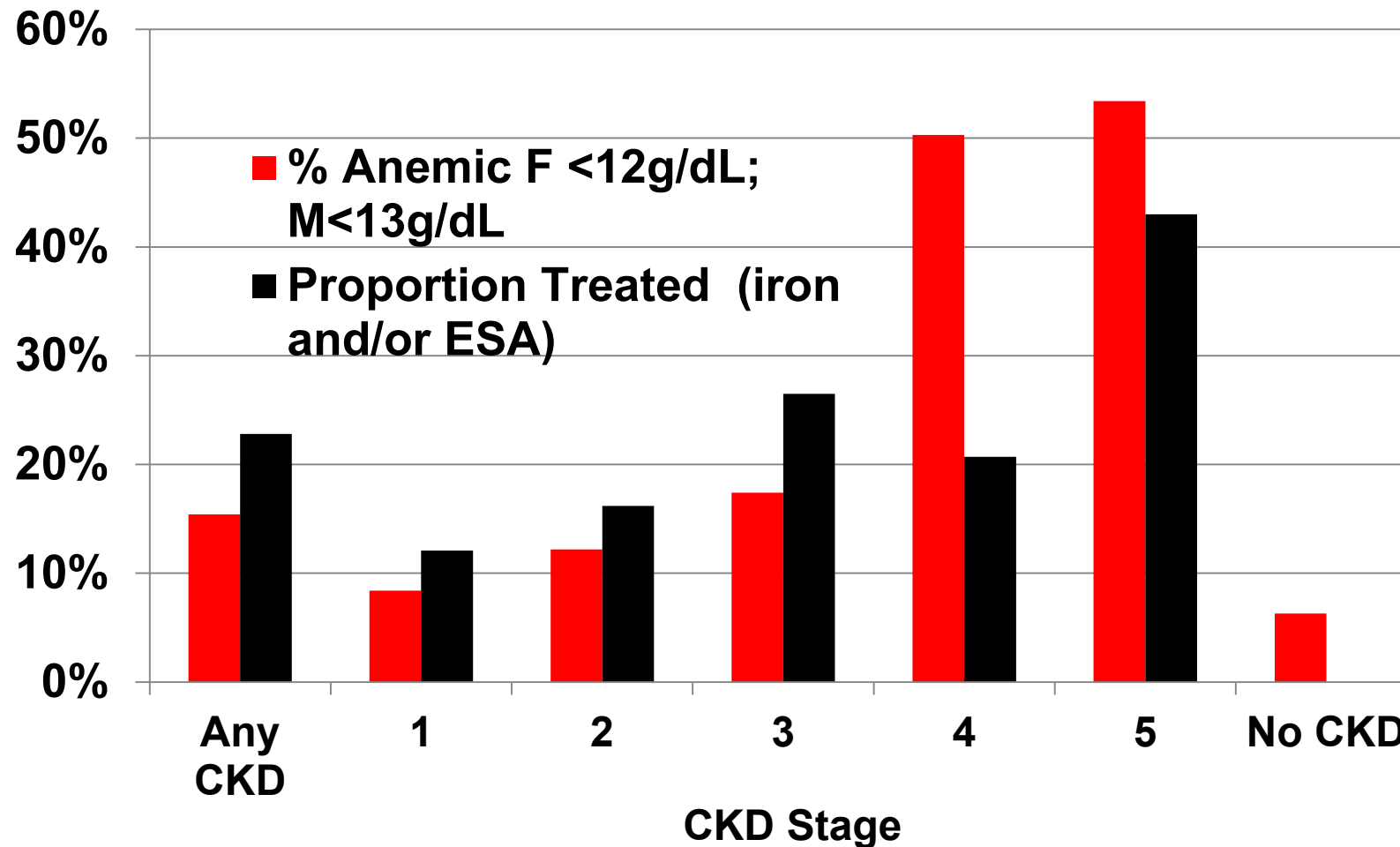
# Blood transfusions in CKD: what are the key questions in 2018?

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- Do blood transfusions still increase the risk of HLA sensitisation?
- Does HLA sensitisation adversely affect outcomes of transplantation?

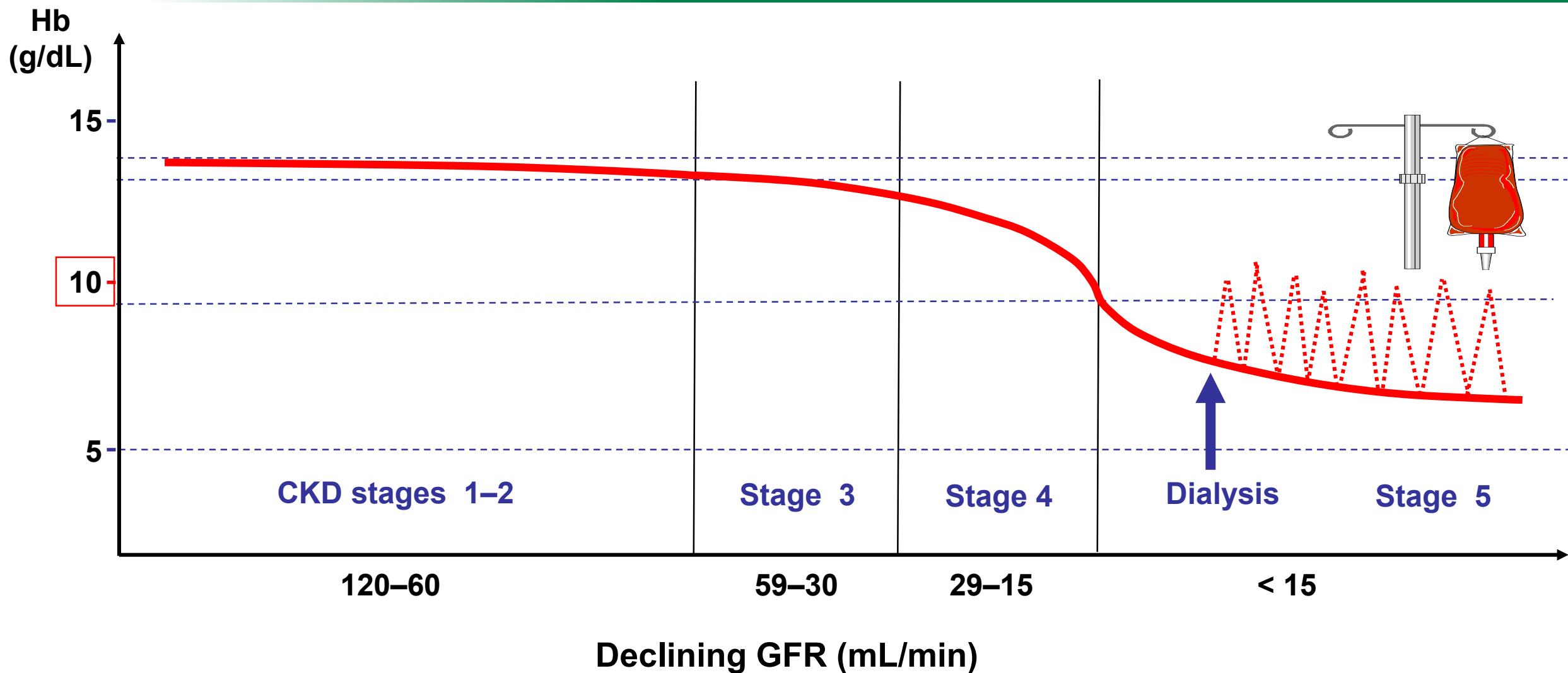


# Anaemia in US CKD Patients and Prevalence of Treatment



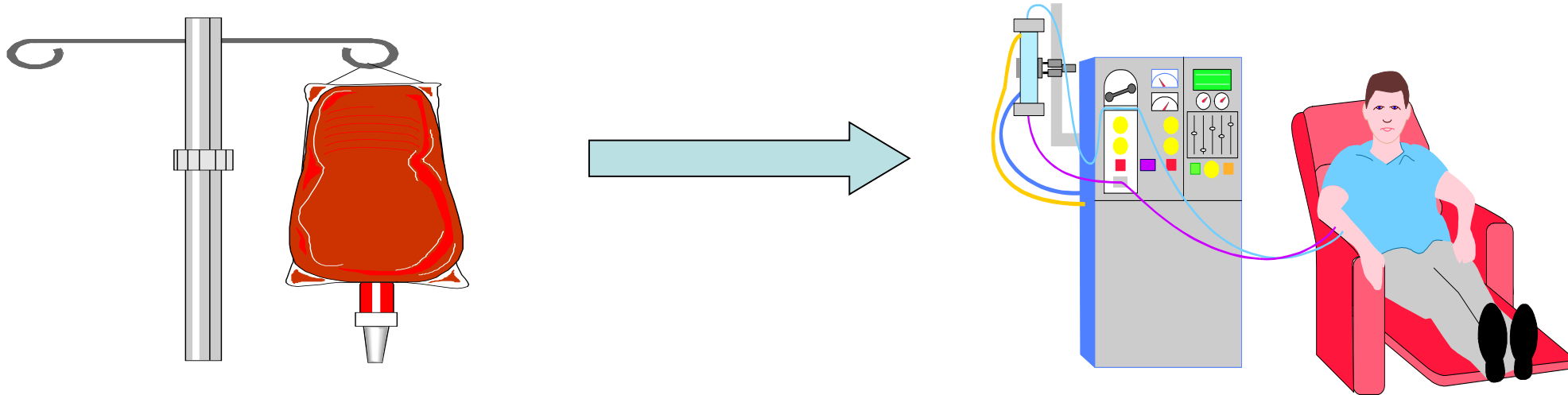
NHANES data 2007–2010

# Renal anaemia prior to EPO availability

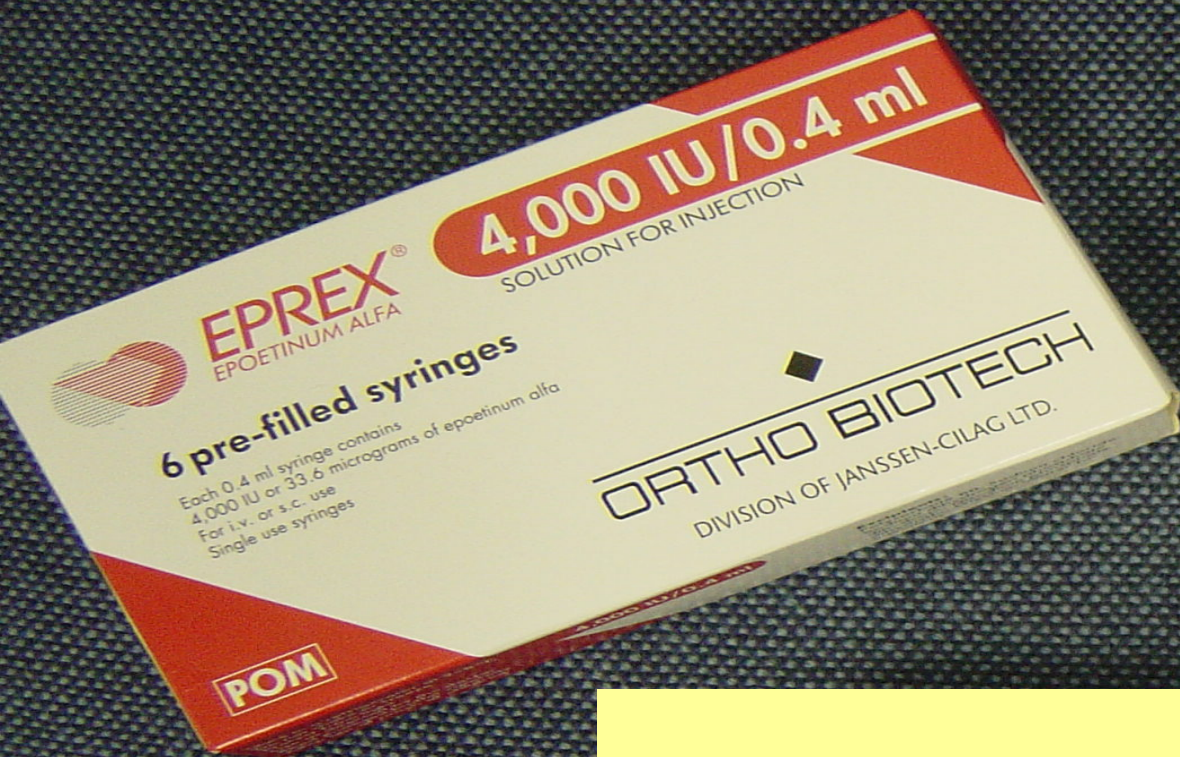


*NHANES 3 data.*

# Management of renal anaemia prior to EPO



- Many dialysis patients had “top-up” transfusions every 2–4 weeks
- Effects transient
- Increased risk of infections, *esp. viral*
- Sensitisation to HLA antigens – transplantation problematic
- Iron overload



**Epoetin alfa (*Eprex*)**

**Epoetin beta (*NeoRecormon*)**

# Early days of EPO therapy

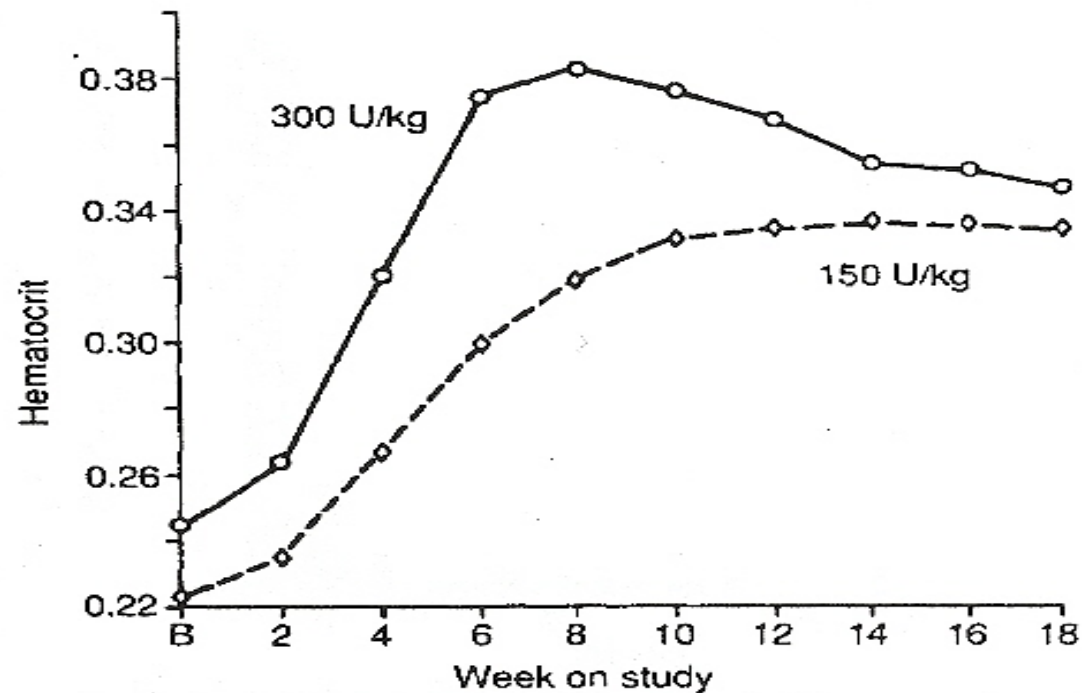


Figure 1. The mean hematocrit values at biweekly intervals for 35 patients receiving 300 U rHuEpo/kg body weight (*circles*) or 201 patients receiving 150 U (*diamonds*) rHuEpo/kg. The rHuEpo was given intravenously three times per week.

