

Mitigating Iron Deficiency in Blood Donors: Issues, Strategies, and Prevention

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■ Disclosures

- PI on NIH IRON protocol
- Co-PI on STRIDE study

■ Conflict of Interest

- None

■ Disclaimer

- Any opinions expressed in this presentation are mine and do not represent the University of Texas System, UTMB, AABB, or SCABB

Iron Deficiency in Blood Donors

- Iron deficiency in 1st time and repeat blood donors is a challenge in transfusion medicine
- Iron is an essential element lost with each blood donation
 - 242 ± 17 mg for men
 - 217 ± 11 mg for women
- Normal iron stores
 - 1000 mg men
 - 350 mg women

Iron Deficiency in Blood Donors

- **In order for a donor to compensate for iron lost in donating blood:**
 - Iron is mobilized from the body's iron stores
 - Increased iron absorption from diet
- **Balance can be difficult to maintain in premenopausal females and regular blood donors since there is ongoing loss**
- **Young blood donors are an additional “at risk” subgroup**

Consequences and Symptoms

- **Consequences of iron deficiency in donors:**
 - Decreased iron stores → decreasing hemoglobin values → donor deferrals
 - Eventually may result in iron deficiency anemia if not treated

Symptoms of Iron Deficiency

- Fatigue
- Decreased exercise tolerance
- Difficulty in concentration
- Cognitive dysfunction
- Pica*
- RLS
- Hearing loss
- Pregnancy related complications
 - Perinatal mortality
 - Preterm delivery
 - Low birth weight
 - Newborn neurodevelopmental abnormalities

(* = strong evidence)



What have we learned from Iron Replacement Studies?

- **IRON Program – NIH**
- **Iron for Women Program - Indiana Blood Center**
- **HEIRS Study**
- **STRIDE Protocol**

Iron Replacement Therapy in the Routine Management of Blood Donors

(I.R.O.N. Protocol: “Iron Replacement or Not”)

Bryant BJ, Yau YY, Arceo SM, et al. Transfusion 2012;52-1566-1575

■ Background

- 8-12% of all WB donor visits to DTM end in deferral for low FS Hgb

■ 39-month study at the NIH

- “Low hemoglobin” donors
 - ◆ Screening capillary fingerstick sample by HemoCue device
- “Control” donors

I.R.O.N. Protocol

- **Additional health history screening**
- **Laboratory testing**
 - CBC
 - Iron studies (ferritin, serum iron, % sat, transferrin)
 - Other
- **Oral iron replacement therapy**
 - FeSO₄, 325 mg (65 mg elemental iron)
 - FeGluconate, 325 mg (38 mg elemental iron)

Iron Stores Definitions

- **Women: Ferritin normal range = 9-120 mcg/L**
 - Fe deficient: ferritin < 9 mcg/L
 - Fe depleted: ferritin = 9-19 mcg/L
 - Fe replete: ferritin ≥ 20 mcg/L
- **Men: Ferritin normal range = 18-370 mcg/L**
 - Fe deficient: ferritin < 18 mcg/L
 - Fe depleted: ferritin = 18-29 mcg/L
 - Fe replete: ferritin ≥ 30 mcg/L

IRON Protocol

- **1236 “Low FS Hemoglobin” donors**
 - 1073 (89%) females, mean FS Hgb 11.8
 - 163 (11%) males, mean FS Hgb 11.9
- **400 “Control” donors**
 - 143 (37%) females, mean FS Hgb 13.7
 - 257 (63%) males, mean FS Hgb 14.9

Results

■ Low Hgb Group

- Females:
 - 30% iron depleted
 - 23% iron deficient
- Males:
 - 8% iron depleted
 - 53% iron deficient

■ Control Group

- Females:
 - 29% iron depleted
 - 10% iron deficient
- Males:
 - 18% iron depleted
 - 21% iron deficient

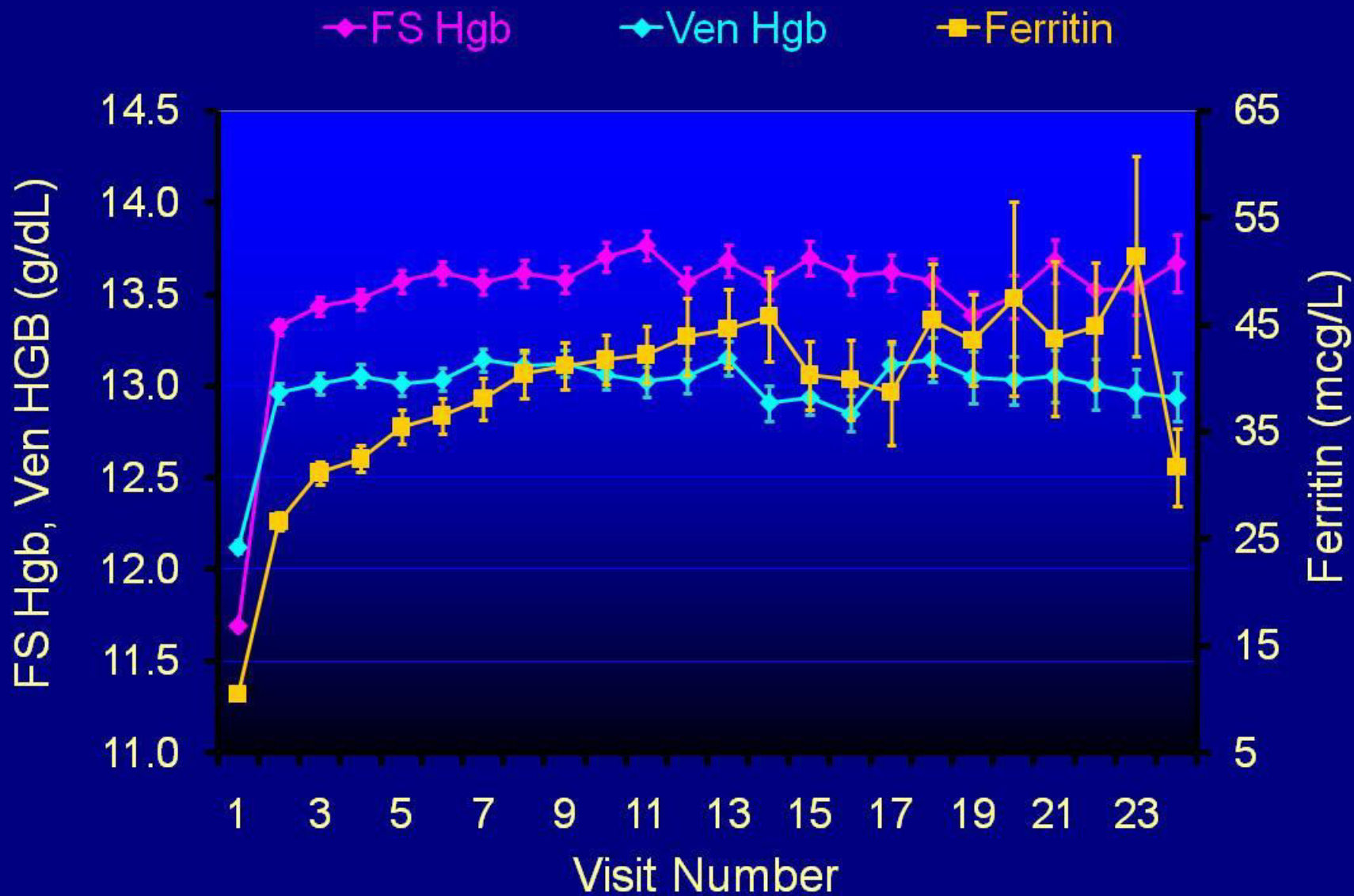
Association of FS Hgb Levels with Iron Status and Venous Hgb in ♀

