

# Apheresis donation and donor safety

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**SALUTE E SICUREZZA DEL DONATORE**  
**Blood Donor Health and Safety**

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# Surveillance of complications related to blood donation

## A1 Blood outside vessel

A1.1 Haematoma

A1.2 Arterial puncture

A1.3 Delayed bleeding

## A2 Arm pain

A2.1 Nerve injury/irritation

*\*D<12m: duration < 12 months*

*\*D>12m: duration > 12 months*

*\*A2.2 Other arm pain*

## A3 Localized infection/inflammation of vein or soft tissues

*\*A3.1 Superficial thrombophlebitis*

*\*A3.2 Cellulitis*

## A4 Other major blood vessel injury

A4.1 Deep Venous Thrombosis (DVT)

A4.2 Arteriovenous fistula

A4.3 Compartment syndrome

A4.4 Brachial artery pseudoaneurysm

## B. Generalized symptoms – Vasovagal Reactions

B.1 Vasovagal Reaction, no loss of consciousness (LOC)

B.2 Vasovagal Reaction, loss of consciousness

*\*<60s: < 60 seconds, no complications*

*\*>60s: ≥ 60 seconds, or convulsions or incontinence*

**Additional Information:**

*\*w/ inj: With injury*

*\*w/o inj: Without injury*

*\*ONSITE: on collection site*

*\*OFFSITE: off collection site*

## C. Related to apheresis

C.1 Citrate reactions

C.2 Haemolysis

C.3 Air embolism

C.4 Infiltration

## D. Allergic reactions

D.1 Local allergic reaction

D.2 Generalized (anaphylactic) reaction

## E. Other serious complications

E.1 Acute cardiac symptoms (other than myocardial infarction or cardiac arrest).

E.2 Myocardial infarction

E.3 Cardiac arrest

E.4 Transient Ischemic Attack (TIA)

E.5 Cerebrovascular accident

E.6 Death

## F. Other (give diagnosis)

**\*Severity Grading:**

*To be classified as **severe**, the adverse event should be life-threatening or leading to hospitalisation, incapacity, chronic morbidity or death. Otherwise, the case be classified more subjectively as **mild** or **moderate**.*

**\*Imputability:**

**Definite:** Conclusive evidence donation caused adverse event

**Probable:** Clearly leans toward donation as cause of adverse event

**Possible:** Could be caused by donation or alternative reason

**Unlikely:** Clearly leans toward other causes for adverse event

**Excluded:** Conclusive evidence something else caused event

# Other complications of donation

## **Whole Blood**

- Iron deficiency
- Restless legs syndrome

## **Apheresis**

- Protein loss
- Exposure to plasticizers (DEHP)
- Iron deficiency
- Impact on platelets / coagulation
- Technical and machine-related problems

# Overall adverse event (AE) incidence (rate /10000 collections)

| AE           | Whole Blood                              | Plasmapheresis | PLTpheresis | Multicomponent | Apheresis mix | Ref  |
|--------------|--|----------------|-------------|----------------|---------------|--|
| Total events | 24 - 3050<br><br>(1029-3050<br>→ 24-340) | 4 - 251        | 81 - 700    | 87 - 600       | 47 - 1250     | Newman 1997<br>McLeod 1998<br>Despotis 1999<br>Tomita 2002<br>Bonomo 2004<br>Winters 2006<br>Bueno 2006<br>Eder 2008<br>Schulzki 2006<br>Crocco 2009<br>Yuan 2010<br>Amrein 2012<br>Goldman 2013<br>Kiessig 2013<br>Heuft 2013<br>Barbosa 2014<br>Diekamp 2014 – 2015<br>Burkhardt 2015- 2019<br>Dogra 2017<br>Catalano 2018 |