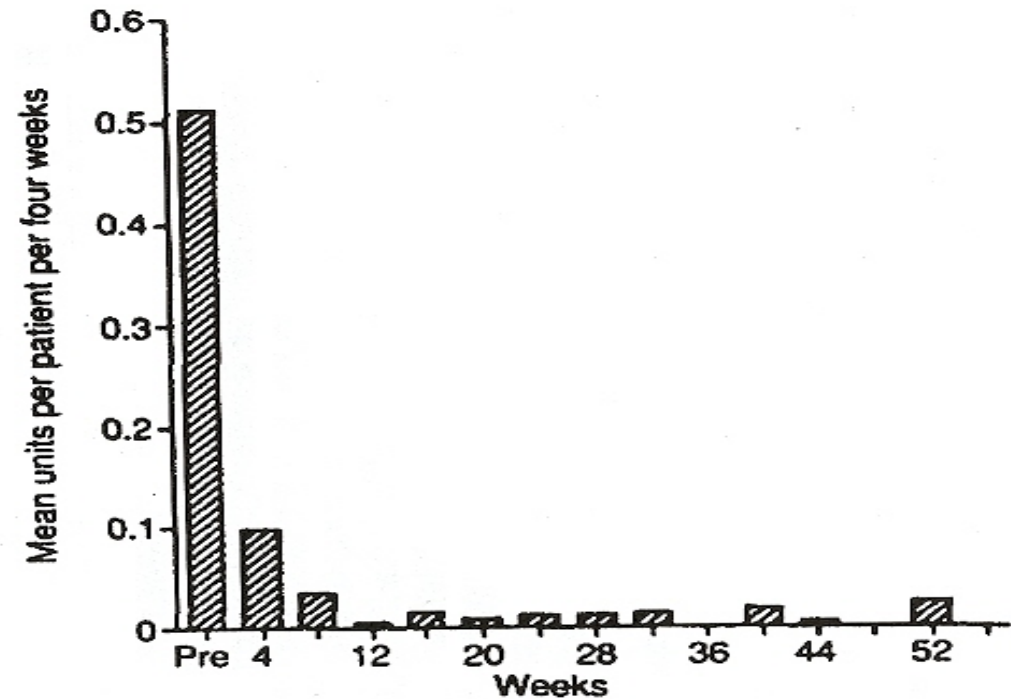
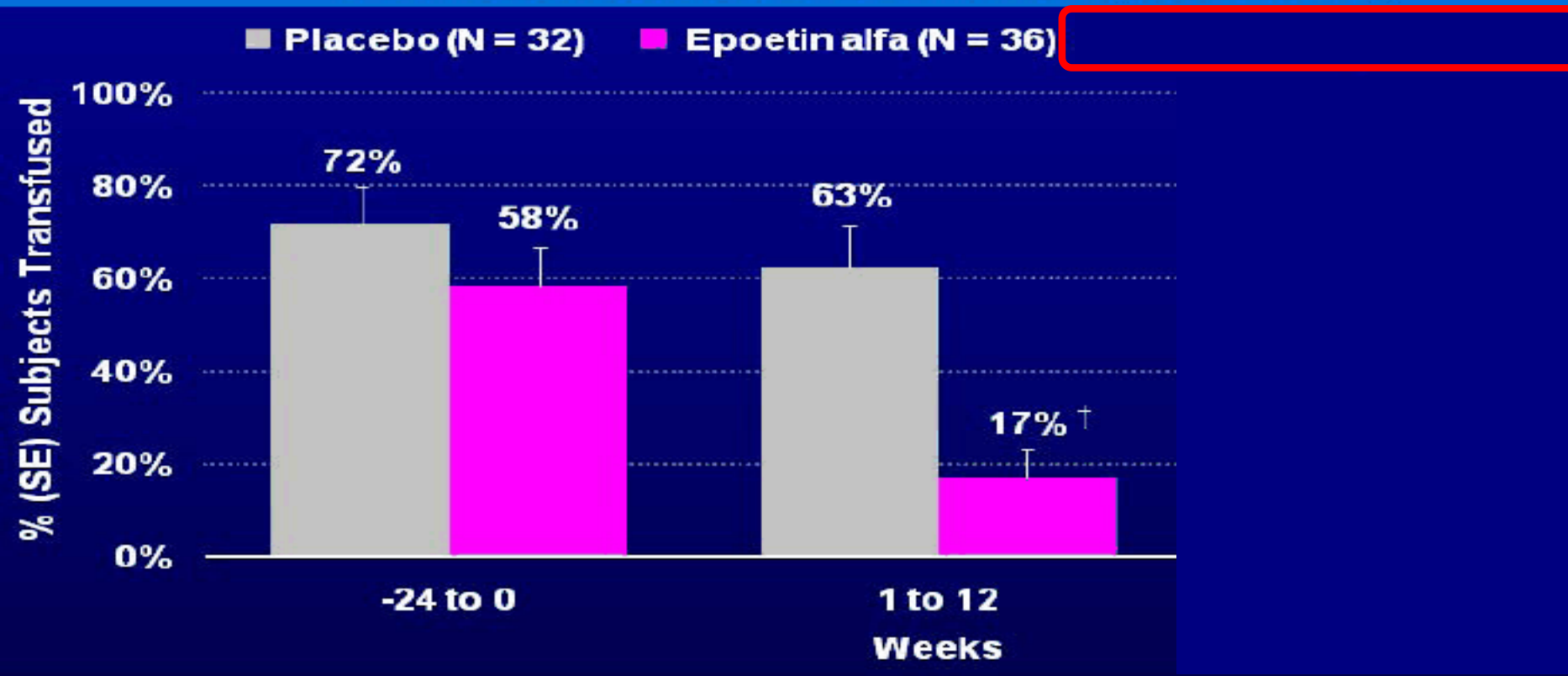


Figure 2. Transfusion requirements (*units/patient*) per month for 6 months before initiation of rHuEpo therapy (*pre*) and at 4-week intervals thereafter. At week 52, one patient autodonated three units in the previous month for elective hip surgery.

# ESAs Decrease Transfusion Burden in Subjects Receiving Dialysis

Transfusion Reduction in Dialysis Study

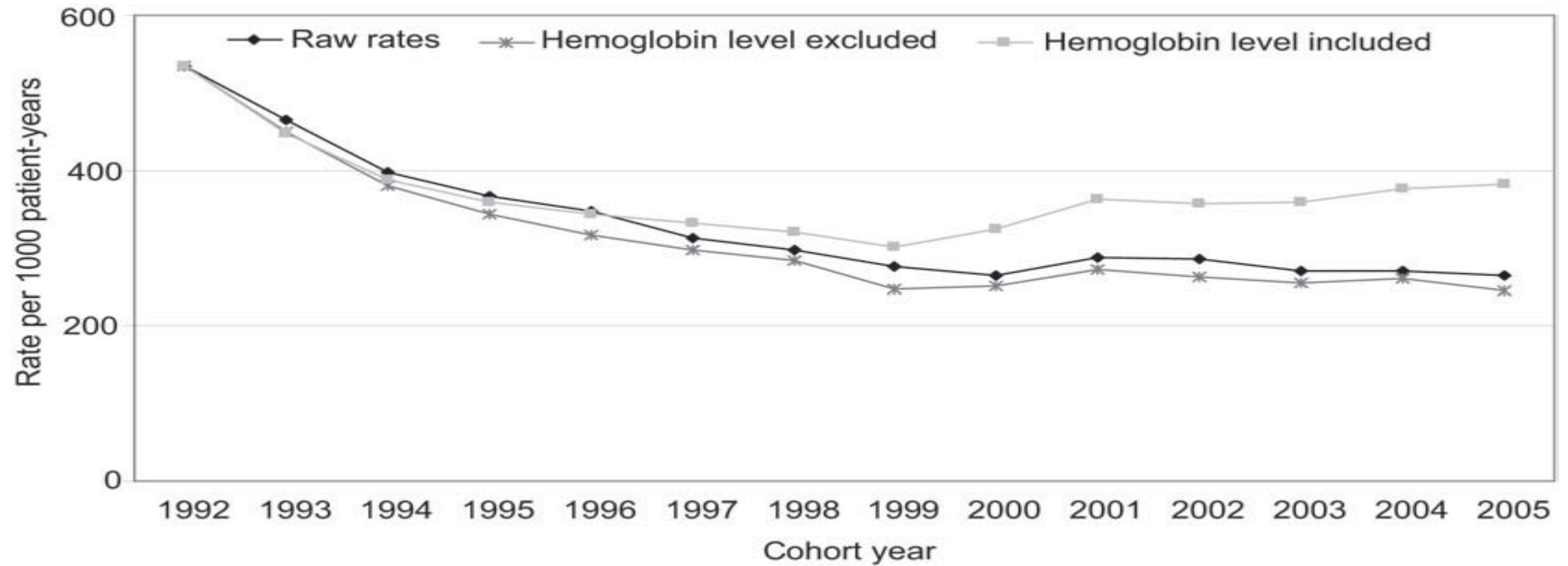


<sup>†</sup>P < 0.01 placebo vs. Epoetin alfa

\*P < 0.05 placebo vs. Epoetin alfa

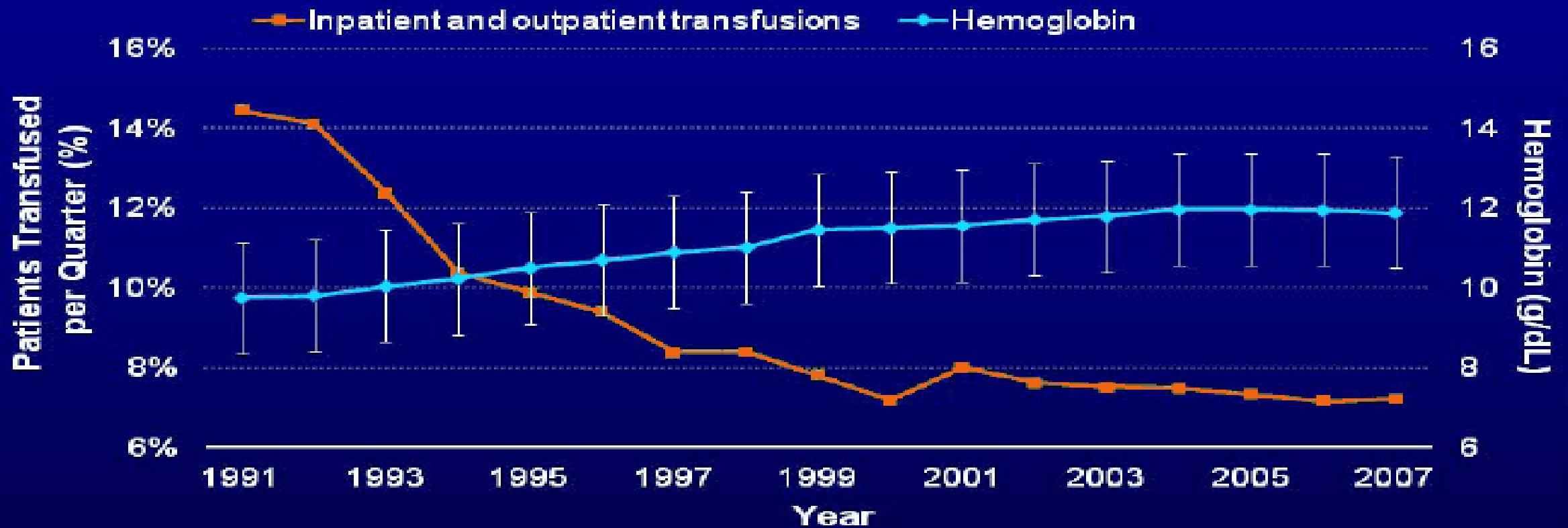
Data on file, Amgen; [Study 8701].