WOMEN (n=1216)	Fingerstick Hemoglobin Levels (g/dL)			
	< 11.5	11.5-11.9	12.0-12.4	≥ 12.5
Iron Status % (n) %Menopause	(n=256)	(n=302)	(n=515)	(n=143)
Fe deficient	40% (102) 4%	24% (72) 4%	14% (70) 1%	10% (14) 3%
Fe depleted	26% (66) 5%	28% (86) 4%	32% (166) 5%	29% (42) 7%
Fe replete	34% (88) 6%	48% (144) 11%	54% (279) 13%	61% (87) 24%
Venous Hgb ≥ 12.5	18% (47)	35% (106)	55% (283)	80% (115)

Association of FS Hgb Levels with Iron Status and Venous Hgb in ♂

MEN (n=420)	Fingerstick Hemoglobin Levels (g/dL)				
	< 12.0	12.0-12.4	12.5-12.9	13.0-13.4	≥ 13.5
Iron Status % (n)	(n=74)	(n=89)	(n=9)	(n=19)	(n=229)
Fe deficient	62% (46)	46% (41)	56% (5)	26% (5)	19% (44)
Fe depleted	6% (4)	10% (9)	22% (2)	26% (5)	18% (40)
Fe replete	32% (24)	44% (39)	22% (2)	48% (9)	63% (145)
Venous Hgb ≥ 12.5	55% (41)	69% (61)	78% (7)	95% (18)	100%(229)

Effect of Iron Therapy in Low Fingerstick Hgb Donors



Pica and RLS

- **Pica was reported in:**
 - 11% donors with Fe depletion/deficiency
 - 4% donors w/out Fe depletion/deficiency
 - Positive predictive value = 73%
- **RLS was reported in:**
 - 16% donors with Fe depletion/deficiency
 - 11% donors w/out Fe depletion/deficiency
 - Positive predictive value = 58%

Long Term Donor Center Operational Effects

- **Interval between visits:**
 - **Low Hgb group**
 - **92 days females**
 - **76 days males**
 - **Control group**
 - **94 days females**
 - **81 days males**
 - **Overall = 87 days**

Operational Effects

- Reduction of donor deferrals not sustained
- However, average productive donor visits/donor/year:
 - 1.3 for entire donor population
 - 1.1 for females
 - 1.6 for males
 - 1.9 for study population
 - 1.5 for females
 - 2.8 for males

Operational Effects

- Although, donors in the IRON protocol had higher deferral rates, they returned to the blood bank more often to attempt donations resulting in a 46% increase in productive visits per donor per years compared to the general donor population
- Thus, donors on iron donated more units of WB per year than the general donor population

Currently at the NIH

- **Iron replacement protocol adopted as routine medical practice with few modifications:**
 - FeGluconate
 - Laboratory testing performed initially and after subsequent deferrals

Indiana Blood Center - Iron for Women (IFW)

- Operational program only
- Carbonyl iron given to menstruating female donors between ages 18-50 yrs
- Donation and Deferral rates
 - Pre-program:
 - 1.9 donations/yr and 2.2 deferrals/yr
 - Currently:
 - 3.5 donations/yr and 1.6 deferrals/yr

HEmoglobin Iron and Recovery Study (HEIRS)

Kiss JE, Brambilla D, Glynn SA, et al. *JAMA* 2015;313:575-583

- **Study Aim: Determine the time to postdonation hemoglobin and ferritin recovery with and without iron**

HEIRS

- **136 female and 79 male donors**
 - No donation in previous 4 month
 - Ferritin levels obtained
 - Upon return donation:
 - Segregated into iron depleted (ferritin \leq 26 ng/dL) vs non-iron depleted groups
 - Randomly assigned to receive 37.5 mg elemental iron daily for 24 weeks or no supplementation
 - Hgb and ferritin measured 7x during study out to 24 weeks

HEIRS Results

- **Compared to donors who did not take iron, donors taking iron returned to 80% of predonation hgb levels faster**
 - Iron-depleted group = 5 weeks vs 23 weeks
 - Non-iron depleted group = 4 weeks vs 11 weeks
- **Return to baseline ferritin results in donors taking iron vs not taking iron**
 - 11 week vs >24 weeks
- **At 24 weeks, 66% of donors not taking iron had not recovered iron lost at donation**