# Moderate/severe adverse event (AE) incidence (rate /10000 collections)

| AE                          | Whole Blood | Plasmapheresis | PLTpheresis | Multicomponent | Apheresis mix | Ref  |
|-----------------------------|-------------|----------------|-------------|----------------|---------------|--|
| Moderate+severe             | 1 - 14      | 21 - 33        | 37 - 54     | 35 - 100       | 4 - 65        | Goncales 2012<br>Goldman 2013<br>Diekamp 2014<br>Yuan 2008 – 2010<br>Danic 2010<br>Wiltbank 2007<br>Gustafson 2019<br>Daurat 2016<br>Narbey 2016 |
| Severe                      | 3 - 8       | 7              | 10 - 15     | 2 - 21         | 1 - 54        | Crocco 2009<br>Danic 2010<br>Yuan 2008 - 2010<br>Ounnoughene 2013<br>Daurat 2016   |
| Severe<br>(hospitalization) | 0.05        | 0.1            | 1           |                |               | Popovsky 1995<br>Despotis 1999<br>Schulzki 2006  |

# AE (%) by donor status

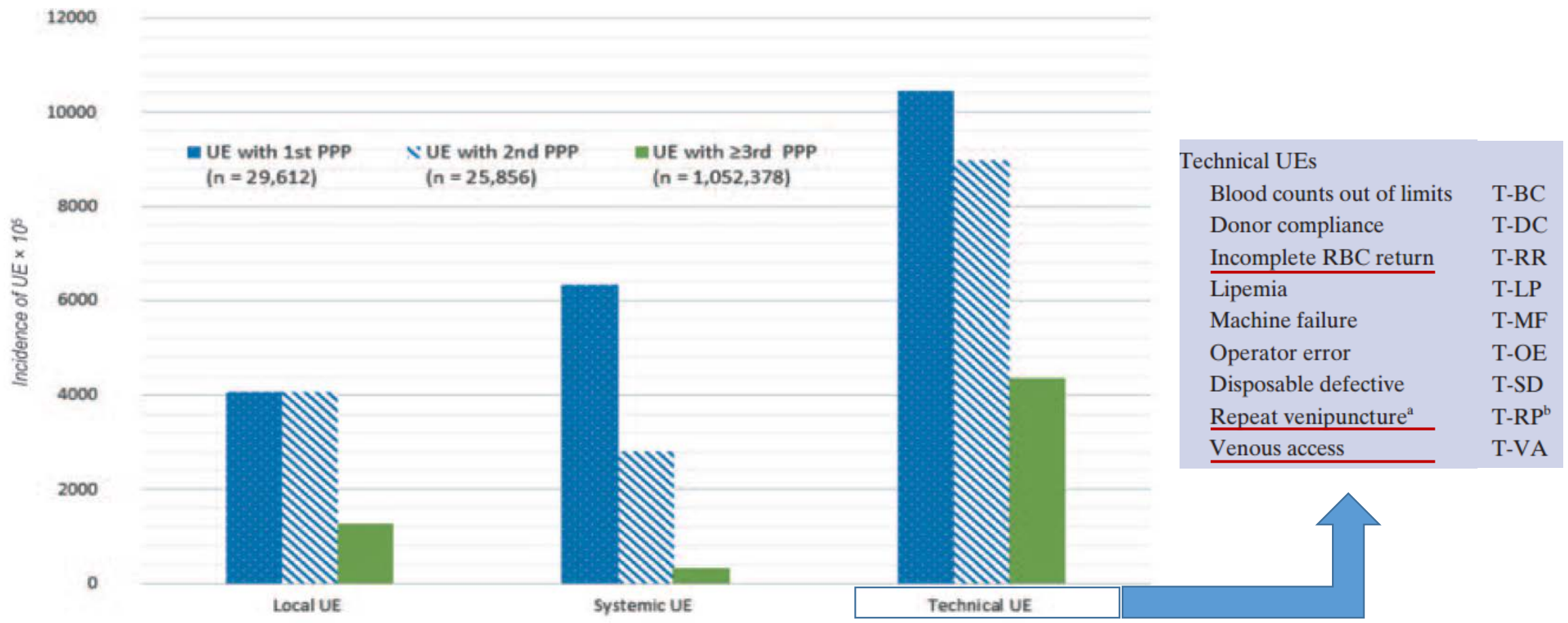
| Adverse events    | Donor status |        | First time vs repeat |
|-------------------|--------------|--------|----------------------|
|                   | First time   | Repeat |                      |
| Venipuncture only | 1,92         | 1,01   | P < 0.05             |
| Non venipuncture  | 2,92         | 0,77   | P < 0.00001          |
| Total             | 4,84         | 1,78   | P < 0.00001          |

