Comparison of immunity in the general population versus blood donors

Dr Joanne Pink

On behalf of TS093 Working Party

Information sources

Sustainable and Safe Plasmapheresis

Summary and key issues for consideration

Several themes and key issues emerge from the available literature on the safety of intensive plasmapheresis:
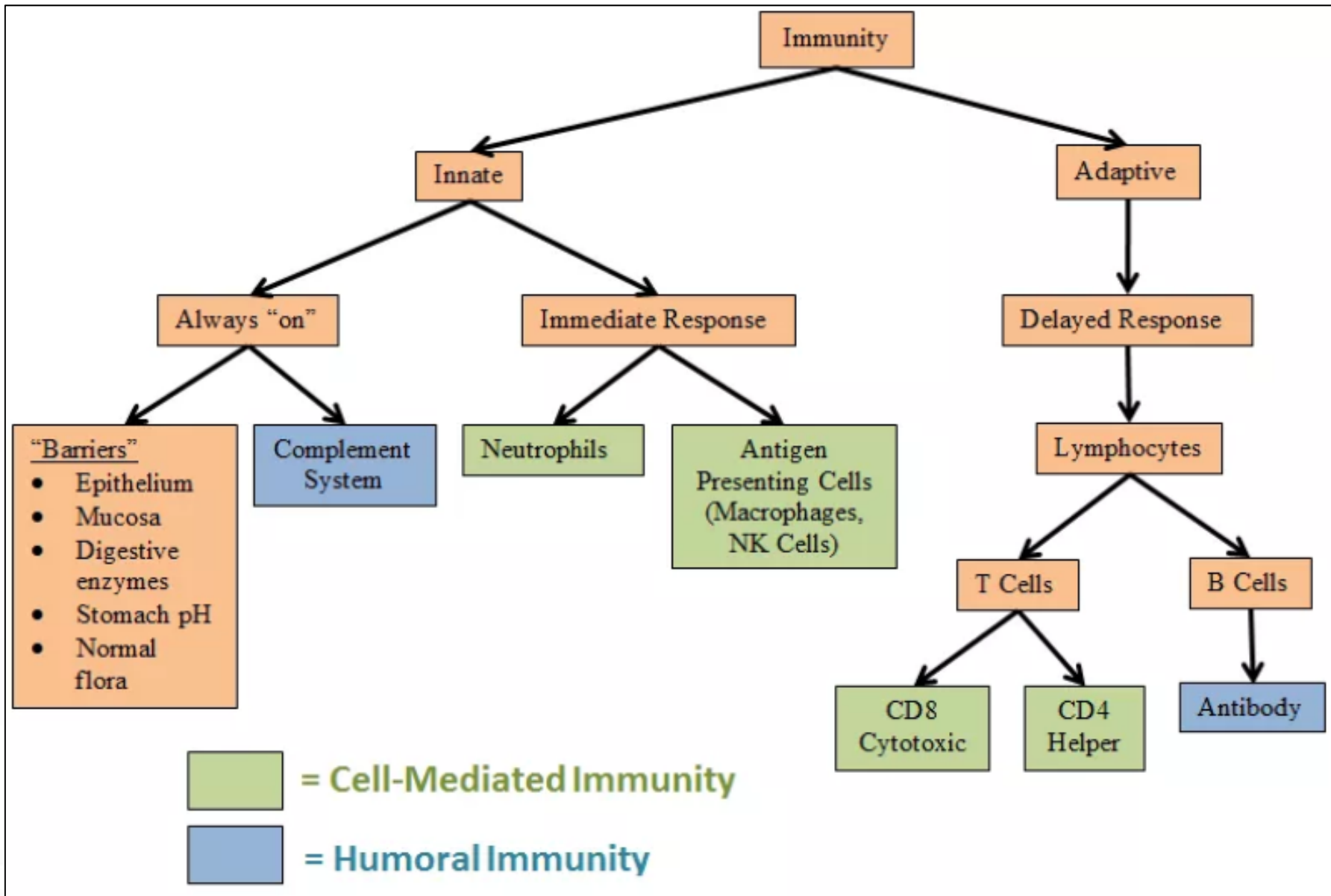
- Definite changes occur in the levels of plasma proteins after a donor enters a plasmapheresis program, and include reduction in total serum protein and immunoglobulin levels. These are most pronounced when comparing plasmapheresis donors to whole blood donors, but they are also evident in some studies when existing plasmapheresis donors have their donation frequency increased.
- Many studies identify proteins that fall below normal ranges, particularly in high intensity plasmapheresis programs when the maximum number of plasma donations exceeds the European Guidelines of 33 donations per annum. Nevertheless, there are no reports of clinical consequences of these proteins falling below normal range other than the need for deferral once limits have been reached.
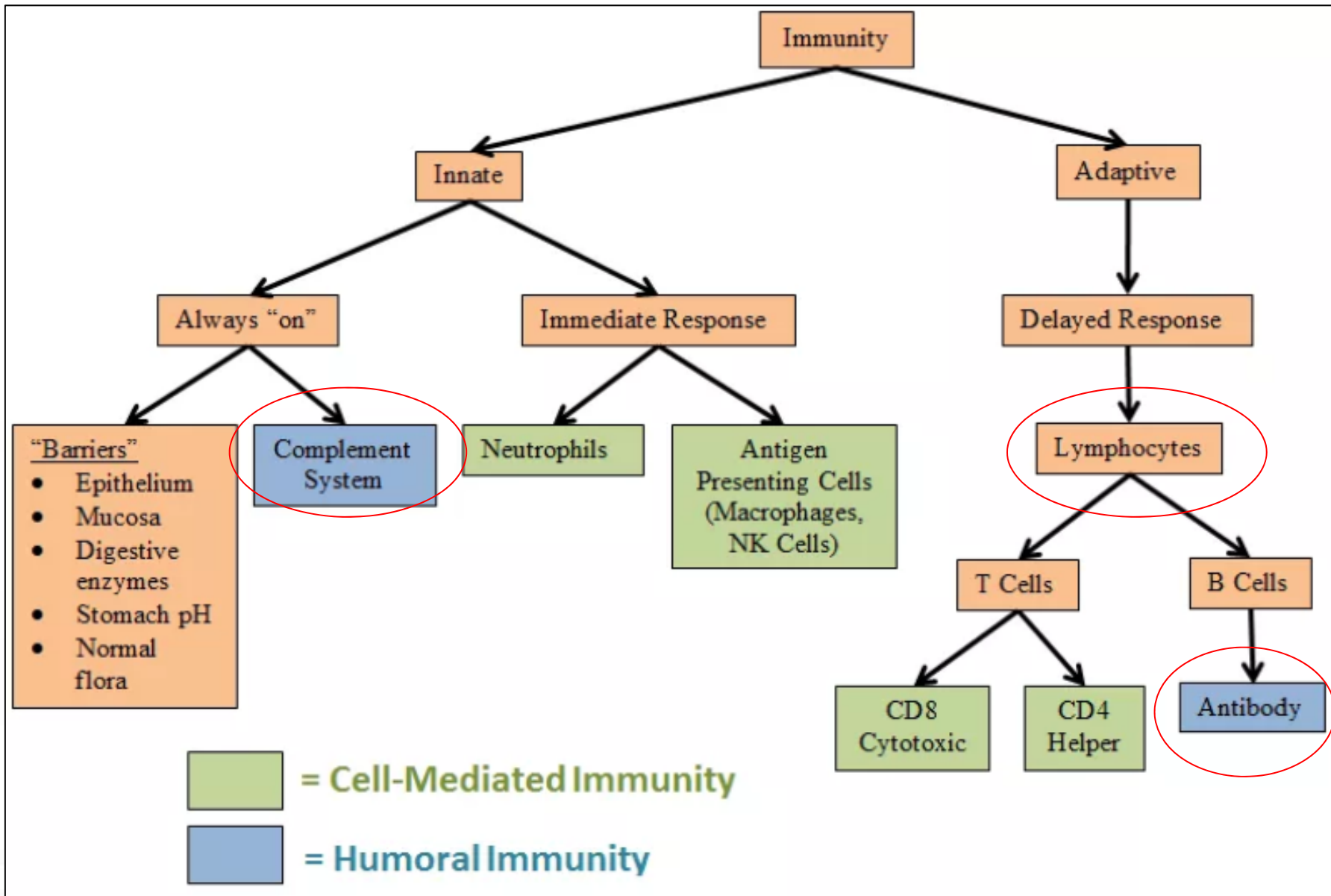
Review by:

- Members of the TS093 Working Party

- Australian immunologists (Dr Jeremy McComish and Dr Melanie Wong)

- Other Danish experts

TS093 core group members

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https://i0.wp.com/www.stomponstep1.com/wp-content/uploads/2014/09/flow-chart.png

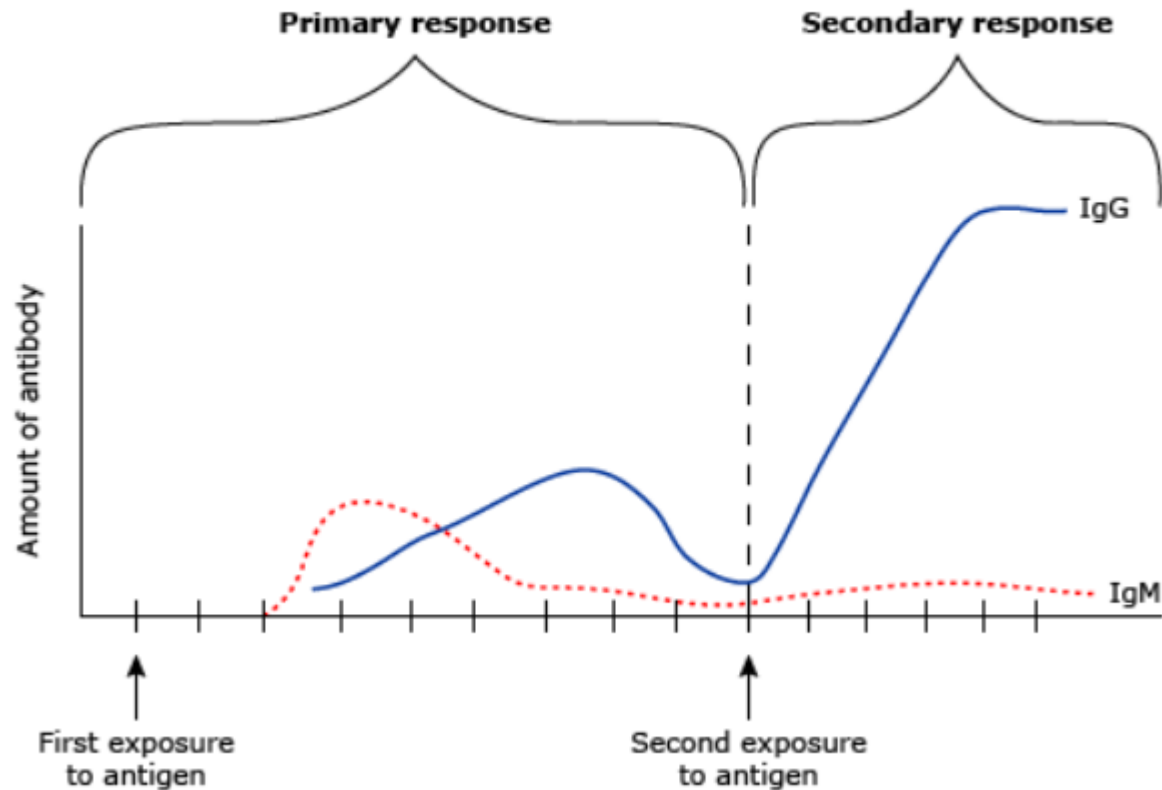https://i0.wp.com/www.stomponstep1.com/wp-content/uploads/2014/09/flow-chart.png

Lymphocytopenia

- Plateletpheresis using early haemopheresis equipment was associated with losses of donor lymphocytes, as much as 5-10 X 10^9/L per procedure

- The loss of lymphocytes over the course of 24 platelet donations using modern hemapheresis equipment is equivalent to the loss of lymphocytes in a single whole blood donation!

- Expect even lower loss with plasmapheresis

JL Winters. *Complications of Donor Apheresis*. Journal of Clinical Apheresis, 2006, Vol 21, Issue 2, 132-141.

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Primary and secondary antibody responses to tetanus and diphtheria antigens

- Course of response varies - antigenic dose, route of administration, and persistence or clearance of antigen.

- Primary response

- Secondary response - much shorter lag period, more rapid and greater response, total amount produced is greater.

- Source: UptoDate 2019

Antibodies in innate immunity

- There is significant cross-talk between the humoral and innate immune systems.

- Includes coating pathogens with IgG and IgA antibodies to enhance phagocytosis (ie, opsonization), use of antibodies as pathogen detectors by innate cells, and antibody-mediated inhibition of activation.

- Polyreactive IgM natural antibodies, which are constitutively produced, play a vital, protective role very early in immune responses before a more specific humoral immune response can be generated.

  - Source: UptoDate 2019

IgG trends in the general population

Table 2 - Reference intervals for immunoglobulins G, A, M (g/L)

Reference intervals may vary with methodology and with the racial composition of the population

	Immunglobulin G	Immunglobulin A	Immunglobulin M
Cord blood	6.4-16.1	0.01-0.04	0.06-0.26
1 month	2.5-9.1	0.01-0.53	0.20-0.87
2 months	2.1-6.0	0.03-0.47	0.17-1.1
3 months	1.8-5.8	0.05-0.46	0.24-0.89
4 months	2.0-5.6	0.04-0.73	0.27-1.0
5 months	1.7-8.1	0.08-0.84	0.33-1.1
6 months	2.2-7.0	0.08-0.88	0.35-1.0
7-9 months	2.2-7.0	0.11-0.90	0.34-1.3
10-12 months	2.9-11.0	0.16-0.84	0.41-1.5
1 year	3.5-12.0	0.14-1.1	0.43-1.7
2 years	4.2-11.0	0.14-1.2	0.48-1.7
3 years	4.4-11.0	0.22-1.6	0.47-2.0
4-5 years	4.6-12.0	0.25-1.5	0.43-2.0
6-8 years	6.3-13.0	0.33-2.0	0.48-2.1
9-10 years	6.1-16.0	0.45-2.4	0.52-2.4
Adult	6.5-16.0	0.6-4.0	0.5-3.0

Source (above): RCPA Manual

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# IgG trends in the general population

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9-10 years	6.1-16.0	0.45-2.4	0.52-2.4
Adult	6.5-16.0	0.6-4.0	0.5-3.0

- IgG tends to be higher in females

- Positive correlation between IgG and age in most studies (not clear whether this represents selection bias as longitudinal studies are not available), some show a decline after 30 years or later.

- Negative correlation with some lifestyle factors eg smoking, alcohol (but small impact <1 g/L)

Source (above): RCPA Manual
Source (right): EDQM Safe and sustainable plasmapheresis

Mean: 1118 mg/dl
Median: 1090 mg/dl
SD: 251 mg/dl
Range: 407–2170 mg/dl
P-2·5: 705
P-97·5: 1745
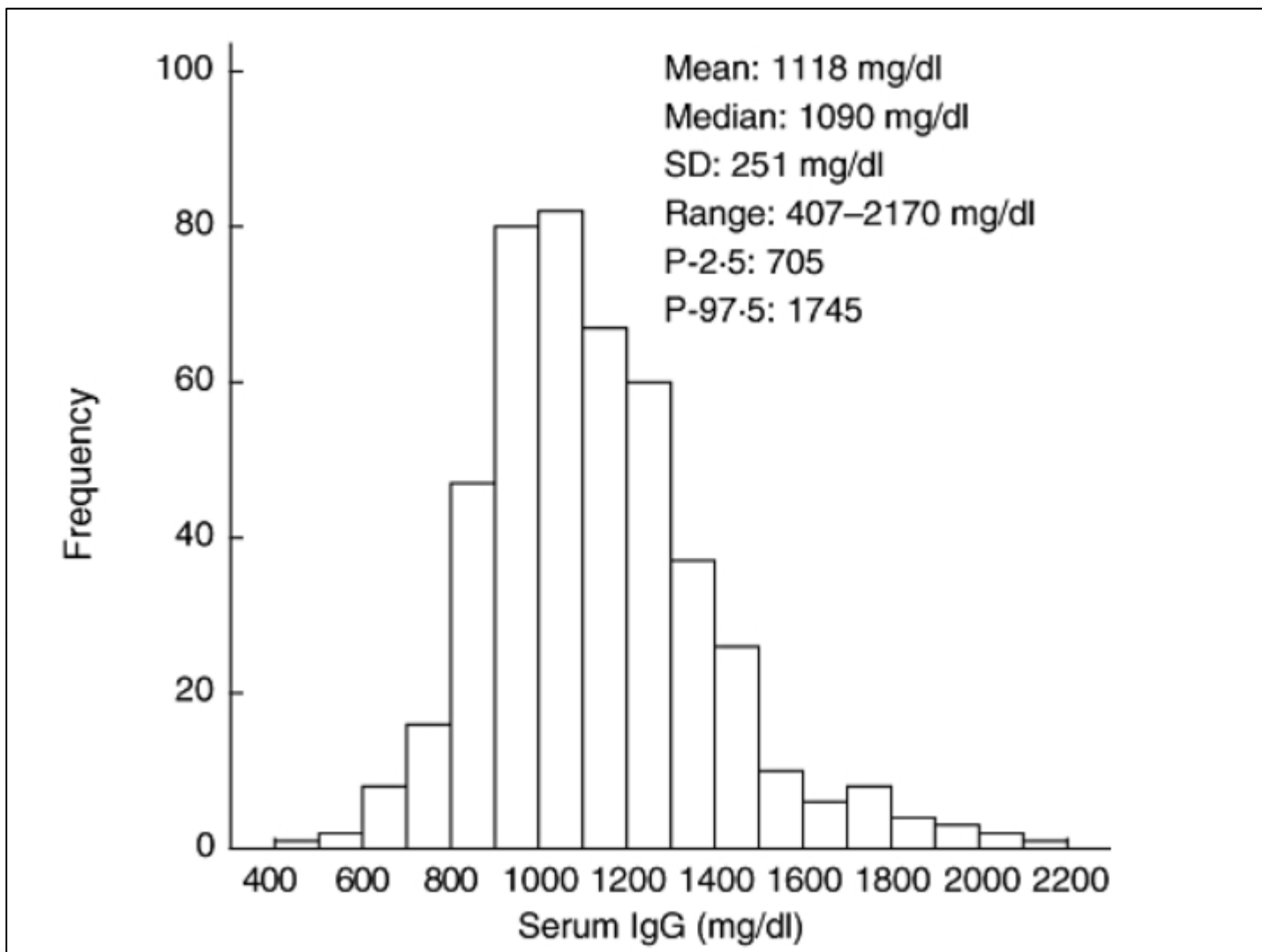
- IgG approximates normal distribution – some skewing to the right.

- Small proportion of normal people will have an IgG level below the 'normal' range.

A Gonzalez-Quintela et al, Clin Exp Immunol 2008 Jan; 151(1): 42–50.

IgG levels in first time Australian WB donors
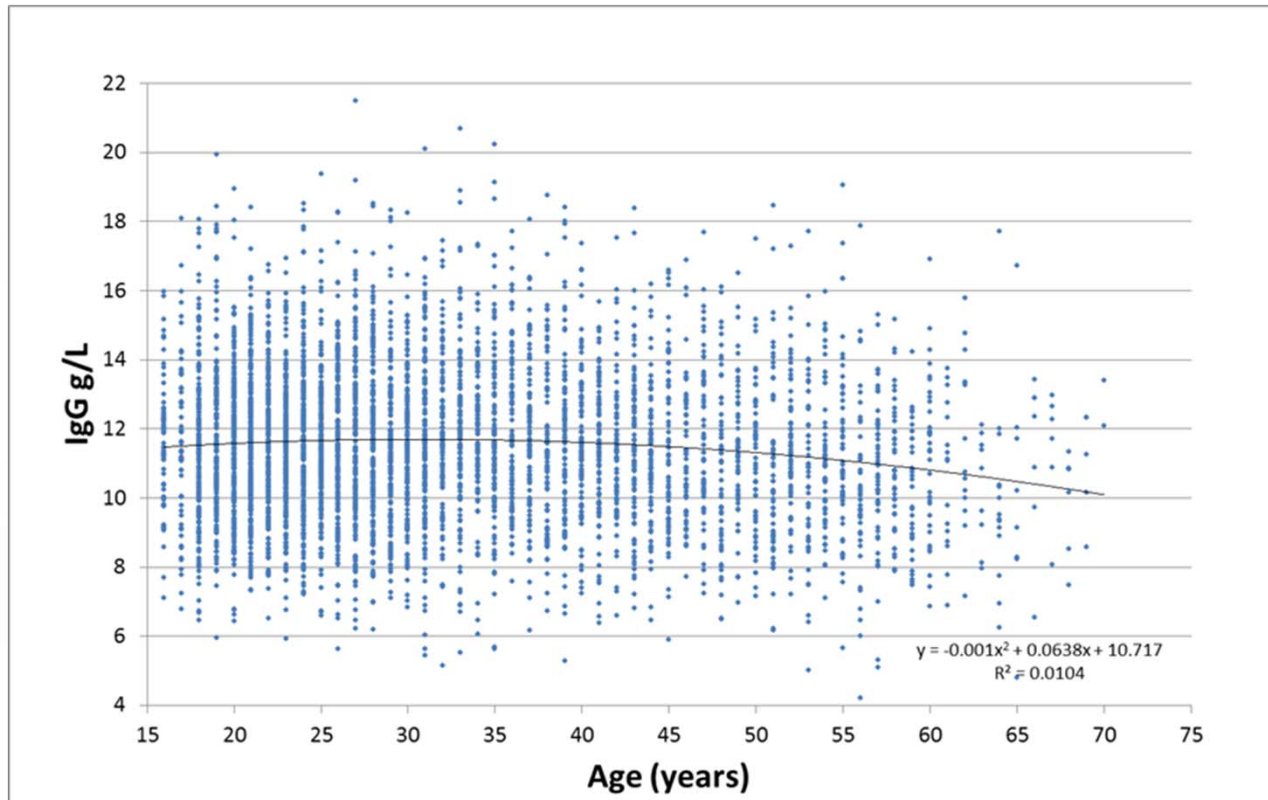
Scatter plot includes 5,058 new whole blood donors

- Normal IgG range is quite broad – opportunity to target donors with higher IgG

- IgG relatively stable until about 50 years of age

- Minor decrease in IgG with donor ageing, particularly after 50 years of age (about 1.5 g/L)

Hypogamma – reduced production

- Primary immunodeficiency – mainly inherited, impaired antibody production because of either a molecular defect intrinsic to B cells or a failure of interactions between B and T cells.

- Secondary - impaired antibody production from medical conditions or infections that alter immune system function, environmental exposures such as radiation or toxic chemicals, or trauma.

  - Drugs – eg rituximab

Source: UptoDate 2019

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Treatment of acquired hypogamma

Diagnosis Requirements	A diagnosis must be made by an Immunologist, Haematologist, Paediatrician, General Medicine Physician or an Oncologist.
Qualifying Criteria for IVIg Therapy	Serum IgG to be measured on two separate occasions (at least one hour apart and at least one sample taken when the patient does not have an active infection). Baseline serum levels of IgA and IgM should be provided to allow assessment of immune recovery at review. • Significant hypogammaglobulinaemia with serum IgG less than 4g/L (excluding paraprotein) regardless of the frequency and severity of infections OR • Serum IgG (excluding paraprotein) greater than 4g/L but less than the lower limit of the age related reference range with at least one life threatening infection in the last 12 months OR • Serum IgG (excluding paraprotein) greater than 4g/L but less than the lower limit of the age related reference range with at least two serious infections in the last six months requiring more than standard courses of antibiotics (e.g. hospitalisation, intravenous or prolonged antibiotic therapy)

The need to treat is not based on IgG level alone – consider frequency / severity of bacterial infections and IgG result.

https://www.blood.gov.au/bloodstar

Analogous to plasmapheresis?

- No

- Plasmapheresis donors have normal IgG production and do not have a blunted immune response

- Rut Norda et al studied immune responsiveness in plasma donors – hep B vaccination, no difference between men and woman in t ½ of antibody response, no correlation between donation frequency, total volume of plasma donated, peak antibody titre or level of titre sustained (ISBT 2018 Poster).

Hypogamma – increased loss

- Protein-losing states such as protein-losing gastroenteropathy and nephrotic syndrome can lead to hypogammaglobulinemia and increased susceptibility to infection.

Analogous to plasmapheresis?

- In part - plasmapheresis removes IgG.

- If the long-term rate of removal of IgG exceeds the rate of donor IgG synthesis, the levels will reduce.

- Easier to stop the loss of IgG - available studies suggest the IgG level returns to the pre-donation level if the donor is deferred.

- There are no reports of adverse clinical consequences (increase risk of infection, delayed wound healing) provided donors are deferred when the levels fall below the reference range to allow recovery.

Source: EDQM Safe and sustainable plasmapheresis

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Safety of long-term intensive plasmapheresis in donors (SIPLA 1)

- Prospective multicentre study

- Intensive plasmapheresis programme (maximum 60 pa)

- Observed over 3 year period

- Donors weighing 50-70Kg donated 750mL plasma including citrate at least weekly, 3 years (Arm I)

- Donors weighing >70Kg, assigned to either Arm I or Arm II (850mL including citrate)

- Determined TSP, Hb (Hct) at each donation; IgG every 5th

- Drop out rates and reasons were analysed.