# Transfusions among US dialysis patients 1992-2005

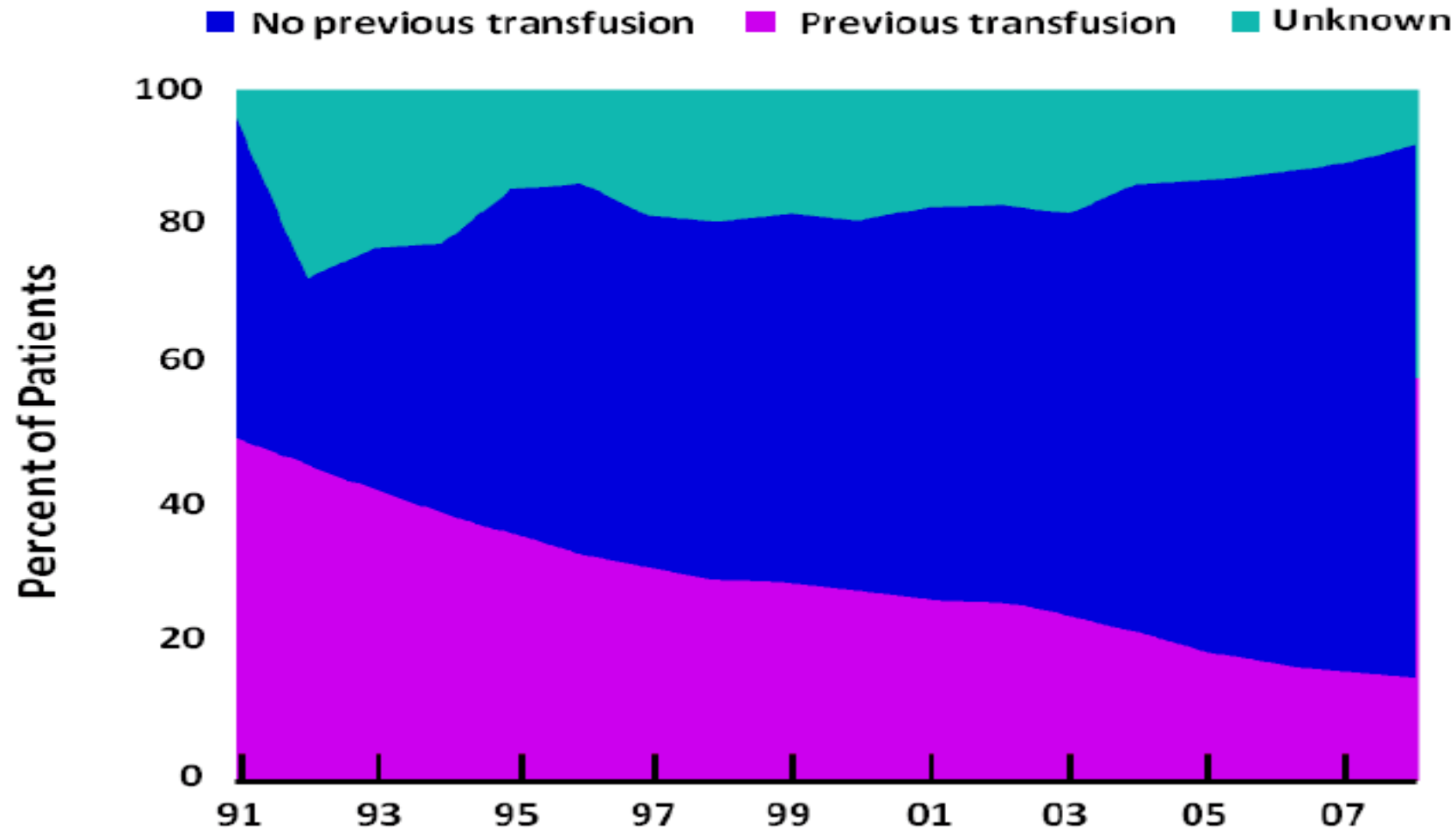


# Time Trend of Transfusions Rates and ESA Use in Hemodialysis Patients

Association of Hb Level and Total Blood Transfusions Over Time

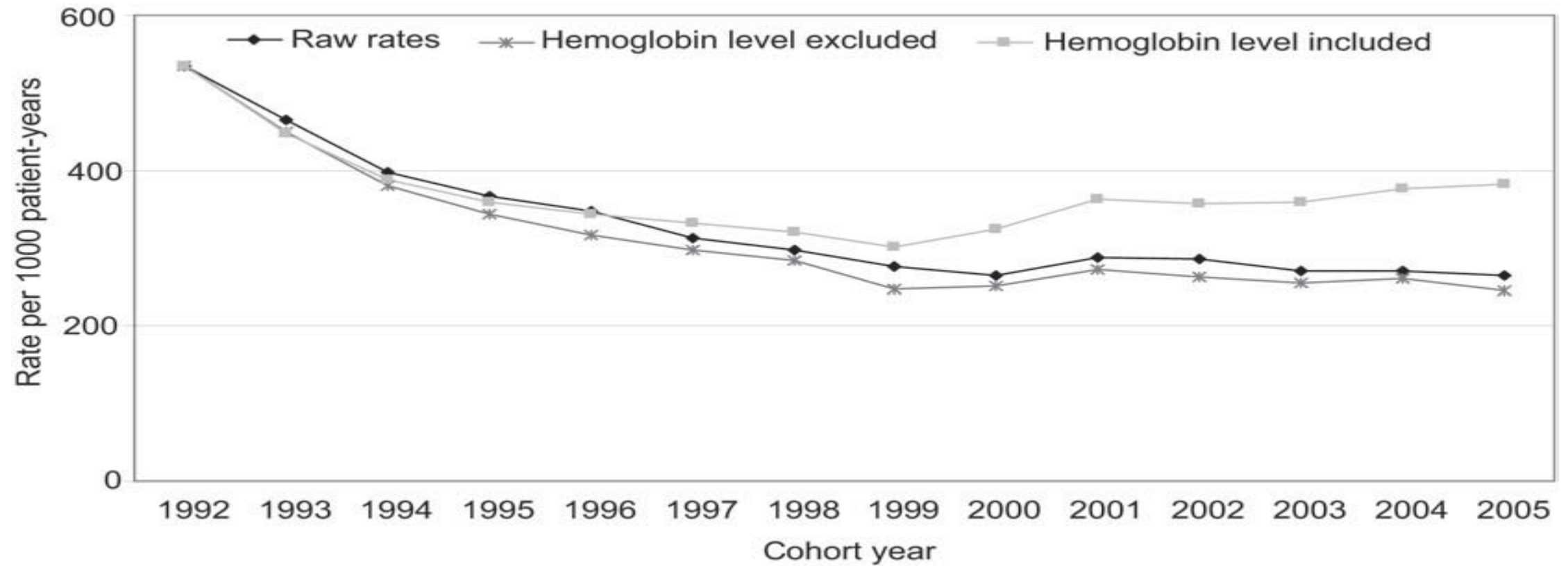


# In Transplanted Patients, the Proportion With Previous Transfusions Have Declined



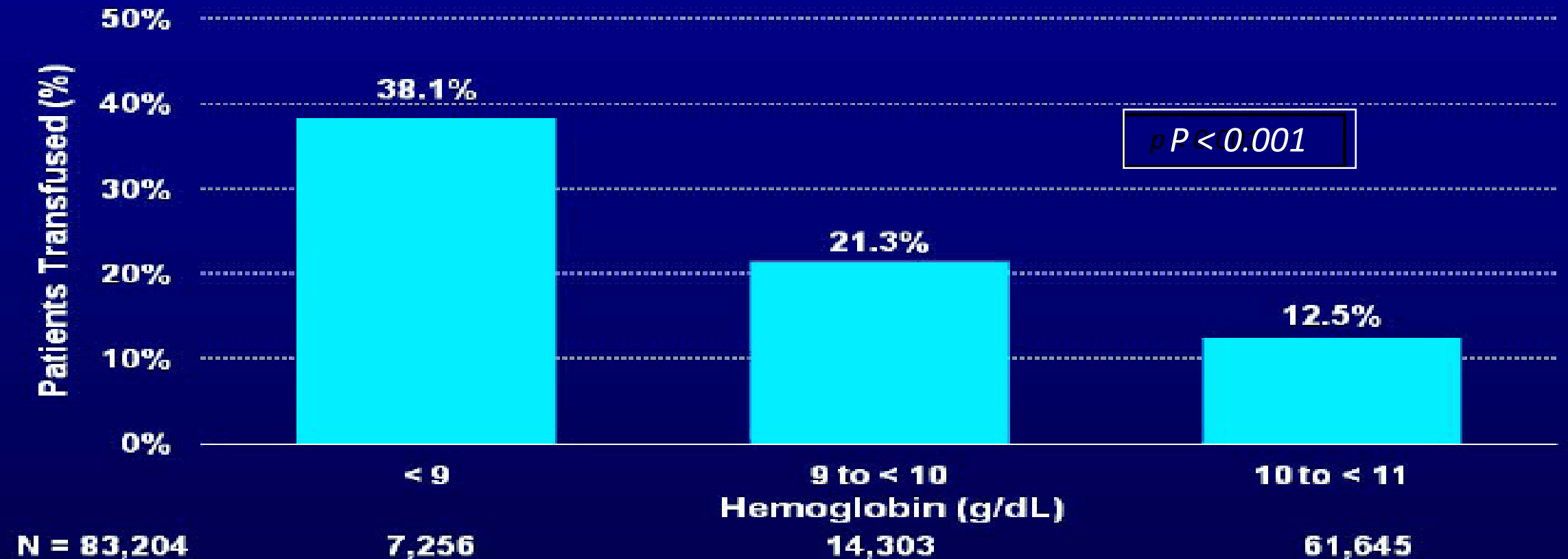
*Adapted from: US Renal Data System 2010 Annual Report.*

# Transfusions among US dialysis patients 1992-2005



# Transfusion Rate Increases as Hemoglobin Declines

Patients Not on Dialysis Transfused within One Year by Baseline Hemoglobin (2002-2007)



Adapted from: Lawler EV et al, *Nephrol Dial Transplant* 2010; 25: 2237-2244.

# The TREAT study (*NEJM* 2009)

## *The* NEW ENGLAND JOURNAL *of* MEDICINE

### A Trial of Darbepoetin Alfa in Type 2 Diabetes and Chronic Kidney Disease

Marc A. Pfeffer, M.D., Ph.D., Emmanuel A. Burdmann, M.D., Ph.D., Chao-Yin Chen, Ph.D., Mark E. Cooper, M.D.,  
Dick de Zeeuw, M.D., Ph.D., Kai-Uwe Eckardt, M.D., Jan M. Feyzi, M.S., Peter Ivanovich, M.D.,  
Reshma Kewalramani, M.D., Andrew S. Levey, M.D., Eldrin F. Lewis, M.D., M.P.H., Janet B. McGill, M.D.,  
John J.V. McMurray, M.D., Patrick Parfrey, M.D., Hans-Henrik Parving, M.D., Giuseppe Remuzzi, M.D.,  
Ajay K. Singh, M.D., Scott D. Solomon, M.D., and Robert Toto, M.D., for the TREAT Investigators\*

#### ABSTRACT

##### BACKGROUND

Anemia is associated with an increased risk of cardiovascular and renal events among patients with type 2 diabetes and chronic kidney disease. Although darbepoetin alfa can effectively increase hemoglobin levels, its effect on clinical outcomes in these patients has not been adequately tested.

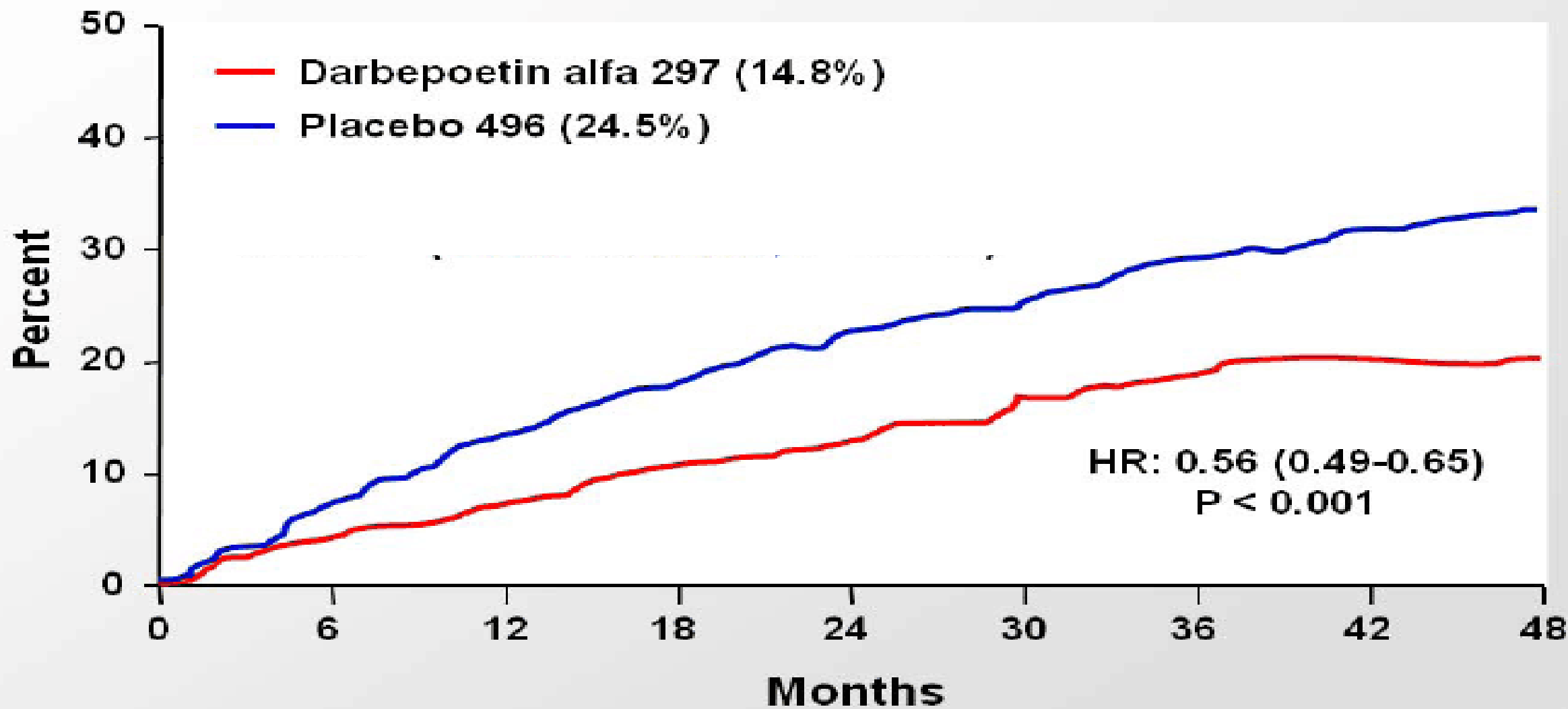
##### METHODS

In this study involving 4038 patients with diabetes, chronic kidney disease, and anemia, we randomly assigned 2012 patients to darbepoetin alfa to achieve a hemoglobin level of approximately 13 g per deciliter and 2026 patients to placebo, with

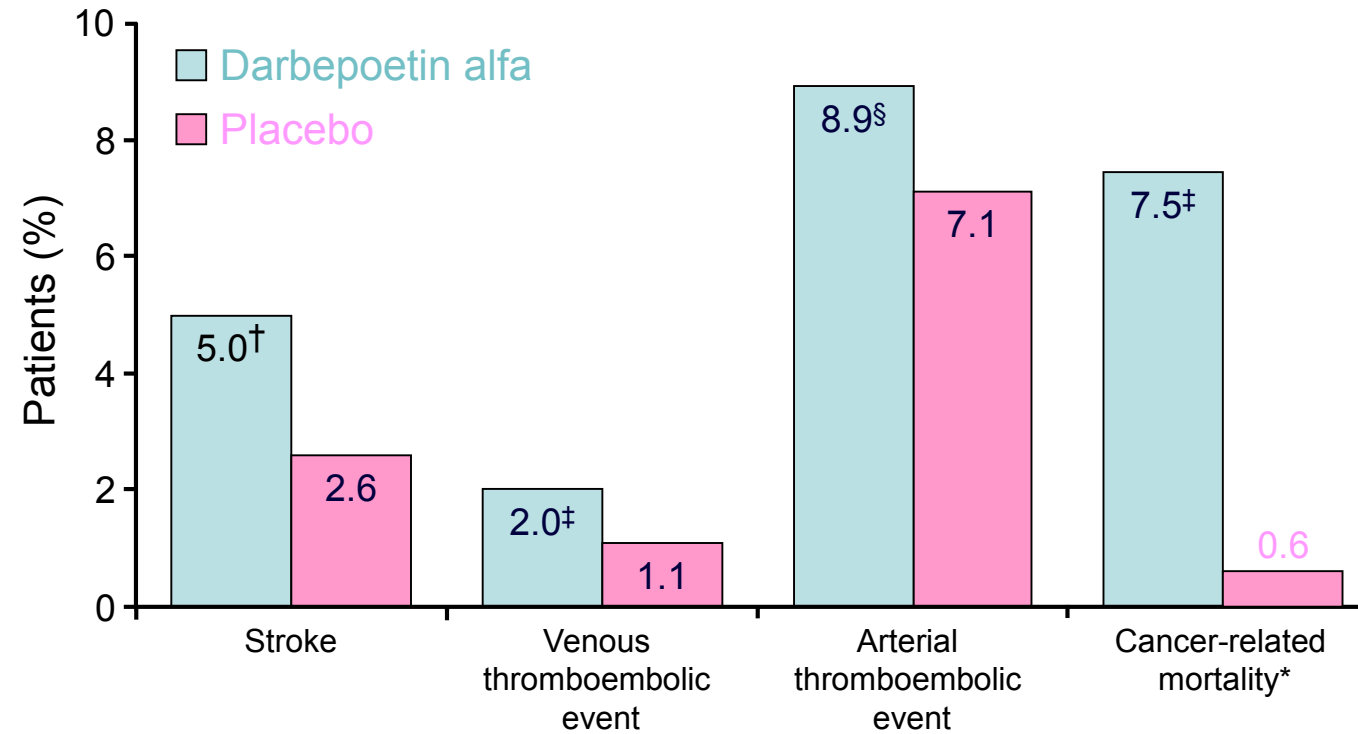
The affiliations of the authors are listed in the Appendix. Address reprint requests to Dr. Pfeffer at the Cardiovascular Division, Brigham and Women's Hospital, 75 Francis St., Boston, MA 02115, or at [mpfeffer@rics.bwh.harvard.edu](mailto:mpfeffer@rics.bwh.harvard.edu).