From: Oral Iron Supplementation After Blood Donation A Randomized Clinical Trial

JAMA. 2015;313(6):575-583. doi:10.1001/jama.2015.119

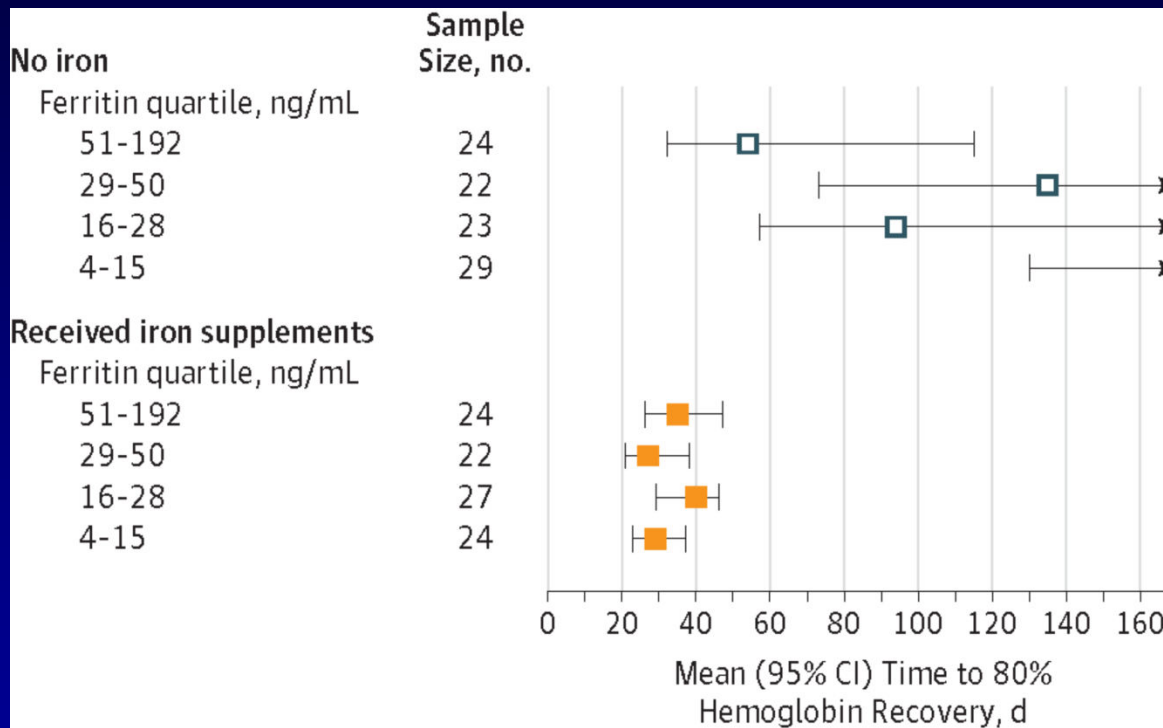


Figure Legend:

Mean Time to 80% Hemoglobin Recovery by Quartile of Ferritin and Treatment Assignment. The confidence intervals are censored at the end of follow-up at 168 days. No mean is shown for the lowest ferritin quartile for participants not taking iron because the mean was longer than 168 days.

HEIRS Conclusions

- **Therefore, extending interdonation interval to 12 or 16 weeks was not sufficient without iron supplementation**
- **Significant effect of supplemental iron was noted in the 1st 8 weeks of iron therapy**
 - Weakly demonstrable in the 2nd 8 weeks in those with iron deficiency
 - Not notable in either donor group in 3rd 8 weeks
- **Low dose iron replacement for 8 weeks likely to be effective**

Strategies To Reduce Iron Deficiency (STRIDE)

Mast AE, Bialkowski W, Bryant BJ, et al. *Transfusion* 2016;56:1588-1597

- The objective of this study was to obtain randomized and placebo controlled data to determine the efficacy of donor education and iron supplementation interventions for preventing iron deficiency in frequent blood donors

STRIDE
Strategies to Reduce
Iron Deficiency
Study



STRIDE

- **Randomized, blinded, placebo-controlled, multi-center study of education and iron supplementation for mitigation of iron deficiency in frequent blood donors**
- **Designed to improve the health of regular blood donors**
 - Through development of effective programs that prevent development of iron deficiency
 - Easily and readily implemented in community blood centers

Study Population

- Donors ≥ 18 years of age
- Donated whole blood or double red cells
 - ≥ 3 times in the past 12 months if male
 - ≥ 2 times in the past 12 months if female
- Commitment to meet (or exceed) donation frequency requirements for 2 more years, give a blood sample at each visit, and complete baseline and follow-up surveys

STRIDE

- **Two year study of 692 frequent blood donors**
- **Ferritin, sTfR and CBC measured at each visit**
- **Two letter arms:**
 - Iron status letter following each donation
 - Thank you (control) letter following each donation
- **Three pill arms:**
 - 38 mg elemental iron for 60 (or 120 days)
 - 19 mg elemental iron for 60 (or 120 days)
 - Placebo for 60 (or 120 days)

Educational Arm: Letters



"thanks for donating!"

*"your iron status is normal"
(ferritin ≥ 26)
or
"your iron status is low"
(Ferritin < 26)*

Interventional Arm: Iron Tablets



38 mg iron

19 mg iron

0 mg iron = placebo



Iron Status Letter Arm

- Donors with ferritin ≥ 26 ng/mL received a letter recommending continued donation
- Donors with ferritin < 26 ng/mL received a letter recommending either:
 - Taking an iron supplement
 - Delaying donation for 6 months
- Donors were allowed to chose to do either, both or neither

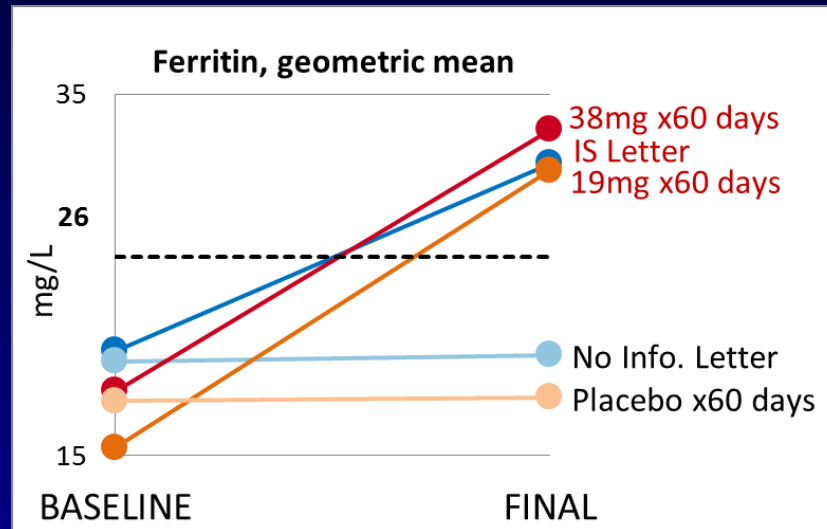
Interventional Arm: Receiving Tablets

- **Double-blinded, placebo controlled**
- **Instructed to take 1 tablet daily**
 - 60 days following each WB donation
 - 120 days following a double red cell donation
- **Unused pills returned to assess compliance**
- **Adverse events reported and tracked**