T.Schulzki etal. *A prospective multicentre study on the sfatey of long-term intensive plasmapheresis in donors (SIPLA).* Vox Sanguinis(2006), 91, 162-173
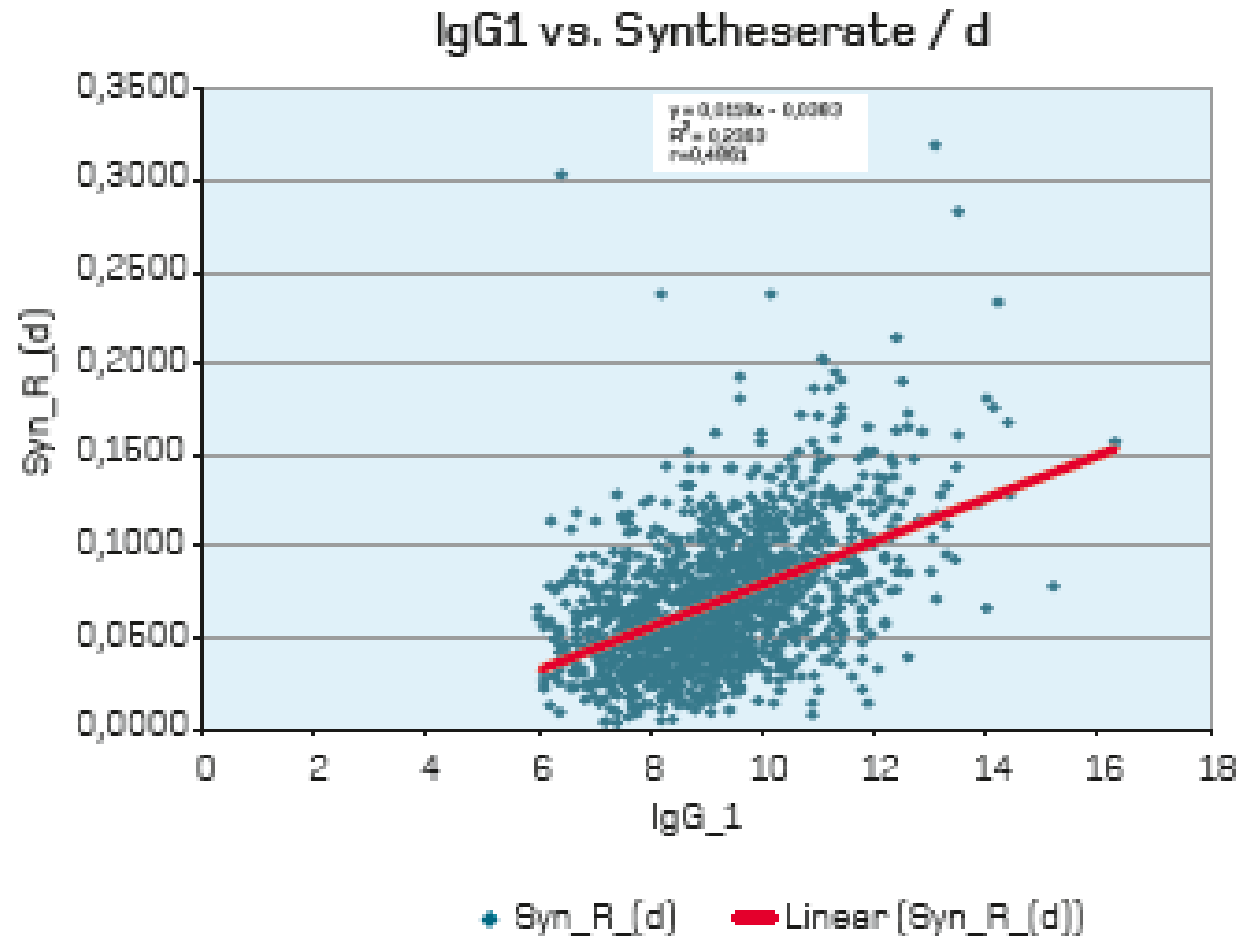
Safety of long-term intensive plasmapheresis in donors (SIPLA 1)

- Drop-outs (overall about 75%):

  - No significant differences between arm I and arm II or between males and females

  - Socio-economic (49.2%) eg lack of time, moved, personal reason

  - IgG/TSP/Hb below threshold (16%) – risk factors = young, female, low initial IgG, high donation frequency

  - Medical, not related to plasma (10.4%) eg pregnancy, surgery

IgG values (SIPLA)

	Initial value	Final value
Females (n=193)		
IgG g/L	8.8 (5.3 – 16.4)	8.0 (4.7 – 18.8)
Number <5.8g/L	2	7 (3.6%)
Males (n=730)		
IgG/L	8.7 (5.5 – 16)	7.9 (5.0 – 17.0)
Number <5.8 g/L	2	32 (4.4%)

Figure 2: Scatter diagram
IgG1 vs. Synthesis rate

IgG1 vs. Syntheserate / d

IgG metabolism in plasma donors depending on individual conditions. Moller et al. Poster ISBT 2010

- Significant variation in the IgG synthesis rate (0.004 – 0.319 g/L per day).

- The daily synthesis rate of IgG correlates moderately positively with the donors initial IgG result.

- Suggests tolerance of donation frequency is influenced by the starting IgG level and donors with lower IgG levels should donate less frequently.

Is it better to have a higher IgG level?

- Correlation between total IgG and risk of disease is unclear for IgG within the population reference range (6 - 16 g/L), in part because autoreactive IgG may form part of the total.

What about the lower IgG limit?

- Donor safety – we know that patients who are constantly losing IgG and have very low IgG levels (eg protein losing enteropathy) have increased susceptibility to infection – we need a lower limit.

- Product quality – whilst every drop of IgG is valuable, it is more cost-efficient to collect plasma with a reasonable amount of IgG in it.

- What should the lower limit be? The lower limit of an established reference range seems reasonable – 6 g/L

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Conclusion

- No evidence of short term blunted immune response in donors, even with intensive plasmapheresis - donors have normal IgG production and respond normally to antigenic stimulation

- Major limiting factor in donor plasmapheresis is the capacity of donors to restore their plasma proteins

- Significant variation in IgG synthesis rate – in general donors with lower initial IgG have lower synthesis rates.

- Important to monitor IgG and defer the donor if the IgG falls below the lower limit of the reference range – protects donor health and plasma quality.

Management of donors using IgG level based donor suitability

EXPERIENCES AND CHALLENGES

Stephan T. Kiessig, MD, PhD
Dr. Kirsten Seidel, MD
Chair ARGE Plasmapherese e.V.

ARGE Plasmapheresis

In 1997 the so called „working group" (ARGE) Plasmapheresis was founded. The objective of this organization is:

the procurement of high quality, safe plasma derived products under economically viable conditions,

the support of growing knowledge about donor suitability and donor safety in plasma by collecting and collating scientific data and background information,

cooperation with scientific organizations and regulating authorities in order to improve the awareness of the differences of plasma collection compared to whole blood and the special requirements regarding donor and product issues.

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PLASMAPHERESE** E.V.

- 1991 TP on every donation, IgG every 15th donation

- 1997 ARGE Plasmapheresis was founded

- 1999-2003 The ARGE carried out the SIPLA study

The importance of IgG as the leading protein regarding donor safety
(as well as product quality) as well as differentiated collection volumes were
recognized.

In 2005, IgG testing frequency was therefore increased to every 5th donation

Schulzki et al.: SIPLA I 2006
Kiessig et al. SIPLA II. ISBT 2013

What is the Recipe?

- IgG levels are highly variable from donor to donor. They depend on gender, age, childhood exposure to antigens, immunizations, recent infections suffered, ethnicity and individual factors

- We see IgG's of first time plasma donors from 0 to 28 g/L.

- Persons with an IgG of <6 g/L or >19 g/L at the first time are sent for further investigation.

- TP is mostly tested in combination with IgG to see the complete picture and observe the donor's protein metabolism over a longer period of time.

- Both proteins are easily tested from the product (plasma anticoagulated with 4% citrate) and can be reconverted to serum values with a validated conversion factor. We so avoid unnecessary blood sampling.

The Art of Keeping Donors above IgG Levels of 6 g/L

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- IgG levels drop by 2-3 g/L with regular donation and take approx. 2 to 3 weeks to recover to original levels.

- TP drops by approx. 8 g/L with regular donation

- Recovery rate to original levels varies significantly and needs individual donation patterns.

IgG in g/l for first time and regular donors

— regular donors
— first time donors
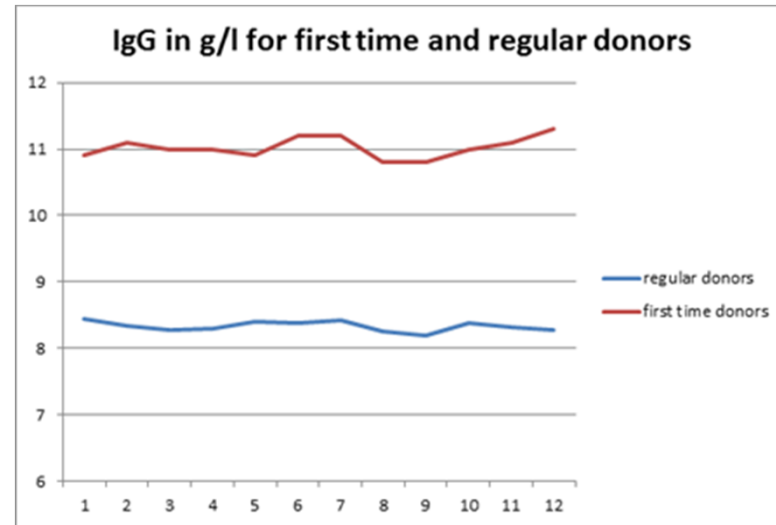
Other Parameters Detected$_2$ → Methods

Germany / SIPLA I & II

- TP: Bredford / Biuret
- IgG: Nephelometry / Turbidometry
- Both: every 5th donation
- Both: has to follow nat. Lab Med Guidelines (precision, recovery, … validated ICH Q2R)

Other regions

- TP: Polarimetry (at each procedure)
- IgG: by Electrophoresis or immune-diffusion (4 monthly)**
- Both: not state of the art***
- Inacceptable precision, recovery, ...
- Too infrequent

Results: up to 24% more IgG in Regions with regular IgG observations*

*Laub et al.: Specific protein content of pools of plasma for fractionation from different sources: impact of frequency of donations. Vox Sanguinis (2010) 99, 220–231

: CFR **§640.65: https://www.ecfr.gov/cgi-bin/text-idx?SID=7d14143c40b0a1459c073878caea3c01&mc=true&node=pt21.7.640&rgn=div5#se21.7.640_165t

***: Weichselbaum TE.: An accurate and Rapid Method for the Determination of Protein in small Amounts of Blood Serum and Plasma. AmJClinPathol (1946) 16, 40-49

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Influenced by plasmapheresis

- IgG
  - Longer recovery
- TP
  - Short recovery

Regulations needed for

- Donor safety and
- Plasma quality

Not influenced by plasmapheresis

- Hemoglobin
- HCT

No need for regulations

The Art of Keeping Donors above IgG Levels of 6 g/L

Fixpoints: either donor's **last / first** IgG

Therefore, in order to achieve sufficient quantities to meet the demand, plasma collectors developed a system to guide donors regarding their donation frequency.

- Manually, according to donor's last/first IgG

- With a fixed donation interval, according to donor's last/first IgG (donation programs with fixed intervals)

- With an electronic system, that increases IgG/TP testing frequency, when levels drop, and reduces donation frequency accordingly, to **avoid dropping at** IgG   < 6 or
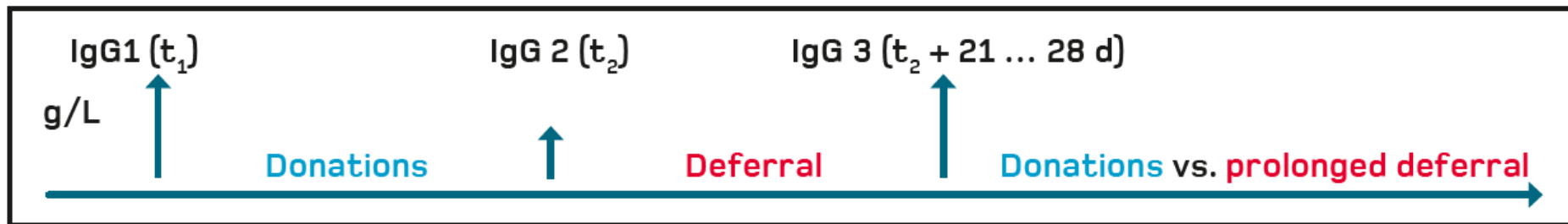 TP   < 60 g/L.

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There are advantages and disadvantages the starting point (First vs last IgG):

First time IgG

◦ Clear definition of possible donation frequencies from the very beginning

◦ Also donors active in more than one center are recognized and therefore thwarted

◦ Avoid cross donations

Last IgG

◦ Continuous adaption to the donors capabilities

◦ Avoid cross donations

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IgG1 (t_1) IgG 2 (t_2) IgG 3 $(t_2 + 21 ... 28 d)$

g/L

Donations   Deferral   Donations vs. prolonged deferral

Möller et al.: ISBT 2010

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	IgG1	IgG2	IgG3
Sample size (n)	6667	6667	6667
Lowest value (g/L)	1.9400	1.9400	2.8900
Highest value (g/L)	16.3000	5.9900	15.4800
Arithmetic mean (g/L)	8.8030	5.5073	6.8547
95% CI for the mean (g/L)	8.7610 to 8.8450	5.4966 to 5.5180	6.8207 to 6.8886
Median (g/L)	8.7000	5.6100	6.6300
95% CI for the median (g/L)	8.6500 to 8.8000	5.6000 to 5.6500	6.6000 to 6.7000
Variance	3.0575	0.1981	2.0003
Standard deviation (g/L)	1.7486	0.4451	1.4143

Beware: Target in the treatment of immunodeficient patients:

IgG > 6 g/L (according to current guidelines)

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There are advantages and disadvantages to all systems:

- **Manual systems:** time consuming, too much room for individual decisions by health professionals and frequency being changed at every visit, loss of potential plasma, insufficient reduction of IgG-deferrals

- **Algorithm system:** might be inflexible, donor is in a fixed donation pattern, loss of potential plasma, sufficient reduction of IgG-deferrals

- **Electronic system:** needs to be programmed in the donor software, but is the ideal system to guide donors and health professionals.

- With this system, a maximum individual donation frequency can be achieved, with deferrals for IgG of less than 2%

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As a result of **guiding** and **individualizing** donors' donation frequency,
(and of course personal reasons) numbers of donations vary greatly:

Average number of donations per year

1-5	36%
6-10	16%
11-20	18%
21-30	12%
31-45	11%
46-55	4%
55-60	3%

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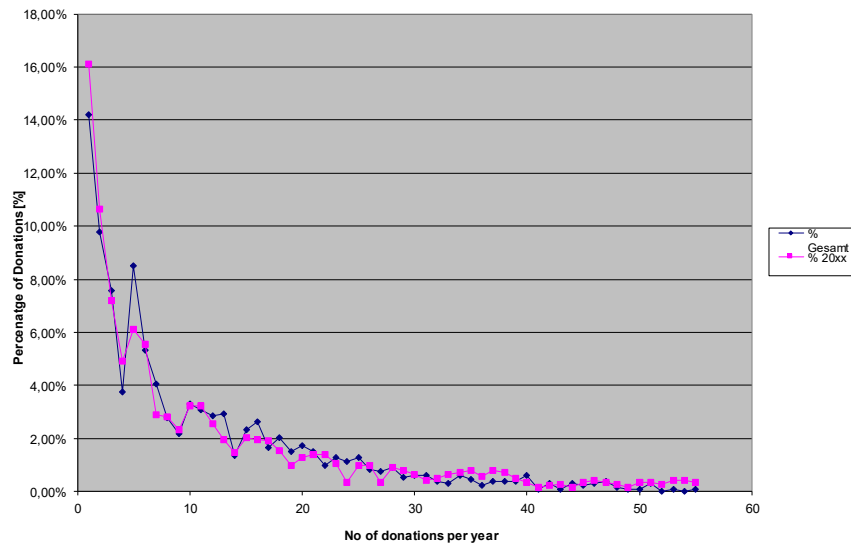
With any of the systems collectors get a good overview over that specific donor's protein recovery rate and can act accordingly and reduce donation frequency, if necessary or encourage higher donation frequency, if protein levels are very high.

We achieve higher donation frequencies than with a rigid interval and still **maintain donor safety** and **adequate plasma protein levels**.

We have collected data on millions of plasma donors over the last 20 years, and have seen an enormous variance in protein loss and recovery among individual donors.

Accordingly, regulatory maximum number of donations are completely arbitrary, be it 33, 60 or 104.

Likewise, annual volume limitations are senseless. Plasma is not an issue of „volumes". <u>**We collect life-saving proteins**</u>, with IgG as the most sought after being the most important one for an increasing number of therapies.

… without impacting the donors safety!

If an IgG/TP monitoring system is in place, requirements to limit number of donations or annual donation volume can be waived.

Any limits should be evidence based!

Achieving as many donations as possible for that specific donor's protein recovery rate with as little deferrals for low IgG as possible and keeping him long-term healthy and happy as a donor, is a proven way to a sufficient plasma supply on an national or European level

Increasing the donation frequency
= product safety

Optimizing the donation frequencies to the donor capabilities
= donor safety
= increases IgG yield in the fractionation process

This allows a better patient supply

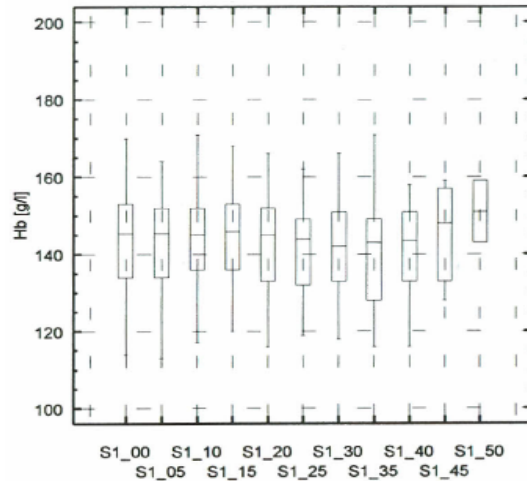There are still a lot of challenges to further optimize safe donations for happy patients !!
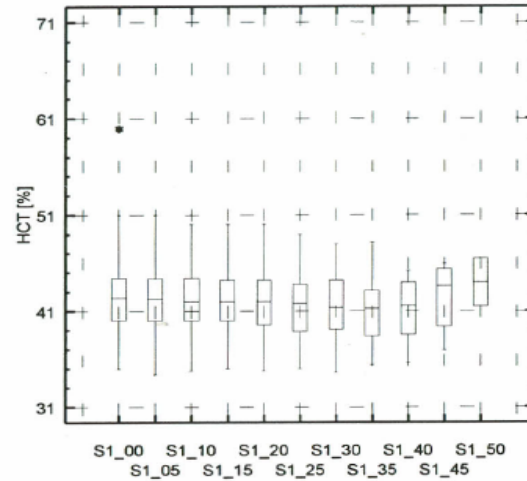
Backup

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Multiple Box-and-Whisker Plot
SIPLA 1, Hemoglobin

Multiple Box-and-Whisker Plot
SIPLA 1, Hematocrit

Multiple Box-and-Whisker Plot
SIPLA 1, IgG
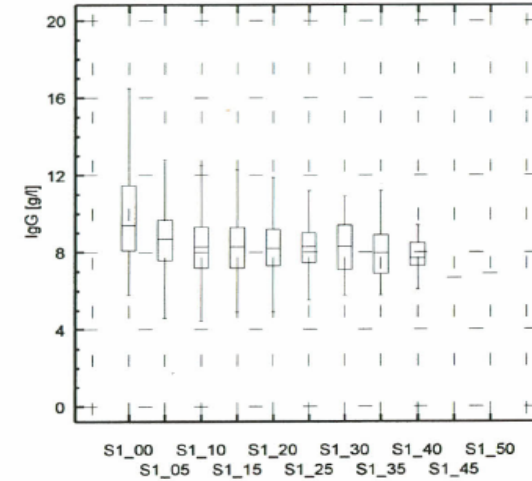
Multiple Box-and-Whisker Plot
SIPLA 1, Body Weight
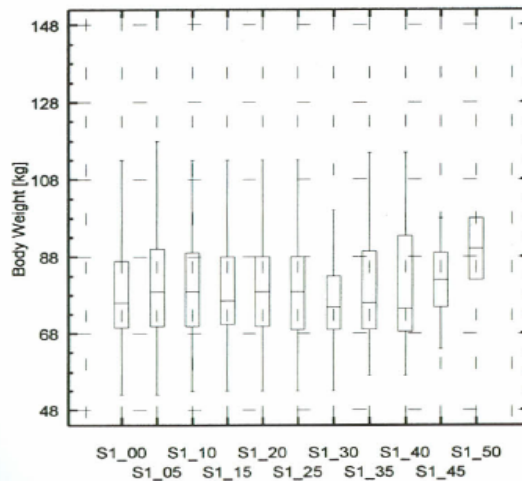
Multiple Box-and-Whisker Plot
SIPLA 1, Total Protein
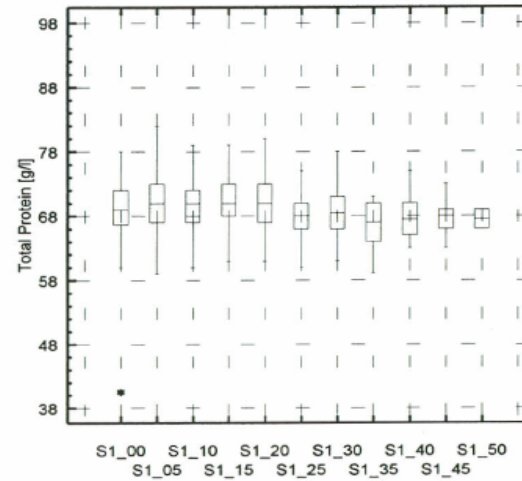
Legend to the figures:

S1 = SIPLA 1

S1_00: Data at starting point
S1_05: Data at the 5th donation
S1_10: 10th donation
S1_15: 15th donation
S1_20: 20th donation
S1_25: 25th donation
S1_30: 30th donation
S1_35: 35th donation
S1_40: 40th donation
S1_45: 45th donation
S1_50: 50th donation
S1_55: 55th donation

Laub et al.: Specific protein content of pools of plasma for fractionation from different sources: impact of frequency of donations. Vox Sanguinis (2010) 99, 220–231

Group I: EU plasma

Group IV: Other plasma

Table 3 Comparison of total protein and specific plasma protein contents in plasma pools collected from Group I and Group IV donors (mean ± SD)

| Protein (g/l) | Content in g/l in donations | | % | P-value |
| | Group I n = 51 | Group IV n = 41 | | |
	A	B	Variation[a] C	D
Total protein	$60\cdot46 \pm 3\cdot46$[b]	$55\cdot20 \pm 2\cdot60$	-9	$< 0\cdot0001$
Albumin	$34\cdot05 \pm 2\cdot24$	$29\cdot05 \pm 3\cdot08$	-15	$< 0\cdot0001$
Total IgG	$8\cdot48 \pm 0\cdot61$	$6\cdot49 \pm 0\cdot51$	-24	$< 0\cdot0001$
IgM	$0\cdot96 \pm 0\cdot13$	$0\cdot69 \pm 0\cdot09$	-28	$< 0\cdot0001$
IgA	$1\cdot64 \pm 0\cdot22$	$1\cdot54 \pm 0\cdot18$	-6	$< 0\cdot05$
Transferrin	$2\cdot23 \pm 0\cdot18$	$2\cdot06 \pm 0\cdot15$	-7	$< 0\cdot0001$
Haemopexin	$0\cdot70 \pm 0\cdot05$	$0\cdot62 \pm 0\cdot06$	-11	$< 0\cdot0001$
α_1 glycoprotein	$0\cdot67 \pm 0\cdot04$	$0\cdot65 \pm 0\cdot07$	-2	$> 0\cdot05$
Retinol-binding protein	$0\cdot03 \pm 0\cdot01$	$0\cdot03 \pm 0\cdot01$	-10	$< 0\cdot05$
C_1 inhibitor	$0\cdot21 \pm 0\cdot01$	$0\cdot232 \pm 0\cdot02$	$+12$	$< 0\cdot0001$
Prealbumin	$0\cdot19 \pm 0\cdot03$	$0\cdot21 \pm 0\cdot02$	$+9$	$< 0\cdot0001$
C-reactive protein	$1\cdot72 \pm 0\cdot29$	$2\cdot08 \pm 0\cdot67$	$+21$	$< 0\cdot05$

- **Female frequent donors have higher ferritin levels than donors with no donations**

- **For males, although frequent donors had lower ferritins than those with no donations, the differences were not statistically or clinically significant**

- **Few SP donors have AIS and for most, ferritin values are well within the normal range**

- **Iron depletion seen with frequent WB donation does not occur with frequent SP donation**

Transfusion 2018;58;951-959

Source Plasma Donors

- Source Plasma (SP) donation is associated with little red blood cell (RBC) loss; there is no information on iron status for frequent SP donors.

- Despite little RBC loss, questions about accumulated loss over a large number of donations were raised during the November 2011 FDA Workshop on Hemoglobin Standards and Maintaining Adequate Iron Stores in Blood Donors.

    - SP industry decided to conduct a large cohort study of the association between frequent donation and ferritin levels

Whole Blood Donors

Effect of 12-month whole blood or RBC donation frequency on the geometric mean of plasma ferritin by males and pre- [age <50 years] or post- [age ≥50 years] menopausal females

Legend:
- Male
- Female ≥50
- Female <50

Y-axis: Geometric Mean of Ferritin (0, 20, 40, 60, 80, 100, 120)
X-axis: Donations in past 12 months (0, 1, 2-3, 4, ≥5)
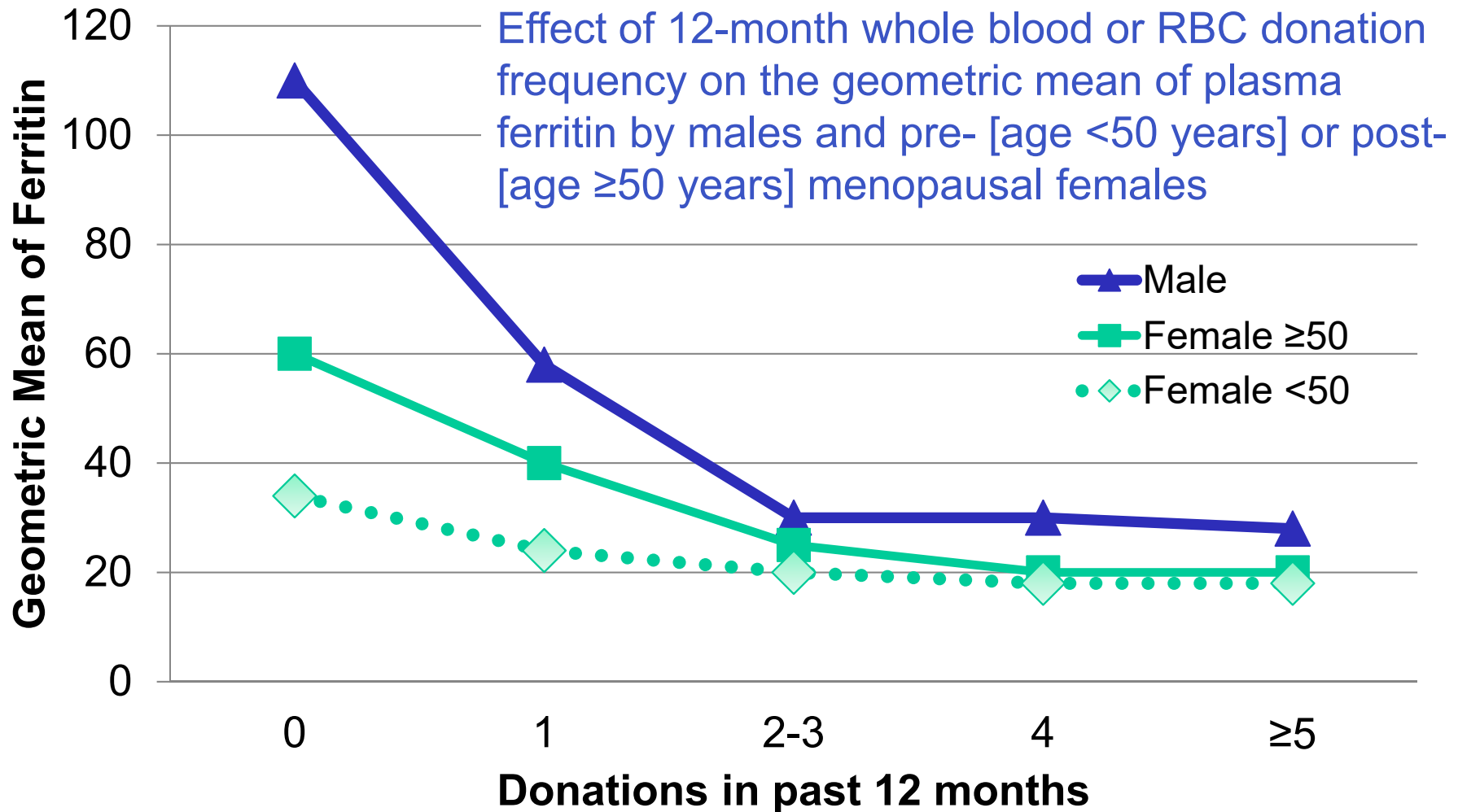
Cable RG, Glynn SA, Kiss JE et al. for the NHLBI Retrovirus Epidemiology Donor Study-II (REDS-II). Iron deficiency in blood donors: analysis of enrollment data from the REDS-II Donor Iron Status Evaluation (RISE) study. Transfusion 2011; 51: 511-22.