\*The Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT) committees and teams are listed in the Appendix, and investigators and individual

# Red Cell Transfusions



# TREAT study: Safety issues



†,  $p < 0.001$  versus placebo

‡,  $p = 0.02$  versus placebo

§,  $p = 0.04$  versus placebo

\*Amongst patients with a history of malignancy at baseline

# NKF meeting, May 2012

## DOPPS (Robinson BM et al)

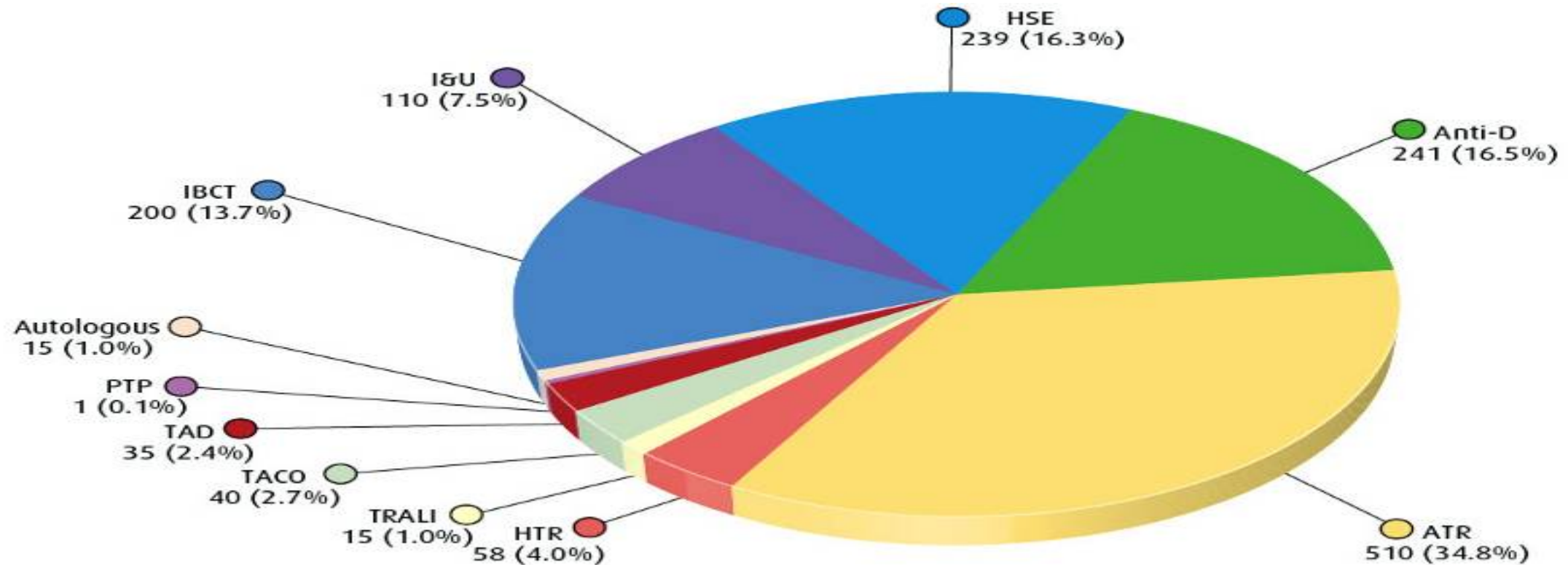
- Median Hb levels fell 0.08 g/dL between August 2010 and July 2011, and by an additional 0.37 g/dL through October 2011
- Weekly ESA doses fell a median of 23% between Aug. 2010 and Dec. 2011
- IV iron use steeply increased from 57% of patients receiving iron in 2010 to 77% in December 2011
- 2.21% of patients transfused in hospital per month in September 2010 increased to 4.87% in September 2011

# Blood transfusions: what are the key questions in 2018?

- What are the risks of reactions / transmitted infections in the modern era?
- Do RBC transfusions increase the risk of HLA sensitisation?
- Is HLA sensitisation bad for the patient?

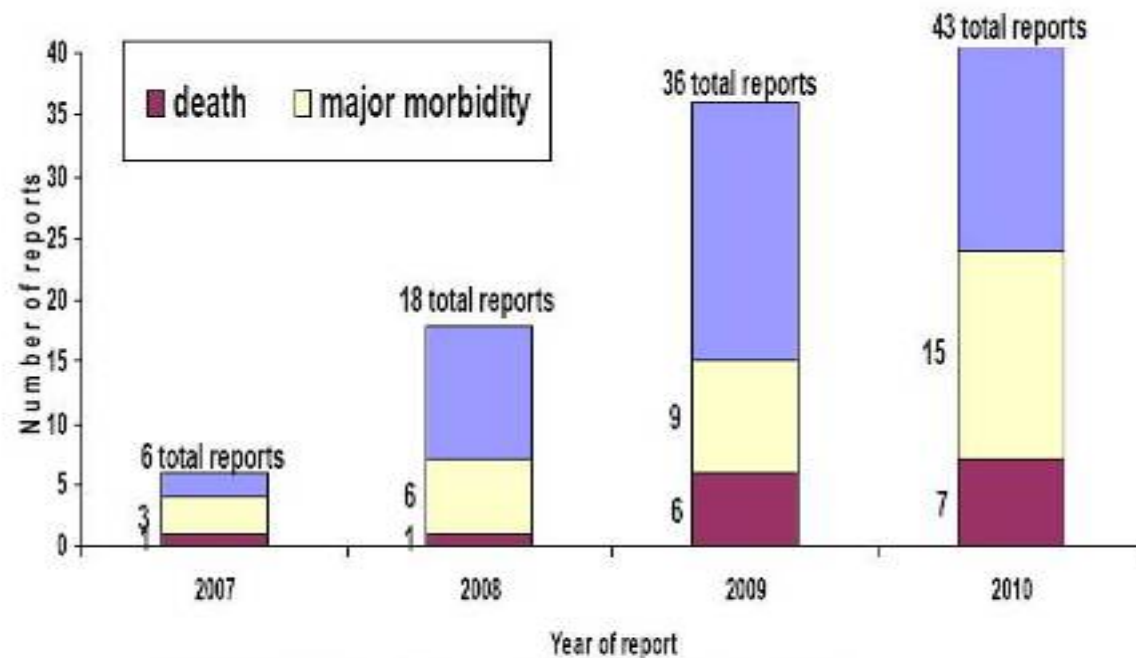
# SHOT UK

- 3200 reports were made of which 2464 were analysed



# Transfusion-associated circulatory overload (TACO)

- 15 TACO-related deaths and 33 cases of major morbidity



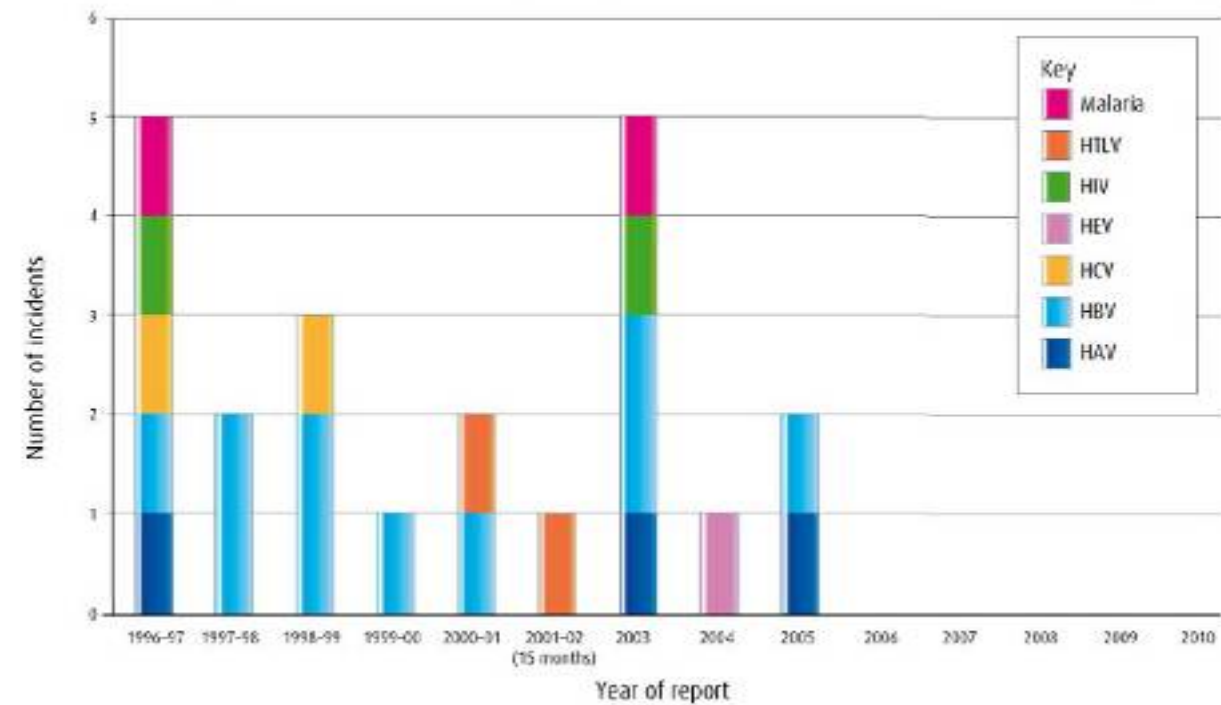
\*Includes 3 deaths and 5 cases of major morbidity from I&U

- Risk factors included:**

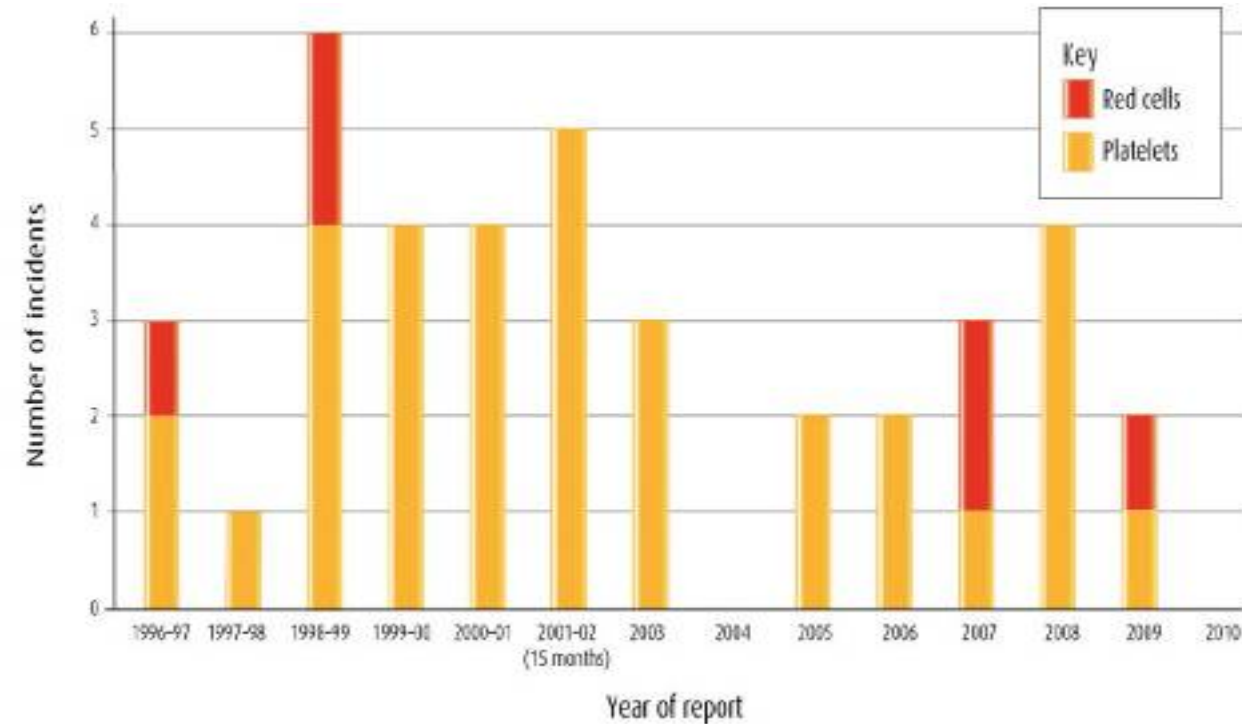
- *age > 70 years*
- *small body size*
- *pre-existing heart failure*
- *chronic renal impairment*
- *hypoalbuminaemia*

# Transfusion-Transmitted Infection (TTI)

## *Viral and Parasitic infections*



## *Bacterial infections*



# Blood transfusions: what are the key questions in 2018?

- What are the risks of reactions / transmitted infections in the modern era?
- Do RBC transfusions increase the risk of HLA sensitisation?
- Is HLA sensitisation bad for the patient?

# How many HLA antigens are expressed on **red** cells?

- A. None
- B. 100 – 2,000 per cell
- C. 6,000 – 30,000 per cell
- D. 40,000 – 100,000 per cell
- E. 100,000 – 200,000 per cell

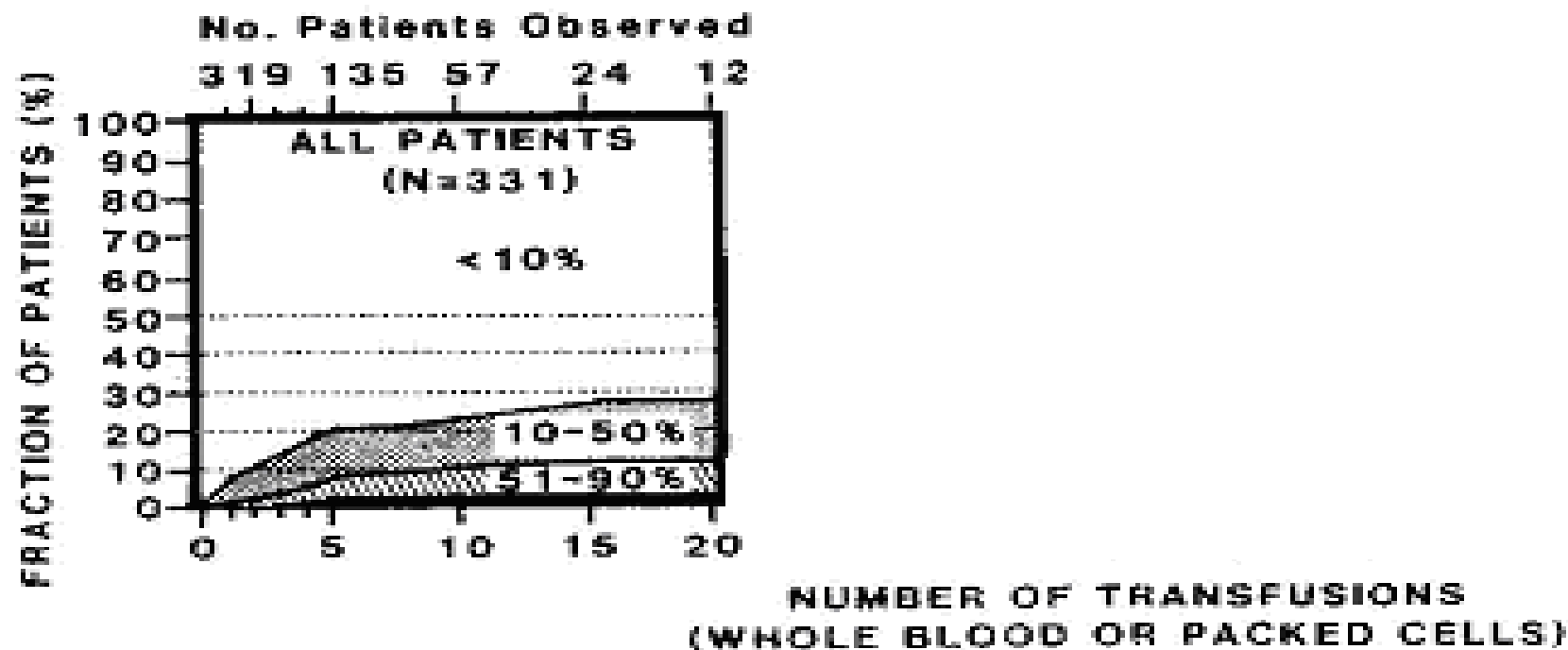
# How many HLA antigens are expressed on **white** cells?

