Donor Safety – View from Plasma Source

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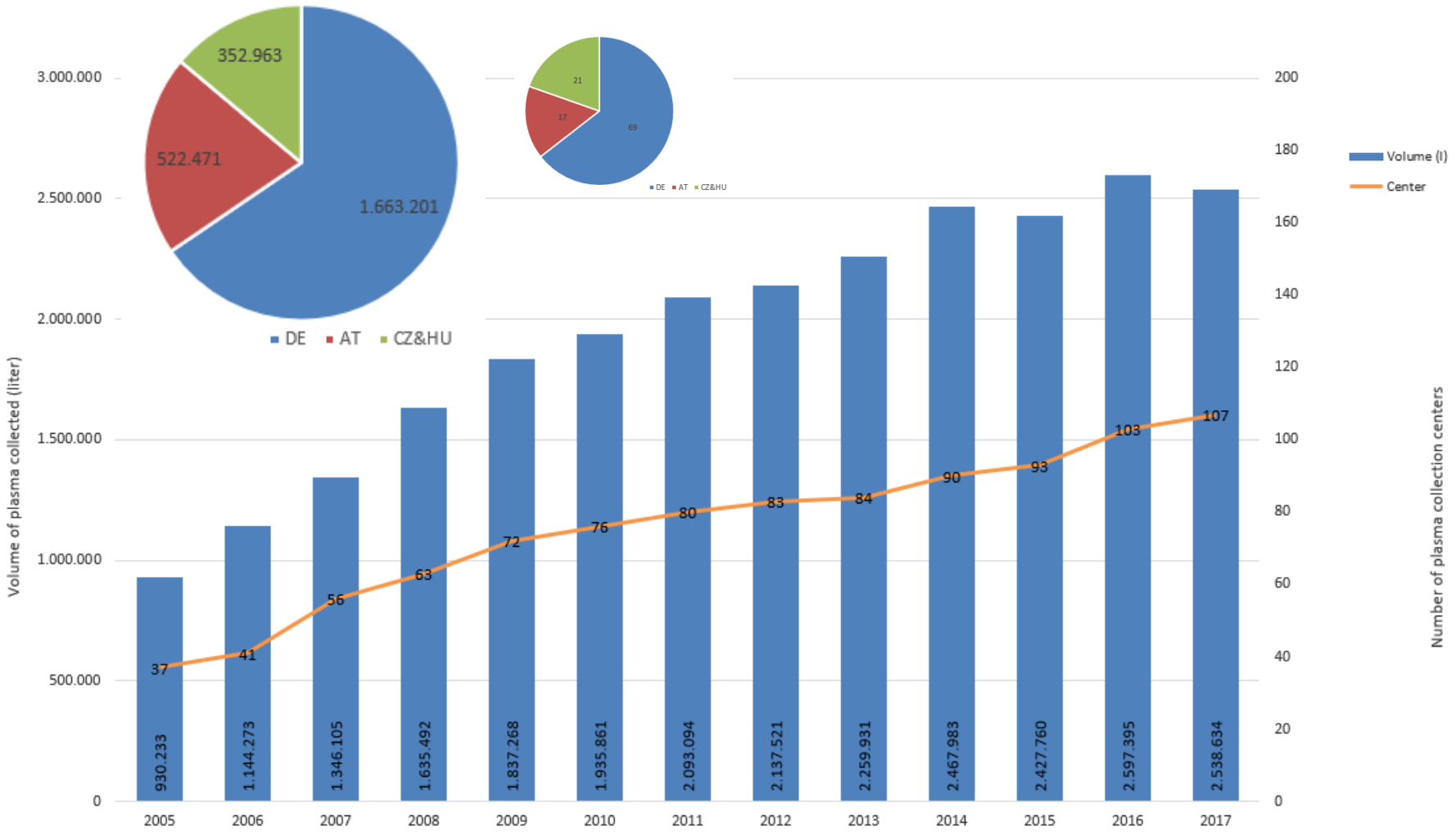
ARGE Plasmapherese Fortbildungsveranstaltung in Göttingen, 23.11.2018

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

Plasma Collection in Europe (2017)



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?