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Ferritin Levels in Plasma Donors (FLIPD) Study

- Examine ferritin levels in SP donors associated with donation frequency

- Protocol received independent IRB approval

- Donors administered informed consent

- Conducted as a delinked cohort study

- Three companies participated (Biolife Plasma Services, CSL Plasma and Grifols)

PPTA
Plasma Protein Therapeutics Association

1,323 Potential Study Subjects

1,272 Agreed to Participate in Study

1,254 Enrolled in Study

51 Refusals

13 Disqualified

5 Withdrawals

4 Donor Frequency Groups

PPTA — Plasma Protein Therapeutics Association
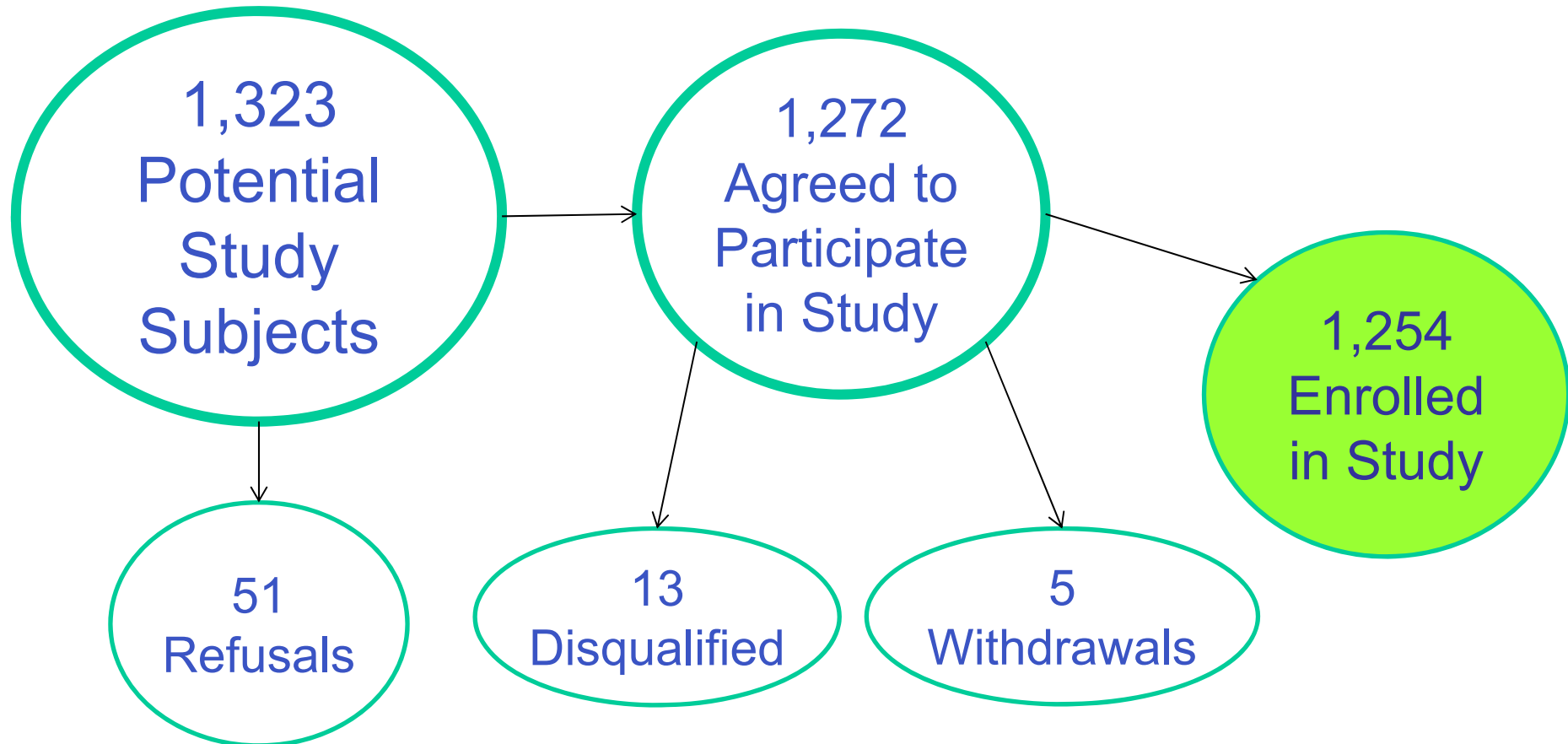
Donor Frequency Group	# Donations Prior 12 Months	# Enrolled in Study	Female	Male
No Prior Donations ("No Donations")	0	309	164 (53%)	145 (47%)
Low Frequency Donors ("Low")	1-24	306	168 (55%)	138 (45%)
High Frequency Donors ("High1")	25-69	342	181 (53%)	161 (47%)
High Frequency Donors ("High2")	≥70	297	156 (53%)	141 (47%)
ALL	ANY	1254	669 (53%)	585 (47%)

Age (years) – Mean

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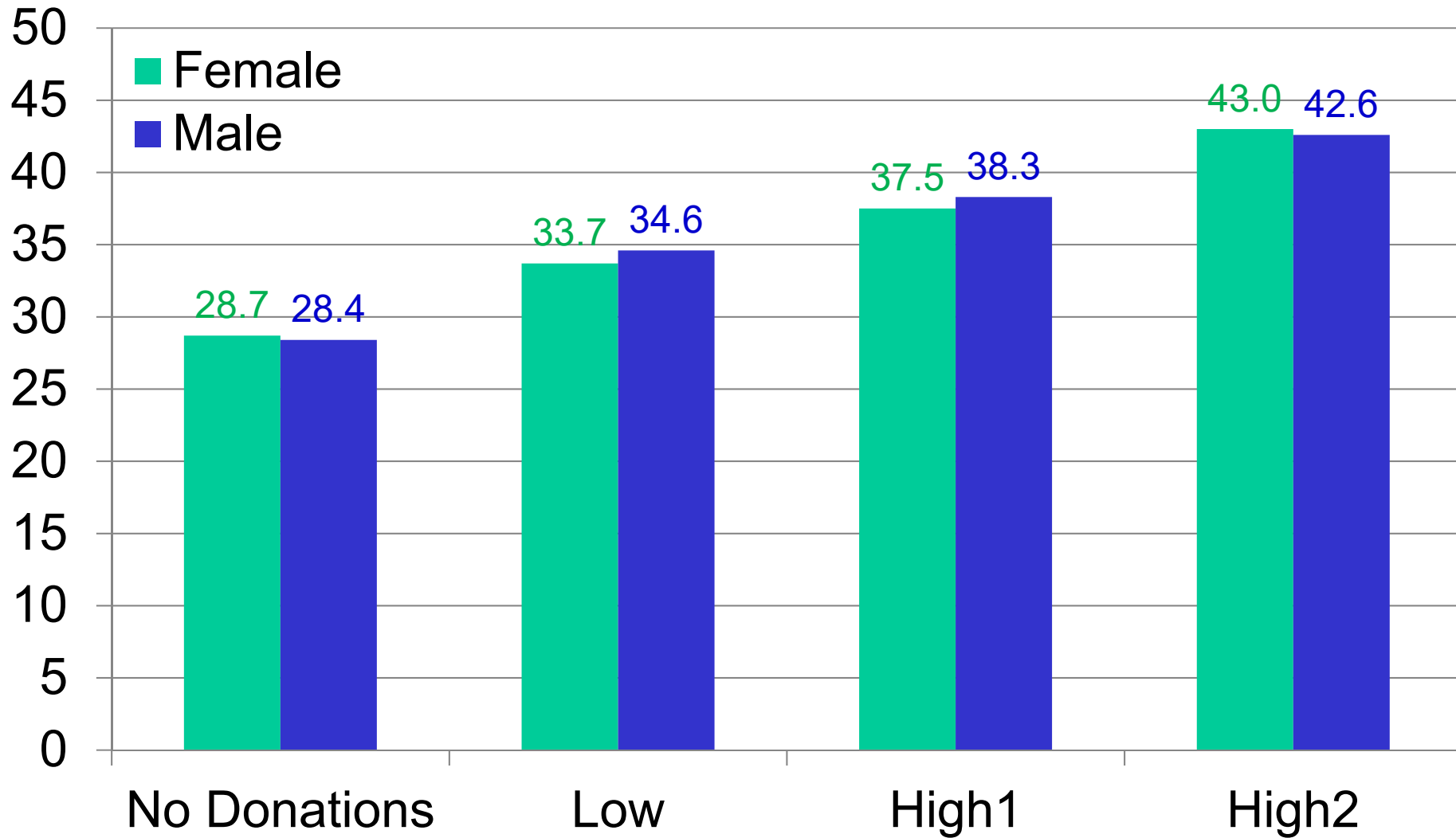
Baseline Hematocrit (%) – Mean

PPTA
Plasma Protein Therapeutics Association

Female
Male

No Donations: Female 42.3, Male 46.1
Low: Female 42.1, Male 45.9
High1: Female 42.2, Male 45.7
High2: Female 42.2, Male 46.0

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Supply Management

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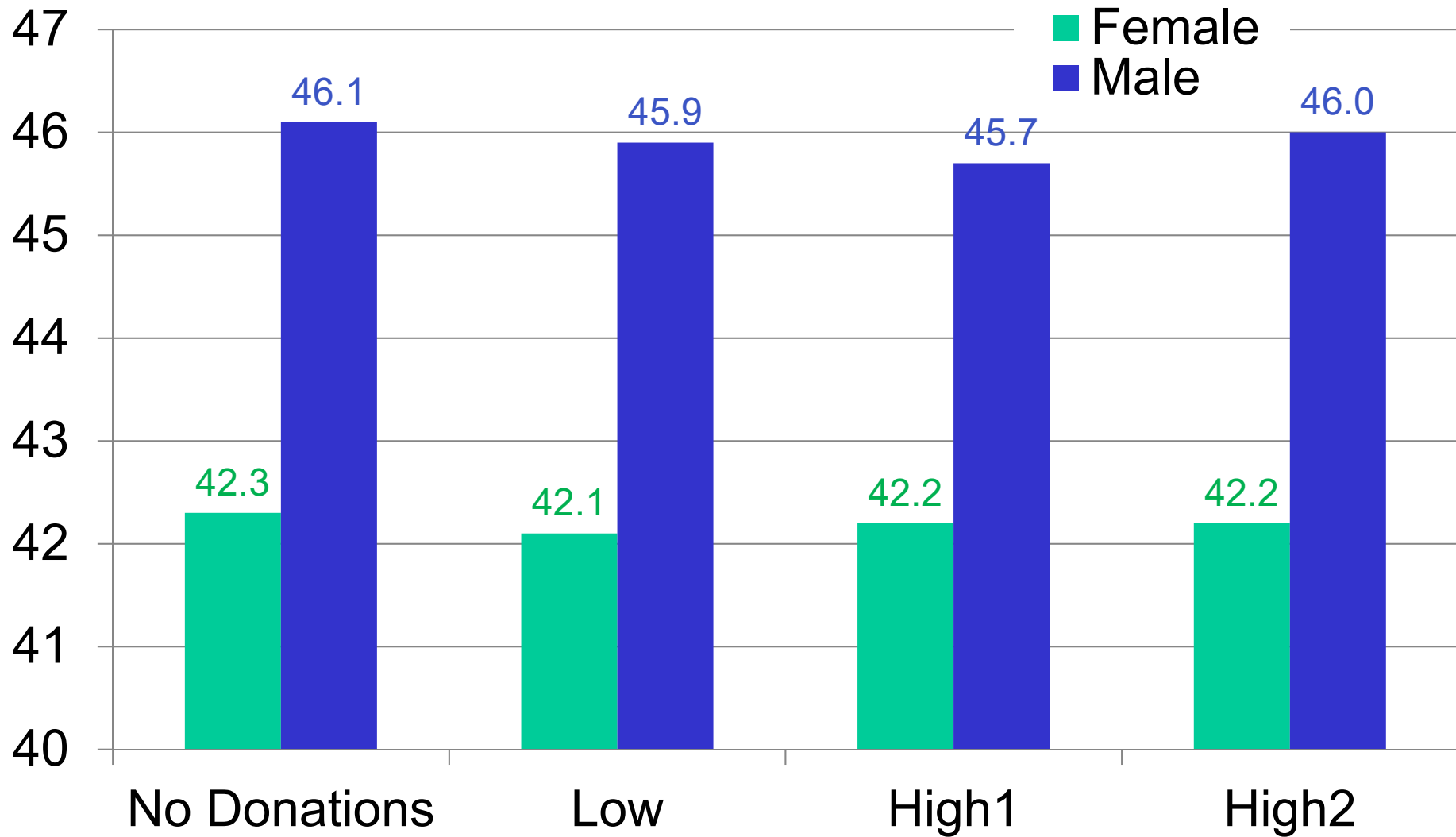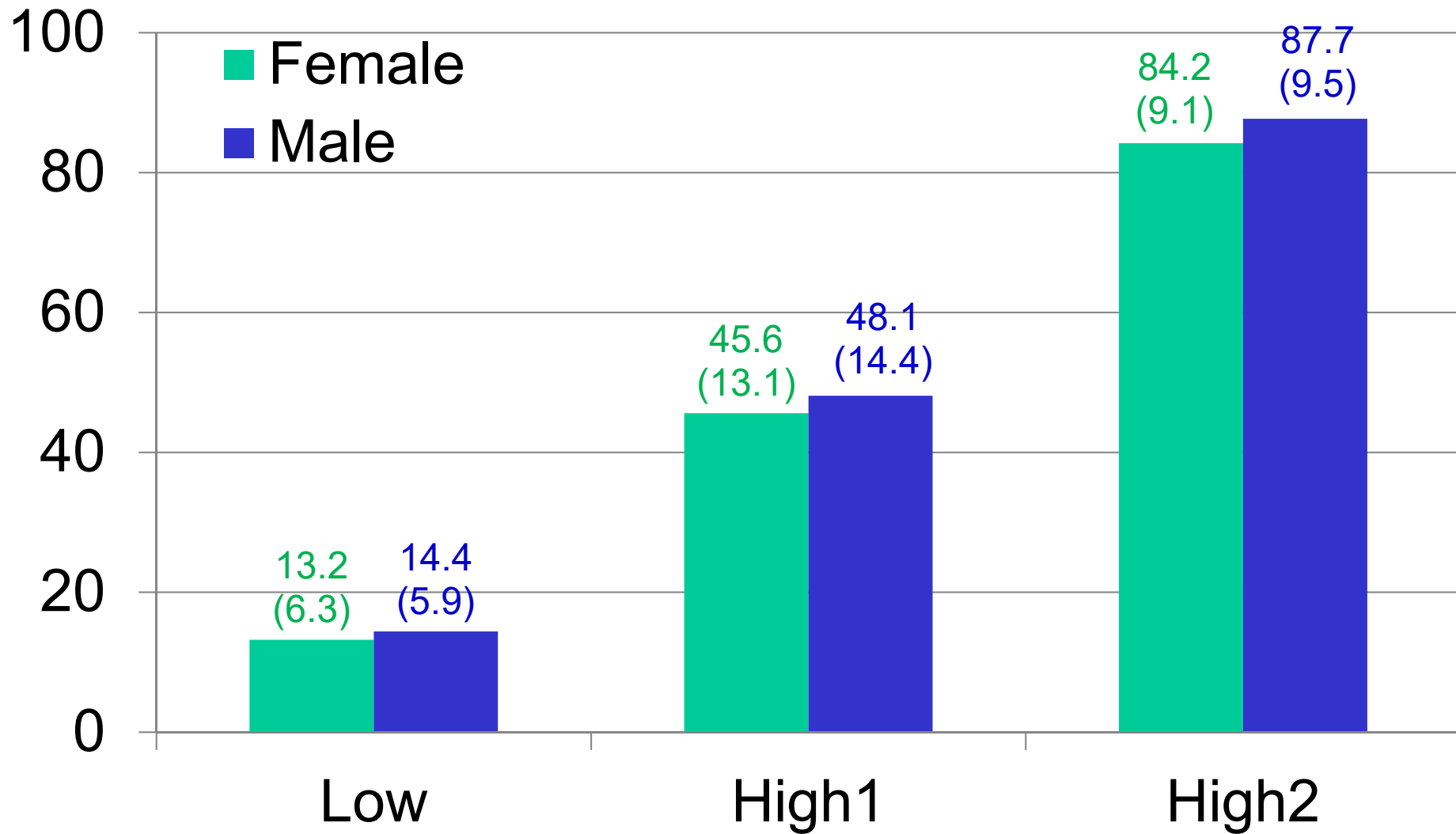
Ferritin (ng/mL) – Mean
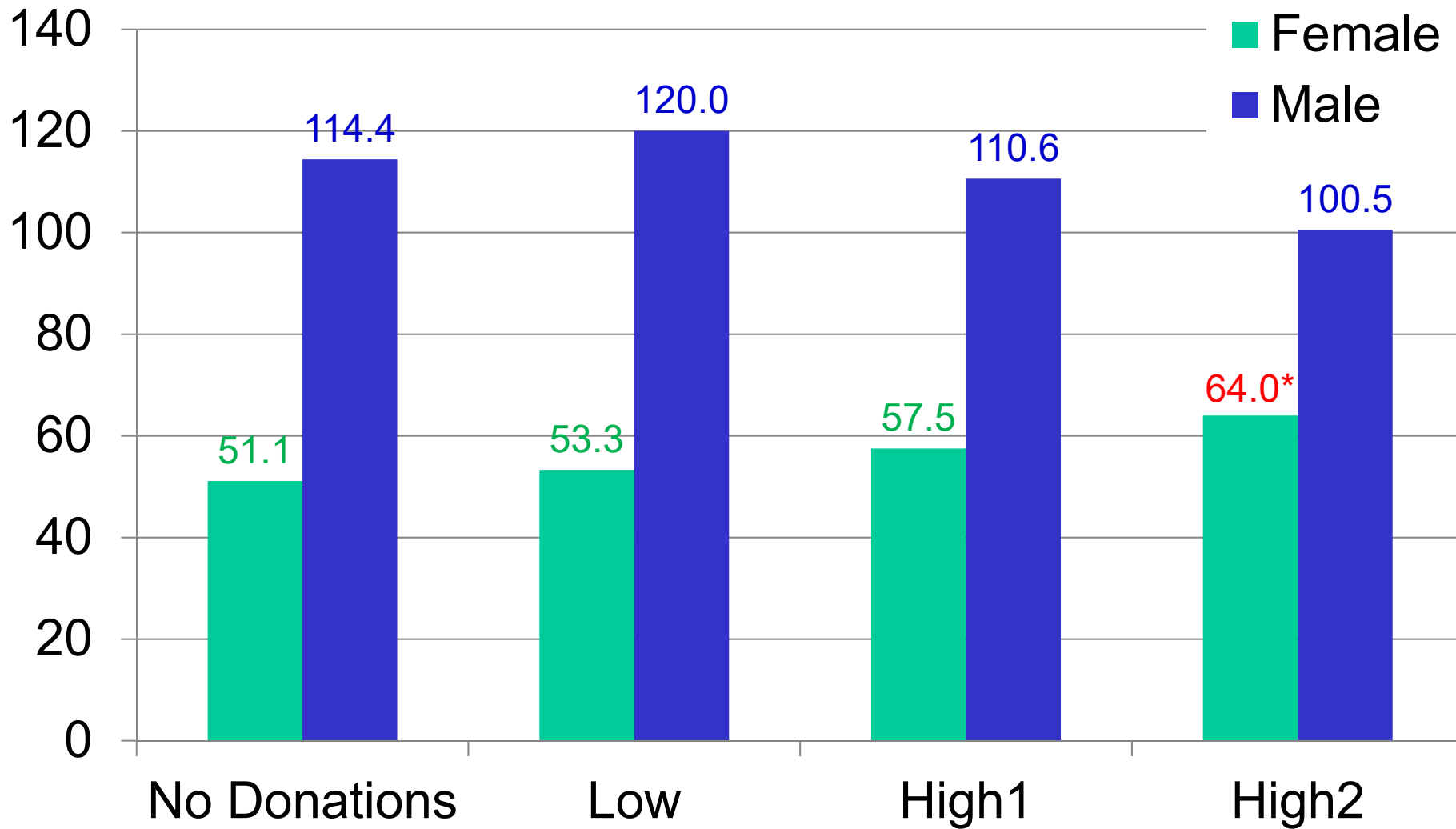
* p ≤ .02; no donations versus high2

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Ferritin* – Mean Differences Between Frequency Groups (Unadjusted)

	N	Mean ± SD	Difference No prior-low/high Mean (95% CI)	p-value (2-sided)
Females				
No donations	164	51.1 ± 41.2		
Low	168	53.3 ± 49.8	-2.2 (-12, 7.7)	0.66
High1	181	57.5 ± 52.9	-6.4 (-17, 3.7)	0.22
High2	156	64.0 ± 57.3	-13 (-24, -2.0)	0.02
Males				
No donations	145	114 ± 73.4		
Low	138	120 ± 75.8	-5.7 (-23, 11.8)	0.52
High1	161	111 ± 77.9	3.7 (-13, 20.8)	0.67
High2	141	100 ± 85.5	13.9 (-4.6, 32.4)	0.14

12   * In ng/mL
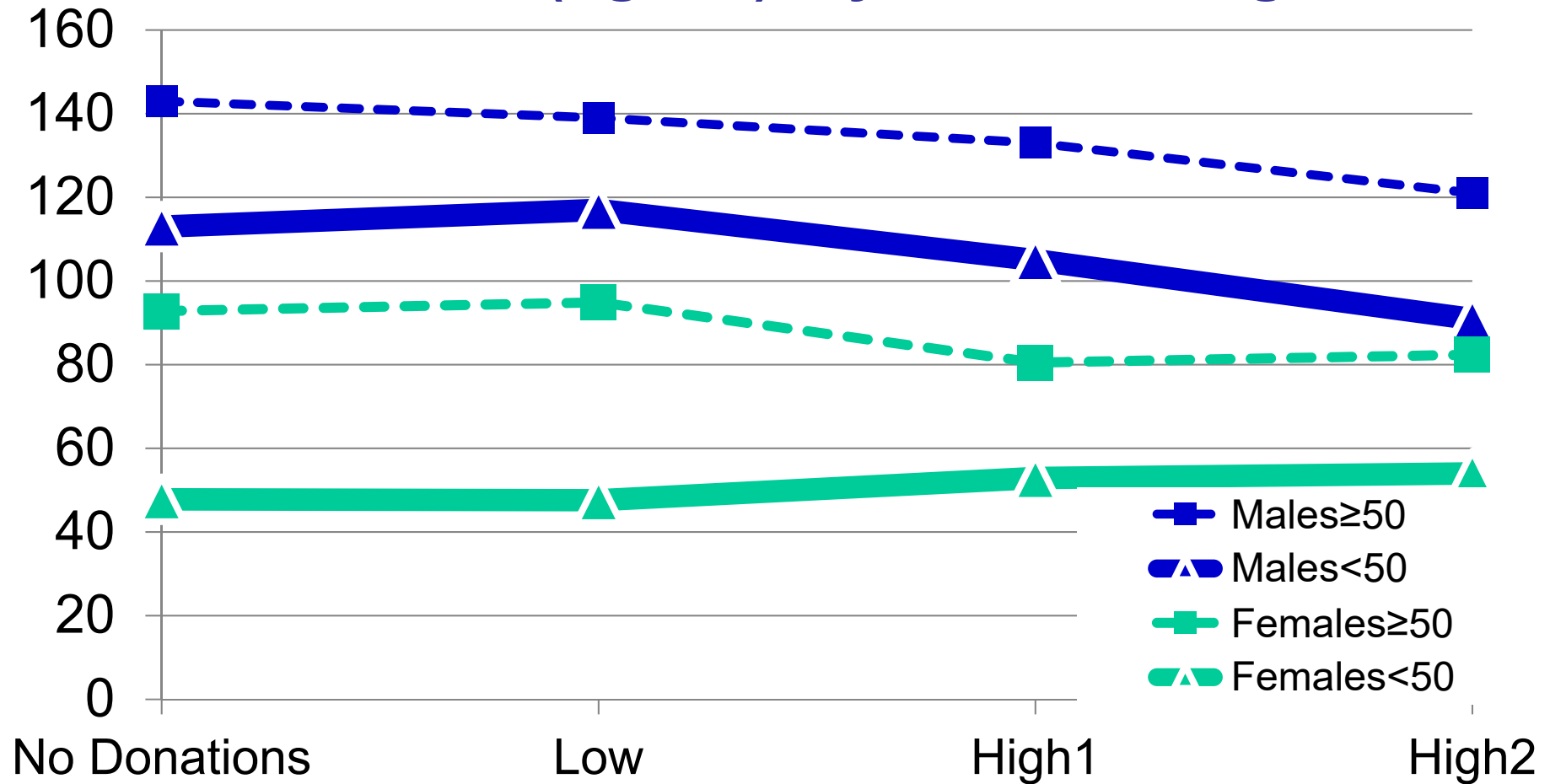
Ferritin

Mean Differences in Ferritin Levels* Between Frequency Groups

	Unadjusted		Adjusted	
	Difference No prior-low/high Mean (95% CI)	**p-value (2-sided)**	**Difference No prior-low/high Mean (95% CI)**	**p-value (2-sided)**
Females				
Low	-2.2 (-12, 7.7)	0.66	0.6 (-10.0, 11.2)	0.91
High1	-6.4 (-17, 3.7)	0.22	3.2 (-7.2, 13.7)	0.54
High2	-13 (-24, -2.0)	0.02	3.5 (-7.7, 14.6)	0.54
Males				
Low	-5.7 (-23, 11.8)	0.52	3.2 (-15.0, 21.3)	0.73
High1	3.7 (-13, 20.8)	0.67	-8.1 (-25.8, -9.5)	0.37
High2	13.9 (-4.6, 32.4)	0.14	-21.3 (-39.9, -2.7)	0.03

* In ng/mL

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Plasma Protein Therapeutics Association

Donors with Absent Iron Stores (AIS) (Ferritin < 12 ng/mL)

	No donations	Low	High1	High2	Total
Females	12/164 (7%)	9/168 (5%)	5/181 (3%)	2/156 (1%)	28/669 (4%)
Males	1/145 (1%)	0/138 (0%)	0/161 (0%)	2/141 (1%)	3/585 (<1%)

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Median Ferritin and Percent of Donors with AIS, for SP (FLIPD) and WB (RISE) Donors, by Donation Frequency and Gender

	Median Ferritin (ng/mL)		AIS (%)	
	No Donations	High Frequency*	No Donations	High Frequency*
Females				
FLIPD	39	45	7.0	2.1
RISE	37	19	6.4	27.1
Males				
FLIPD	100	84	1.0	0.7
RISE	108	25	0.0	16.4

* High Frequency:
    FLIPD: ≥ 25 donations in 12 months
    RISE: Females ≥ 2 donations in 12 months
              Males ≥ 3 donations in 12 months

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Hematocrit Deferral Rates (%) by Gender and Donation Frequency

	Low	High1	High2
Females*	3.7	2.5	1.9
Males	0.1	0.3	0.2

* p ≤ .005

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For both female and males, correlation is low between hematocrit and donation frequency and ferritin level.