Mc Leod 1998

|                | Total events |        | Circulatory |
|----------------|--------------|--------|-------------|
|                | First time   | Repeat | Repeat      |
| Whole blood    | 2,78         | 0,56   | 0,30        |
| Plasmapheresis | 7,96         | 1,01   | 0,49        |

Burkhardt 2015

# Incidence of unexpected events (UE) in plasmapheresis by category and donor status.



# Apheresis donation and donor status

In France, apheresis donations are performed after a donor has experienced several successful WB donations. So no apheresis donors are first-time donors.

Daurat 2016

Within Australia, plasmapheresis donors are only recruited if they have completed at least one WB donation without complication.

Bagot 2013

- This strategy is intended to maximize donor safety and retention as first-time donors are more likely to experience a vasovagal reaction than experienced donors and those who experience a vasovagal reaction are less likely to donate again.
- Operationally, a novice donor's initial WB donation provides an opportunity for the blood collection staff to assess the donor's blood type and vein suitability for plasmapheresis.

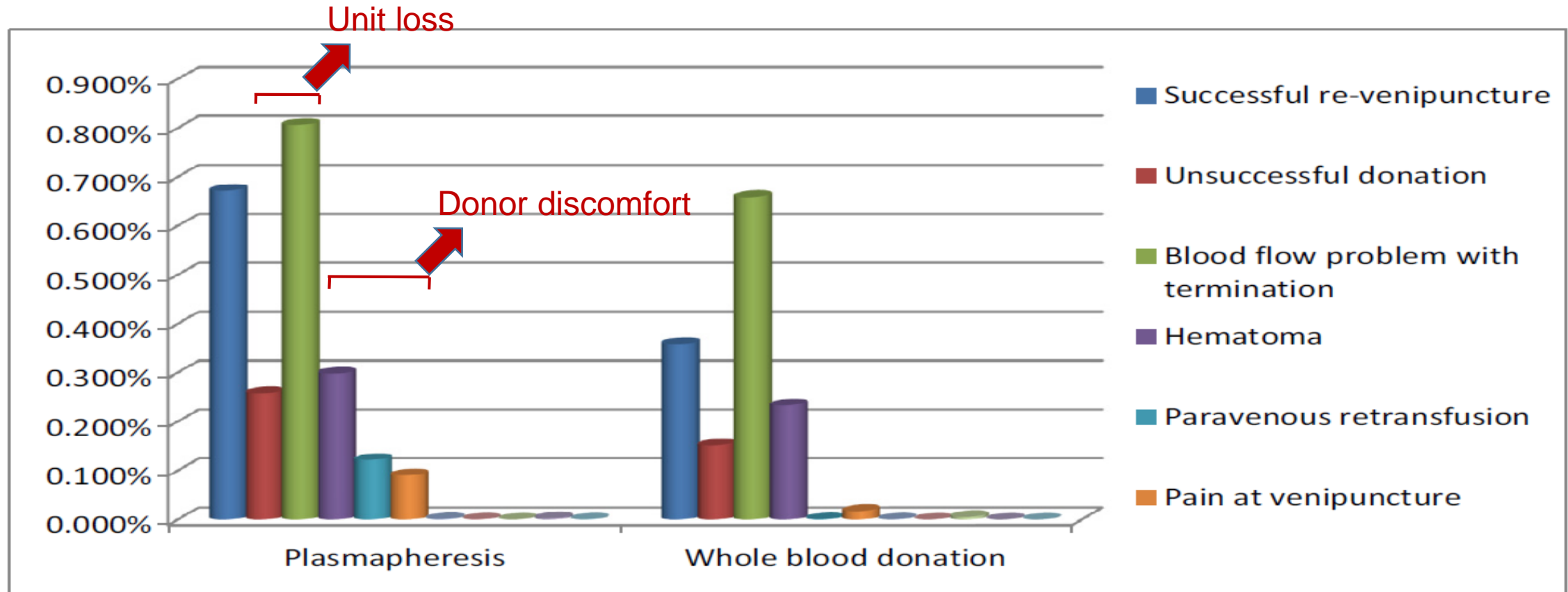




# Venipuncture-related side effects

| Problems with venous access /10.000 donations |    |
|---|----|
| Plasmapheresis                                | 52 |
| Whole blood donation                          | 26 |

Burkhardt 2015



Burkhardt 2015

# Apheresis donors: recruitment and retention strategies

- Focus on providing relevant and sufficient **information** and **educating** donors on the additional value of plasmapheresis donation to the collection agency, wider community, patients and him/her self.
- Emphasize **safety** of plasmapheresis donation, including the return process.
- Ensure **positive early experiences** with additional attention, including efficiency of the pre-donation process, providing an experienced phlebotomist and reducing perception of donation time.
- Offer **flexibility in scheduling** plasmapheresis appointments, tailoring to suit donors' varying schedules, initially mimicking WB frequency.
- Follow-up promptly to keep donation salient for donors to support **regular donation patterns**

# Citrate toxicity

Neuromuscular hyperactivity related to reduced ionized calcium levels secondary to anticoagulant (citrate) infusion during apheresis

## Symptoms and signs:

- Numbness or tingling of lips, feelings of vibrations, numbness or tingling in the fingers, metallic taste, chills, shivering, light-headedness, feeling of tightness, muscle twitching, rapid or slow pulse, shortness of breath.
- Symptoms may progress to carpopedal spasms and vomiting.
- In severe reactions: generalised muscle contractions (tetany), shock, irregular pulse and cardiac arrest.