General Distribution of Number of Donations achieved per 12 month

Objectives of Regulations

- Main Objectives
  - Donor safety
  - Product safety

- Less in focus
  - Product quality

STUDIES ON DONOR SAFETY:

SIPLA I

SIPLA II

IPS

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SIPLA I

SIPLA I: Volume per donation and frequency

- 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
  - Volume (incl. citrate):
    - < 70 kg: 750 ml/donation
    - ≥ 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% (no relevant diff. between gender)
    - Hb: 1,5% (female sign. more often, $p < 0{,}0001$)
    - Other: 0,1%

SIPLA I: Adverse events

- Severe AEs (gr. 3, related to plasmaph.):
  - 5 of 304.836 donations
  - Reasons:
    - Vein puncture related: 4
    - Metacarpal fracture after dizziness: 1
    - No severe collapse
- Other AEs (grade 1 & 2, possibly or probably related): 132 (0,04%)
  - Hematoma or bleeding from vein puncture
  - Citrate reactions
  - Nausea, dizziness, vomiting

SIPLA I: Cardiovascular Safety I

- Non-fatal Stroke (all unrelated): 2
  - In 2 males (47, 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 (47, 59 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)

SIPLA I: Cardiovascular Safety II

- 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/y vs. general population: 340 events/10^5 males/year
    → 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

SIPLA I: Safety

- 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

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

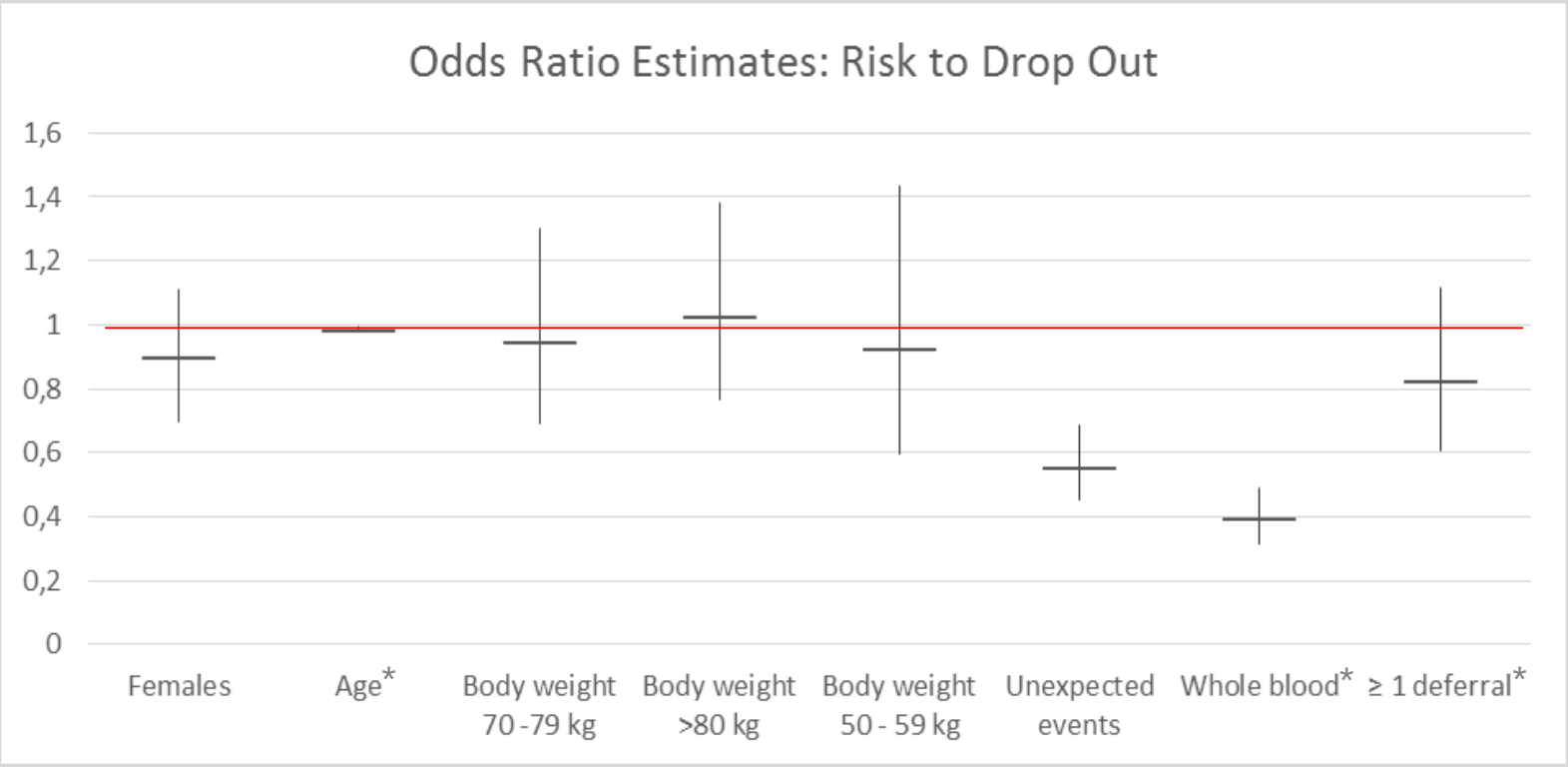
- **STUDY DESIGN:**
  - Open prospective 2-y. multi-center GCP study
  - 2.379 donors (1.284 males, 1.095 females)
  - Mixed collection
    - 71.006 donated units
      → 65.118 plasma donations collected
      → 4.251 whole blood donations
      (and 1.637 incomplete donations)
    - IgG and total protein was tested every 5th donation.
- Drop-outs: 29,3%
- Frequency: 29,8/y (plasma); 1,9/y (blood)
- Avg. volume/year: 19,1 liter (plasma)