- **Frequency of donation; r<0.03 males and females**
- **Ferritin level; r = -0.02 males, r= 0.11 females**

- Few SP donors are AIS and for most, ferritin values are well within normal range.

- Frequent SP donation is not associated with:
    - Lower plasma ferritin values
    - Reduced body iron stores

- Unlike the situation with WB and Platelet donation, iron depletion is neither a short-term nor long-term issue associated with SP donation.

- Our data confirm that iron depletion and deficiency are not outcomes of Source Plasma Donation. Thus, measures needed to protect whole blood and platelet donors are not needed for Source Plasma Donors.

Data on donor adverse reactions and short introduction of utilised adverse reactions/ adverse effects classification for plasma donations : the European view

Aims of the donor vigilance

- Reduce the number (frequency) of adverse events and donor injury

- Improve donor satisfaction

- Improve donation frequency

- Improve the donation process and

- improve the training of the medical staff

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In order to be able to make a reliable statement on the risks of plasma donation, it is necessary to include the country-specific and local conditions.

Important donation conditions for this evaluation

➢ Selection of plasma volume depending on body weight

➢ No saline compensation

➢ Request for fluid intake before and during donation

➢ Use of equipment from Fresenius/Fenwal (A200) and Haemonetics (PCS2 and MCS+)

➢ Definition of the adverse events according to the "Standards for Surveillance of Complications Related to Blood Donation (Rev. 2014)"
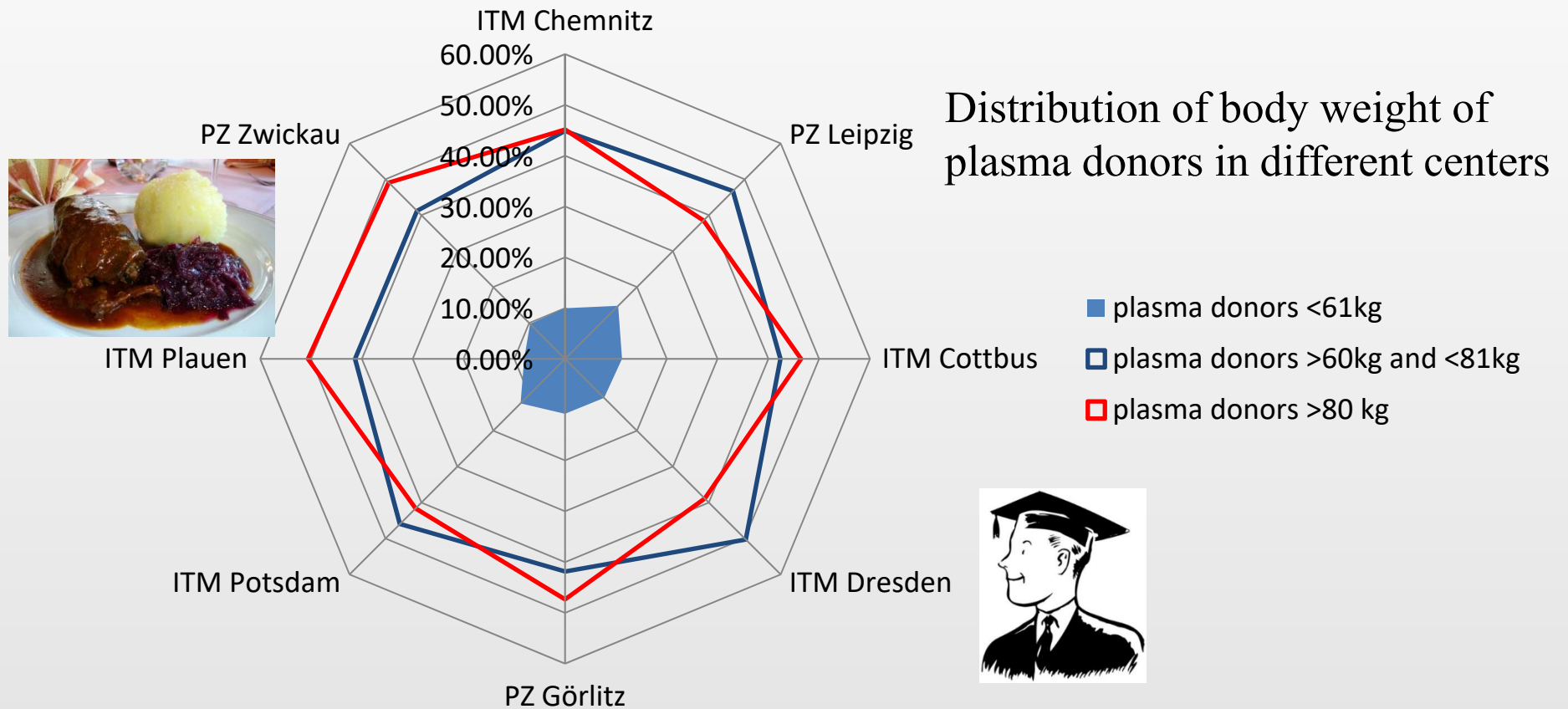
Important changes since the beginning of 2018

(new guidelines for hemotherapy 2017)

➢ Increasing the maximum number of plasma donations per year to 60

➢ Changes in maximum donation volume

- Donors with a body weight over 70 kg can donate 850 ml plasma (previously with a body weight over 80 kg).

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For an evaluation of individual centers, it is important to know different center-specific conditions

Distribution of body weight of plasma donors in different centers

- plasma donors <61kg
- plasma donors >60kg and <81kg
- plasma donors >80 kg

Data basis for donor vigilance statistics
2011-2017

➢ 2.068.233 Whole blood donations

➢ 169.360 first time donors, 1.898.873 donations from multiple donors

➢ 851861 Plasma donations

➢ 16464 first time donors, 835397 donations from multiple donors

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Comparison of side effects of whole blood and plasma donation

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Overview of adverse reactions to whole blood and plasma donations (multiple donors)

	venipuncture-related side effects	Systemic (Vasovagal) adverse reactions
Plamsapheresis	0.432%	0.299%
Whole blood donation	0.233%	0.323%

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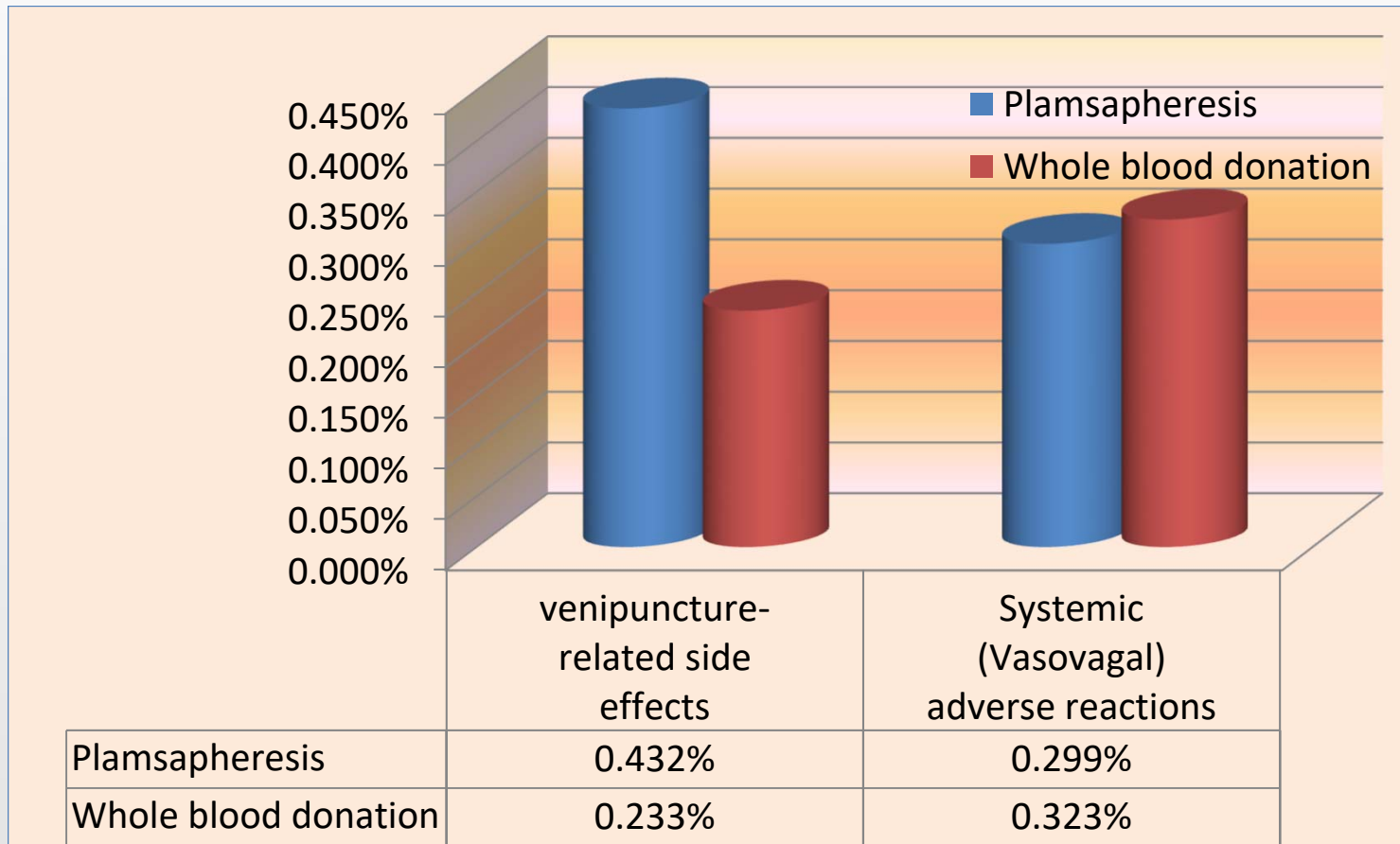
most frequent local side effects in comparison

	haematoma	Infiltration	Nerve injury/rritation	other arm pain	Arterial puncture
whoole blood donation	0.2112%	0.0000%	0.0009%	0.0196%	0.0067%
plasmapheresis	0.2654%	0.0985%	0.0010%	0.0749%	0.0004%

Dr. med. Thomas Burkhardt

local side effects due to venipuncture in first-time donors

	Haematoma	Infiltration	Nerv injury/irritation	ohther arm pain	Arterial puncture
whoole blood donation	0.28%	0.00%	0.00%	0.02%	0.01%
plasmapheresis	1.04%	0.26%	0.02%	0.09%	0.01%

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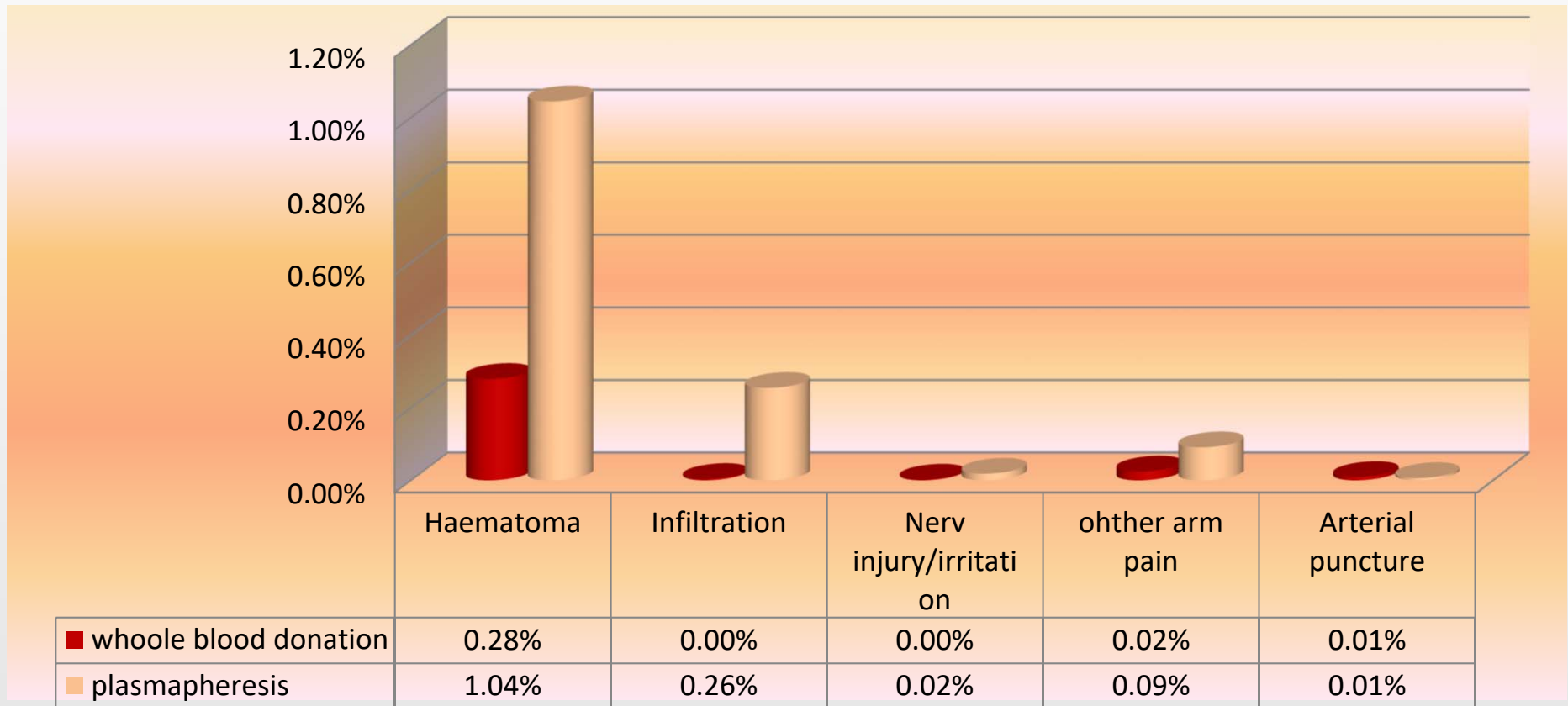
Comparison of vasovagal reactions occurring in first-time donors

	mild VVR without therapie and LOC	VVR with therapie/ without LOC	VVR with LOC <60 seconds	VVR with LOC >60 seconds
■ whoole blood donation	1.38%	0.97%	0.14%	0.01%
▢ plasmapheresis	3.78%	0.16%	0.01%	0.05%

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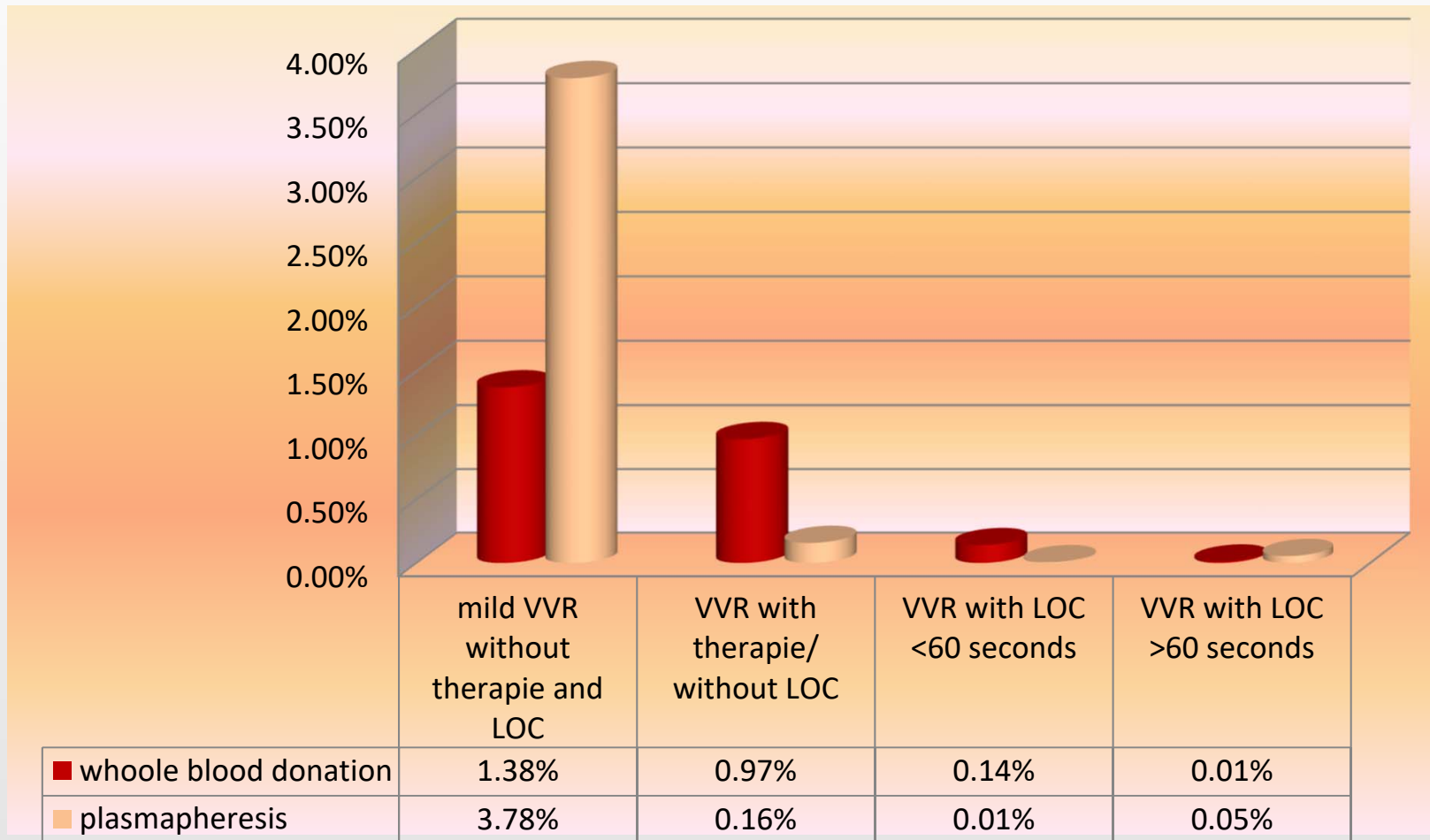
short summary from the comparison of whole blood
donation and plasmapheresis

➢ Both types of donation rarely have side effects, which
are usually mild in nature

➢ More venipuncture-related side effects are observed in
plasma donation, mainly caused by different procedures.

➢ Vasovagal reactions are rarer in plasmapheresis than in
whole blood donation and usually progress slightly.

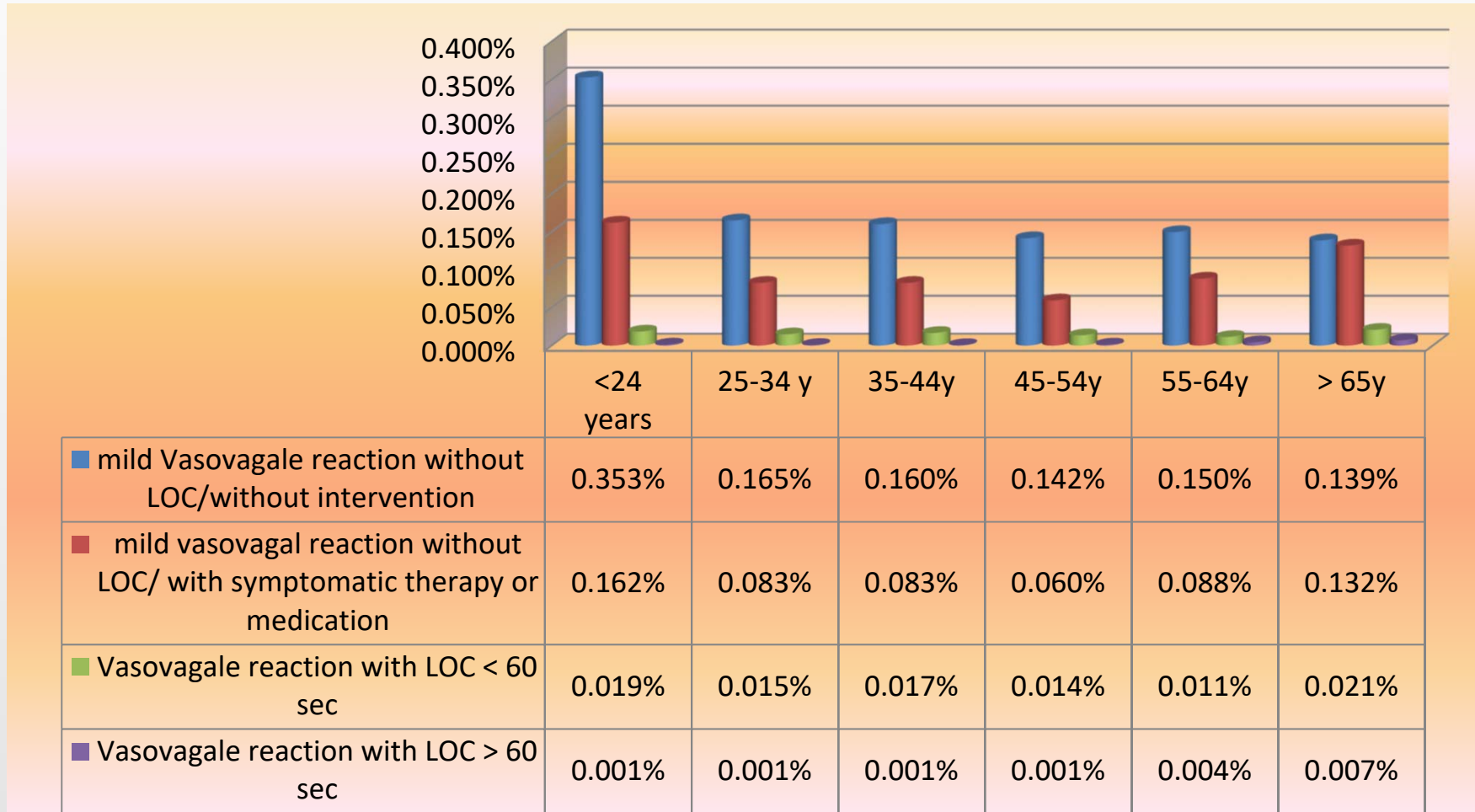➢ severe side effects occur very rarely in both types of
donation

Systemic (vasoavagal) side effects of plasma donors (multiple donors) (835397 donations)

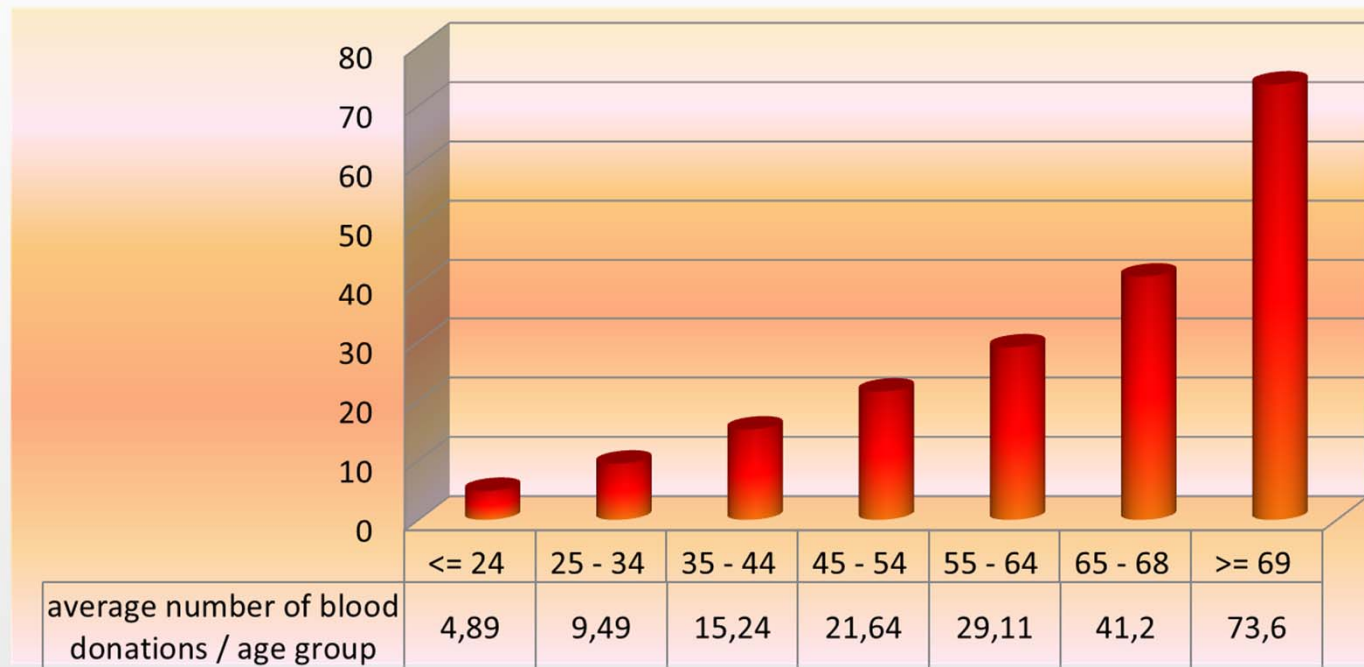|	
mild Vasovagale reaction without LOC/without intervention	1579
mild vasovagal reaction without LOC/ with symptomatic therapy	775
Vasovagale reaction with LOC < 60 sec	128
Vasovagale reaction with LOC > 60 sec	14
Hypertension	3
Citrate reaction	71
nausea / emesis	88
convulsive fit	6
injury in donors with a vasovagale reaction	5
injury/accidents related to blood donation/plasmapheresis	3
Haemolysis	14
other side effects	0

Local side effects of plasma donors (multiple donors) (835397 donations)

Haematoma	2179
Delayed bleeding	38
Infiltration	823
Nerve Injury	8
Other Painful arm	626
Arterial puncture	3
Local allergic reaction	10
local inflammation	2
Thrombophlebitis	5
other local side effects	0

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vasovagal reactions in plasma donation depending on age?