STRIDE Analyses

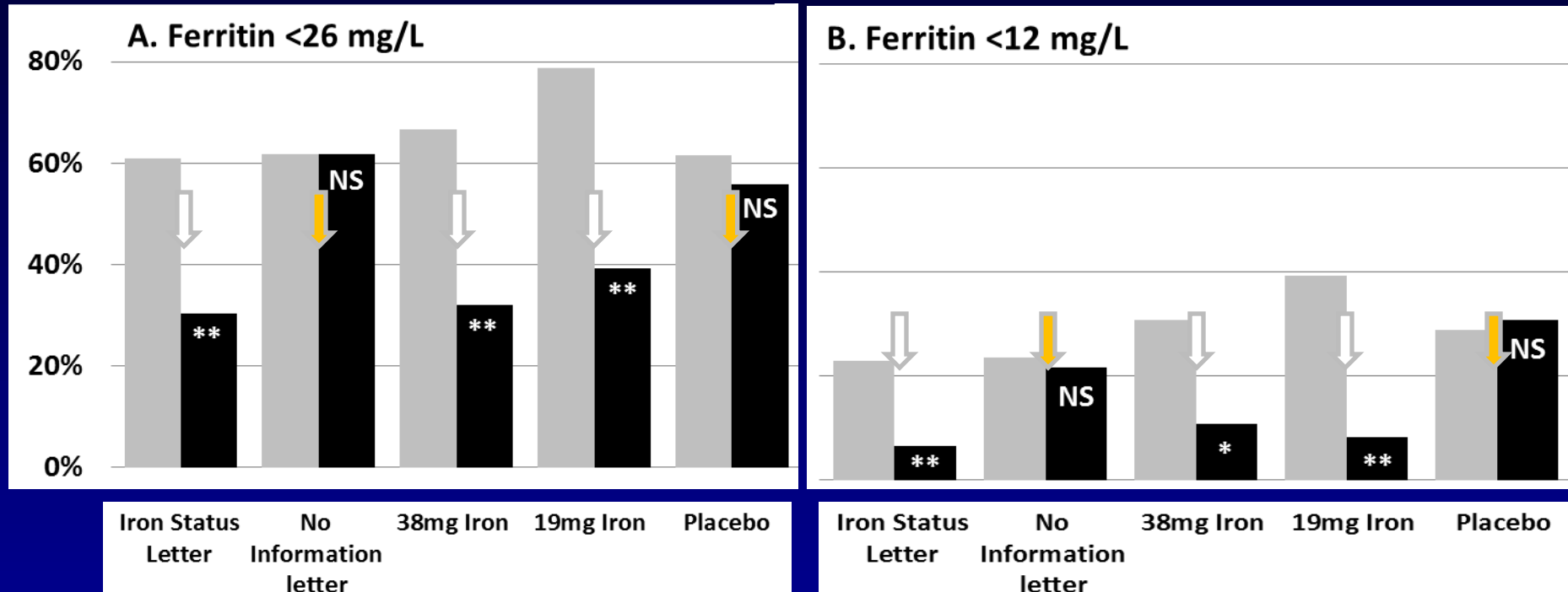
- **Comparison of status at the final visit**
 - 393 subjects
- **Comparison of changes between enrollment and final visit**
 - 393 subjects
- **Longitudinal analyses of all visits**
 - 692 subjects

Change in Iron Status between Enrollment and Final Visit



- Final iron status was mostly equivalent for the 19 and 38 mg iron groups.
- Iron status letter arms and better than control arms.

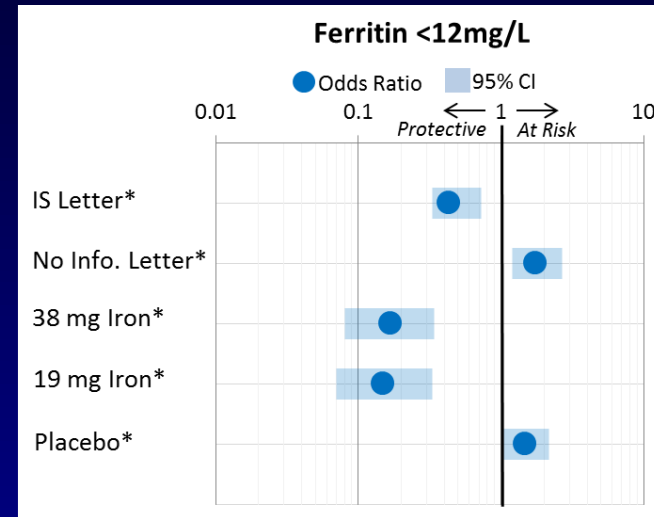
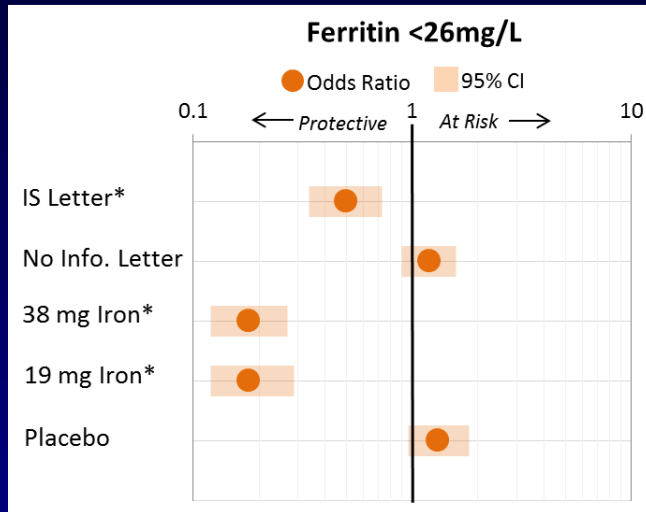
Change in Ferritin Cut-off Status between Enrollment and Final Visit