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 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

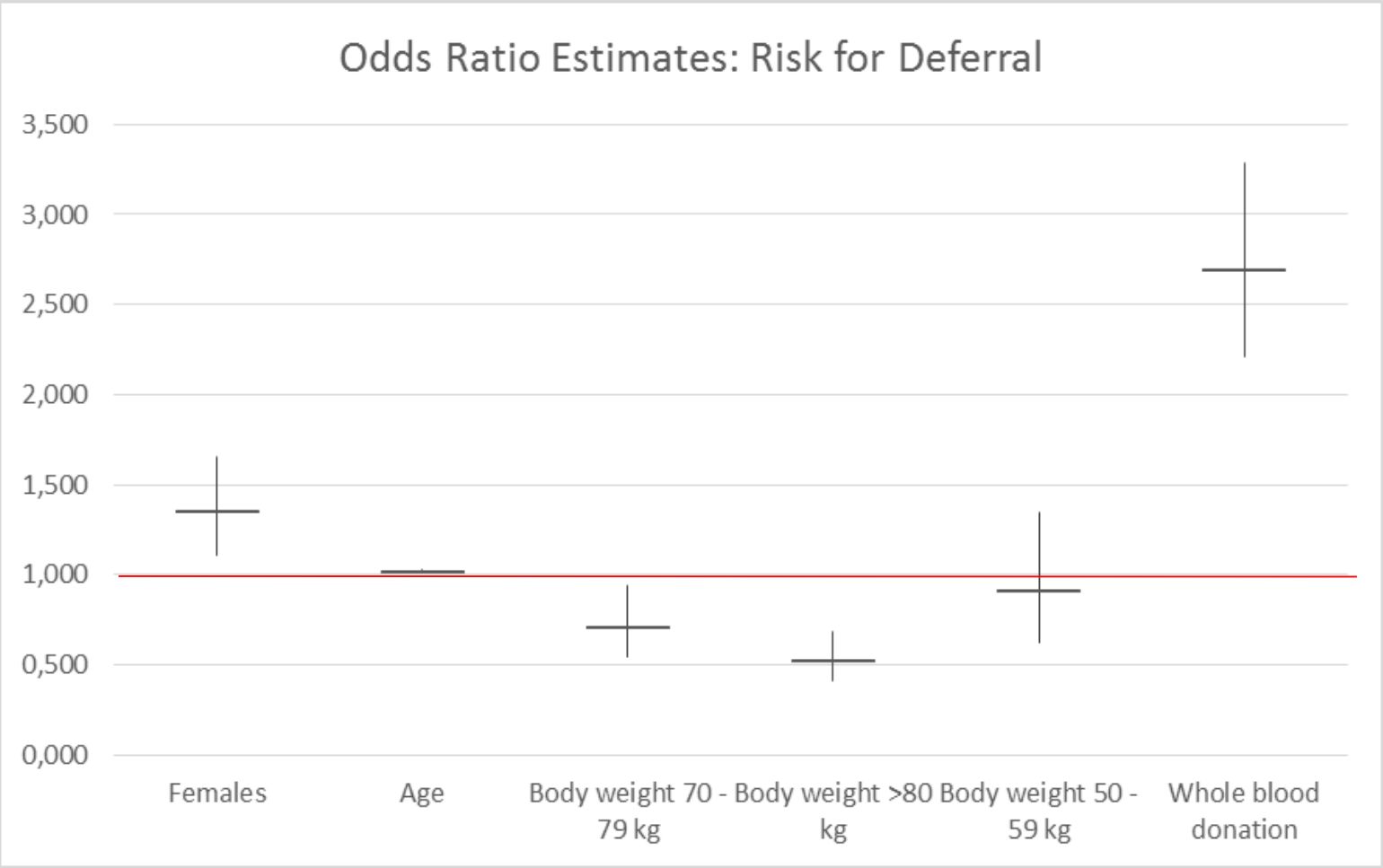
SIPLA II Risk factors to drop out



Multiple logistic Regressions (final point: drop out; full model)