- A. None
- B. 100 – 2,000 per cell
- C. 6,000 – 30,000 per cell
- D. 40,000 – 100,000 per cell
- E. 100,000 – 200,000 per cell

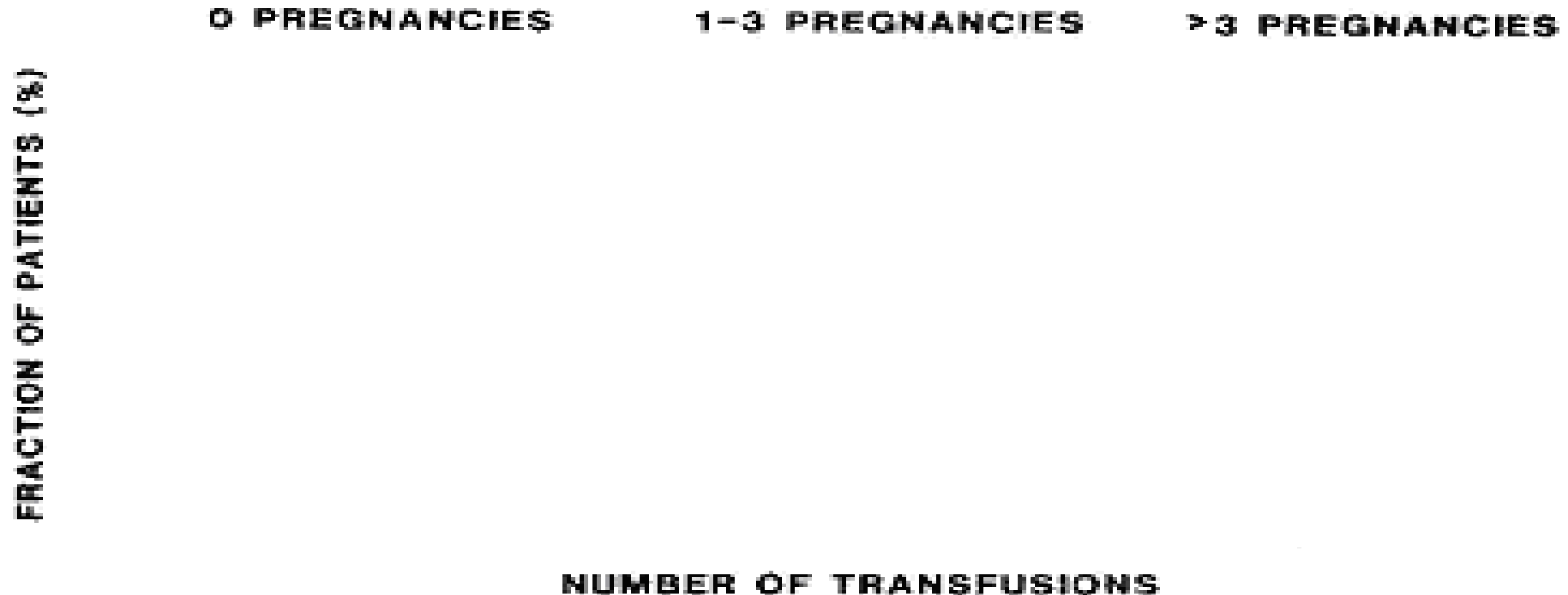
# How many HLA antigens are expressed on **platelets**?

- A. None
- B. 100 – 2,000 per cell
- C. 6,000 – 30,000 per cell
- D. 40,000 – 100,000 per cell
- E. 100,000 – 200,000 per cell

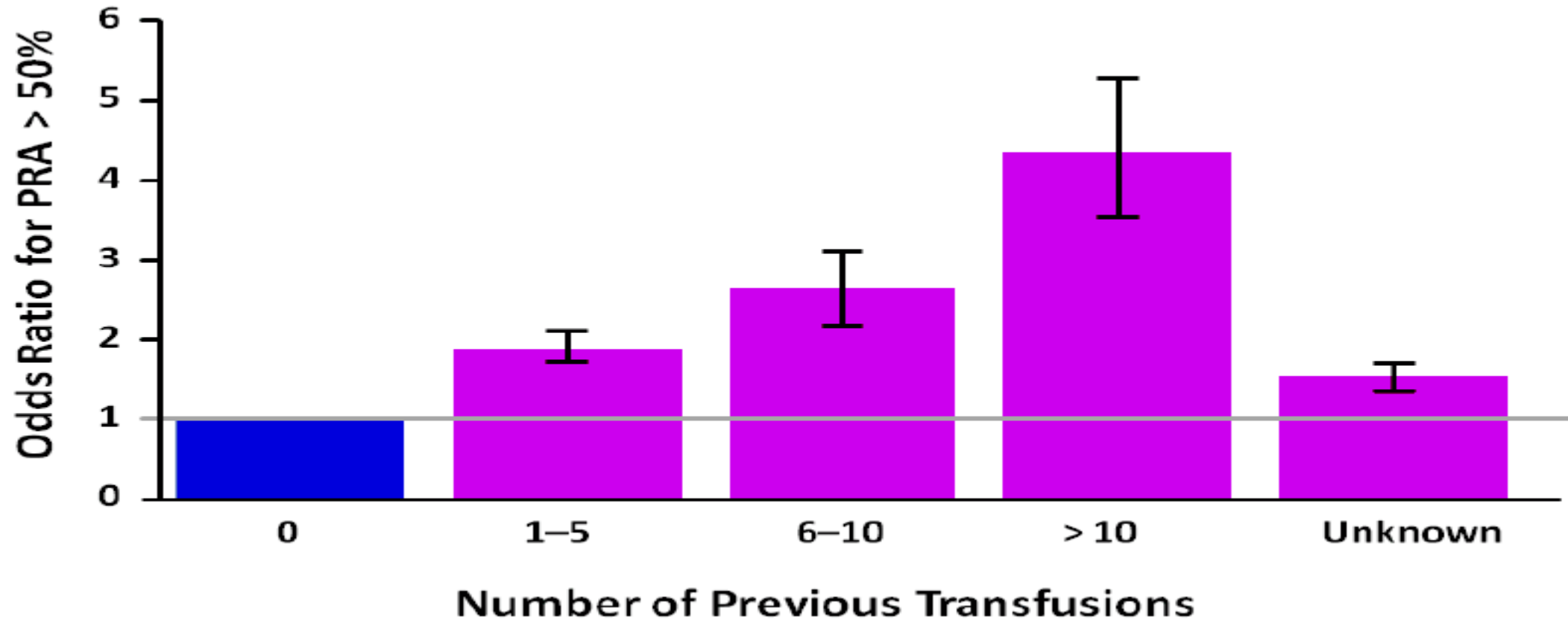
## Lymphocytotoxic antibody reactivity against random donor test panel in relation to the number of blood transfusions



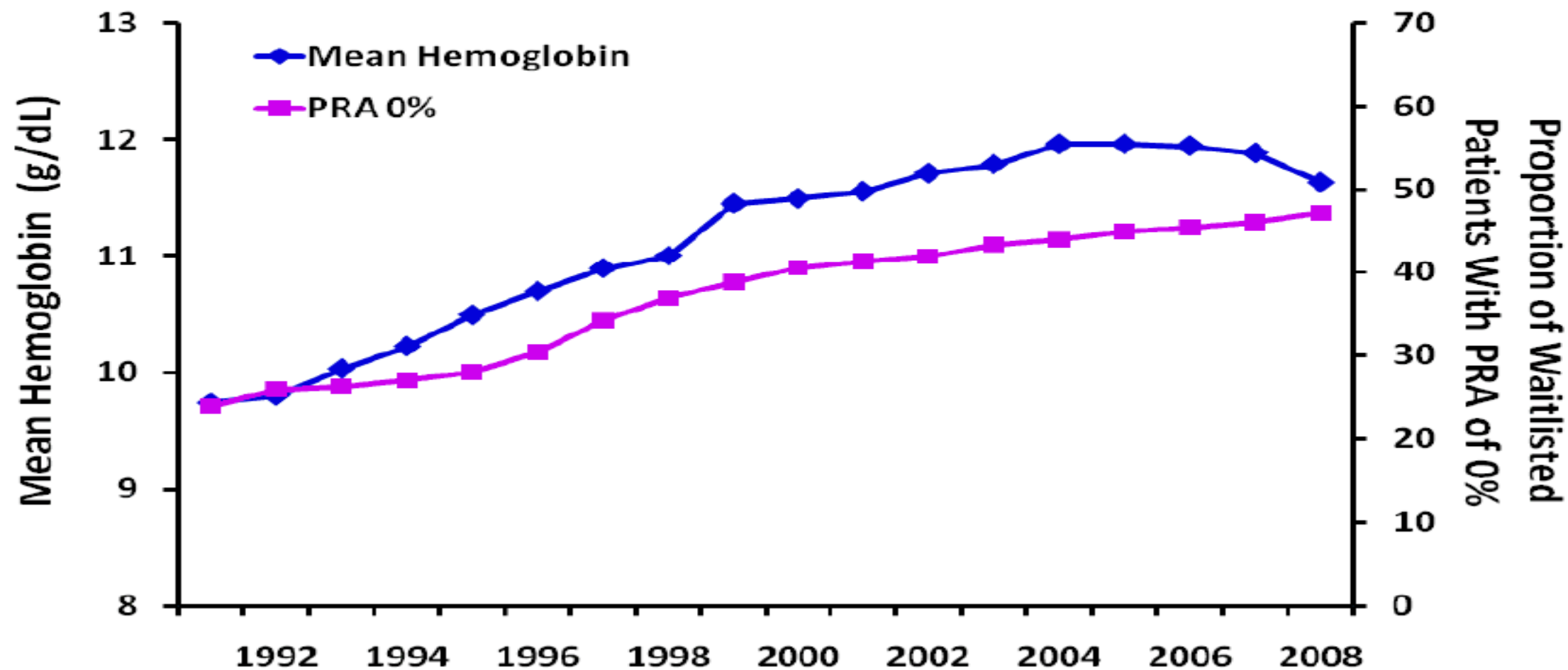
# Lymphocytotoxic antibody reactivity against random donor test panel in relation to the number of blood transfusions



## Risk of PRA > 50% with cumulative transfusion



# Percent of Waitlisted Patients with PRA = 0% Has Increased as Hemoglobin Levels Have Increased in US Dialysis Patients



# Sensitization from transfusion in patients awaiting primary kidney transplant

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Deborah Kim<sup>4,\*</sup>,

Brian D. Bradbury<sup>4</sup>,

Calvin D. Lou<sup>2</sup>,

Jeffrey Petersen<sup>4</sup>,

Jerome Rossert<sup>4</sup>,

Glenn M. Chertow<sup>1</sup>

and Dolly B. Tyan<sup>2</sup>

<sup>1</sup>Division of Nephrology, Department of Medicine, Stanford University, Stanford, CA, USA,

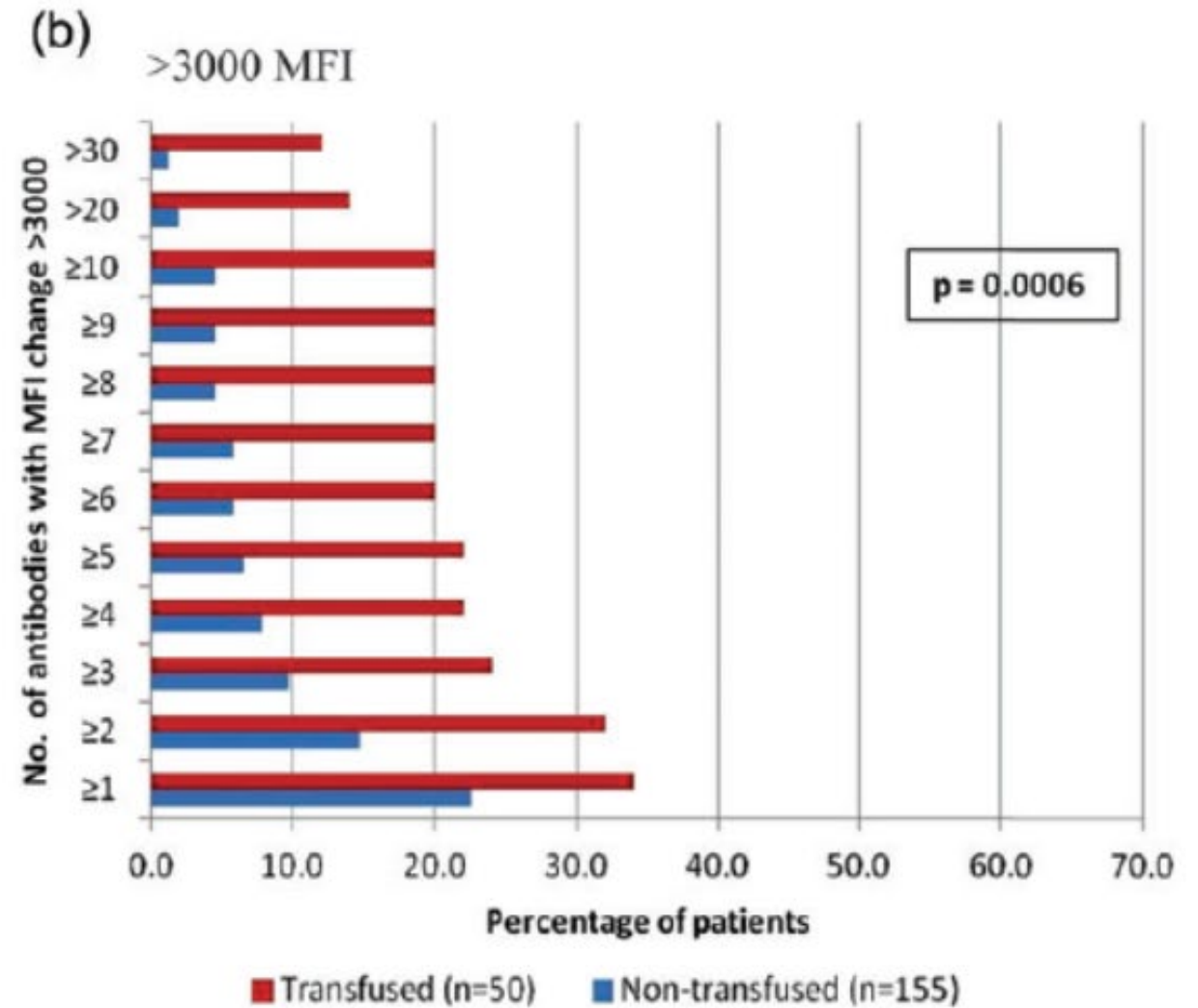
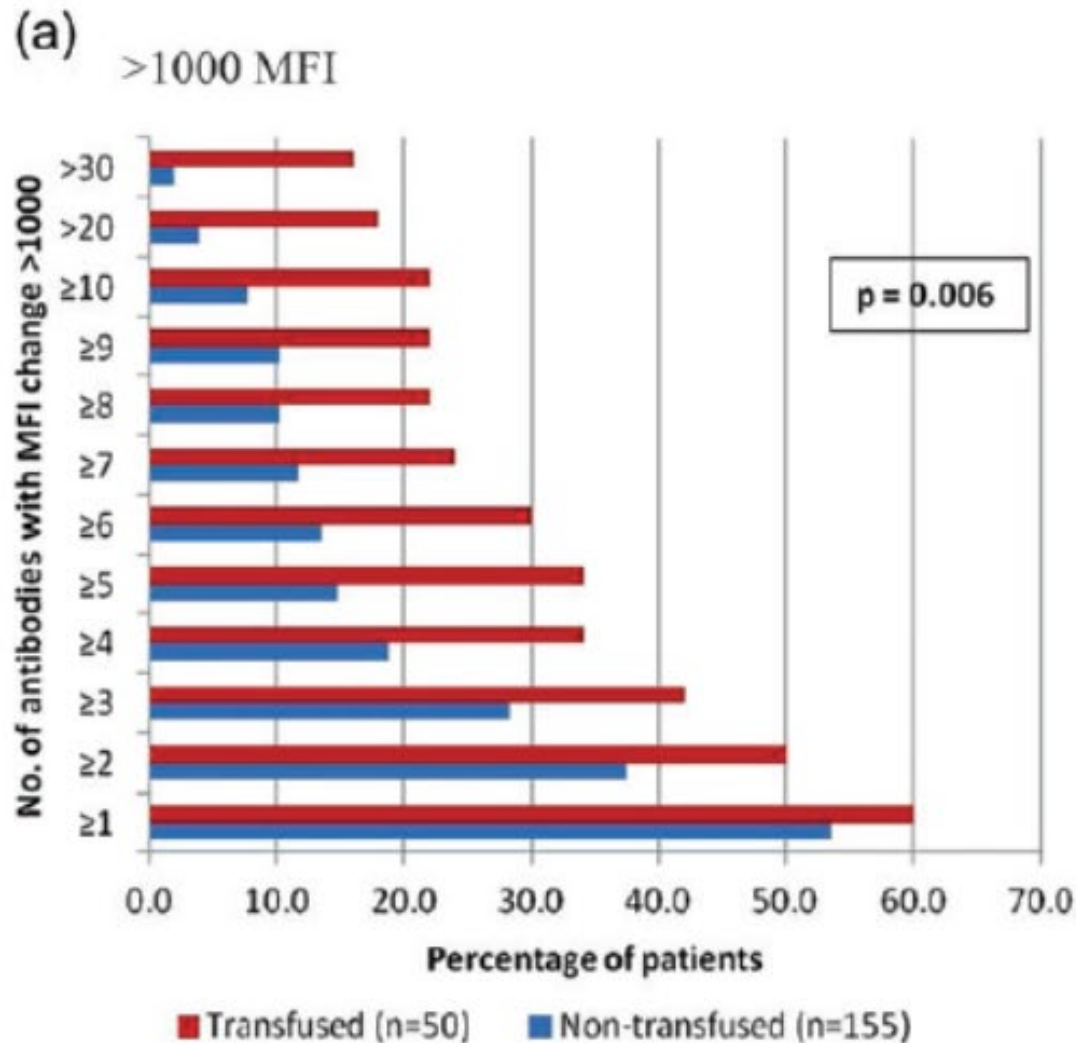
<sup>2</sup>Histocompatibility, Immunogenetics, and Disease Profiling Laboratory, Department of Pathology, Stanford University, Palo Alto, CA, USA,