Ferritin <26 mg/L declined over 50% in all 3 intervention groups
 Ferritin <12 mg/L declined over 70% in all 3 intervention groups
 No change in control groups

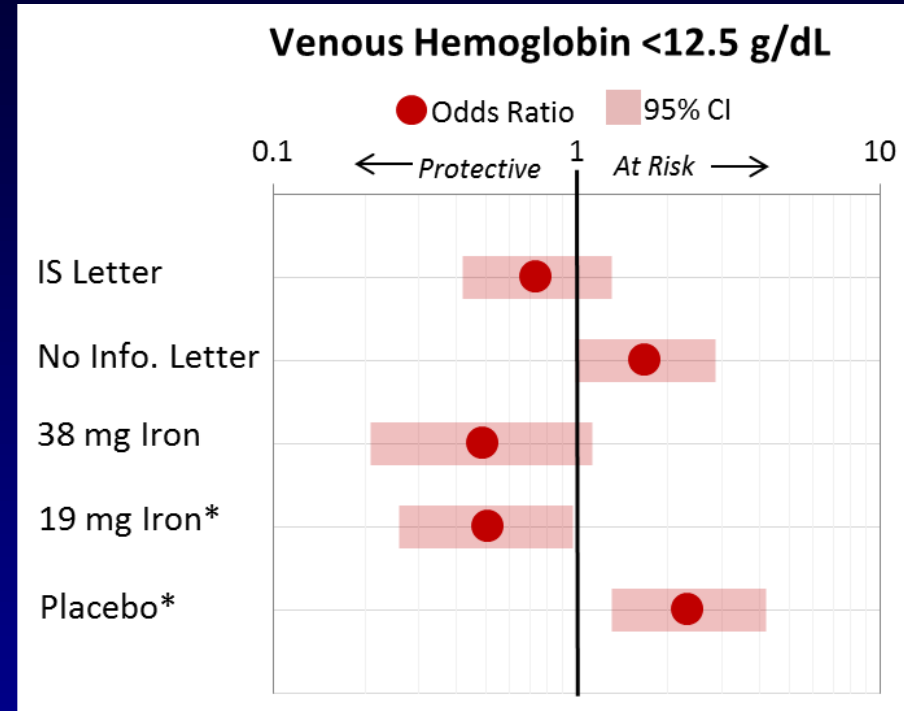
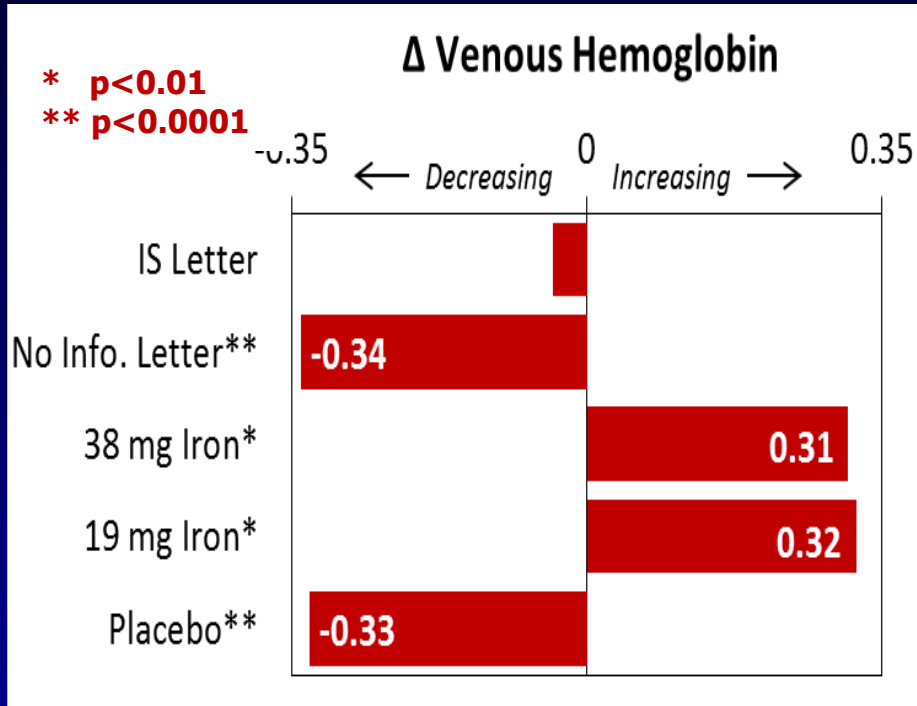
**p<0.0001, *p<0.01, NSp>0.05