ISBT 2014

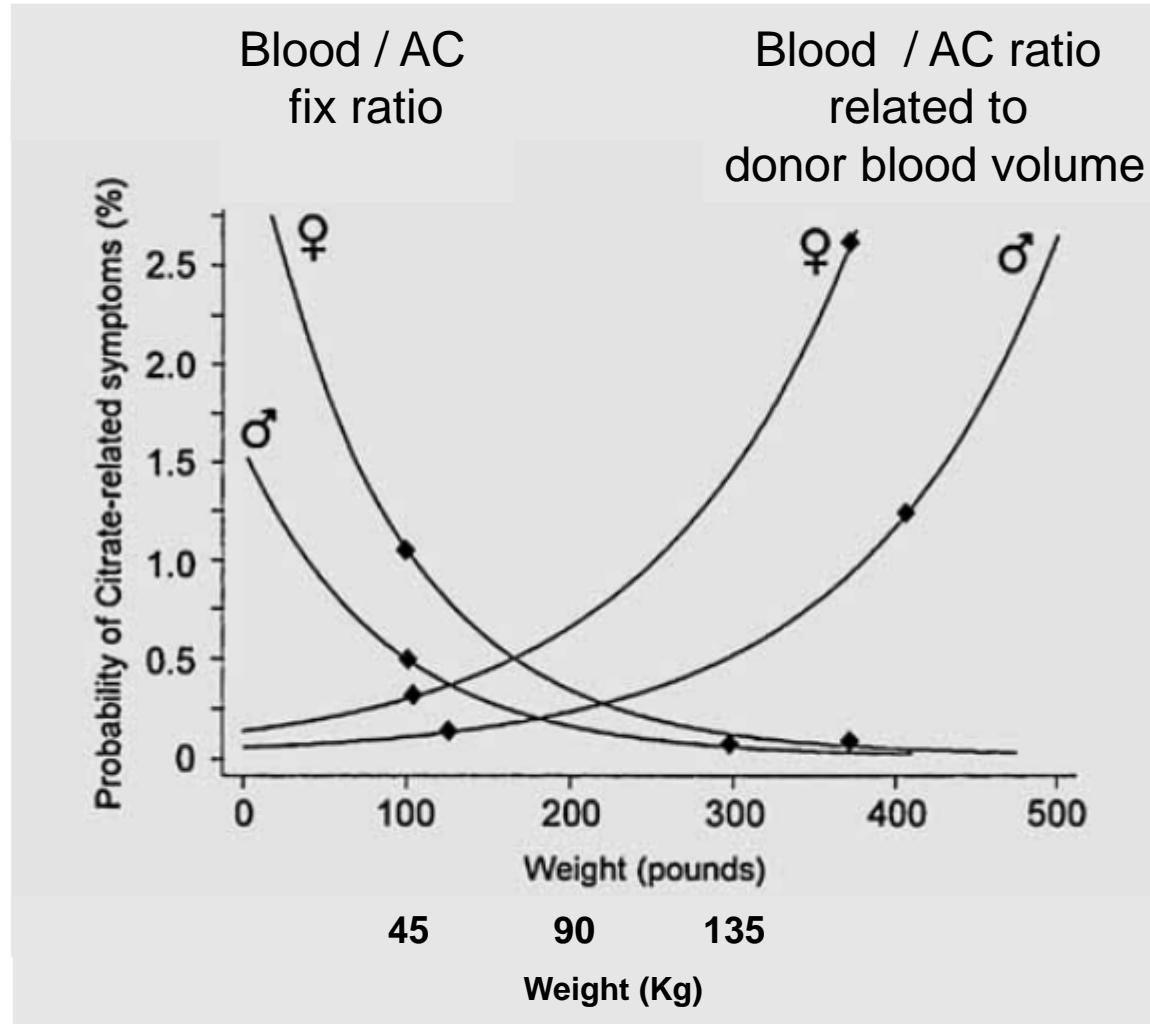
## Predisposing factors:

- low body weight (blood volume < 4 liters) and/or high hematocrit
- low baseline level of Albumin, Mg, vitamin D
- alkalosis due to hyperventilation
- type of anticoagulant solution (ACD-A)
- intermittent flow hemapheresis

# Anticoagulant (AC) infusion protocols and probability of citrate related reactions

- Whole blood flow rate
- Procedure duration

! Donor blood volume in female with low body weight



- Donor weight and height
- Volume processed
- Procedure duration

! Ideal body weight in female obese donors

# IgG serum / plasma ratio and plasma volume

- Confidential survey in 8 plasma center companies (2014)
- Ratios IgG s/IgG p between 1.1 – 1.32
- Strong inter-individual variation
- Dependent on hematocrit and procedure duration
- The individual donation volume without citrate AC cannot be exactly determined

Burkhardt 2019

| Collection volume<br>(ml) | Serum IgG<br>(g/l) | Plasma IgG<br>(g/l) | Ratio<br>S IgG/ P IgG | Citrate<br>consumed<br>(ml) | Citrate in<br>collected<br>plasma<br>(ml) | Citrate<br>delivered<br>to the donor<br>(ml) | Plasma<br>donated<br>by the donor<br>(ml) |
|---------------------------|--------------------|---------------------|-----------------------|-----------------------------|---|--|---|
| 760                       | 6.0                | 5.1                 | 1.17                  | 130                         | 110                                       | 20   | 650                                       |
| 760                       | 6.0                | 5.4                 | 1.1                   | 85                          | 70  | 15   | 690                                       |
| 760                       | 6.0                | 4.5                 | 1.32                  | 215                         | 185                                       | 30   | 575                                       |