	<24 years	25-34 y	35-44y	45-54y	55-64y	> 65y
■ mild Vasovagale reaction without LOC/without intervention	0.353%	0.165%	0.160%	0.142%	0.150%	0.139%
■ mild vasovagal reaction without LOC/ with symptomatic therapy or medication	0.162%	0.083%	0.083%	0.060%	0.088%	0.132%
■ Vasovagale reaction with LOC < 60 sec	0.019%	0.015%	0.017%	0.014%	0.011%	0.021%
■ Vasovagale reaction with LOC > 60 sec	0.001%	0.001%	0.001%	0.001%	0.004%	0.007%

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average number of blood donations / age group

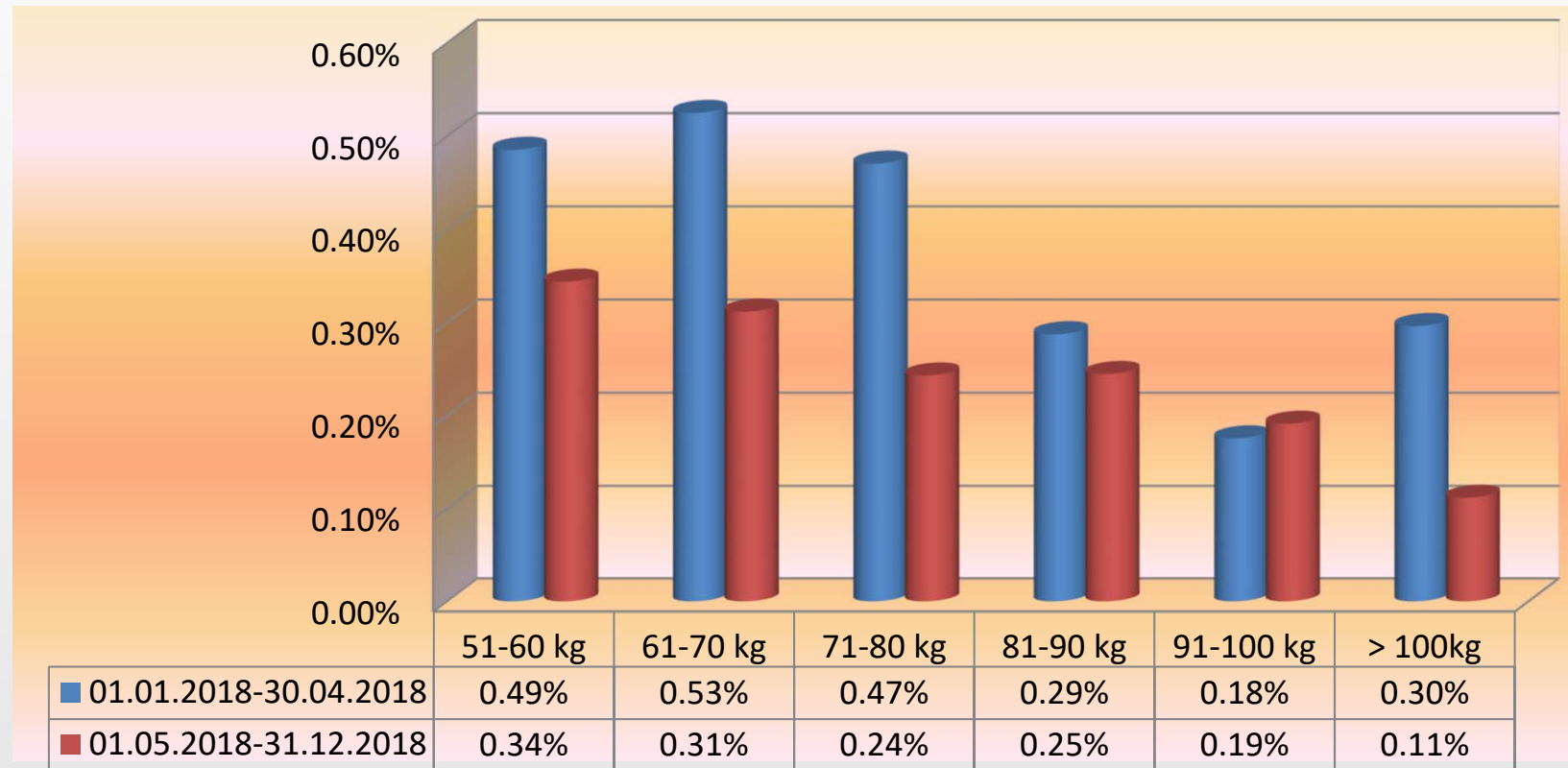|	<= 24	25 - 34	35 - 44	45 - 54	55 - 64	65 - 68	>= 69
average number of blood donations / age group	4,89	9,49	15,24	21,64	29,11	41,2	73,6

- older donors usually have a much higher donation experience
- many donors with side effects leave the donation process

Comparison of the vasovagal reactions 2017/2018 after increasing the collection volume to 850 ml for donors with a body weight of 71-80 kg (First time and repeat donors)

2017: 128936 plasma donation
2018: 117045 plasma donation

	51-60 kg	61-70 kg	71-80 kg	81-90 kg	91-100 kg	>101 kg
2017	0.449%	0.427%	0.287%	0.220%	0.327%	0.190%
2018	0.456%	0.450%	0.377%	0.300%	0.214%	0.208%

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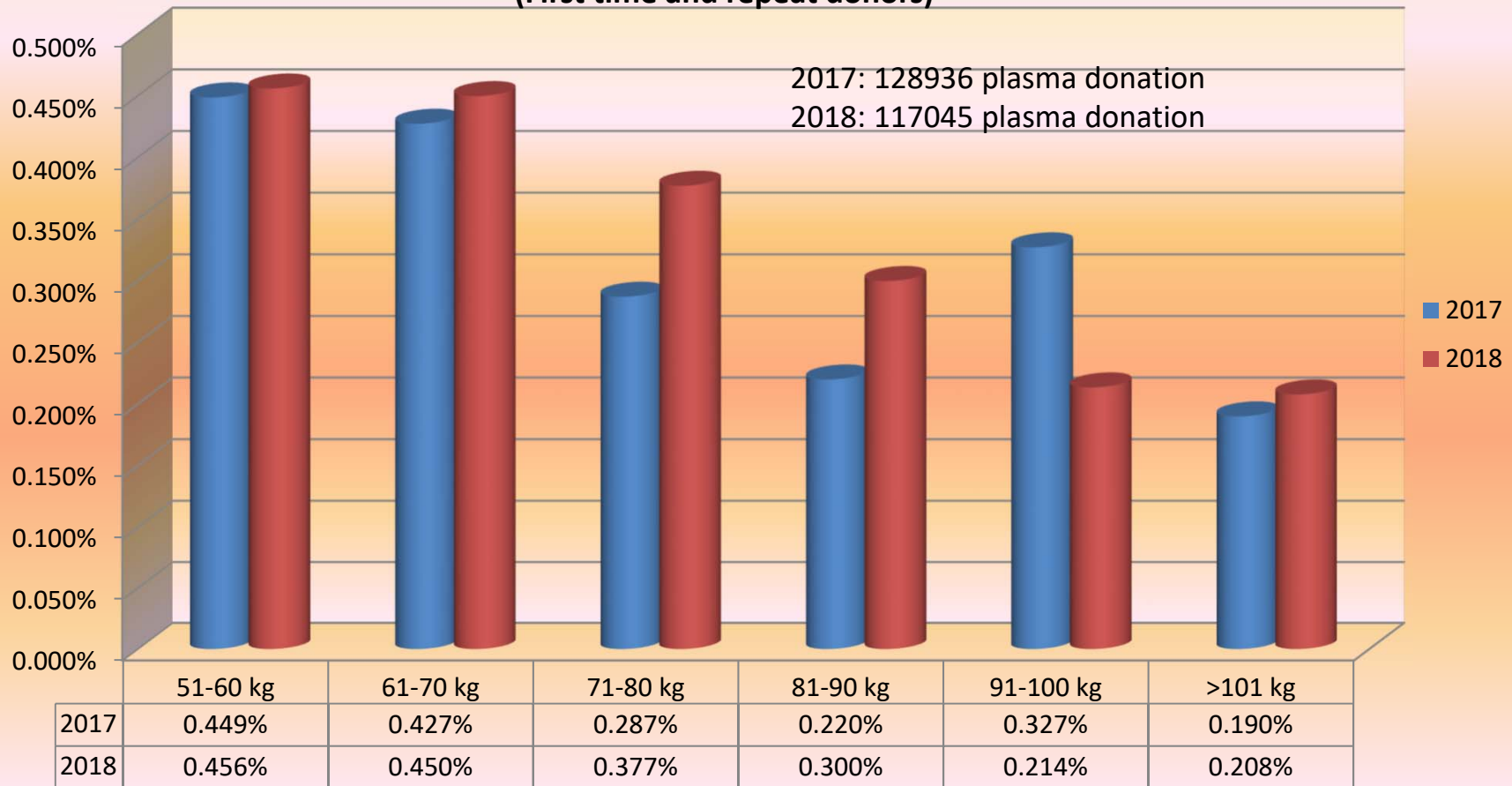
Development of detected VVR in the first year after changes in collected plasma volume

	51-60 kg	61-70 kg	71-80 kg	81-90 kg	91-100 kg	> 100kg
■ 01.01.2018-30.04.2018	0.49%	0.53%	0.47%	0.29%	0.18%	0.30%
■ 01.05.2018-31.12.2018	0.34%	0.31%	0.24%	0.25%	0.19%	0.11%

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amount of plasma collected and frequency of vasovagal reactions

- If the plasma volume is adapted to the body weight of the plasma donor, moderate or severe side effects are very rare
- Even with donors in the 71-80 kg weight group, only a few vasovagal reactions occur after increasing the donation volume
- The comparison of the VVR from the years 2017 and 2018 is an indication but not a certain statement - there are not enough data and the differences between the centres are too great
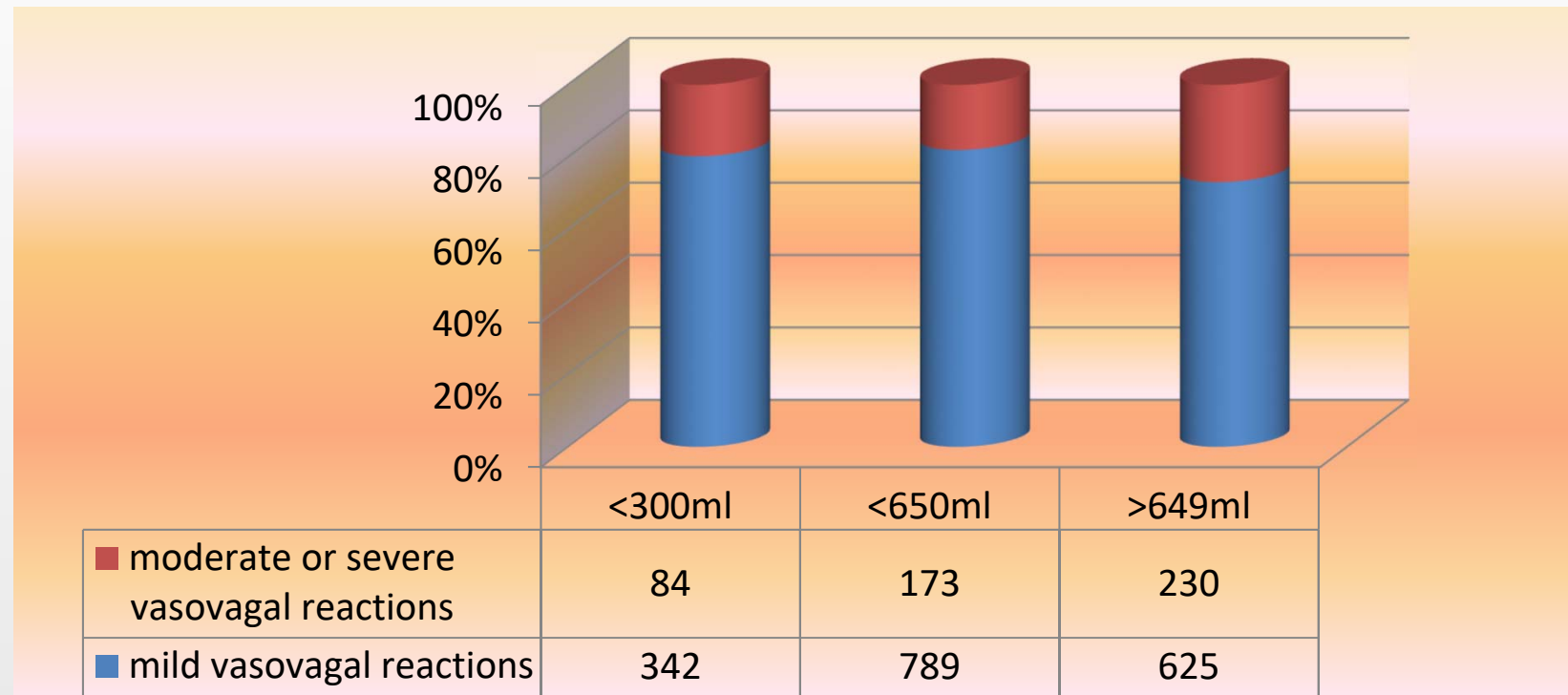
plasma volume achieved at the time of VVR occurrence
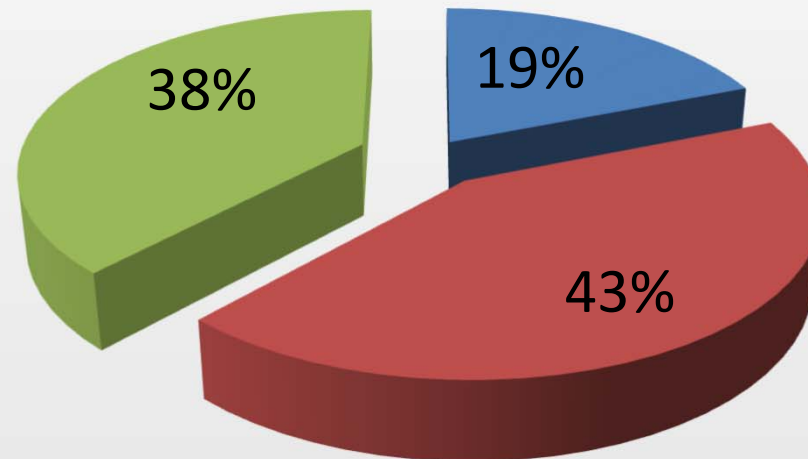
VVRs do not always occur after the donation has been completed.

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plasma collected up to the time of occurrence of a vasovagal reaction

	<300ml	<650ml	>649ml
■ moderate or severe vasovagal reactions	84	173	230
■ mild vasovagal reactions	342	789	625

- especially the VVR occurring at the beginning of the plasma donation could also be the result of a too high plasmapheresis speed.

Grading Severity of Plasma donor adverse events

-   it would be a good idea to introduce a uniform system for assessing the severity of an adverse reaction
-   The severity of a side effect can often only be assessed retrospectively.
-   this measure could allow a better assessment of adverse reactions that occur

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**Donor vigilance meets
Donor management**

In order to reduce side effects,
comprehensive care of plasma donors
by well-trained staff is required !

Donor vigilance meets Donor management

important points to reduce side effects

- good and comprehensive donor education
- quiet and professional working employees
- the knowledge of how to minimize the individual donor risk
- a perfect management of side effects

Training of (medical) staff to manage side effects

- to treat the donor
- to reassure other donor
- to show that professional work is done

Recommendations for an intensified and safe plasma donation from the point of view of own practical experience

- the maximum number of 60 plasma donations per year and a new plasma donation after 3 days is safe if the haemoglobin content is tested on the occasion of the donation and the IgG is tested every 5th donation
- the best is a procedure individually adapted to the plasma donor
- a withdrawal quantity adapted to the body weight of the plasma dispenser (650ml - <61kg bodyweight/750ml - < 71kg body weight /850ml - > 70kg body weight) is safe and practicable
- For donors with a lower body weight, the sampling speed should be adjusted.

thank you for your interest
still having a good meeting
without side effects

Dr. med. Thomas Burkhardt

Assessing Donor Health

Just as patient's health and safety, donor health is a top priority for the plasma collection industry. Donor Health & Safety is addressed by:

- Selection/Monitoring per FDA and EU Blood Directive, requirements of other countries (depending on where the final is product used)

  - Annual physical exam

  - BP / pulse / temperature / total protein / hematocrit / weight on each donation

  - Consultations with personal healthcare provider as needed

- PPTA Voluntary Standards;

  - International Quality Plasma Program (IQPP) certification

- Hemovigilance (PlasmaVigilance);

IQPP Donor Adverse Events Recording Standard

- Provides a common language to classify donor adverse events (DAE) within the industry
  - Each plasma organization has procedures in place to safeguard and monitor the health and safety of donors
  - The terminology between organizations was similar, but the definitions were not standardized.
  - Standardization was necessary for data aggregation and benchmarking.

PPTA
Plasma Protein Therapeutics Association

- Detailed categories that are applicable to the plasma industry

- Easy to use with objective definitions based on simple and common signs and symptoms

- Strengthens the power of the data representing the entire plasma industry

- Standard implemented April 1, 2015 (pilot 2016)

- Revised based on pilot April 1, 2018

- Available on PPTA's website:
  http://www.pptaglobal.org/safety-quality/standards/iqpp

DAE Classifications

- The *Donor Adverse Event Classification Guide* provides the signs and symptoms that set the boundaries defining each category and sub-category.

- Eight (8) major categories were selected for recording of events.

- Most categories have sub-categories providing granularity to better reflect the severity spectrum within a category.

DAE Classifications

Category	Recording Requirement (* = record)	Sub-Category
Hypotensive Event (vasovagal/Hypovolemia)		
		Prefaint, No LOC (Minor)
	*	Prefaint, No LOC (Moderate)
	*	LOC approximately less than 60 Seconds
	*	LOC approximately 60 Seconds or longer
	*	Severe (With or Without LOC)
	*	Injury

DAE Classifications

PPTA — Plasma Protein Therapeutics Association

Category	Recording Requirement (* = record)	Sub-Category
Major Cardiovascular or Respiratory Event	*	
Local Injury Related to Phlebotomy Event		
	*	Nerve Irritation
		Hematoma/Bruise (Uncomplicated)
	*	Hematoma/Bruise (Complicated)
	*	Infection
	*	Arterial Puncture
		Infiltration
	*	Major Blood Vessel Injury
Citrate Reaction Event		
		Minor
	*	Moderate
	*	Severe

DAE Classifications

Category	Recording Requirement (* = record)	Sub-Category
Hemolysis/Hemoglobinuria Event		
	*	Uncomplicated
	*	Complicated
Air Embolus Event		
		Uncomplicated
	*	Complicated
Allergic Event		
	*	Local
	*	Generalized
	*	Anaphylaxis
Hyperventilation Event	*	
Other Event	*	

- Assess performance of the Standard by reviewing operational data

- Obtain a snapshot of events recorded over a 3-month period post-implementation

  - 01 March – 31 May 2016

  - Only DAE that occurred during or post donation were evaluated

- 6 companies participated in the pilot study

- Nearly 7.6 million donations were collected; ~79% of industry

- 15,300+ DAE were recorded

Top 6 DAE

Rank	Classification	% of DAE	Rate per 10,000 donations
1	Hypotensive: Prefaint, No LOC (Moderate)	57.3%	11.98
2	Local Injury Related to Phlebotomy: Hematoma/Bruise (Complicated)	18.2%	3.81
3	Hypotensive: LOC (brief)	9.0%	1.88
4	Hypotensive: Severe (with or without LOC)	3.2%	0.66
5	Local Injury Related to Phlebotomy: Nerve Irritation	3.2%	0.66
6	Citrate Reaction: Moderate	3.1%	0.65
All others		4.3%	1.29
	TOTAL	100%	20.93
	TOTAL DAE: 15,300+		

DAE major category reaction rates

Events per 10,000 donations

- Hypotensive: 14.77
- Major Cardiovascular or Respiratory…: 0.03
- Local Injury Related to Phlebotomy…: 4.56
- Citrate Reaction Event: 0.68
- Hemolysis/Hemoglobinuria: 0.011
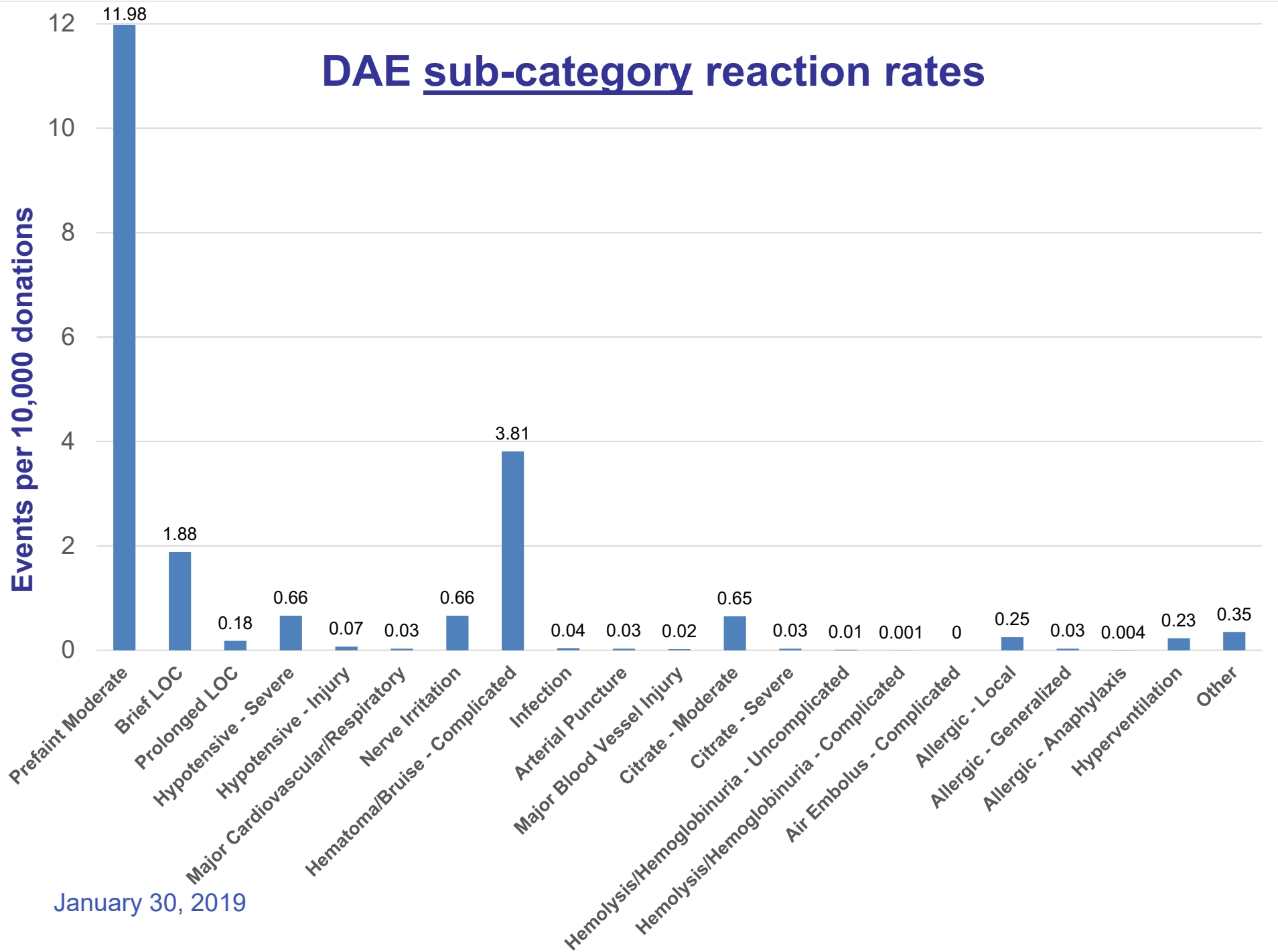- Allergic Event: 0.284
- Hyperventilation Event: 0.23
- Other Event: 0.35
- *
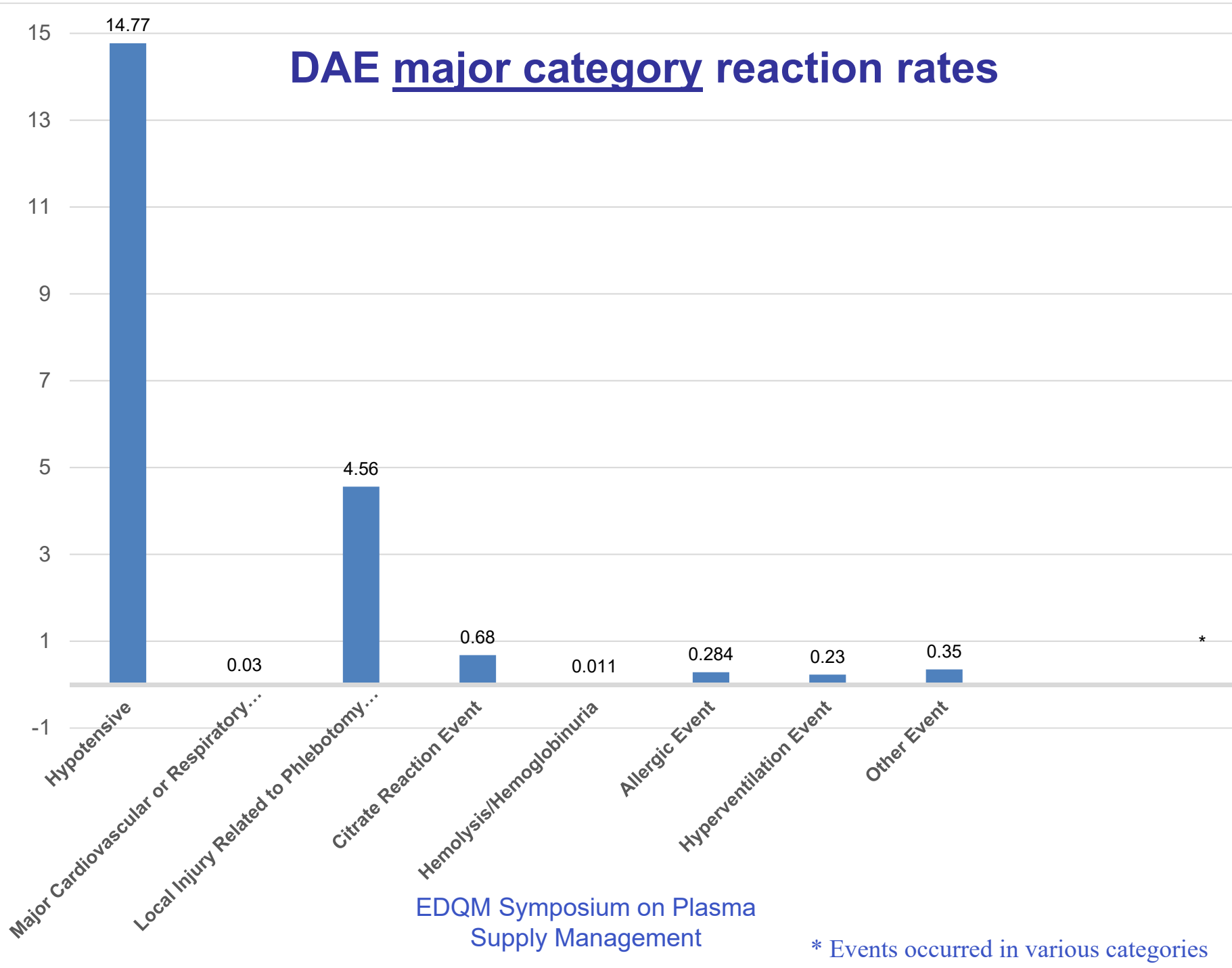
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* Events occurred in various categories

DAE sub-category reaction rates

Events per 10,000 donations

Category	Value
Prefaint Moderate	11.98
Brief LOC	1.88
Prolonged LOC	0.18
Hypotensive - Severe	0.66
Hypotensive - Injury	0.07
Major Cardiovascular/Respiratory	0.03
Nerve Irritation	0.66
Hematoma/Bruise - Complicated	3.81
Infection	0.04
Arterial Puncture	0.03
Major Blood Vessel Injury	0.02
Citrate - Moderate	0.65
Citrate - Severe	0.03
Hemolysis/Hemoglobinuria - Uncomplicated	0.01
Hemolysis/Hemoglobinuria - Complicated	0.001
Air Embolus - Complicated	0
Allergic - Local	0.25
Allergic - Generalized	0.03
Allergic - Anaphylaxis	0.004
Hyperventilation	0.23
Other	0.35

January 30, 2019

- Hypotensive – Prefaint no LOC (moderate) was most prevalent reaction (11.98/10,000 donations)

  This reaction:

  a. requires medical staff (physician substitute) intervention, OR

  b. involves signs/symptoms that did not resolve quickly (e.g. within approximately 10 minutes), OR

  c. additional signs/symptoms may be present.