Odds Ratios for Iron Deficiency in Longitudinal Modeling of All Visits



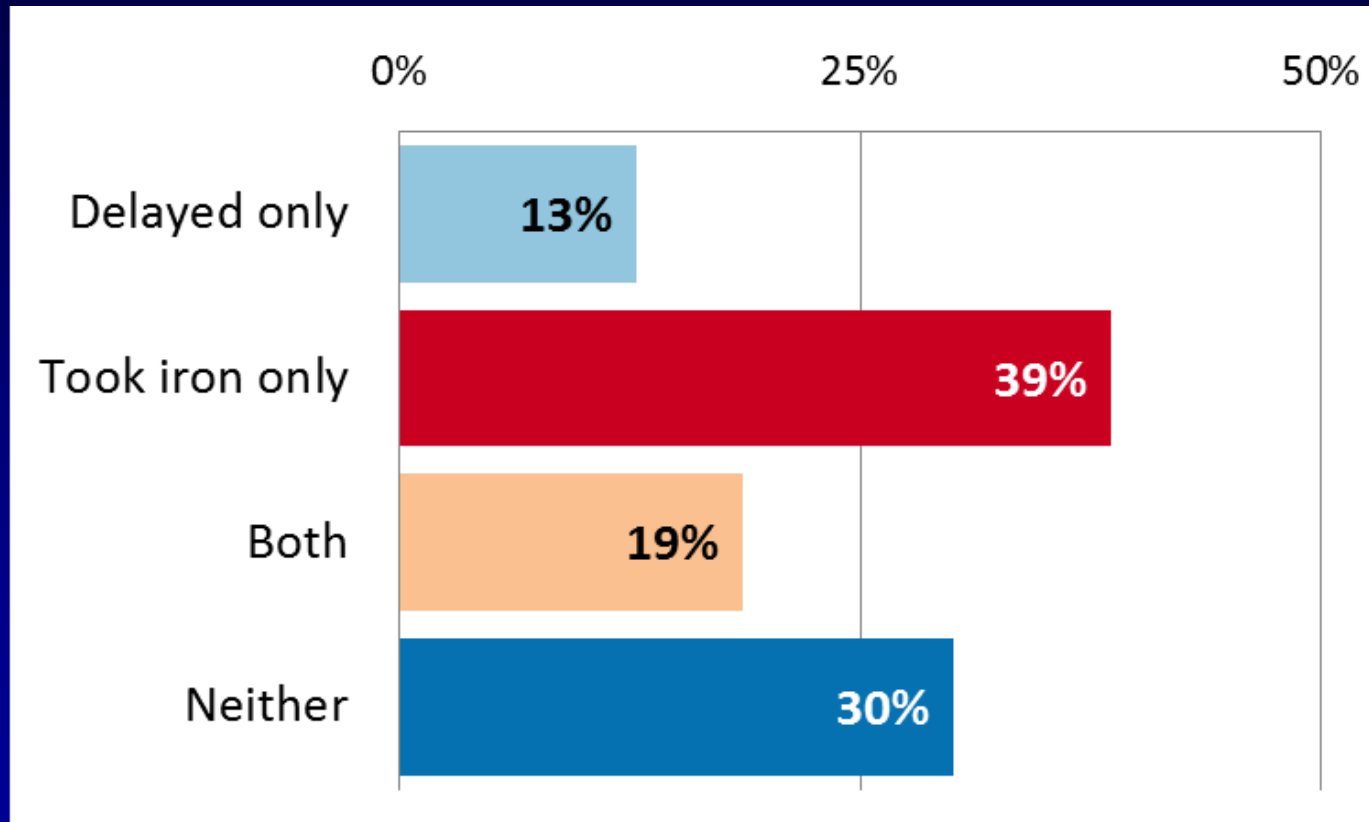
- The odds for iron deficiency decreased >80% in the 19 and 38 mg iron groups
- The odds for iron deficiency decreased ~50% in the iron status letter group
- The risk for ferritin <12 mg/L increased 48 to 76% in control groups

Longitudinal Modeling of Hemoglobin



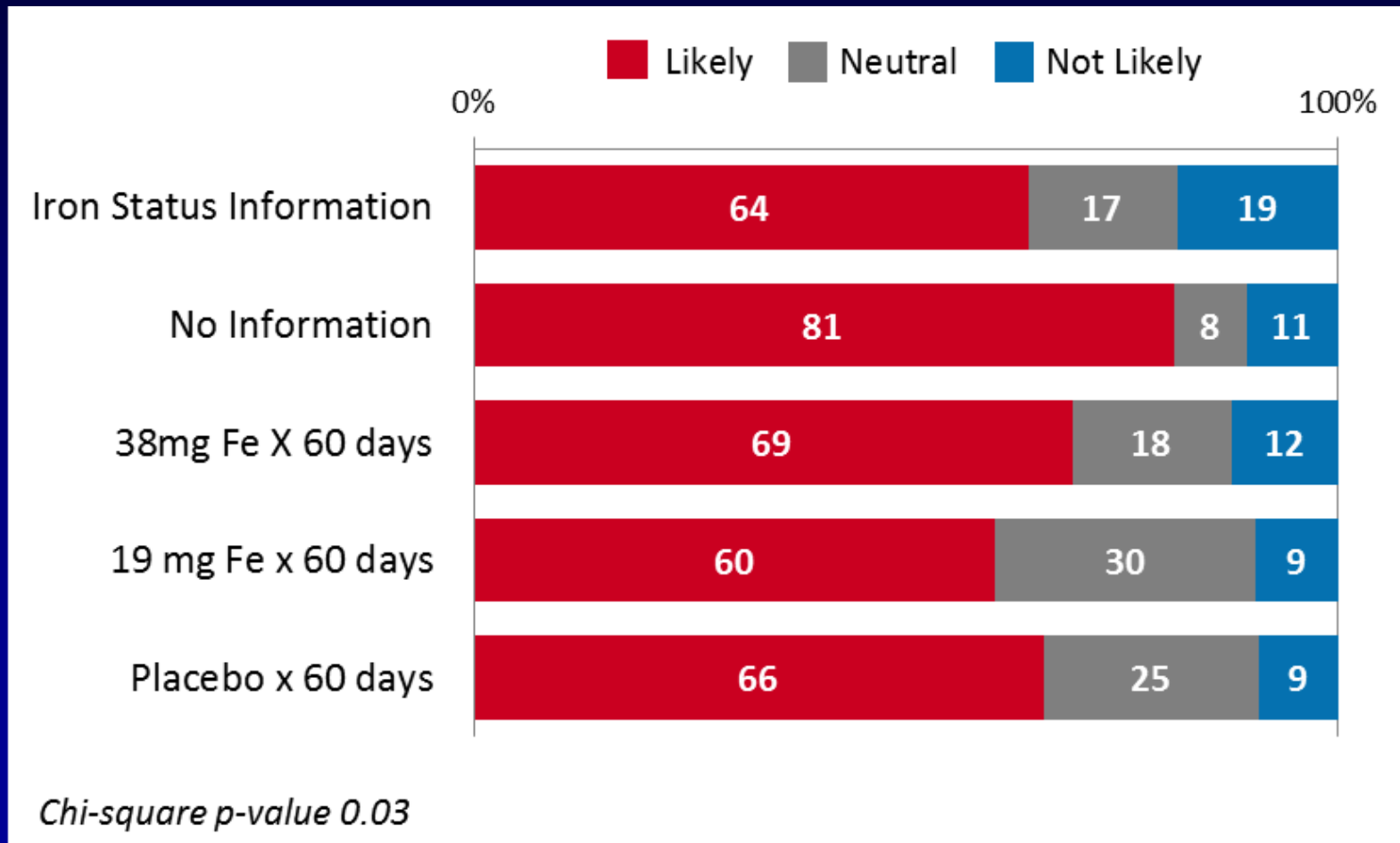
- Hb increased >0.3 g/dL in 19 and 38 mg iron groups, decreasing the odds for low Hb deferral about 50%
- Hb decreased >0.3 g/dL in control groups, increasing the odds for low Hb deferral about 70%