# Citrate AE incidence (rate /10000 collections)

| AR                  | WB | Plasmapher | PLTpheresis | Multicomp | Apheresis mix | Ref   |
|---------------------|----|------------|-------------|-----------|---------------|---|
| Total               | -  | 0.14 - 2   | 8 - 96      | 24        | 3.5 - 40      | Winters 2006<br>Yuan 2008<br>Amrein 2012<br>Philip 2013<br>Diekamp 2014<br>Daurat 2016<br>Catalano 2018<br>Burkhardt 2019 |
| Moderate+<br>severe | -  | 0 - 0.68   | 3           | 2         | 1.5           | Makar 2002<br>Yuan 2008<br>Diekamp 2014<br>Catalano 2018<br>Gustafson 2019  |

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

*Katrine Grau,<sup>1</sup> Senthil K. Vasan,<sup>2</sup> Klaus Rostgaard,<sup>1</sup> Walter Bialkowski,<sup>3</sup> Rut Norda,<sup>4</sup>  
Henrik Hjalgrim,<sup>1,5</sup> and Gustaf Edgren,<sup>2,6</sup>*

*for the National Heart, Lung, and Blood Institute (NHLBI) Recipient Epidemiology and Donor Evaluation Study-III (REDS-III)*

|                                | Number of apheresis donations                          |            |                  |                  |                  |
|--------------------------------|--|------------|------------------|------------------|------------------|
|                                | 1 - 8  | 9-24       | 25 - 49          | 50 - 99          | ≥ 100            |
| <b>Both sexes</b>              | <i>Incidence rate ratios (95% confidence interval)</i> |            |                  |                  |                  |
| 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) |
| <b>Women</b>                   |  |            |                  |                  |                  |
| 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) |
| <b>Men</b>                     |  |            |                  |                  |                  |
| 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) |



# Citrate toxicity

- **Prevention**

- (for donors with a prior history of clinically significant citrate-related effects, or at high risk)
- oral Ca carbonate, citrate or phosphate (0.5 - 2 g) ± vitamin D, the day before and/or 30 minutes before apheresis and/or at 20 minute intervals during donation

- **Treatment**

- **Minor**

- slow re-infusion rate
- increase donor blood /citrate ratio

- **Moderate**

- give oral calcium (carbonate - antacids, 1000-2000 mg/day) effective on paresthesias
- consider procedure interruption

- **Severe**

- interrupt procedure
- give intravenous calcium (gluconate or chloride, 1-2 x 500 mg=5 ml, in bolus or continuous infusion)
- if ineffective, hospitalization

# Syncope: non cardiac etiology

| <i>Syncope type</i>                         | <i>Scenario</i>  | <i>Clinical features</i>  |
|---|--|---|
| <b>Neurally mediated (reflex) syncope</b>   |  |   |
| Carotid sinus syndrome/<br>hypersensitivity | Head rotation or pressure on the carotid sinus (e.g., from shaving or tight collar) can reproduce symptoms; consider in patients with unexplained falls                  | Ventricular pause or decreased systolic blood pressure after carotid sinus massage; may coincide with syncope |
| Situational                                 | Brought on by coughing, defecation, gastrointestinal stimulation, or urination; may occur after exercise or meals  | Absence of heart disease; history of similar syncope; prolonged standing, eating, or voiding                  |
| <u>Vasovagal</u>                            | Mediated by fear, heat exposure, noxious stimuli, pain, or stress  | Prodromal symptoms (e.g., diaphoresis, dizziness, nausea), precipitating factors                              |
| <b>Orthostatic hypotension syncope</b>      |  |   |
| Drug induced                                | Alcohol, antianginal agents, antidepressants, antidiabetic agents, antihypertensives, antiparkinsonian agents, diuretics, flibanserin (Addyi), insulin                   | Initiation or change in dosage  |
| Postural tachycardia syndrome               | Young adults (predominantly female); associated with chronic fatigue syndrome and mitral valve prolapse  | Severe orthostatic intolerance with marked tachycardia  |
| Primary autonomic failure                   | Multiple sclerosis, multiple system atrophy (e.g., Shy-Drager syndrome), Parkinson disease/parkinsonism, Wernicke encephalopathy   | Orthostatic hypotension with postural change  |
| Secondary autonomic failure                 | Amyloidosis, chronic inflammatory demyelinating polyneuropathy, connective tissue diseases, diabetes mellitus, Lewy body dementia, older age, spinal cord injury, uremia | Orthostatic hypotension with postural change  |
| <u>Volume depletion</u>                     | Acute blood loss (e.g., gastrointestinal bleeding, ectopic pregnancy), diarrhea, inadequate fluid intake, vomiting   | Hypotension, tachycardia, history of volume/blood loss, dehydration on examination                            |