- Hematoma/bruise (complicated) had second highest rate (3.81/10,000 donations)

  A hematoma/bruise that is approximately >2" x 2."

Additional Findings – Hypotensive

- Brief LOC (<60 sec) occurred in 1.88/10,000 donations

- Prolonged LOC (≥60 sec) was rarely observed: 0.18/10,000 donations

- Severe hypotensive events (with or without LOC) occurred in 0.66/10,000 donations

- Hypotensive injury occurred in 0.07/10,000 donations

Illustrative Results: Rate per 10,000 donations and number of events (N)*

	ALL reactions	Hypotensive	Phlebotomy
Gender			
Female	38.31 (N=9427)	30.48 (N=7501)	5.38 (N=1325)
Male	11.45 (N=5882)	6.46 (N=3319)	3.89 (N=1997)
No events with <u>unknown</u> gender			
Donor status			
First time	85.65 (N=4607)	68.45 (N=3682)	12.21 (N=657)
Repeat	15.16 (N=10,702)	10.11 (N=7138)	3.77 (N=2665)
Events with <u>unknown</u> donor status were distributed using the ratio of first time to repeat events			
Age [years]			
18-20	57.00 (N=2900)	45.79 (N=2328)	8.52 (N=433)
21-24	27.55 (N=3317)	21.65 (N=2487)	5.13 (N=589)
25-44	16.00 (N=6372)	11.00 (N=4376)	3.67 (N=1461)
45-64	13.70 (N=2634)	8.27 (N=1590)	4.15 (N=798)
65+	21.00 (N=86)	9.51 (N=39)	10.00 (N=41)
Events with <u>unknown</u> age were distributed using the ratio of events by age group			

* Data limited to centers that could provide detailed variable distributions

- Females are 3.3 times more likely than males to have a DAE

  - Hypotensive reactions are 4.7 times more likely to occur in females than in males

  - Females are 1.4 times more likely to experience phlebotomy reactions than males

Hypotensive DAE / 10^4 donations, by donation type and age

	Female	Male
Donor status		
First time	130.2 (N=2784)	30.61 (N=992)
Repeat	20.98 (N=4716)	4.80 (N=2327)
Events with <u>unknown</u> donor status were distributed using the ratio of first time to repeat events		
Age [years]		
18-20	101.30 (N=1695)	18.59 (N=634)
21-24	48.63 (N=1704)	9.81 (N=783)
25-44	22.57 (N=2893)	5.50 (N=1483)
45-64	18.22 (N=1179)	3.22 (N=411)
65+	20.84 (N=31)	3.06 (N=8)
Events with <u>unknown</u> age were distributed using the ratio of events by age group		

Hypotensive DAE / 10^4 donations by weight

PPTA — Plasma Protein Therapeutics Association

Weight [pounds]	Female	Male
110-124	58.68 (N=623)	44.96 (N=66)
125-149	34.53 (N=1469)	8.94 (N=402)
150-174	39.48 (N=2000)	8.10 (N=844)
175+	23.97 (N=3409)	5.58 (N=2008)

Events with <u>unknown</u> weight were distributed using the ratio of events by weight group

Findings

- For hypotensive reactions:

  - First-time female donors had rates 6.2 times higher than repeat donors; similar to males, where the rate was 6.4 times higher

  - For first-time donors, female rate is 4.3 times that of males

  - For repeat donors, female rate is 4.4 times that of males

  - For both genders, younger and lighter donors have higher rates

Current Health Initiatives

- DAE data collection with revised standard
  - 01 May – 31 August 2018
  - 10 million donations/3 companies/70% total donations
  - Data sets recently transmitted for analysis
  - Analysis to be completed mid-summer 2019
- Donor Health Study (in planning stages)
  - SF-36 health assessment augmented with questions focused on immune health
  - 4000 donors
  - Initial survey/6 months/12 months
  - Follow up to include active/ lapsed donors

Thank You

Analysis of donor safety data from the TS093 survey to inform revision of the Guide

Dr Joanne Pink
On behalf of the TS093 Working Party

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TS093 core group members

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BUDZYNSKI Lukasz	Regional Blood Center in Poznan	PL
CASTREN Johanna (Chair)	Finnish Red Cross Blood Service	FI
EPSTEIN Jay	FDA - U.S. Food and DRUG Administration	USA
LARREA Luis	Centro de Transfusion de la Comunidad Vanlencia	ES
LIUMBRUNO Giancarlo	Italian National Blood Center	IT
MARANO Giuseppe	Italian National Blood Center	IT
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Guide to the preparation, use and quality assurance of blood components EDQM 19th edition 2017

- Total blood volume of each donor must be estimated

- Maximum ECV must never be higher than 20%

- Collected volume (excluding anticoagulant) for each procedure must not exceed 16% of estimated TBV and should never exceed 750mL, unless fluid replacement is undertaken

- *Consider survey data for DAE rate (pre-syncope, syncope) and donor retention rate and some relevant literature*

Human model of haemorrhage
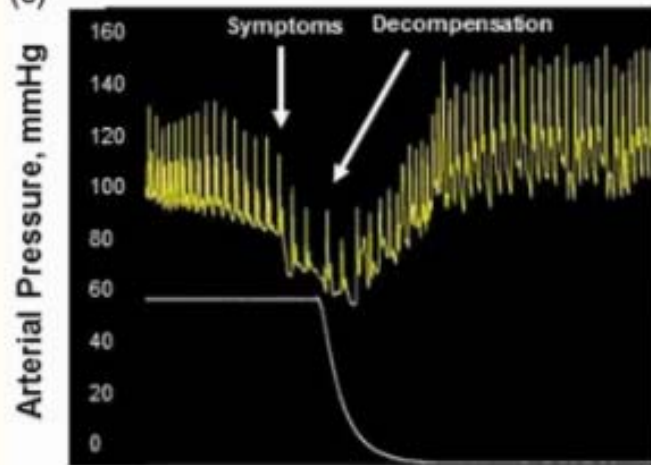
- Healthy human placed in a pressure chamber with the torso exposed and waist wrapped in a neoprene skirt

- Stepwise reductions in pressure inside the chamber which produces a reduction in central blood volume

- Continue until pre-syncope attained

4

Human model of haemorrhage

- Significant individual variability in the compensatory response to blood loss

- 1/3 have low tolerance (decompensate at <21.8% reduced central blood volume) and 2/3 display high tolerance ability to compensate for reduced central blood volume (>21.8%). Some don't tolerate even a 10% loss.

- Overall females demonstrate lower tolerance to central hypovolaemia compared to males
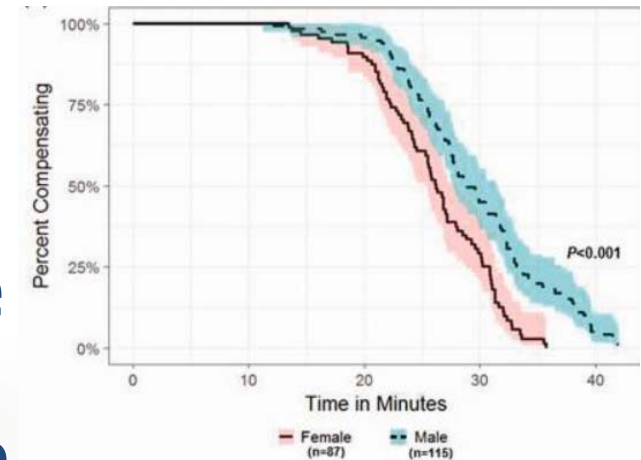
Pros and cons of estimating the TBV

- % of actual TBV lost is correlated with development of syncopal symptomatology

- Main benefit of estimating the TBV is to attempt to equalise the risk of syncopal reactions between large and small donors, and males and females.

- TBV is not perfect – over-estimated in shorter / overweight donors and under-estimated in tall / thin / muscular donors

- Increases operational complexity – height and weight

- Weight alone has poorest correlation with TBV

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Maximum collection volume per procedure versus immediate LOC rate (per 10,000 collections)

Volume Limit (mL) vs. VVR Immediate LOC Rate (/10,000 collections)
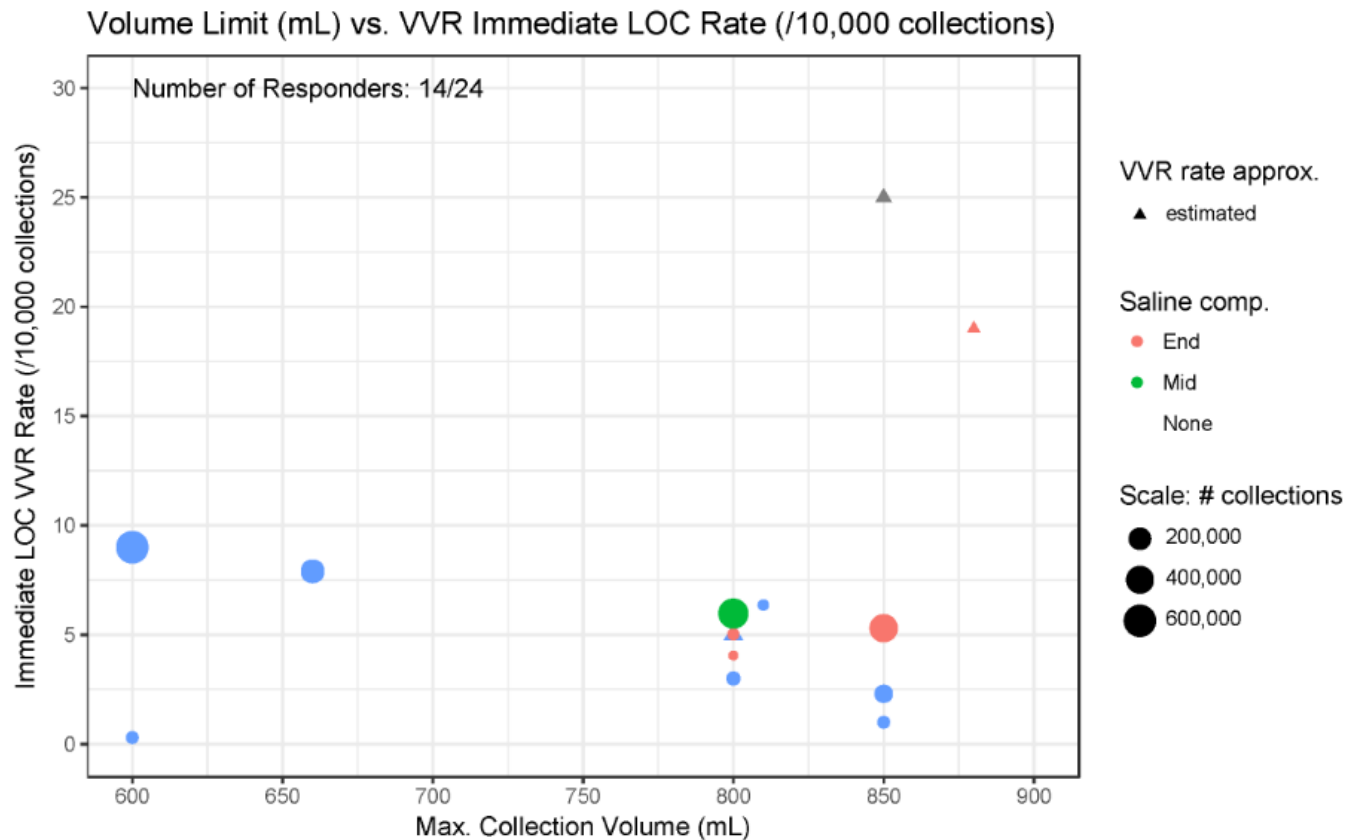
- LOC rate mainly < 10 / 10,000 collections

- Small trend towards reduced LOC rate with larger collection volume

- Likely due to differences in operating model, donor demographics (% of new, female) and perhaps apheresis platform (smaller ECV)

- Saline compensation unrelated

- 850mL are all remunerated

Retention rate versus immediate LOC rate (per 10,000 collections)

Number of Responders: 11/24

VVR Rate Approx
- • No
- ▲ Yes

Remuneration
- • No
- • Yes

Scale: # collections
- ● 200,000
- ● 400,000
- ● 600,000

Retention Rate (y-axis)
Immediate LOC VVR Rate (/10,000 collections) (x-axis)
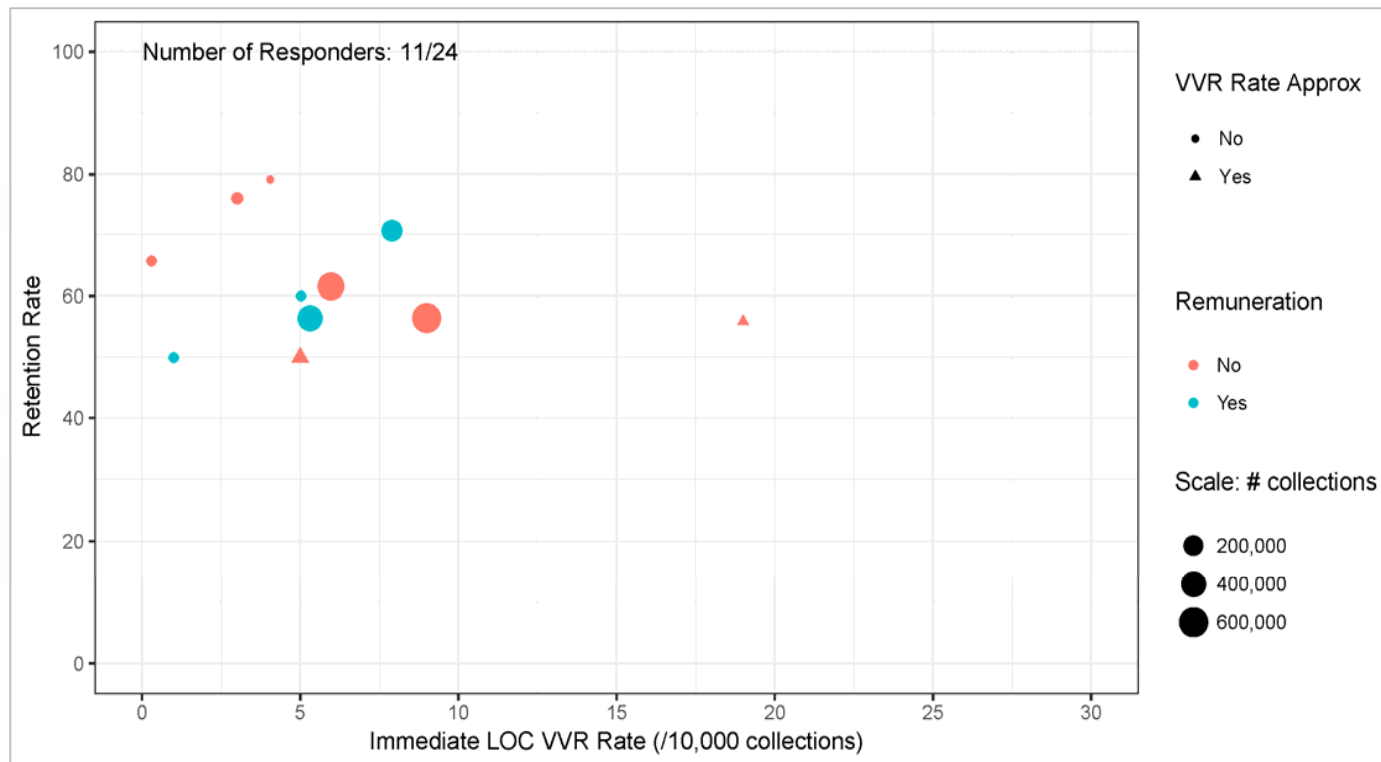
- Retention rate banded in the range of 50%-80%.

- Not correlated with LOC rates, saline compensation or remuneration.

- Caution - small data sample size, variation in reporting

Retention rate versus maximum yearly plasma collection (in Litres)

Max. Collection Volume (L) vs. 12mth Retention Rate (%)

Number of Responders: 16/24

Remuneration
- No
- Yes

Scale: # collections
- 200,000
- 400,000
- 600,000
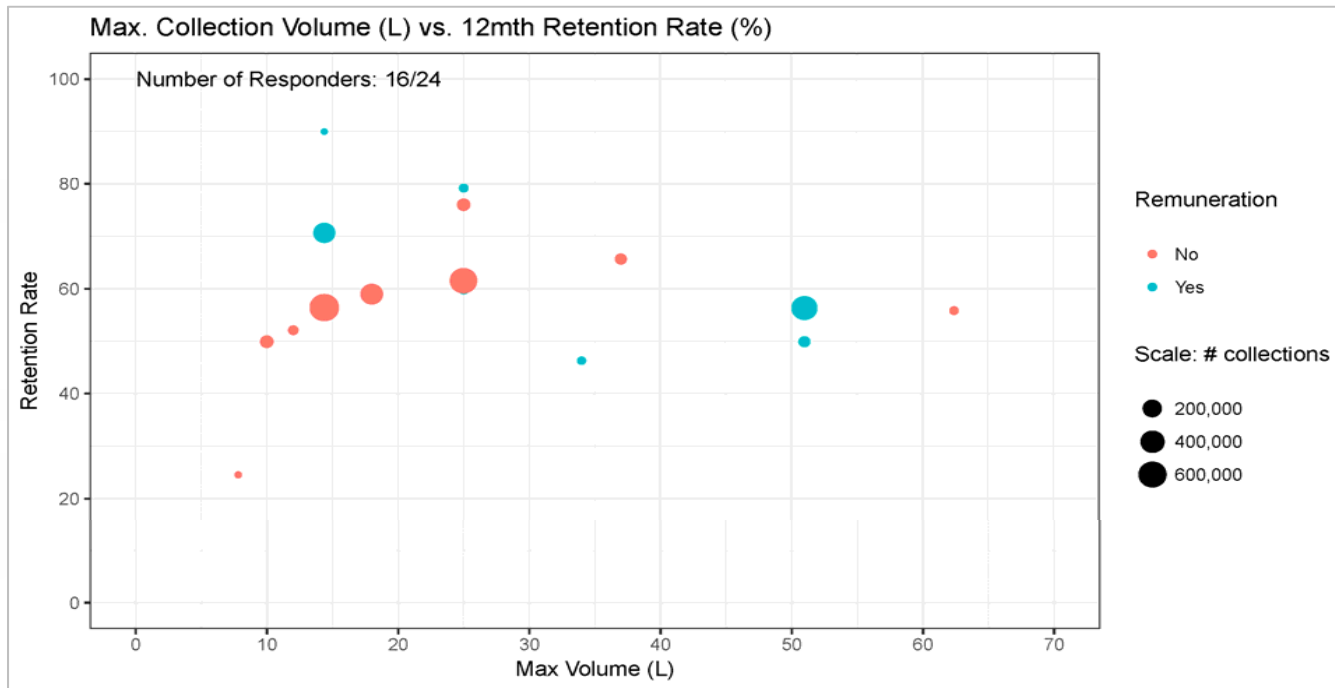
- Retention rate appears to be reasonably constant
- Remunerated collection agencies that restrict yearly collection volumes to 10L-25L appear to have on average a higher retention rate, however limited data points.

Considerations (ECV)

- There is variation in the ability of donors to tolerate plasma collection. Not possible to have zero risk, even at low collection volumes.

- The methodology for calculation of the ECV has limitations and for this reason does not always give a reliable estimate.

- The apheresis procedure is of short duration, the donor is under direct supervision and the additional impact of orthostatic hypotension is not relevant here.

- Physiological compensation with interstitial fluid shifts commences early and is rapid - there are limits though.

Implications for the Guide (ECV)

- Does estimating the ECV add to donor safety?

- Could the requirement for estimating the ECV be removed if we can take care of donor safety another way?

  - Rely on collection volumes?

  - Should we provide guidance that apheresis platforms should minimise the ECV?

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Determining the collection volume

- Inevitably there will be some donor attrition.

- Different methodologies are in place.

- *Survival of the fittest approach* – aim to achieve a panel of the most tolerant donors only, as quickly and simply as possible. Weed out less tolerant donors early.

- *More inclusive approach* – find the sweet spot for each donor, willing to tailor collection to the donor's tolerability - less efficient, more inclusive, but requires more complicated collection algorithms.

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Impact of collection volume target on donor adverse event rate
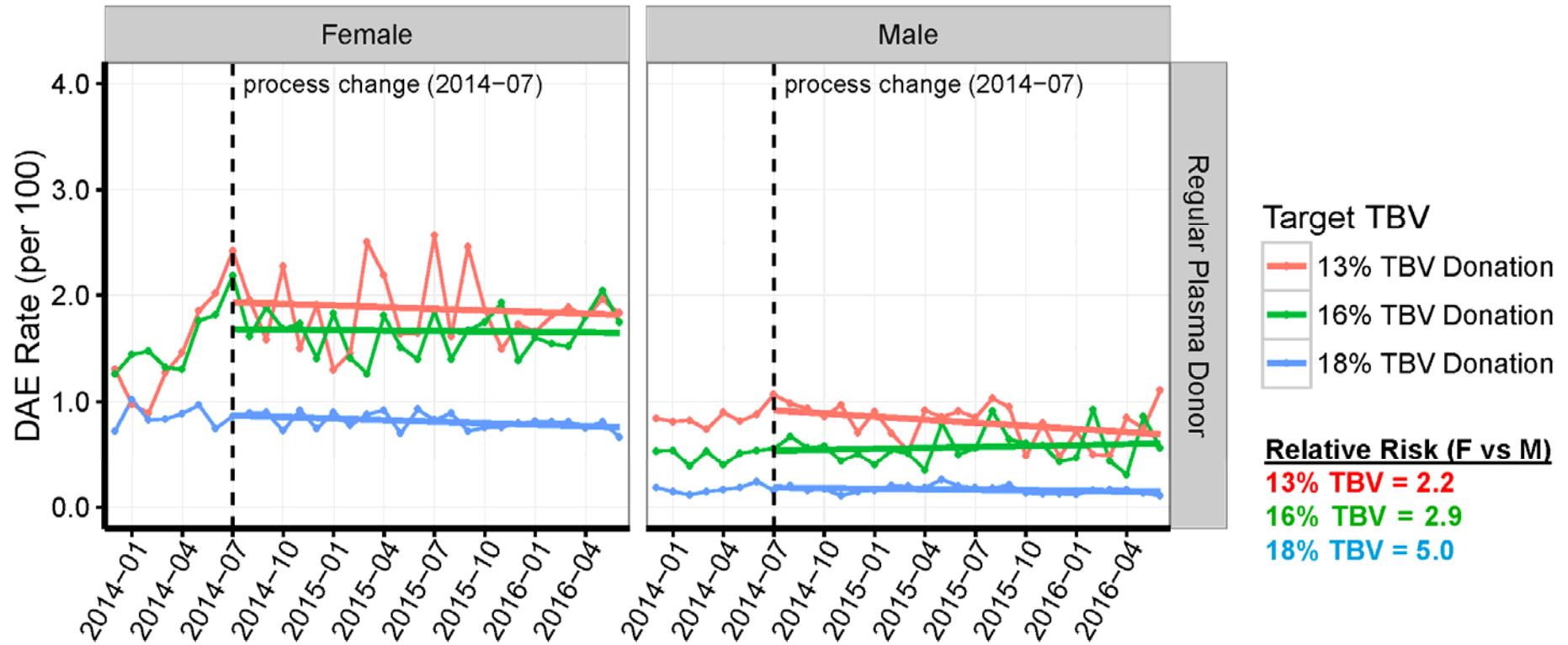
ANALYSIS: Actual Collected TBV percentage (Mid-Saline)
DATE RANGE: 01-2013 to 06-2016
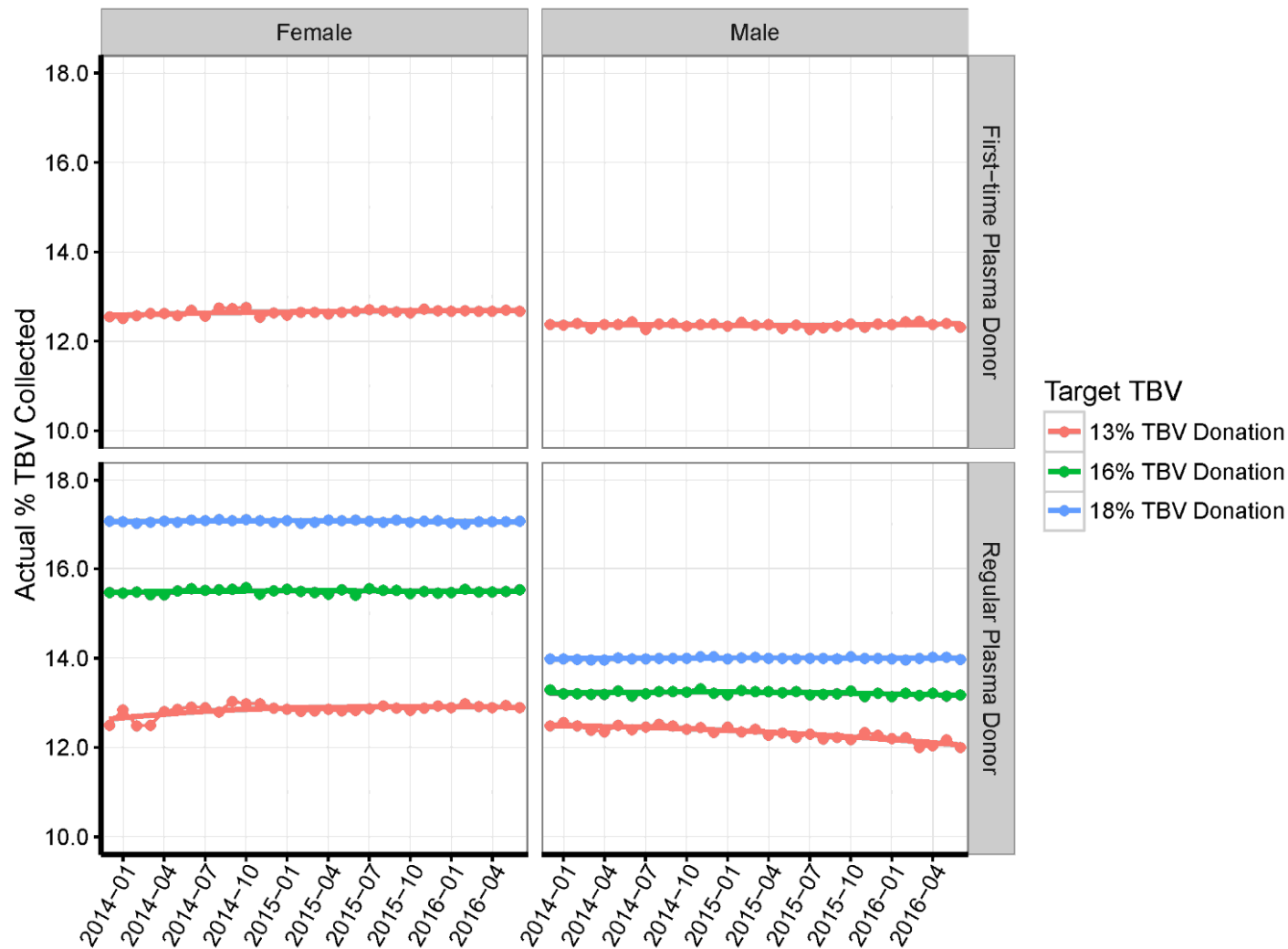
- Impact of the 800mL maximum collection volume limit.
- Actual % TBV collected in females is greater at all collection protocols because females are smaller

Implications for the Guide (TBV)

- What is the best practice methodology for determining the collection volume for a particular donor?