Fewer low ferritin letter donors chose to delay donation than to take iron

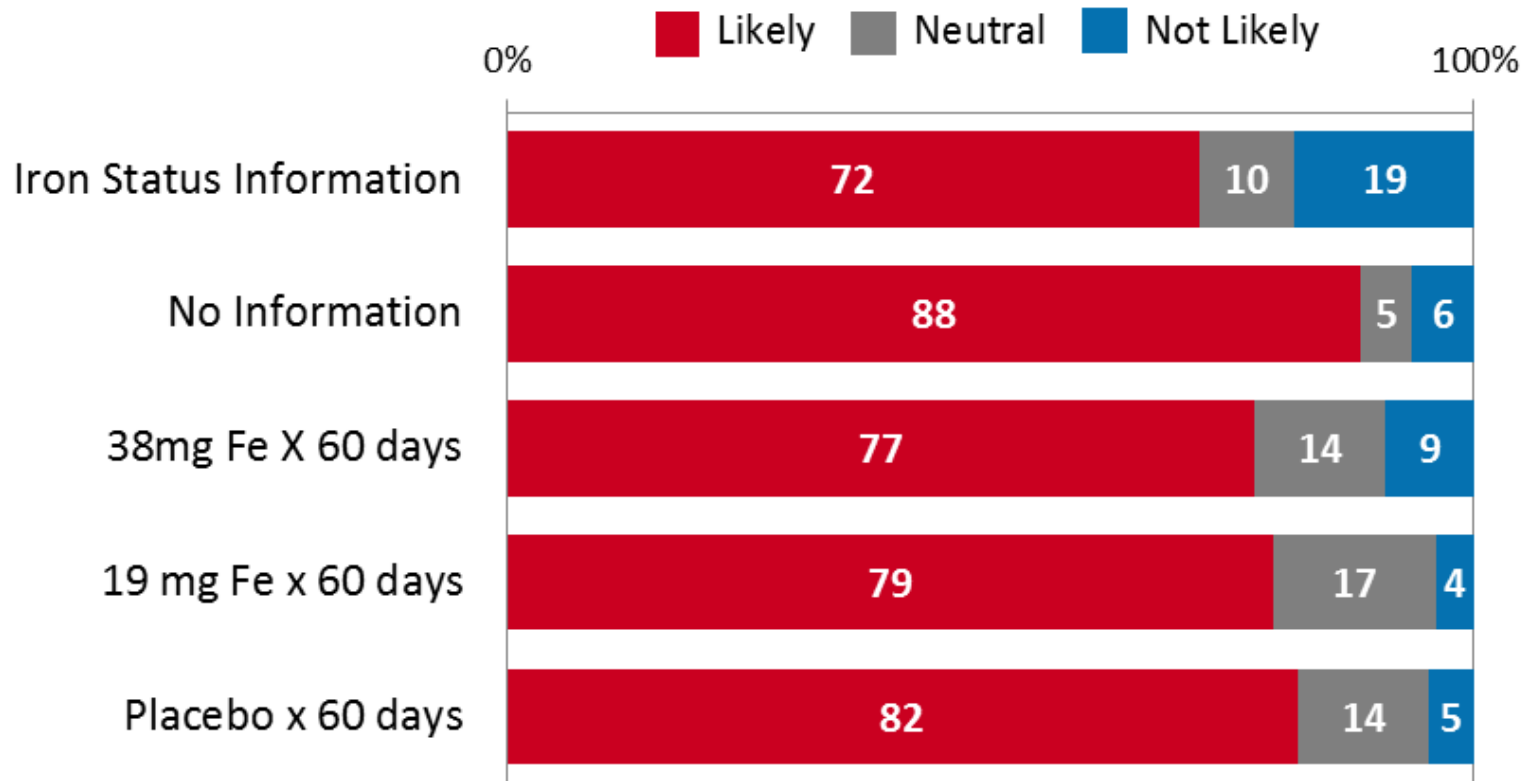


McNemar's Test
p=0.004

Will donors buy and take recommended iron replacement?



Will donors take iron replacement if provided by the blood center?



Chi-square p-value 0.02

STRIDE Conclusions

- A 60-day course of once daily 19 mg iron pills are as effective as 38 mg iron pills for mitigation of iron deficiency in regular blood donors
- Providing accurate information about iron status to donors through ferritin testing and allowing the donor to act on their own is effective for mitigation of iron deficiency in regular blood donors

STRIDE Conclusions

- Providing 19 or 38 mg iron pills improves donor hemoglobin status
- Frequent donors who do not take actions to prevent iron deficiency become progressively more iron deficient with continued donation
- Data from STRIDE as well as several previously published studies from other groups provide ample data for design of operationally feasible programs to mitigate donor iron deficiency

Summary

- **Blood centers are confronted with the on-going challenges of iron deficiency in blood donors**
 - Pre-existing
 - Resultant
- **Altruistic donors come to Blood Centers in order to “give the gift of life” and this is an opportunity for the Blood Centers to give something of value back to these donors**

Summary (cont'd)

- **Iron replacement therapy is a cheap, safe, and effective method of preventing iron deficiency in donors**
- **Advantages to the donor:**
 - Increases successful donor visits
 - Enhances donor well-being by preventing symptomatic iron depletion/deficiency
 - Increases overall donor satisfaction

Summary (cont'd)

- **Advantages to the donor center of establishing iron-replacement programs include:**
 - Results in more productive donor visits (blood donations)
 - Improves donor retention
 - **Cheaper to retain than to recruit**
- **Win-Win situation**

Implications for WBB Programs

- Limited donor pool
- High performance requirements post-donation
- Iron replacement extremely important



Thank You

Extra Slides

Comparison of the History of Donation and Iron LeveLs in Teen Blood Donors (CHILL)

Spencer BR, Bialkowski W, Cable RG, Kiss JE, et al.