<sup>3</sup>Blood Center of Wisconsin, Milwaukee, WI, USA and

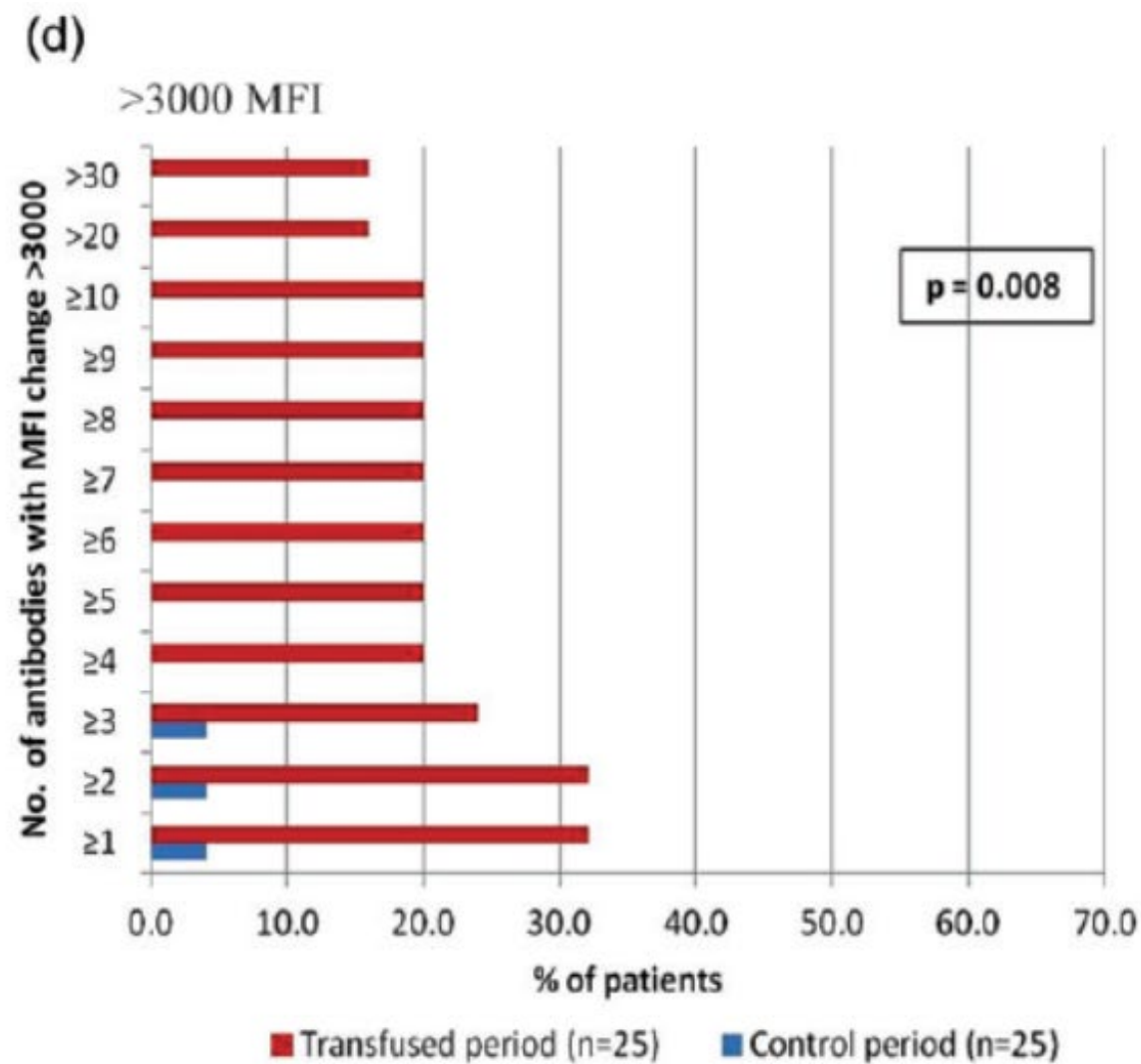
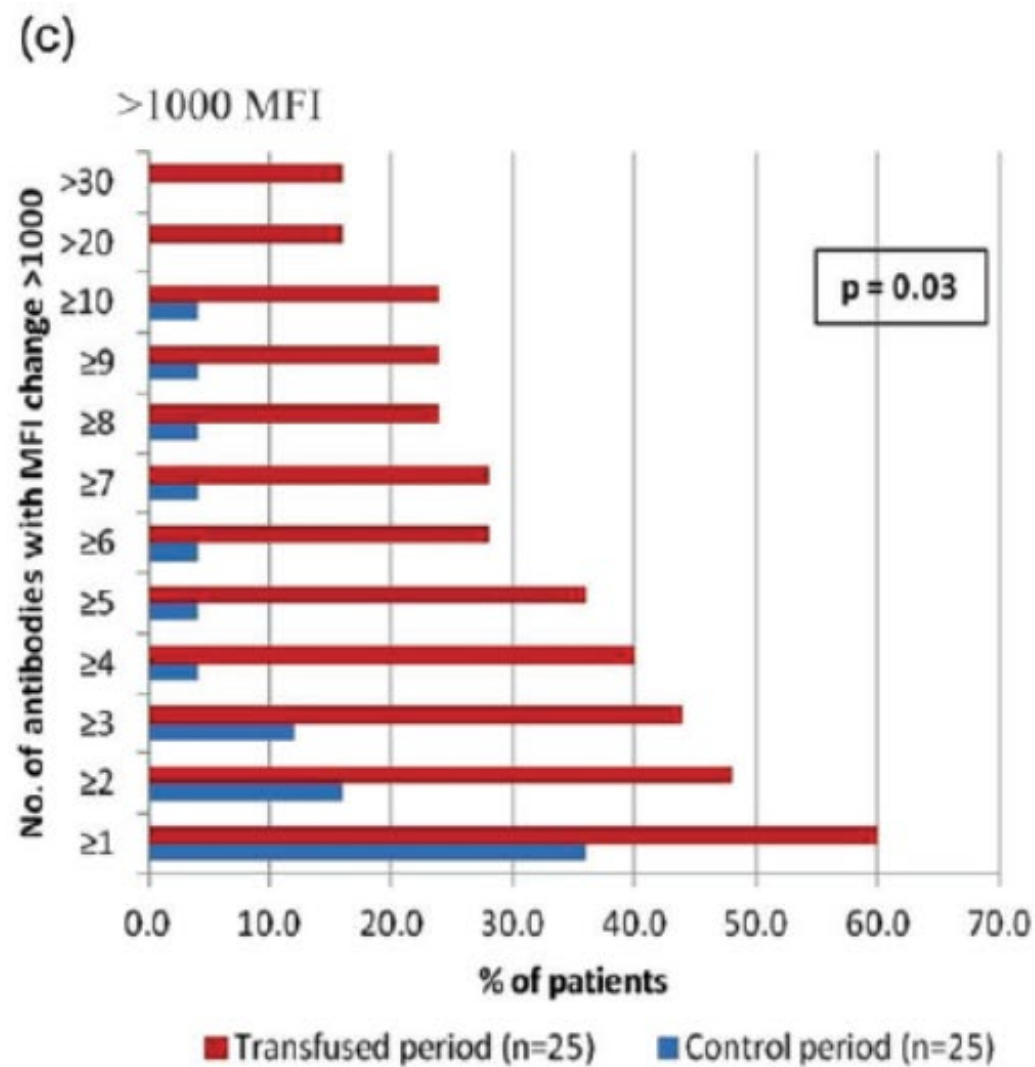
<sup>4</sup>Clinical Development and Center for Observational Research, Amgen, Inc., Thousand Oaks, CA, USA

- US Renal Data System
- On dialysis
- Awaiting kidney transplantation
- Luminex single-antigen bead assay
- 2 cohorts: (i) matched transfused and non-transfused  
(ii) crossover (pre- and post-transfusion)

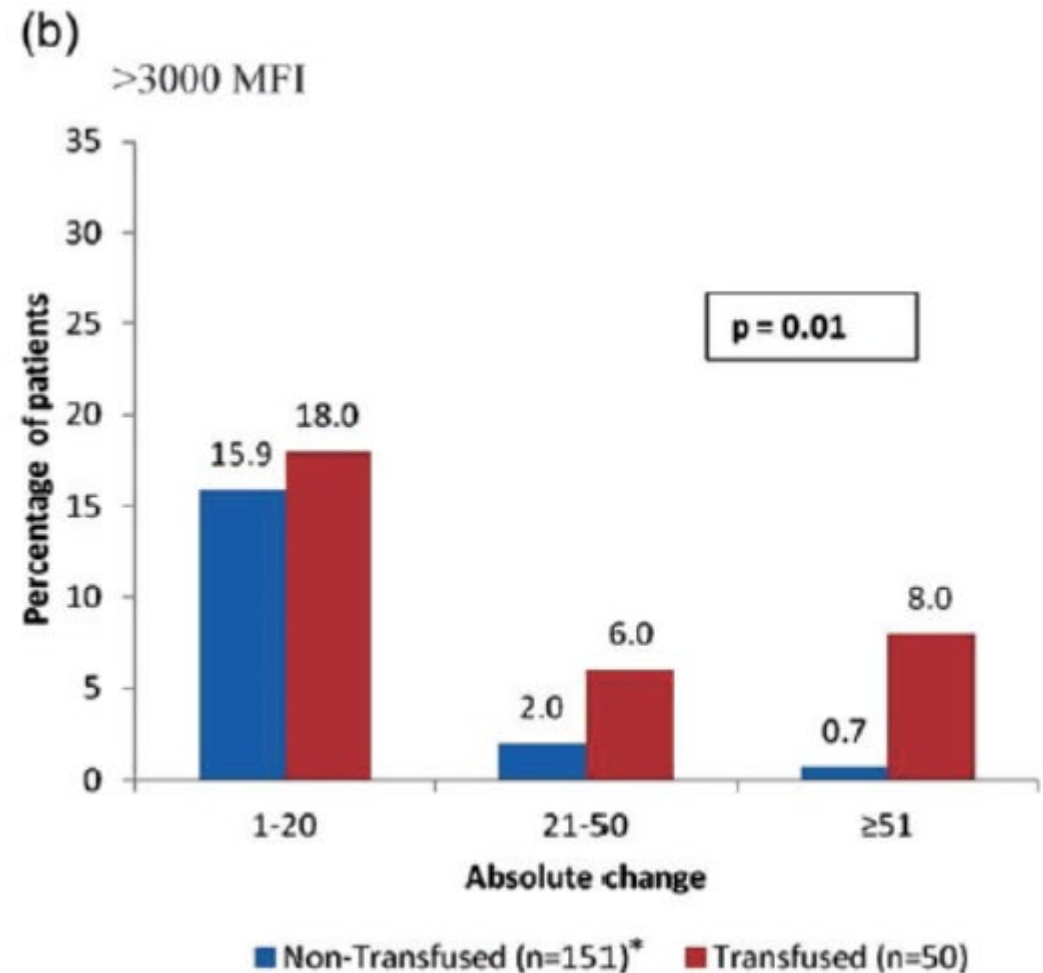
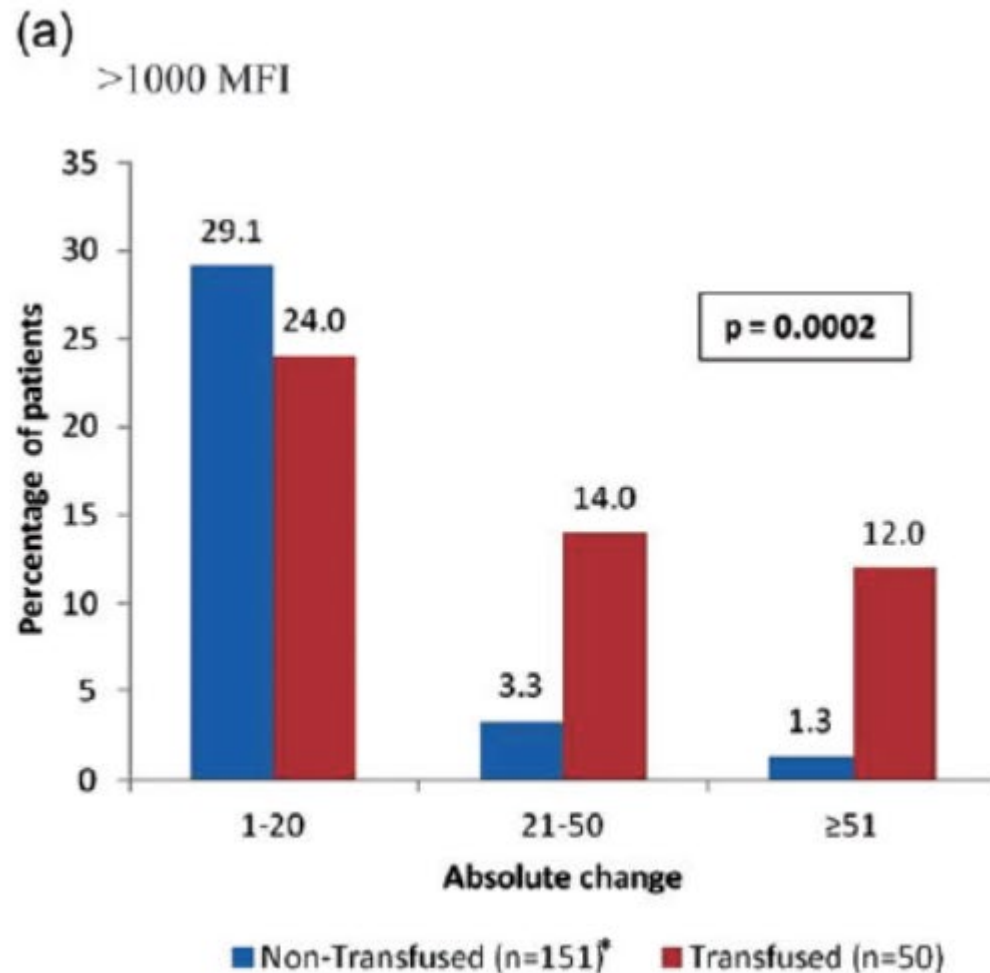
# Change in MFI for each unique HLA antibody in both transfused and matched non-transfused groups