- Height, weight, gender etc

- Should we retain TBV?

Implications for the Guide (maximum collection volume)

- Survey includes 9 Blood Establishments with a collection volume of 800mL or 850mL (excluding anticoagulant), with comparable donor safety data to those with lower collection volumes.

- Should the maximum 750mL limit be increased to a maximum 800 - 850mL (excluding anticoagulant)?

- What is the role of saline replacement? End-saline certainly reduces red cell loss.

Guide to the preparation, use and quality assurance of blood components EDQM 19th edition 2017

- A maximum of 33 procedures may be performed per year (33 X 750mL = 24.75 L)

- Maximum annual collection volume = 25 L

- Not more than 1.5L of plasma may be collected from any one donor per week.

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Maximum yearly plasma collection (in Litres) allowable versus average donation frequency
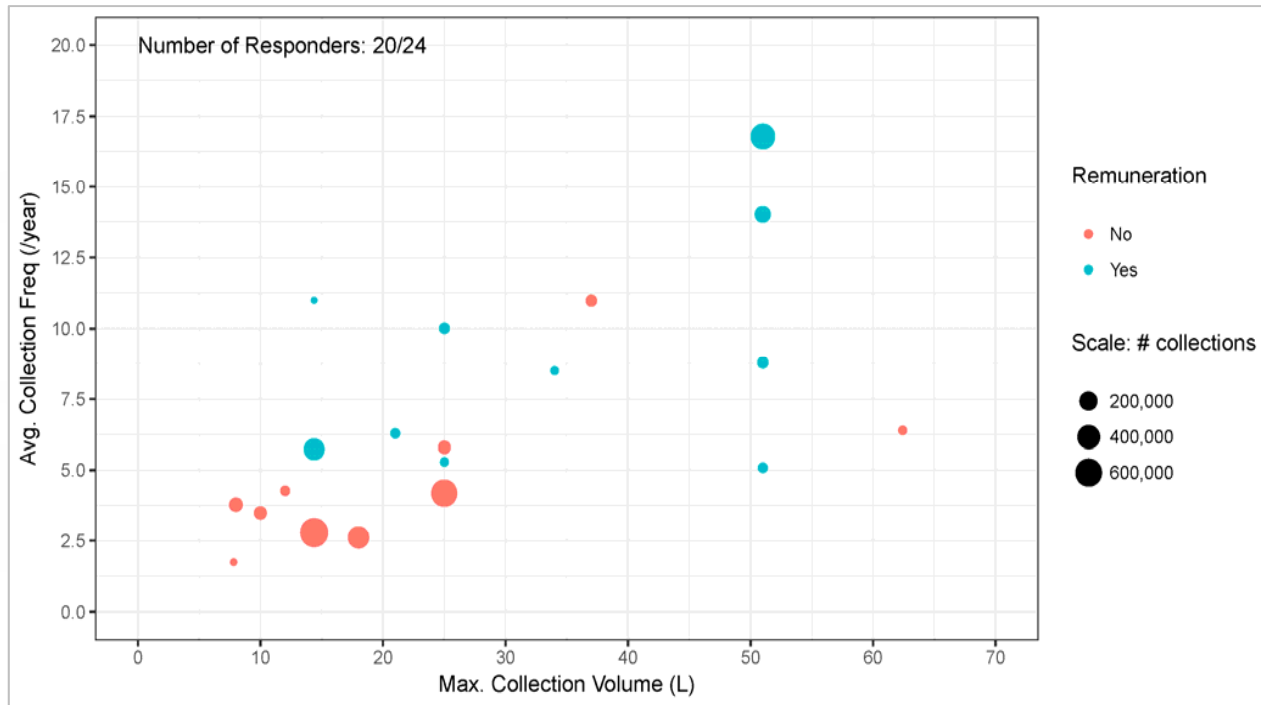
- Positive correlation

- Nearly 50% have an annual maximum collection volume less than that allowed by current Guide (9/20).

- Maximum *average* annual donation frequency still significantly less than that allowed by current Guide (17.5 vs 33).

- Donation frequency is likely influenced by the business model – higher for remunerated

Considerations
(annual collection volume)

- Almost half Blood Establishments are currently collecting less plasma then is already allowed for in the Guide and some are collecting more.

- An upper annual collection limit requires some Blood Establishments to limit collections to every 2 weeks to avoid exceeding 25 L/year, even though this is less conservative than the current guide.

- There is no evidence that more intensive plasmapheresis results in short or longer term donor harm provided there is tailored IgG monitoring with appropriate deferrals and measures are taken to reduce red cell loss (eg end-saline wash back).

Implications for the Guide
(annual collection volume)

- Does a 25L annual collection limit provide additional protection for donor if IgG monitoring and end-saline wash back is in place?

- Should we remove the 25L annual collection limit if collection frequency is tailored based on donor's initial IgG level and regular monitoring (to protect donor and product quality)?

Considerations (donor frequency)

- Significant variation in allowable donation frequency - up to 104 donations pa

- In reality, the major limiting factor in donor plasmapheresis is the capacity of donors to restore their plasma proteins.

- Significant variation in IgG synthesis rate – in general donors with lower initial IgG have lower synthesis rates.

- Maximum average annual donation frequency was 17.5

Considerations (donor frequency)

- Do we need a minimum donation interval to allow time for donation recovery and venepuncture site healing? Perhaps twice weekly?

- Do we need a maximum number of donations per year if donation frequency is determined by the donor's IgG? Perhaps 60?

Thank you

SIPLA Studies

Dr. med. Stephan Walsemann
Chairman, European Plasma Alliance

EDQM Symposium on Plasma Supply Management, 30.01.2019

European Plasma Alliance

- Alliance of 12 European private sector plasma collectors
- 110 centers (2018):

    Germany: 71

    Austria: 16

    Czech Republic: 6

    Hungary: 17

- 2,5 million liter collected (2017)

Mission: Promote safe plasma collection practices in the EU with focus on donor health and safety to ensure patients access to safe products

Dr. med. Stephan Walsemann
EDQM Symposium on Plasma Supply Management, 30.01.2019

Dr. med. Stephan Walsemann
EDQM Symposium on Plasma Supply Management, 30.01.2019

Introduction
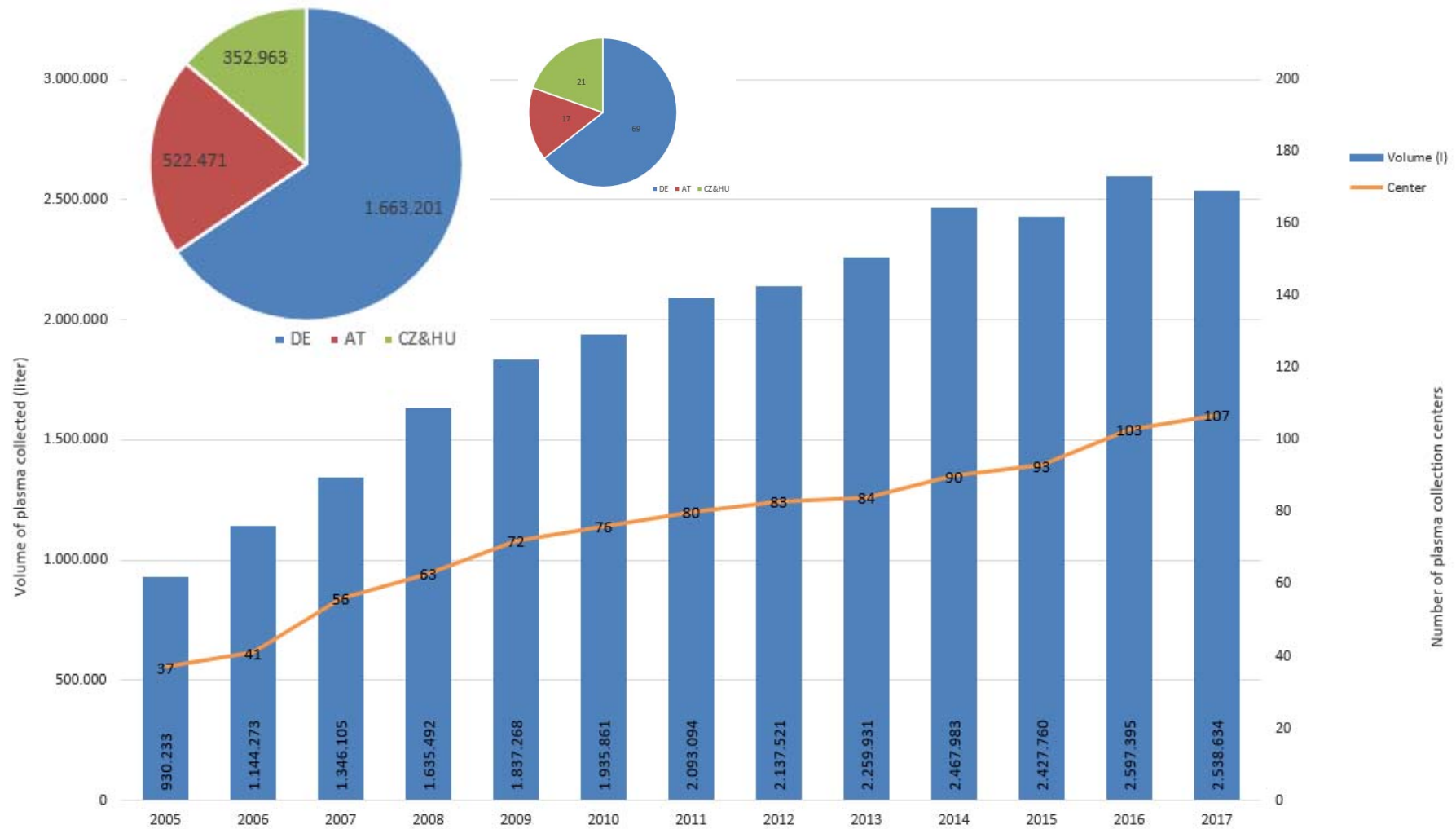
- Donor health is a top priority for the plasma collection industry.
    - Globally, the industry has collected over 130,000,000 plasma donations over the past 5 years with an extraordinary safety record.

- The Dublin Consensus Statement 2011 … , O'Mahony & Turner: "… The health of the donor should not be compromised by their donation."

- A data-driven, scientific rationale is needed to help, inform and guide decisions regarding policies.

- In this presentation: Several key points and highlighted outcomes from several studies involving our sector.

European Regulations

- Due to the lack of scientific data in the late '90s, European regulations on plasmapheresis were based on best knowledge of transfusion experts.

- Since then the scientific knowledge has improved in order to ensure donor safety. Key parameters were:
  - Volume per donation & frequency
  - Monitoring of donor safety
    - Adverse Events during/after plasmapheresis & outside
    - Laboratory & medical care
    - Documentation

Plasmapheresis Regulations

Lack of consistent regulations worldwide:

Country	Volume/Donation (ml)	Donations/Year
US	650 - 880	104
Germany	650 - 850	60
Austria	700 (excl. Citrate)	50
Hungary	650 - 850	45
Czech Republic	650	26

→ Where is the evidence base for these different regulations?

SIPLA I

Dr. med. Stephan Walsemann
EDQM Symposium on Plasma Supply Management, 30.01.2019

- A prospective multicenter study on the safety of long-term intensive plasmapheresis in donors (Schulzki et al. 2006):

  – 3.783 *experienced* donors, 3-years period, 304.836 donations

  – Study Arms based on volume (incl. citrate 1:16):

    • Arm I: < 70 kg: 750 ml/donation, ≥ 70 kg: 850 ml/don.

    • Arm II (voluntary decision): ≥ 70 kg: 850 ml/donation

  – Frequency: Up to 60 times/year

  – Donor-Safety-Monitoring

    • Every donation: Hb ≥ 115 g/L, total protein ≥ 60 g/L

    • Each 5th donation: IgG ≥ 5,8 g/L

SIPLA I: Results

- Avg. volume (incl. citrate) donated:
    - 750 mL/donation: 41 liters/year
    - 850 mL/donation: 47 liters/year

- Donations / donor / 3 years: 65 (5 – 180)

- Donors completing full 3-year period: 923 (24,4%)

- Why experienced donors only?
    - The inclusion of first time donors had required >40.000 participants (limited budgets)
    - Faster way to results

- What were the reasons for drop-out?

SIPLA I: Drop-outs

- Total drop-outs: 2.860 (75,6% of donors)

- Reasons:

  - Socioeconomic: 49,2%

  - Medical unrelated to plasmapheresis: 10,4%

  - Plasmapheresis-related: 16%

    - Low IgG: 12,4% (no diff. re. 750 – 850 mL or gender)

    - Total protein: 2,0% (male sign. lower, $p < 0,0001$)

    - Hb: 1,5% (female sign. more often, $p < 0,0001$)

    - Other: 0,1%

European Plasma Alliance

- **Non-fatal Stroke (all unrelated): 2**

  – In 2 males (57, 59 years)

  – Annual incidence rate /1.000 donors: 0,53
    vs. general population: 0,94
    → Incidence in donor population sign. lower than in general population (P < 0,005)

- **Deep Vein Thrombosis (all unrelated): 3**

  – In 2 females (60, 61 years) & 1 male (54 years)

  – Annual incidence rate /1.000 donors: 0,60 vs. general population: 1,92 /1.000 person-years
    → Incidence in donor population lower than in general population (P < 0,0001)

- Acute Coronary Syndromes (all unrelated):
  - In 9 males (41 -61 years):
    - Fatal: 4, Non-fatal: 5
  - Corresponds to 239 age-adj. events/10^5 males (donors)/year vs. general population:
  340 events/10^5 males/year
  $\rightarrow$ Incidence in donor population sign. lower than in general population (P < 0,0001)

SIPLA I: Long-term safety

		Initial values	Final values	P-value
Female	IgG	8,8	8,0	<0,0001
	TP	68	69	ns
	Hb	133	134	ns
Male	IgG	8,7	7,9	<0,0001
	TP	69	70	ns
	Hb	147	149	<0,001

- Avg. IgG was found to be sign. lower after the end of the study period, but well above lower limit

- Safety also confirmed by Bechtloff et al. (2005) through bio-vascular risk markers taken at baseline and every 30th donation in subpopulation (n=72) for 3 years.

- No significant changes during the observation period (avg. 48 don./year) for:

  - Cardiovascular:

    - LDL, HDL, triglycerides, fibrinogen

  - Red cells and iron metabolism:

    - Hb, ferritin, transferrin (also confirmed by Schreiber et al. Transfusion 2018)

  - Proteins

    - Albumin, TP, IgG (3 drop-outs due to low TP)

SIPLA II

Dr. med. Stephan Walsemann
EDQM Symposium on Plasma Supply Management, 30.01.2019

SIPLA II

- Comparison of safety of *first time* and *experienced* donors in intensified plasmapheresis (Kiessig et al. ISBT, 2013)

- Volume/donation:
  - 50-59 kg: 700 mL
  - 60-69 kg: 750 mL
  - ≥ 70kg: 850 ml

- Frequency: Up to 60 times/year

- Donor-Safety-Monitoring
  - Every donation: Hb ♀ < 125 g/L, ♂ < 135 g/L,
  - Each 5th donation: total protein ≥ 60 g/L, IgG ≥ 6,0 g/L

SIPLA II: Design & Results

- Open prospective 2-year multi-center GCP study

- 2.379 donors (1.284 males, 1.095 females)

- Mixed collection (whole blood & plasma):

  - 71.006 donated units
    - → 65.118 plasma donations collected
    - → 4.251 whole blood donations
      (and 1.637 incomplete donations)

- Frequency (avg.):

  - 29,8/year (plasma)

  - 1,9/year (blood)

- Avg. volume/year: 19,1 liter (plasma)

- Drop-outs: 29,3%

Dr. med. Stephan Walsemann
EDQM Symposium on Plasma Supply Management, 30.01.2019

SIPLA II: Safety

- Hb low in 11,1% male and 10,4% female

- TP low in 25,4%

- IgG low in 27,1 (female > male, no reason for drop-out)

- Adverse reactions (% of donors with an AR during the study):

  - Grade 4 or 5: None

  - Grade 3:   1,6%

  - Grade 2:   2,1%

  - Grade 1: 27,7% (e.g. small hematoma)

  → 69% of AEs were technical

  → 27% local reactions

  → 4% systemic reactions of which
     3,5% hypovolemic, 0,3% vasovagal

→ Plasmapheresis under intensified conditions appears safe

Overall Summary & Conclusions

- Scientific studies have shown there is no significant adverse effect on donor health by long-term intensified plasmapheresis, if Hb, TP and IgG are monitored regularly

- The risk for adverse events decreases with the number of individual donations

- Cardiovascular risk of donors remains unaffected by plasmapheresis as evidenced by established biochemical cardiovascular risk markers

- Future developments might lead to more individualization based on individual IgG status

- The industry is committed to protecting donor health and minimizing any potential risk

Dr. med. Stephan Walsemann
EDQM Symposium on Plasma Supply Management, 30.01.2019

Recommendations...

- **Chapter 2 of Blood Guide:**
  - The SIPLA-protocols have been shown to be safe for the donors
  - The inclusion of the SIPLA protocol in the German Transfusion Guidelines (in 2017) have given evidence of safety of intensified plasmapheresis in daily routine

- **Increase availability of plasma for fractionation:**
  - Plasmapheresis will be the main source to meet growing demand for plasma in EU: Develop plasmapheresis programs in EU MS
  - The plasma sector needs a specific recognition and framework in the EU legislation
  - Standards programs (IQPP) contribute to the safety and quality of plasma therapies by augmenting regulatory requirements
  - Coexistence of private and public collectors like successfully done in AT, CZ, DE, HU
  - Awareness Campaigns in member states, like „How is Your Day?" (www.HowIsYourDay.org)
  - Respect differences between blood and plasma donors and address accordingly

Dr. med. Stephan Walsemann
EDQM Symposium on Plasma Supply Management, 30.01.2019

Health effects of plasma donation: SCANDAT experience

Gustaf Edgren MD PhD

Associate professor of epidemiology

Karolinska Institutet

Outline

- Intro to Scandinavian Donations and Transfusions (SCANDAT) database

- Challenges in donor health outcomes

- Plasma donation and risk of adverse outcomes:
  - Apheresis donation and risk of lymphoma
  - Apheresis donation and risk of lymphoma, redux (ongoing)
  - Apheresis donation and risk of fractures

The SCANDAT database

- The SCANDAT (Scandinavian Donations and Transfusions) database is a compilation of all electronic data on blood donations and transfusions in Sweden and Denmark

- Linkage between donors and recipients, as well as with detailed clinical follow-up

- Bi-nationally (nearly) complete since mid 1990's
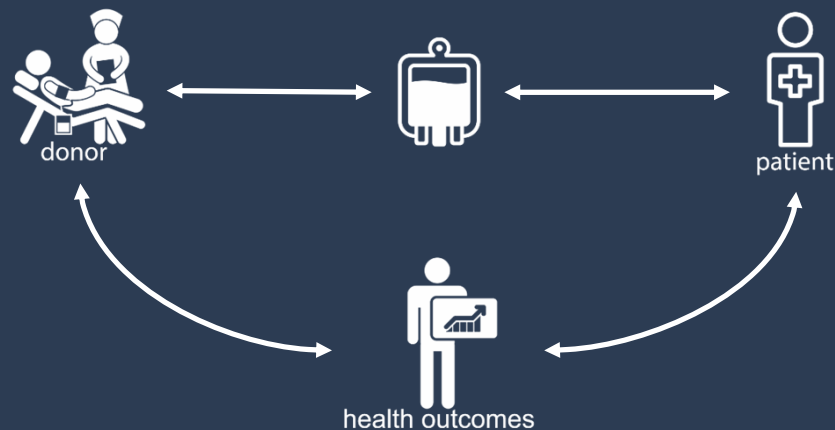
Big data?