- **High school blood donors at 2 US blood centers**
- **Primary objectives:**
 - Assess prevalence of low ferritin (<12 and <26 ng/mL) in high school age donors
 - Assess the impact of blood donations

CHILL

- **6219 donations from 4265 donors**
 - 3714 teen donors (age 16-18) making 5439 donations
 - 551 control donors (age 19-49) making 780 donations
- **Ferritin levels measured at 1st and subsequent donations during an academic school year**

CHILL

- Younger donors (age 16-18 yo) had a risk for ferritin <12 or <26 ng/mL that was more than 2 or 3 fold higher, respectively, compared to control donors
- Risk for low ferritin levels extended up to 1 year with those donating at intervals of 24 - 52 weeks having an odds ratio $\sim 2x$ those donating at intervals > 1 yr

CHILL

■ Conclusions:

- Baseline iron deficiency higher in teenagers before donation
- Exacerbated to greater extent by blood donation than in adult donors
- For some donors, an interdonation interval of up to 12 months may be needed to avoid iron deficiency

A Large National Study of Ferritin Testing in Canadian Blood Donors

Goldman M, Uzicanin S, Osmond L, Scalia V, O'Brien SF. *Transfusion* 2017;57:564-570

- Feasibility and efficacy of ferritin testing in a large blood center
- Donors from centers representative of entire donor base were assessed for iron deficiency
- 17 month study
- Ferritin measured on retention samples

Canadian Study

- **Donors with ferritin <25 µg/L were sent letters**
 - Given results of ferritin test
 - Advised donors to see their health care provider for further investigation and possible iron supplementation
 - Told they should stop donating blood for 6 months
 - Return to donate after their ferritin level had been rechecked by MD and it had returned to normal
- **These donors received an email questionnaire 6 months later asking if they had followed instructions**
- **Follow-up ferritin tested done on donors previously tested**

Canadian Study Results

- **12,595 donors tested (2.6% of entire donor base)**
 - More likely to be male repeat donors with more donations in past 12 months
 - 90% repeat donors
 - 23% had donated 4-6 time in previous 12 months
- **Absent iron stores (ferritin < 12 µg/L) found in**
 - 30% female donors
 - 12% male donors
- **Low iron stores (ferritin 12-24 µg/L) found in**
 - 30% female donors
 - 21% male donors

Canadian Study Results

- **Low ferritin donors (ferritin < 25 µg/L)**
 - First time and reactivated (no donations in past yr) donors
 - **Males = 2.9%**
 - **Females = 32.2%**
 - Repeat donors
 - **Males = 41.6%**
 - **Females = 65.1%**
- **Return rates 11.7 months (mean) after index donation**
 - 76% normal donors
 - 58% low ferritin donors (made approx. 1 less donation/yr)

Canadian Study Results

- **Retest rates upon return**
 - 53% of low ferritin donors still had low ferritin
 - 32% of normal ferritin donors had low ferritin
- **Ferritin increased in low ferritin donors by**
 - 16.3 $\mu\text{g/L}$ in males
 - 12.1 $\mu\text{g/L}$ in females
- **Ferritin decreased in normal ferritin donors by**
 - 17 $\mu\text{g/L}$ in males and females

Canadian Study Conclusions

- Minimum hemoglobin level for male donors increased from 12.5 g/dL to 13.0 g/dL
- Minimum donation interval for females donors changed from 56 days to 84 days (= maximum 4 WB donations/yr)
- Ferritin testing and notification costs = \$4/donor

Canadian Study Conclusions

- **Consequences of informing donors of low ferritin results**
 - Return rates were 18% lower
 - Returning donors donate approximately 1 unit less/yr
 - Ferritin levels improved to some degree compared to decline in donors with initially normal results
- **Analysis of donor actions (questionnaire) to follow**
- **Of note, Canada has a publically funded health care system, and majority of donors have family physician and get annual checkups**

AABB Association Bulletin #17-02 Updated Strategies to Limit or Prevent Iron Deficiency in Blood Donors

- **Supersedes AB #12-03 and recommends actions**
- **Based on:**
 - Possibility that some donors may develop iron deficiency anemia
 - Known progression of iron deficiency that occurs with ongoing frequent donations
 - Potential for adverse effects of iron deficiency
- **Develop policies beyond development of educational materials for all donors on the risk of postdonation iron deficiency**

Recommendation #1

■ Comprehensive Educational Materials

- Risk of iron deficiency and applicability to at-risk donor subgroups
- Benefit of iron supplementation following donation
 - Type of iron
 - Dosage
 - Length of supplementation
- Donors with personal or FH of HH, familial polyposis, colorectal CA should check with PCP before starting iron
- Check with PCP or pharmacist about effect of iron absorption and other meds

Recommendation #2

- **Facilities should implement one or more interventions or strategies in all blood donors or in subgroups at high risk**
- **Subgroups at risk:**
 - Young donors (age 16-18) and possibly into early 20's
 - Premenopausal females
 - Frequent donors
 - **Males donating ≥ 3 times/year**
 - **Females donation ≥ 2 times/year**
 - Donors with Hb near cut off
 - **Males 13-13.5 g/dL**
 - **Females 12.5-13.0 g/dL**

Interventions/Strategies

(1 or more of the following)

- **Donor iron supplementation**
 - Dosage
 - Length (WB vs double RBC)
 - Provide iron vs vouchers
 - Define # apheresis procedures that results in approximate loss of red cells as in WB donation
- **Lengthening interdonation interval or decreasing number of donations/year**
 - ≥ 26 weeks or 2x/yr (without other intervention)
 - All young donors (and possibly premenopausal female) = 1 donation/year

Interventions/Strategies (cont'd)

- Donor ferritin testing as a basis for advising donors about further actions
 - All donors or at-risk subgroups
 - Test at time of donation
 - Personalized recommendations for iron supplementations or delay in subsequent donations
 - Provide info in writing with ferritin results
 - Repeat ferritin testing based on previous testing and operational capabilities

Recommendation #3

- **Blood Collection Establishments should consider post-implementation monitoring**
 - Collect, track, tabulate, and publish data

Where Do We Go From Here?



Next Steps

- **Risk Based Decision Making Process**
 - **Assessment Report of the Ad Hoc Iron Deficiency Working Group**
 - **Thorough assessment of the breadth, risks, and benefits of various options to respond to iron deficiency**
 - **Evaluated the impact on donors, blood providers and blood supply**
 - **Evaluated the tolerability of each management option**
- **Listening Session/Information Session**