* was significant

SIPLA II Risk factors for Deferral



Multiple logistic Regressions (final point: donors with minimal one deferral; full model)

SIPLA II: CONCLUSIONS

- The preparative plasmapheresis procedures (max. 60 donations/year & volume depending on body weight) were found to be safe.
  - Limiting parameters which required a good donor guidance
    - Presence of whole blood donations
    - IgG and total protein were also reasons for deferrals, but not for drop out.
- The possible donation frequency should depend on initial IgG and should be discussed with the donor at the very first donation
- Regular IgG monitoring is required
- Better donor guidance results in better donor safety & higher plasma quality

IPS-STUDY

IPS-Study (ongoing)

Individualized **P**lasma Donation Program **S**tudy (Taborski et al. 2017)

- The first study validating 104 donations / year
- 9 Arms based on body weight and initial IgG:

	BW 50 – 60 kg	BW 61 – 70 kg	BW > 70 kg
IgG 6 – 8 g/L	650 mL 26/year 2 x /month	750 mL 26/year 2 x /month	850 mL 26/year 2 x /month
IgG 8.1- 10 g/L	650 mL 52/year 4 x /month	750 mL 52/year 4 x /month	850 mL 52/year 4 x /month
IgG > 10 g/L	650 mL 104/year 8 x /month	750 mL 104/year 8 x /month	850 mL 104/year 8 x /month

Control Group: Regimen according to German Guidelines (2010):

- Frequency: 45x/year
- Volume per Donation: 50-59kg: 650ml; 60-79kg: 750ml; >= 80kg: 850 ml

IPS-Study: Interims Safety

- Period 2011 to 2016
- 5.978 donors, 1.394.825 donations
- Unwanted Events / Serious Incidents:
  - Evaluated from severity 1 to 5 (light to fatal)
  - Causality with plasma donation from 1 to 4 (no causality to causality assured)
  - 28.323 UEs/SIs were recorded:
    - Grade 1: 22.781
    - Grade 2: 5.198
    - Grade 3: 314
    - Grade 4: 23
    - Grade 5: 7 (all unrelated to plasma donation)
  - Incidence (per 100 donations) of grade 3-5 UEs/SIs do not differ between control group (0,026) and verum (0,023)

→The IPS donation program is as safe as standard regimen

(Taborski et al. Transfus Med Hemother 2017; 44 (suppl 1))

IPS-Study: First Results awaited

- Average volume per donation:
  - Expected to increase compared to standard regimen
- Donor deferrals:
  - Expected to be lower for IgG and total protein than with standard regimen

COMPARISON OF SAFTETY:
BLOOD
VS.
PLASMA DONOATION

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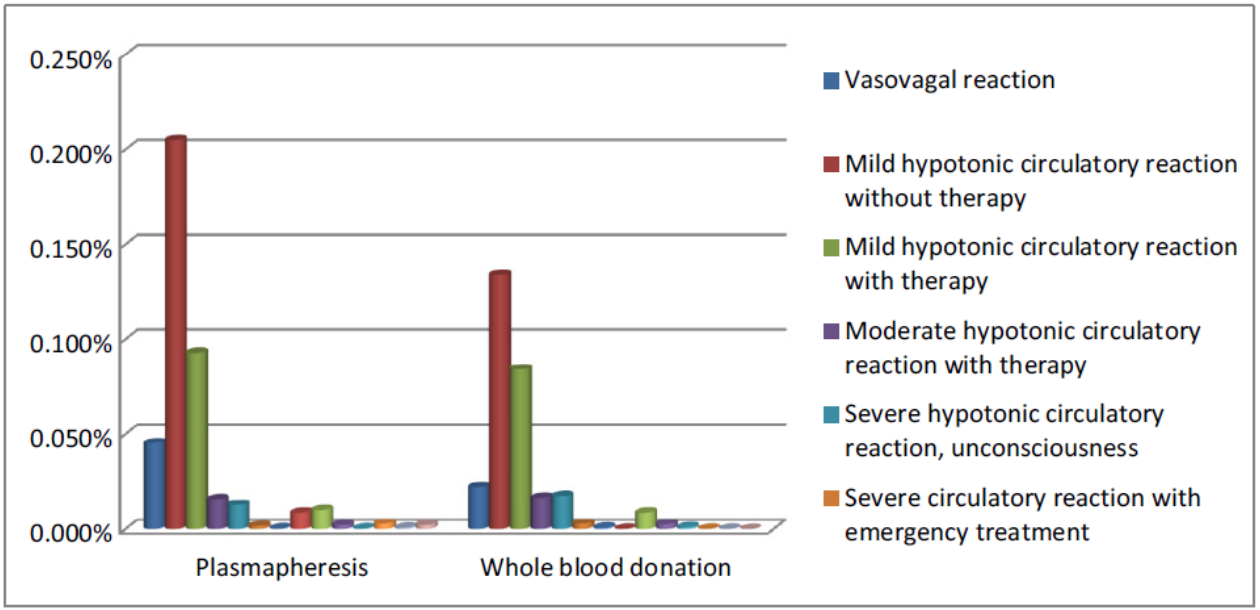
Comparison of safety in blood and plasma donation