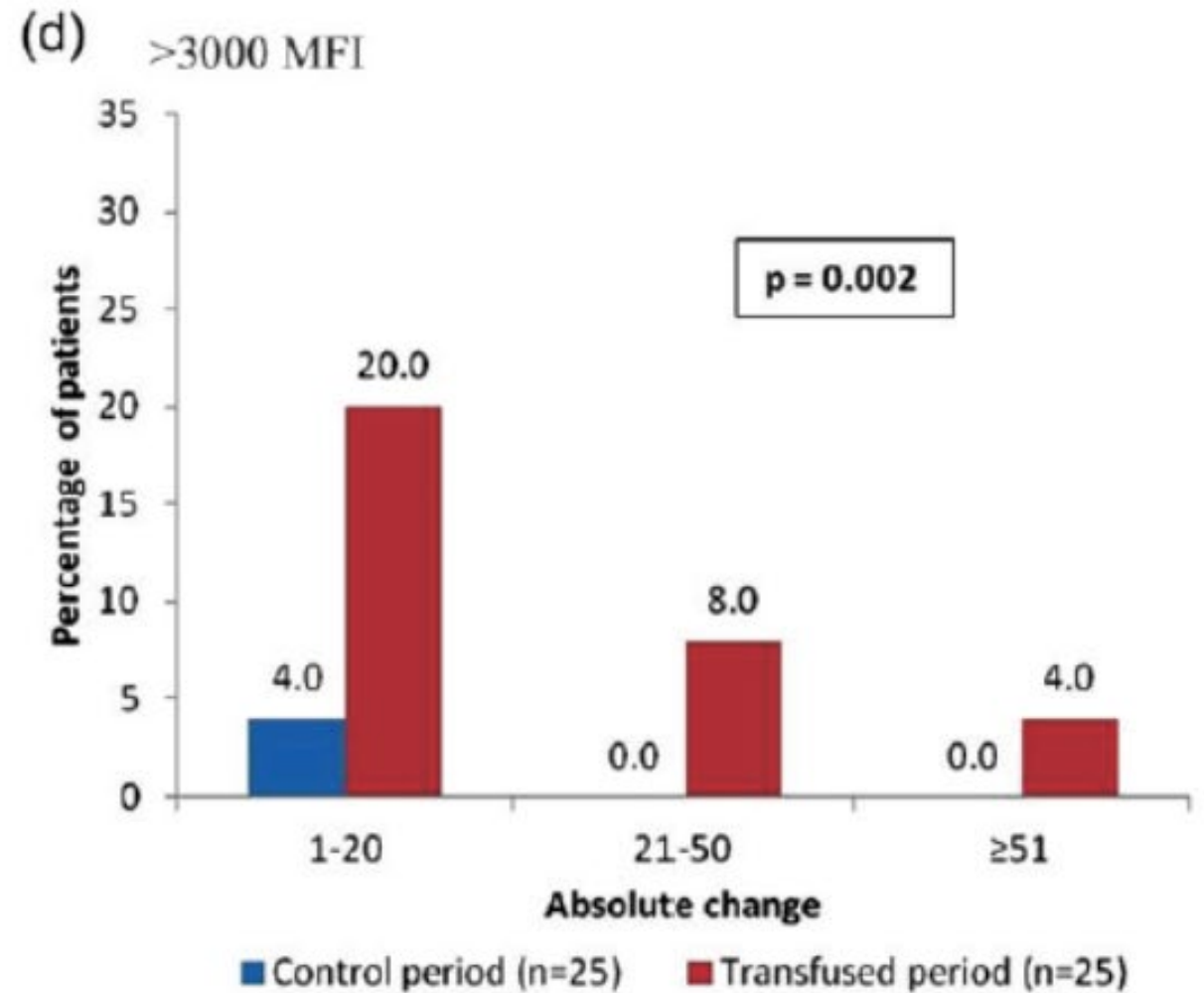
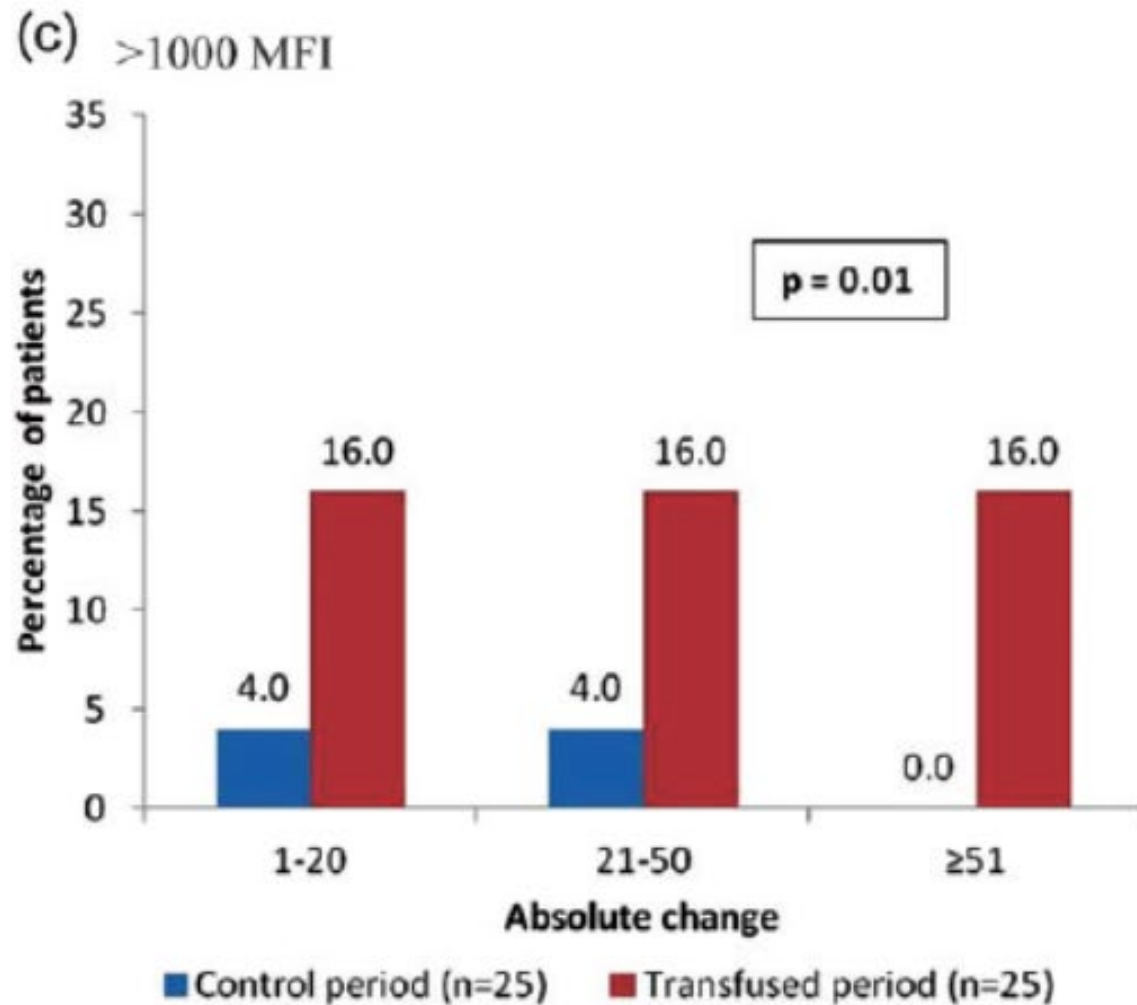
# Change in MFI for each unique HLA antibody in the crossover cohorts



# Absolute change in cPRA levels for all patients in transfused and matched non-transfused groups



# Absolute change in cPRA levels for all patients in crossover cohorts

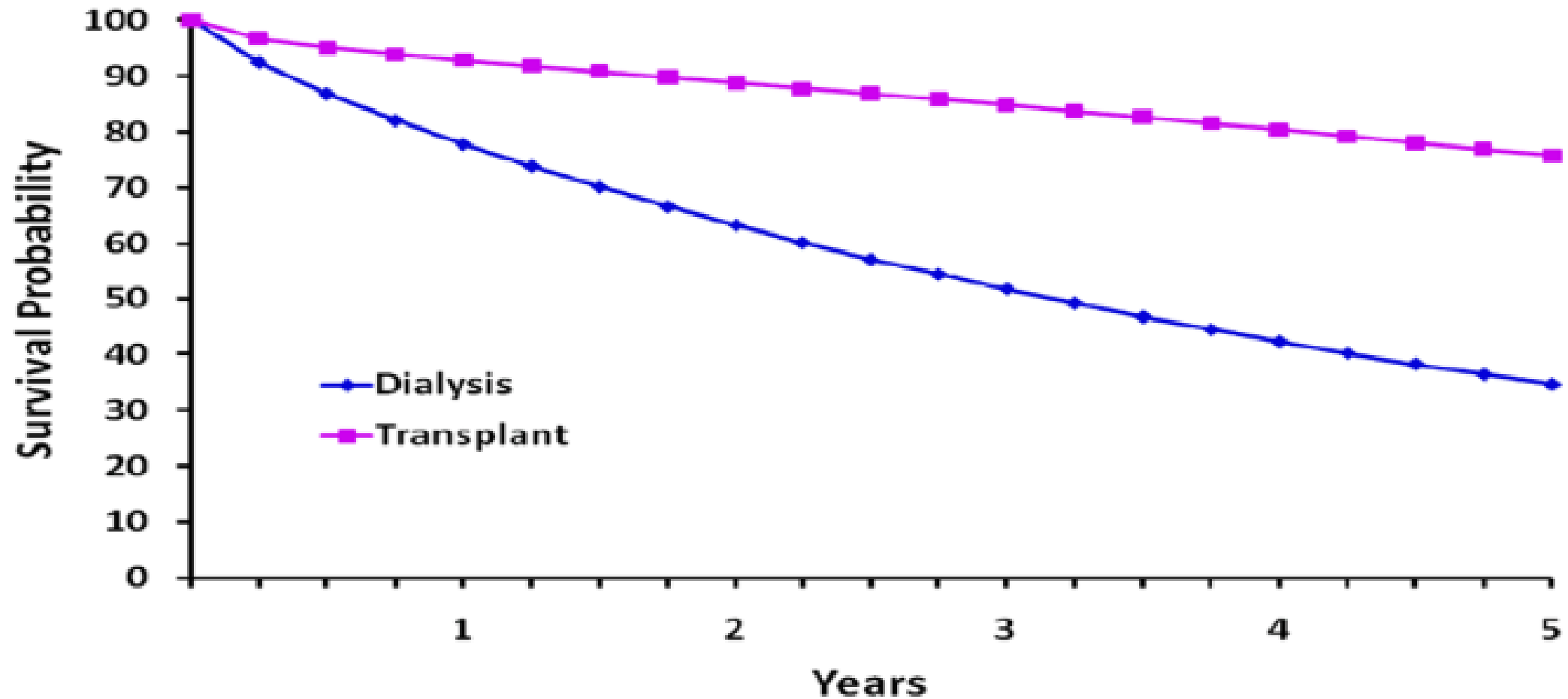


# Blood transfusions: what are the key questions in 2018?

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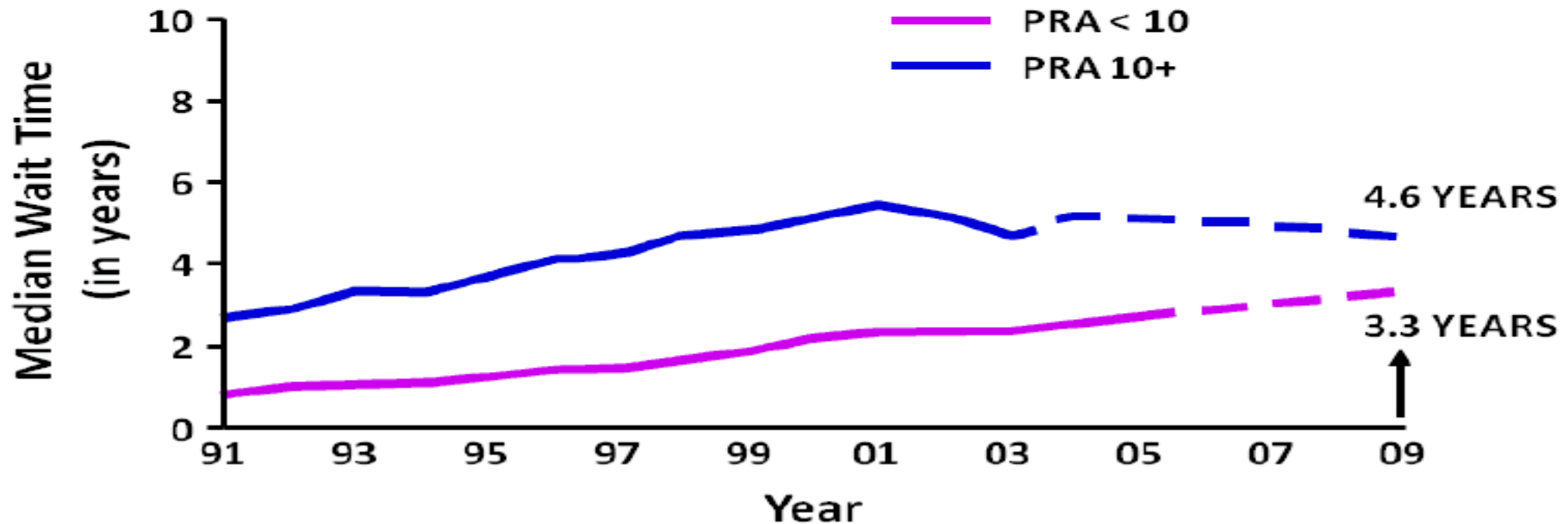
- What are the risks of reactions / transmitted infections in the modern era?
- Do RBC transfusions increase the risk of HLA sensitisation?
- Is HLA sensitisation bad for the patient?