- The database currently holds data on 1.7 million donors and 2.1 million patients

- Data going back to the 1960's in Sweden and 1980's in Denmark

- Complete traceability between donors and recipients through >20 million donations and transfusions

- Linkages with health outcome registers providing unbiased follow-up for wide range of health outcomes

- Ongoing update will add another 0.5 million donors and 1 million patients through 2018
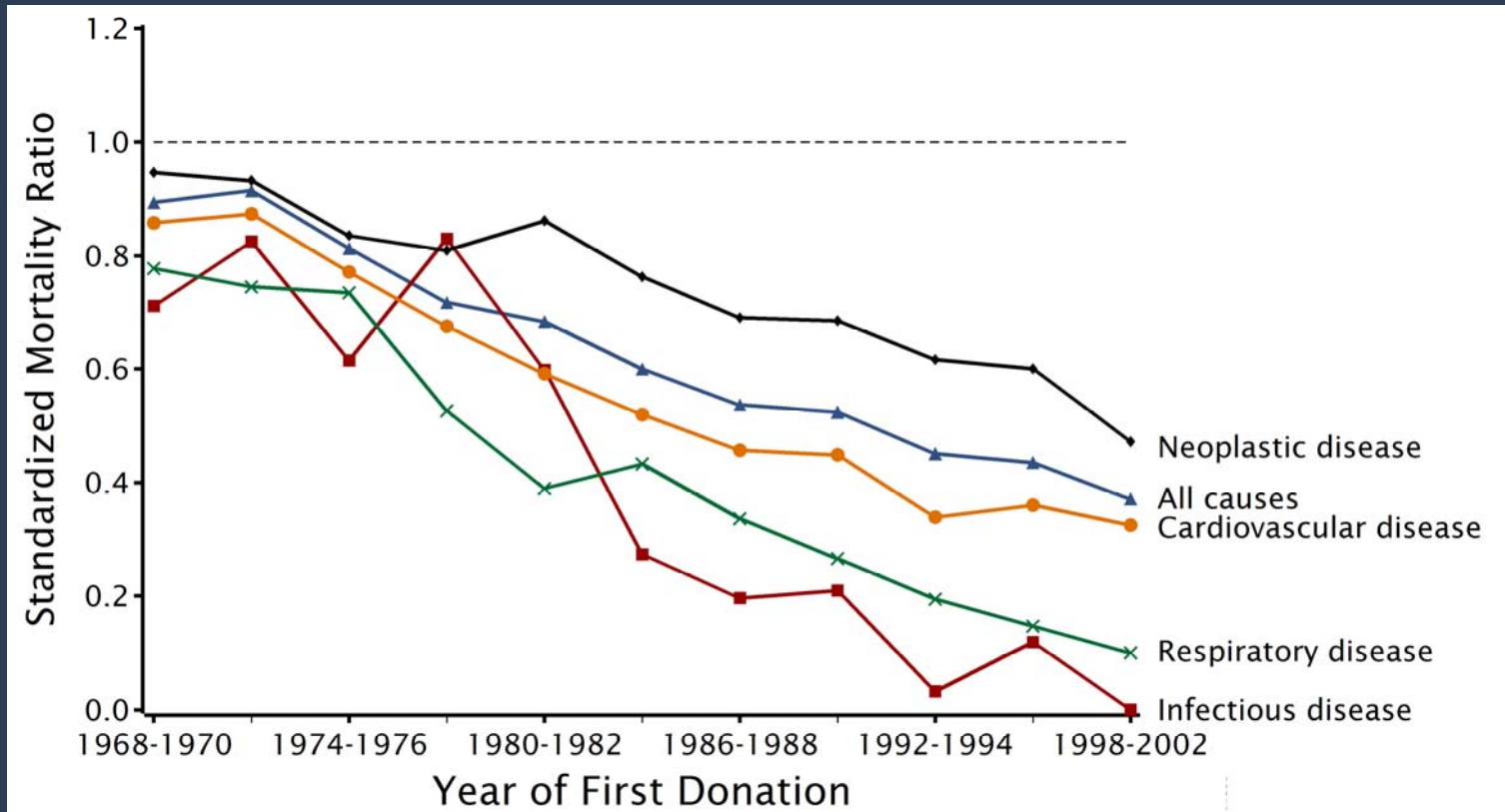
Three main areas of research

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┌──────────┐   ┌────────────┐   ┌──────────────┐   ┌───────────┐
│  DONORS  │───│ DONATIONS  │───│ TRANSFUSIONS │───│ PATIENTS  │
└────┬─────┘   └────────────┘   └──────────────┘   └─────┬─────┘
     │              ┌──────────────┐                      │
     └──────────────│ HEALTH DATA  │──────────────────────┘
                    └──────────────┘
```
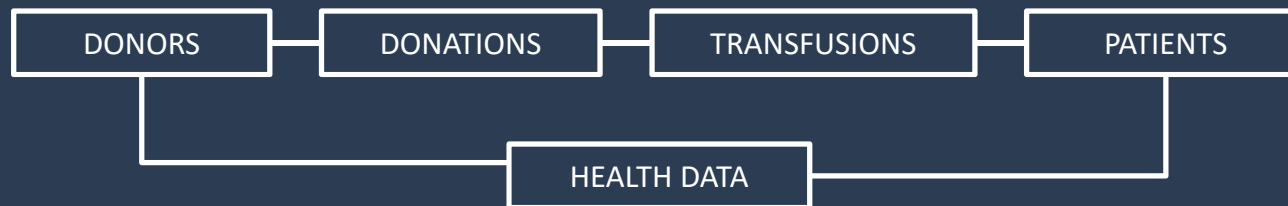
1. Donor health and health effects of blood donations

2. Health effects of blood transfusions

3. Transmission of disease between donors and recipients
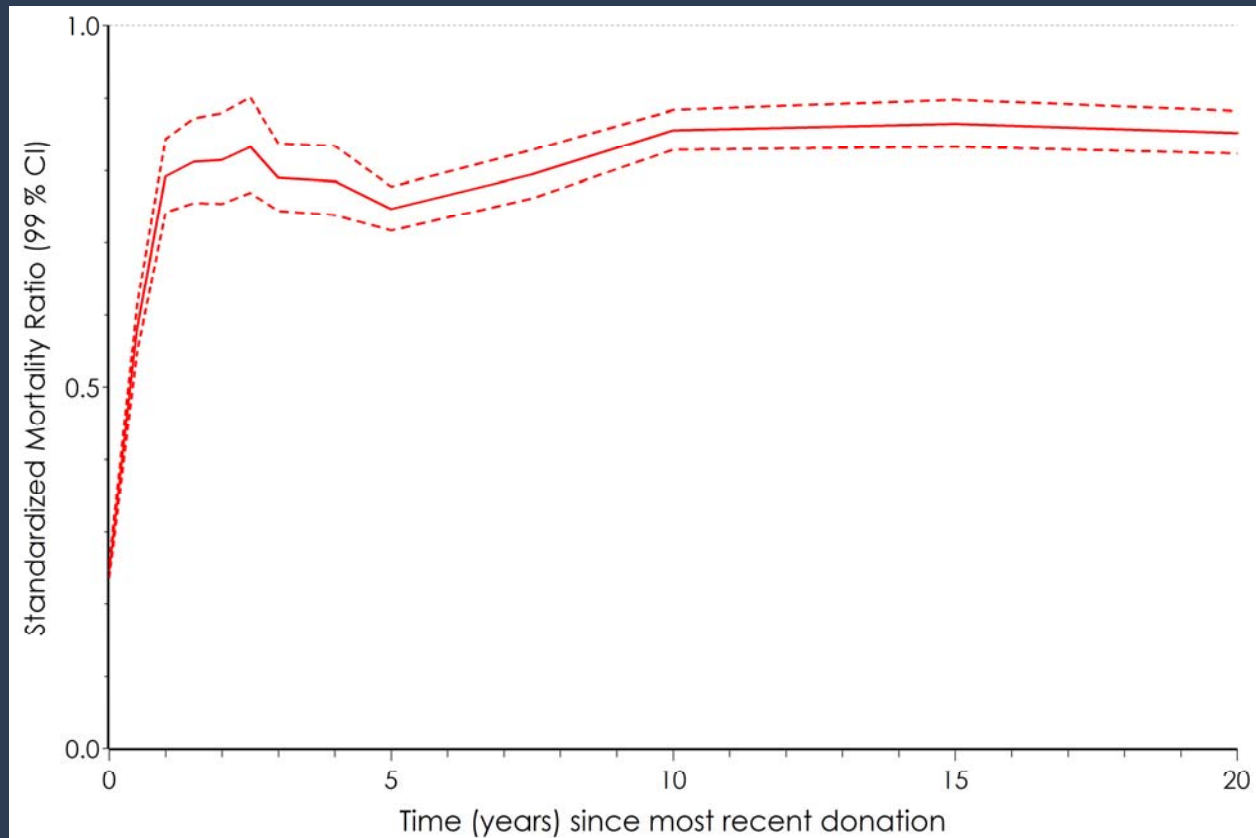
Challenges posed by "universal laws" of transfusion research

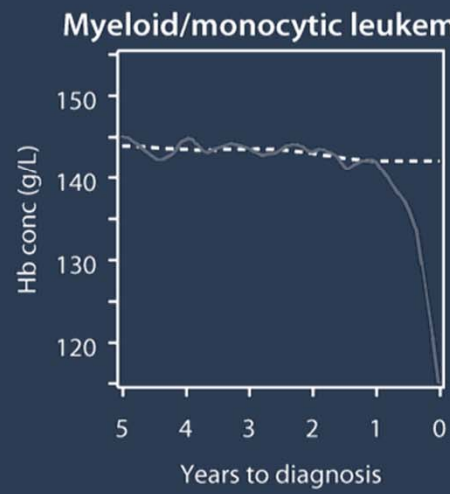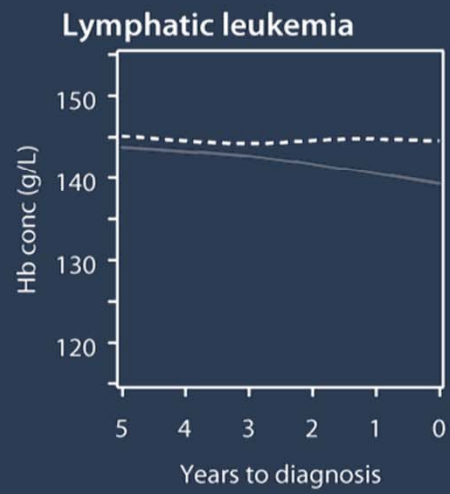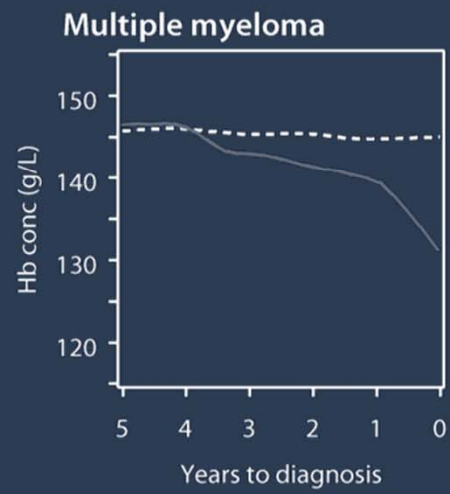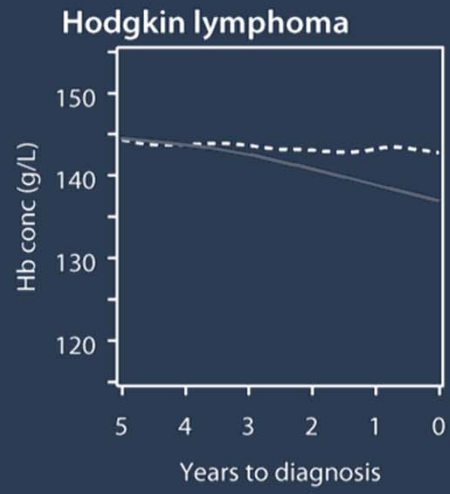- Donors are healthy

- Transfused patients are not

Avoid by finding workarounds, or by studying outcomes where these "laws" don't apply!

Healthy donor effect

Edgren G, et al. Transfusion, 2007

Donor self-selection matters!

Non-Hodgkin lymphoma

Hb conc (g/L)

Years to diagnosis

Hodgkin lymphoma

Hb conc (g/L)

Years to diagnosis

Multiple myeloma

Hb conc (g/L)

Years to diagnosis

Lymphatic leukemia

Hb conc (g/L)

Years to diagnosis

Myeloid/monocytic leukemia

Hb conc (g/L)

Years to diagnosis
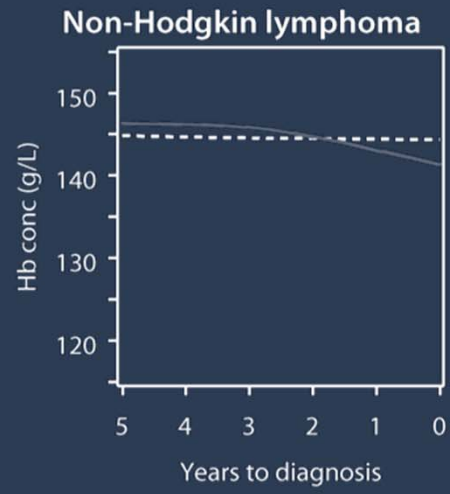
ARTICLE

Donation Frequency, Iron Loss, and Risk of Cancer Among Blood Donors

Gustaf Edgren, Marie Reilly, Henrik Hjalgrim, Trung Nam Tran, Klaus Rostgaard, Johanna Adami, Kjell Titlestad, Agneta Shanwell, Mads Melbye, Olof Nyrén

- Objective:
  - To assess if repeated blood donation, or iron loss thence induced, has an effect on the cancer risk of blood donors.

Analytical considerations

- Analyses considered:
    1. Number of donations overall
    2. Number of donations by type (whole-blood/plasma)
    3. Iron loss experienced through blood donation

- Exposure was divided into three (two, really) windows:

Index date, t_0

$t_0 - 12$ yrs. $t_0 - 7$ yrs. $t_0 - 2$ yrs.
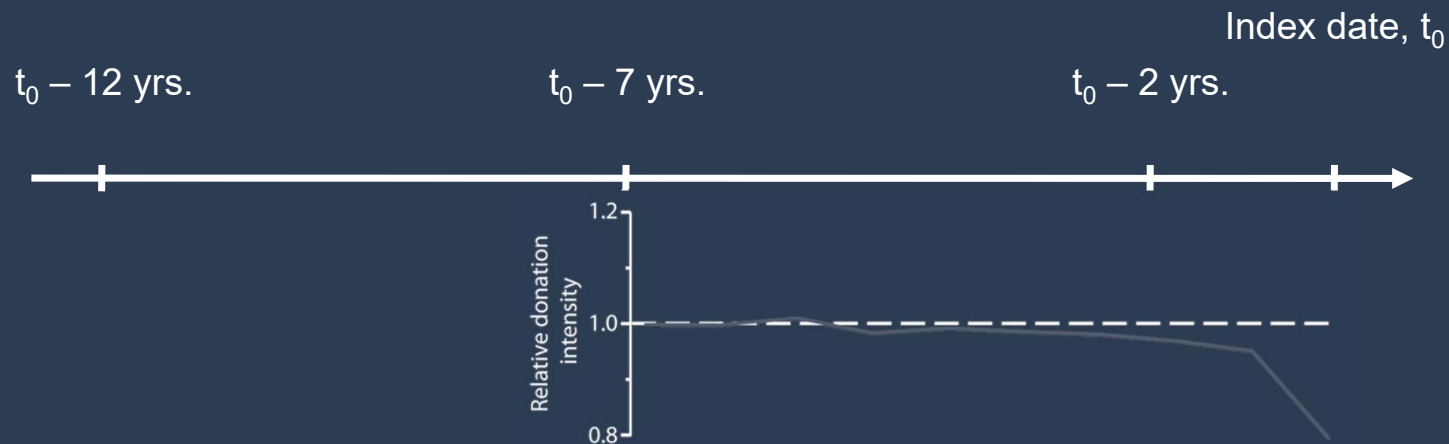
Donation intensity and cancer – results

- Out of 30,729 observed cases of cancer, 10,866 remained after exclusion of donors with insufficient register coverage or insufficient donation activity.
  - For these cases, we selected 107,140 controls.
- There was no clear dose-response dependent association between number of donations of any type and risk of cancer overall.
- This lack of association persisted (more or less) in both exposure windows and for both sexes.
- However, there was one noteworthy exception

Specific results

Cancer overall	Number of donations				
3-12 years before diagnosis	**1-8**	**9-16**	**17-25**	**>25**	**P for trend**
Both sexes	1.00 (ref)	0.98 (0.91-1.05)	0.97 (0.89-1.05)	0.99 (0.90-1.10)	0.84
Women	1.00 (ref)	0.96 (0.86-1.07)	0.99 (0.87-1.13)	0.98 (0.83-1.17)	0.78
Men	1.00 (ref)	0.99 (0.90-1.09)	0.96 (0.86-1.07)	1.00 (0.88-1.13)	0.68

Non-Hodgkin lymphoma	Number of apheresis donations			
3-12 years before diagnosis	**1-8**	**9-25**	**>25**	**P for trend**
Both sexes	1.00 (ref)	0.47 (0.15-1.52)	2.14 (1.22-3.74)	0.05

So what?

- At the time of publication, we toned down the finding of an increased risk of NHL in apheresis (plasma) donors, and speculated that it may be a chance finding

- However, there are possible biological mechanisms relating to immunodeficiency, infections, pthalate exposure, etc

- As such, we wanted to replicate these findings with other methods and more modern data

Apheresis donation and risk of lymphoma 2.0

- Based on newer version of SCANDAT, with follow-up through 2012

- Analyses set up as a cohort study, with time-dependent exposures

- Donors followed from first apheresis donation (of any time), accumulating exposures over time, with careful adjustment for time since most recent donation (strong risk determinant!)

- Analyses conducted using Cox regression, restricted to 1996 and onwards to stick to cases classified using ICD-10 (allowing removal of "benign" conditions such as MGUS and Waldenström's disease)

ORIGINAL RESEARCH

No association between frequent apheresis donation and risk of fractures: a retrospective cohort analysis from Sweden

Katrine Grau,[1] Senthil K. Vasan,[2] Klaus Rostgaard,[1] Walter Bialkowski,[3] Rut Norda,[4] Henrik Hjalgrim,[1,5] and Gustaf Edgren,[2,6] for the National Heart, Lung, and Blood Institute (NHLBI) Recipient Epidemiology and Donor Evaluation Study-III (REDS-III)

- Objective:
  - To assess if apheresis donors are at increased risks of fractures

Background

- All apheresis procedures involve donor exposure to anticoagulants – typically citrate

- Citrate exposure results in
  - **Hypo-calcaemia,** -magnesaemia, –phosphataemia
  - Hypo-albuminaemia, -immunoglobulinaemia
  - **Increase in parathyroid hormone concentration**

- Changes usually transient, lasting 24-48 hours after donation

Apheresis profile examples SCANDAT 1
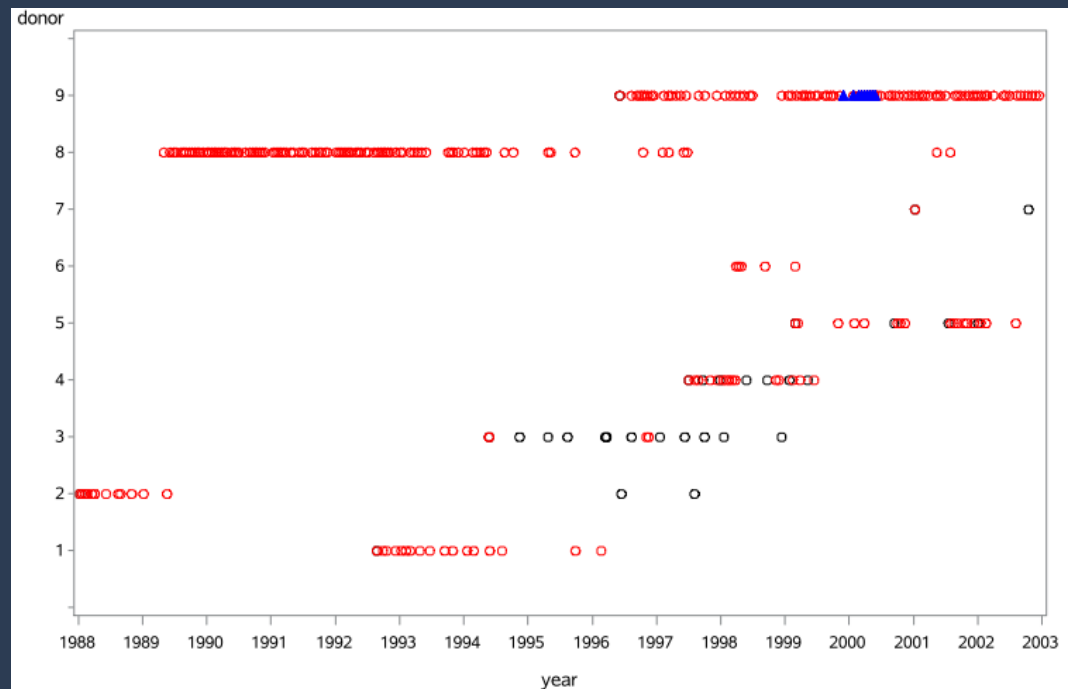
- Up to 26 apheresis donations per year
- Long-term effects on calcium homeostasis and bone density?

Donor self-selection doesn't always matter!
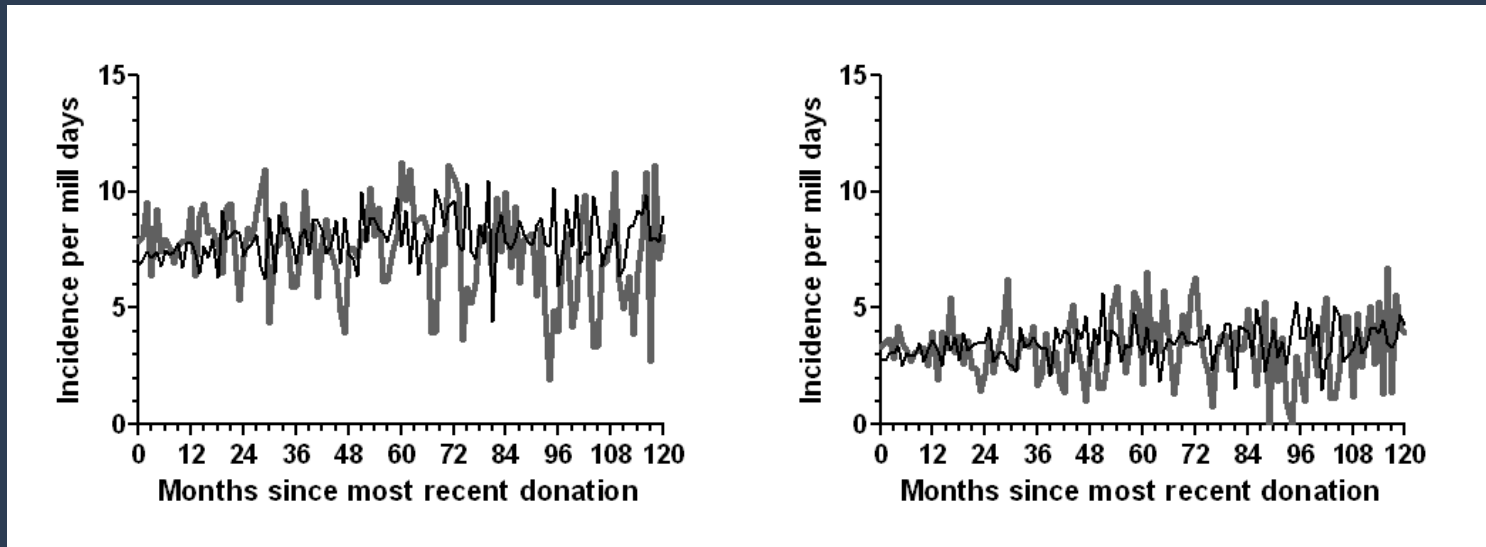
- Incidence of fractures overall (left) and "osteoporosis-related" fractures (right) in apheresis (grey line) and whole blood donors (black line) by time since most recent donation

Grau K, et al. Transfusion, 2016

Study methods

- Inclusion
  - At least one apheresis donation after 1980 in Sweden or Denmark
  - Donors 18 years of age or older

- Exposures
  - Number of apheresis donations

- Outcomes
  - Any fractures; "osteoporosis-related" fractures
  - Distinction approximated by ICD codes

- Follow-up period
  - From date of most recent donation or 1987, whichever occurs last
  - To date of first of fracture, therapeutic donations, death, emigration, and end of 2012

Statistical analyses

- Poisson regression with time since most recent apheresis donation as main time axis

- Adjusted for sex, attained age, country and calendar period

- Men and women considered together and separately

- Fractures analyzed overall and specifically for osteoporosis-related fractures

- Apheresis donations considered both as total number and in 'sliding' time windows of 2, 5, or 10 years

Demographic characteristics

- Apheresis donors
  - ~ 144,563 persons
  - Women: 48 %
  - Median age at first apheresis donation: 30 years (IQR 23-40)
  - Median period of donation : 2.8 years (IQR 0.6-6.1)
  - Most active donors (5 %): >12 years of donation, >90 apheresis donations
  - +2600 fractures; +1100 (43%) "osteoporosis-related" fractures

No overall effect

Table 2. Incidence rate ratios of fracture and osteoporosis related fracture in apheresis donors by cumulative number of apheresis donations and stratified by sex.

	Number of apheresis donations				
	1 - 8	9-24	25 - 49	50 - 99	≥ 100
Both sexes	*Incidence rate ratios (95% confidence interval)*				
All fractures	1.03 (0.99-1.06)	1.00 (ref)	0.99 (0.94-1.04)	0.96 (0.91-1.01)	0.98 (0.91-1.05)
Osteoporosis related fractures	1.05 (1.00-1.11)	1.00 (ref)	1.01 (0.94-1.08)	1.02 (0.94-1.11)	1.03 (0.93-1.15)
Women					
All fractures	1.06 (0.98-1.14)	1.00 (ref)	1.03 (0.94-1.13)	1.00 (0.89-1.12)	1.00 (0.86-1.16)
Osteoporosis related fractures	1.06 (0.98-1.14)	1.00 (ref)	1.03 (0.94-1.13)	1.00 (0.89-1.12)	1.00 (0.86-1.16)
Men					
All fractures	1.05 (0.96-1.14)	1.00 (ref)	0.98 (0.87-1.09)	1.04 (0.92-1.18)	1.06 (0.92-1.23)
Osteoporosis related fractures	1.05 (0.96-1.14)	1.00 (ref)	0.98 (0.87-1.09)	1.04 (0.92-1.18)	1.06 (0.92-1.23)

Donations per time window (all)

Table 3. Incidence rate ratios of all fractures in apheresis donors by number of apheresis donations in past time window, overall and stratified by sex.

	Number of apheresis donations in time window			
	1-3	4-7	8-15	≥16
Past 2 years	Incidence rate ratios (95% confidence interval)			
Both sexes	1.00 (0.92 - 1.08)	1.00 (ref)	0.95 (0.87 - 1.04)	0.94 (0.85 - 1.03)
Women	1.00 (0.88 - 1.14)	1.00 (ref)	0.98 (0.85 - 1.14)	0.89 (0.76 - 1.05)
Men	0.99 (0,90 - 1,10)	1.00 (ref)	0.93 (0.84 - 1.04)	0.96 (0.85 - 1.09)
Past 5 years	1-9	10-19	20-39	≥40
Both sexes	1.05 (0.99 - 1.12)	1.00 (ref)	1.05 (0.97 - 1.13)	0.97 (0.88 - 1.06)
Women	1.09 (0.99 - 1.21)	1.00 (ref)	1.08 (0.95 - 1.23)	0.97 (0.83 - 1.13)
Men	1.03 (0.95 - 1.11)	1.00 (ref)	1.03 (0.93 - 1.13)	0.97 (0.86 - 1.08)
Past 10 years	1-19	20-39	40-79	≥80
Both sexes	0.99 (0.94 - 1.04)	1.00 (ref)	0.94 (0.88 - 1.01)	0.95 (0.87 - 1.04)
Women	0.97 (0.90 - 1.05)	1.00 (ref)	0.92 (0.82 - 1.03)	0.92 (0.79 - 1.08)
Men	1.01 (0.94 - 1.07)	1.00 (ref)	0.96 (0.88 - 1.05)	0.96 (0.86 - 1.08)

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Donations per time window (osteoporosis)

Incidence rate ratios of fracture and osteoporosis related fracture in apheresis donors by number of apheresis donations in past time window, overall and stratified by sex.				
	Number of apheresis donations in time window			
	1-3	4-7	8-15	≥16
Past 2 years	Incidence rate ratios (95% confidence interval)			
Both sexes	1.05 (0.92-1.20)	1.00 (ref)	1.00 (0.86-1.15)	0.98 (0.84-1.15)
Women	1.08 (0.90-1.31)	1.00 (ref)	1.04 (0.84-1.28)	0.98 (0.78-1.23)
Men	1.02 (0.84-1.23)	1.00 (ref)	0.96 (0.78-1.18)	0.98 (0.79-1.23)
Past 5 years	1-9	10-19	20-39	≥40
Both sexes	1.07 (0.97-1.19)	1.00 (ref)	1.08 (0.96-1.23)	1.05 (0.91-1.22)
Women	1.05 (0.92-1.21)	1.00 (ref)	1.04 (0.87-1.24)	1.01 (0.82-1.24)
Men	1.10 (0.95-1.28)	1.00 (ref)	1.13 (0.94-1.35)	1.10 (0.89-1.34)
Past 10 years	1-19	20-39	40-79	≥80
Both sexes	1.04 (0.96-1.12)	1.00 (ref)	1.04 (0.93-1.16)	1.07 (0.94-1.23)
Women	1.02 (0.92-1.14)	1.00 (ref)	1.03 (0.89-1.20)	0.99 (0.81-1.21)
Men	1.06 (0.94-1.19)	1.00 (ref)	1.04 (0.89-1.22)	1.16 (0.96-1.41)

Discussion and conclusion

- Overall message: No evidence of any association between number of apheresis donations and risk of fractures

- No difference in effects in men/women, for osteoporosis related fractures

- No age interaction, i.e. no increased effects also in older donors