- Burkhardt et. al (2015) evaluated DRK North-East‘s safety records for the years 2011-2013:
  - 335.832 plasmapheresis donations
    - Of which 6.461 1st-time donations
    - 650-850 mL/donation
    - Hb ≥ 12,5 female, ≥ 13,5 male
    - Avg. 14,2 donations/year
    - In 4 of 7 plasma centers, 300 mL saline solution was given

Burkhardt et. al (2015): Safety



- „… In summary, our donor vigilance data shows that both whole blood and plasmapheresis donations are safe with low incidences of adverse events.“
- No difference in incidence in UEs was found between centers with and without saline usage (personal communication from Prof. Moog)

Analysis of AEs in an database of 1.107.846 plasma donations

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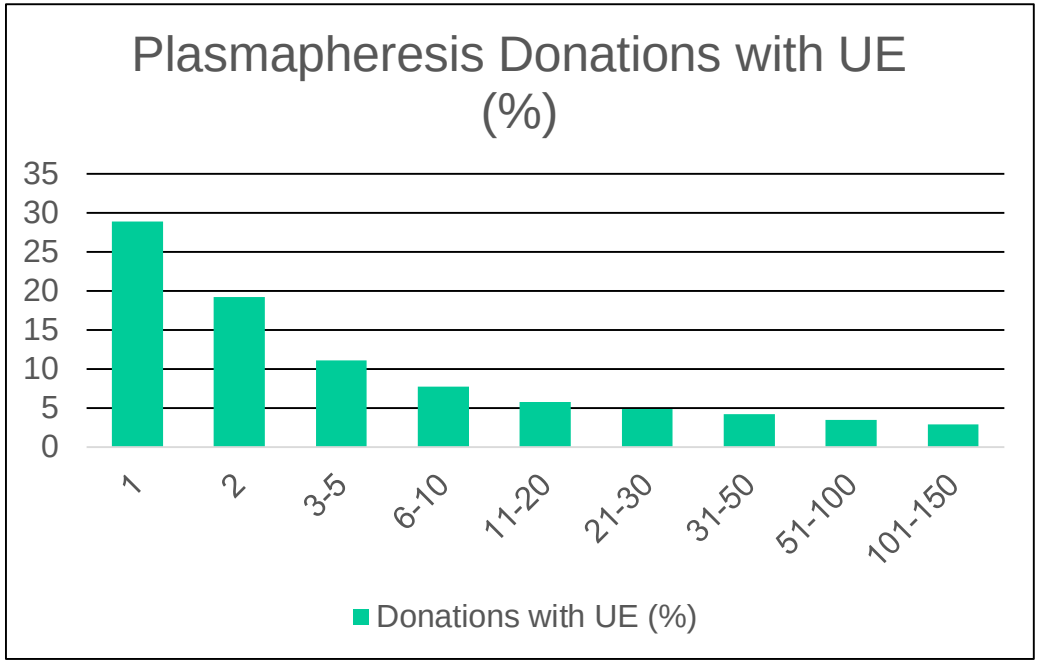
1st & 2nd time donors have the highest risk for UEs