# 5-year survival probability for Transplant vs. Dialysis patients

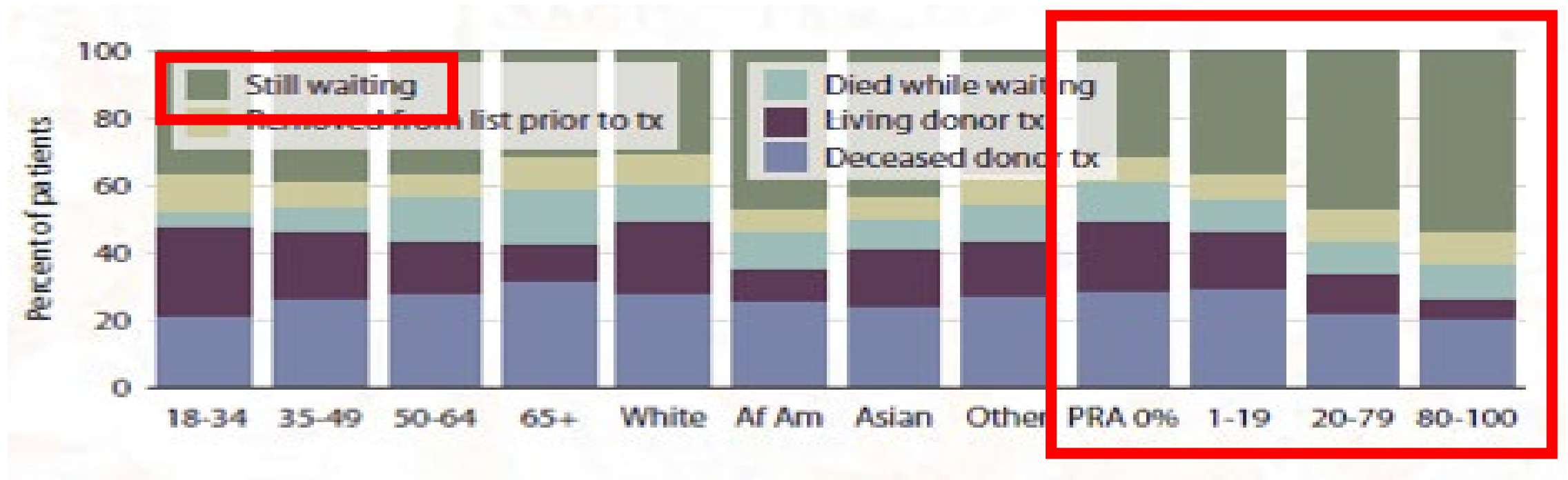


# Association of PRA With the Time to Kidney Transplantation

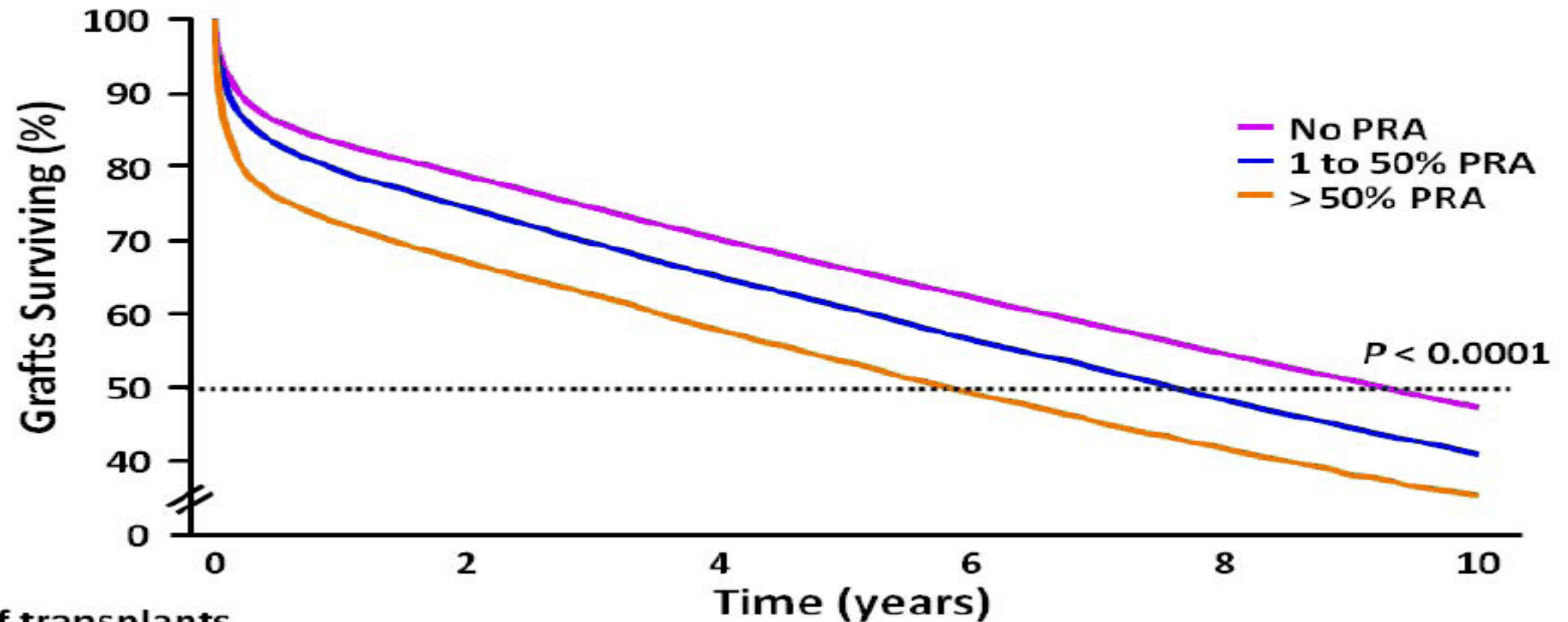
Projected median wait times for kidney transplantation based on PRA levels among patients 18 years and older listed for a first-time kidney-only transplant. Dashed lines show projected times.



# Outcomes for first-time wait-listed patients 3 years after listing, 2005, by age, race, and PRA



# Long-Term (10-Year) Survival of Cadaver Kidney Transplants According to Pre-Transplant PRA



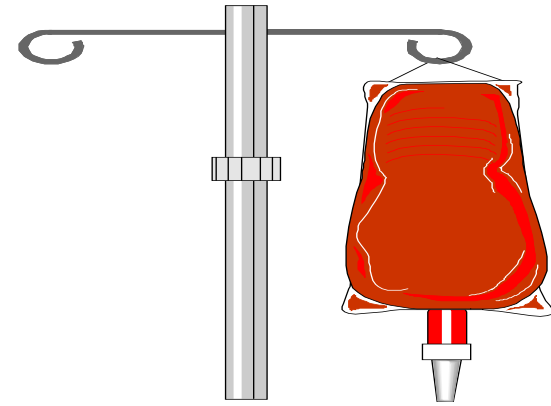
No. of transplants

No PRA	116562	83720	62516	44887	30819	20674
1-50% PRA	36314	25005	18402	12842	8590	5586
> 50% PRA	7610	4712	3582	2579	1817	1242

# What else can be done to reduce HLA sensitisation from blood transfusions?

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- Washed red cells
- Leukodepleted red cells
- HLA-matched red cells



## Leukocyte Reduction of Red Blood Cell Transfusions Does not Decrease Allosensitization Rates in Potential Kidney Transplant Candidates

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WILLIE LAIDLAW,<sup>†</sup> JAMES ZACHARIAS,\* and PETER NICKERSON\*<sup>†</sup>

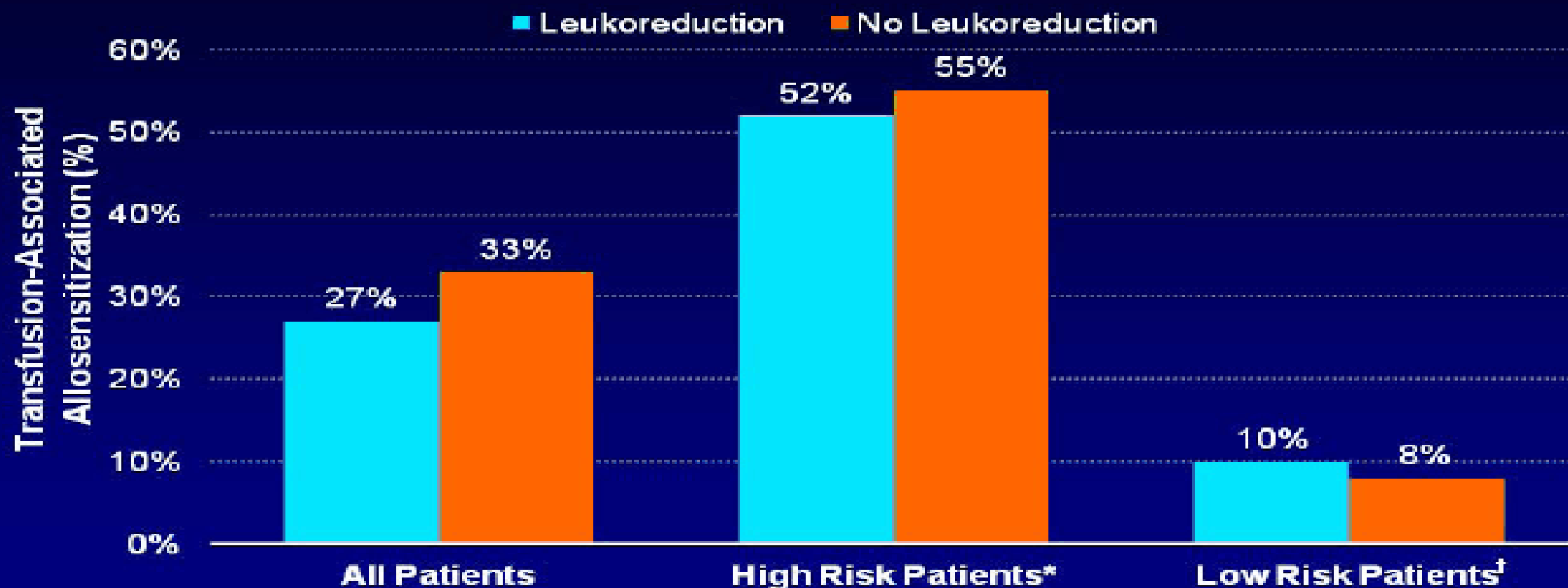
*\*Department of Medicine, University of Manitoba, Winnipeg, Manitoba, Canada; and <sup>†</sup>Immunogenetics Laboratory, Winnipeg Blood Center, Winnipeg, Manitoba, Canada*

[Pediatric Nephrology](#)

..... October 2014, Volume 29, [Issue 10](#), pp 2005–2011 | [Cite as](#)

Washing red cells after leucodepletion does not decrease human leukocyte antigen sensitization risk in patients with chronic kidney disease

# Effect of Leukoreduction of Transfused Blood on Allosensitization



P = NS for all comparisons

\*High risk patients had a history of pregnancy, transplantation, or  $\geq 5$  transfusions

†Low risk patients had no history of pregnancy, transplantation, or transfusions

Karpinski M, et al. *J Am Soc Nephrol*. 2004;15:818-824.

Transplantation Journal. 94(11):1111–1116, DEC 2012

DOI: 10.1097/TP.0b013e318271d776, PMID: 23111496

Issn Print: 0041-1337

Publication Date: 2012/12/15

# Effects of HLA-Matched Blood Transfusion for Patients Awaiting Renal Transplantation

Bernadette A. Magee; Jeanie Martin; Miceal P. Cole; Kieran G. Morris; Aisling E. Courtney

## Abstract

### Background

HLA sensitization in potential renal transplant recipients hinders opportunities of receiving suitable organs. To alleviate this, we sought to determine if supplying closely HLA Class I matched leukodepleted blood would minimize sensitization.

### Methods

Patients received HLA selected or random units of packed red cells. Selected units were sourced from blood donors included in the British Bone Marrow Registry and had no HLA-A and HLA-B mismatches where available, or alternatively, no HLA antigens with more than five immunogenic triplet mismatches as determined by the HLAMatchmaker algorithm. Posttransfusion antibody screening confirmed development of de novo Class I and Class II HLA-specific IgG antibody(s) or increases in preexisting antibody levels of at least 20%.

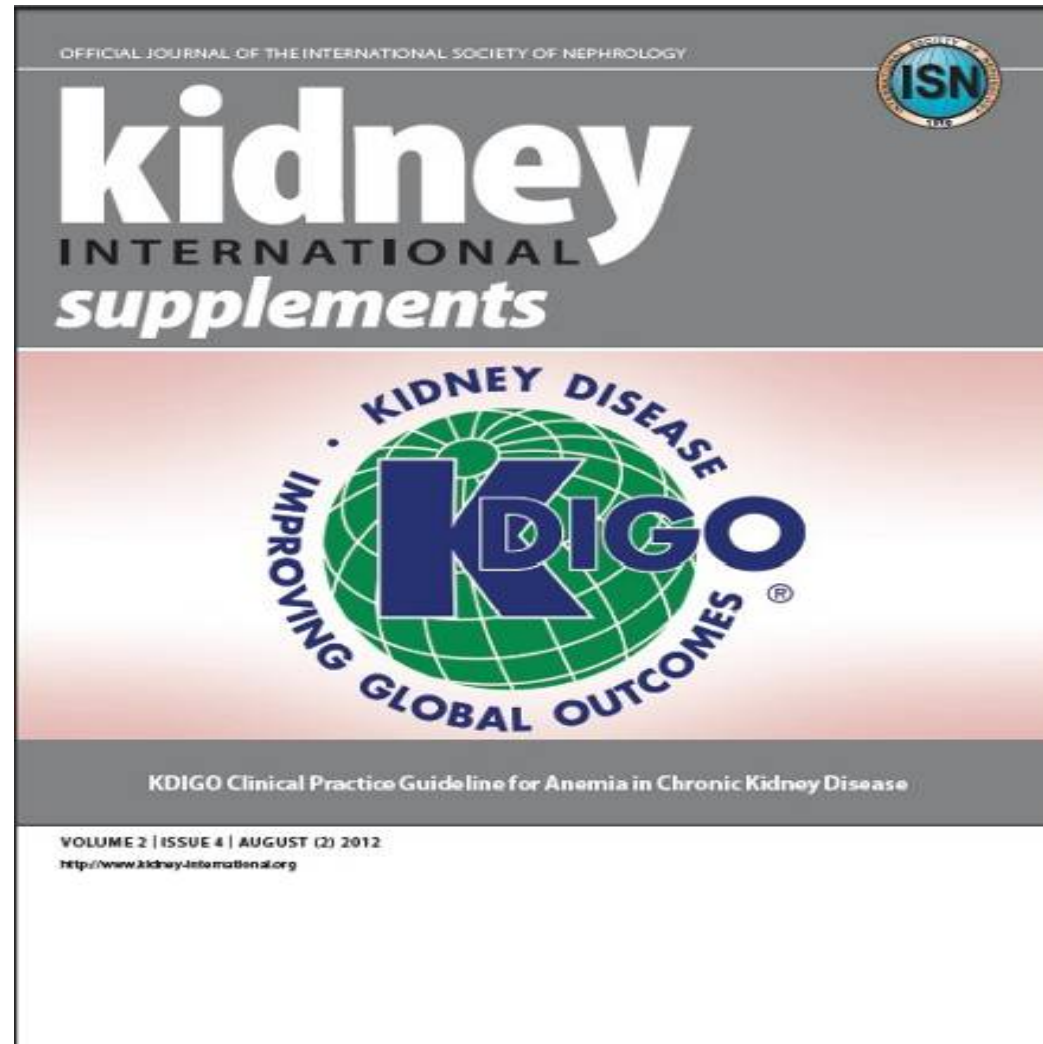
### Results

Thirty-seven and 31 patients received HLA selected (mean, 2.5 units) and random (mean, 3.4 units) blood, respectively. A total of 20 of 37 (54.1%) patients receiving selected units and 10 of 31 (32.3%) patients receiving random units were previously sensitized. No patient receiving HLA selected units demonstrated any change in antibody levels. In patients who received random units, 7 of 31 demonstrated changes in antibody levels with three developing de novo HLA-specific antibodies and four an increase in panel reactive antibody (PRA) of at least 20% ( $P=0.002$ ).

### Conclusions

The risk of developing HLA-specific antibody is significantly reduced in renal patients awaiting transplantation when transfused with HLA selected units of blood compared with random units. With planning, access to HLA typed blood is achievable as many blood transfusion centers recruit donors for stem cell donor registries.

# Who to transfuse?



# Who to transfuse?



- Chronic anaemia
- $\text{Hb} \geq 7 \text{ g/dl}$
- Young
- Already sensitised
- Transplant candidate

# Who to transfuse?



- Chronic anaemia
- Hb < 7 g/dl, symptomatic
- Resistant to ESA
- Marrow disorders, *e.g. MDS*
- Underlying malignancy

# Who to transfuse?



- Actively bleeding
- Hb < 7 g/dl
- Haemoglobinopathies, *e.g. sickle cell disease*
- Elderly
- Not a transplant candidate

# Conclusions

- Blood transfusions carry a very small but definite risk of transfusion reactions and transmission of infection
- ESA therapy has unquestionably reduced transfusion need
- RBC transfusions increase the risk of HLA sensitisation, which in turn has a negative effect on transplantation outcomes
  - *Increased time on waiting list*
  - *Increased rejection*
  - *Worsened graft survival*