- Diekamp et al. (2014) analysed UEs in a database of 1.107.846 plasmapheresis donations (2008-2011)
  - Volume 660, 760, 860 ml depending on body weight
  - 500 ml saline solution given
  - Total UEs: 5,55%, of which:
    - 4,6% technical
    - 1,4% local
    - 0,55% systemic
    - Severe: 0,00036% (female > male)
    - 1st and 2nd time donors have the highest risk for UEs

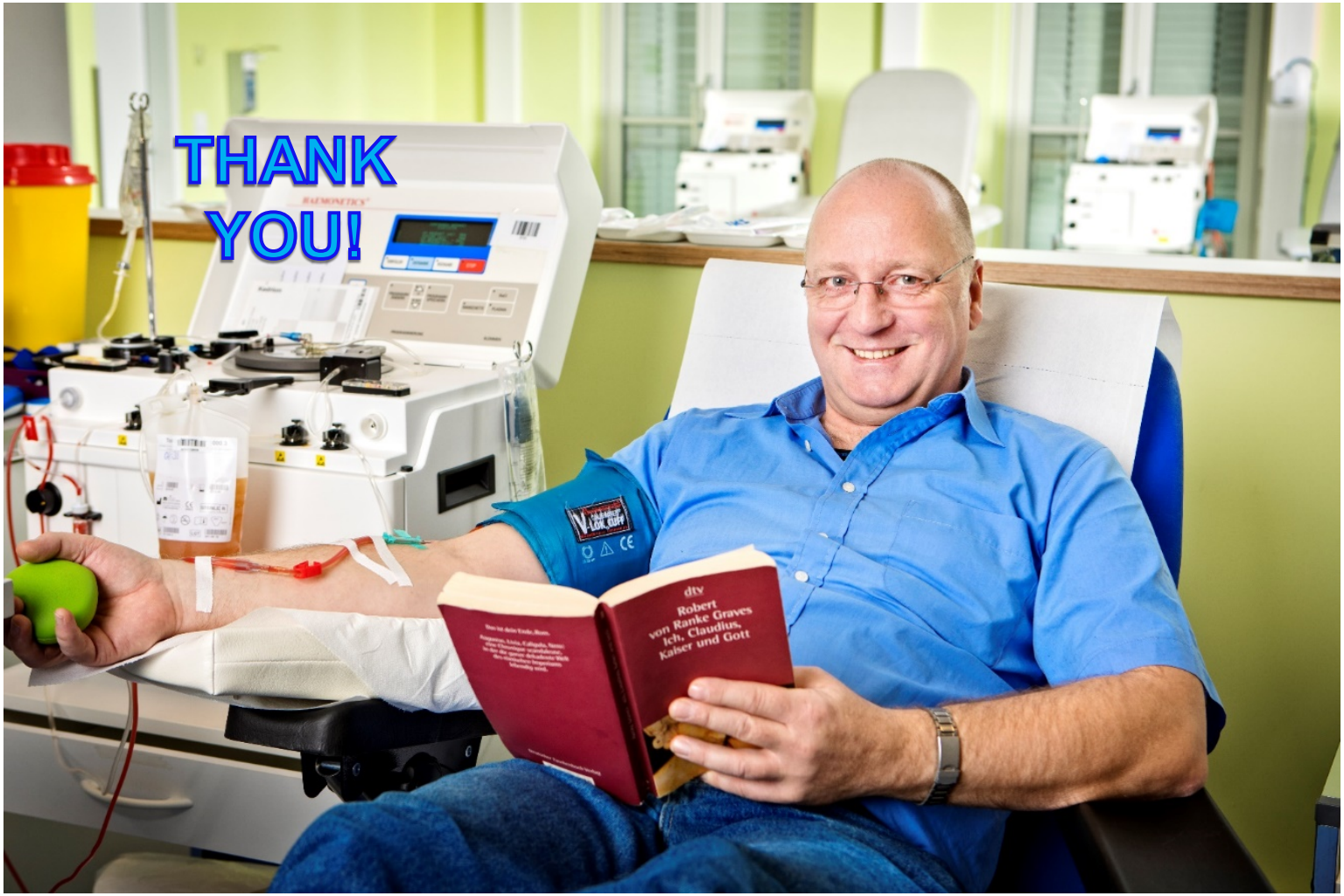
1st & 2nd time donors have the highest risk for UEs

- Diekamp et al. 2014: "…UEs accompanied first and second donations significantly more frequently than for subsequent donations."



- In 2015, Diekamp et al. also confirmed for whole blood donations that first and second time donors have significantly more UEs than subsequent donations. Total UEs occurred in 4,3%

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

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