# Plasmapheresis vs Whole Blood Donation

| Plasmapheresis   | Multicomponent apheresis   | Whole blood donation   |
|--|--|--|
| 30 – 60 min.   | 20 – 70 min.   | 7 – 15 min.  |
| Multiple cycles  | Multiple cycles  | Single phase collection  |
| 600 – 700 ml collected   | Max 700 ml collected   | 405 – 495 ml collected   |
| Gradual intravascular volume changes   | Gradual intravascular volume changes   | Rapid intravascular volume changes                                 |
| Compensatory transcapillary refilling may occur during the procedure (0,5 – 2 ml/min.) | Compensatory transcapillary refilling may occur during the procedure (0,5 – 2 ml/min.) | Minimal compensatory transcapillary refilling during the procedure |
| Can include IV procedural volume replacement   | Can include IV procedural volume replacement   | No procedural volume replacement                                   |
| Only plasma collected  | Erythrocytes and/or platelets and/or plasma are collected                              | Erythrocytes, platelets, leucocytes, plasma are collected          |
| Erythrocytes (almost) entirely returned to donor                                       | Selective return. Possible reduction of erythrocytes and iron                          | Reduction of erythrocytes and iron                                 |
| Small amount of AC returned to donor   | Small amount of AC returned to donor   | No AC returned to donor  |

# Plasmapheresis volume and frequency

## International overview

|  | Max plasma volume (ml) | AC       | Minimal lapse between two donations (hours-days) | Max donations/year (N) | Max volume/year (L) |
|--|------------------------|----------|--|------------------------|---------------------|
| <b>FDA / CBER Guidelines</b> 1992              | 650 - 880              | included | 48 h   | 104                    | ≈ 78                |
| <b>German Guidelines</b> 2017                  | 650 - 850              | included | 48 h   | 60                     | ≈ 45                |
| <b>EDQM</b> 19th Edition 2017                  | 750                    | excluded | 48 h   | 33                     | 25                  |
| <b>Australian Red Cross Blood Service</b> 2012 | 800                    | excluded | 14 d   | 26                     | ≈ 21                |
| <b>French Arrêté</b> 2017                      | 750                    | excluded | 14 d   | 24                     | ≈ 18                |
| <b>Italian Decree</b> 2015                     | 700                    | excluded | 14 d   | ≈ 20                   | 12                  |

# Principles of donor selection

## Frequency of apheresis donation and maximal amount of collected plasma

| Donor Weight / TBV   | ECVmax  | Collection Volume  |
|--|---|--|
| <ul style="list-style-type: none"><li>• TBV of each donor should be estimated based on gender, height and weight<sup>2</sup></li><li>• Alternatively, collection volume based on 10.5 mL/kg of body weight broadly equates to 16% of estimated TBV</li></ul> | <ul style="list-style-type: none"><li>• Must never be higher than 20% of TBV with a recommended guidance of 16%</li></ul> | <ul style="list-style-type: none"><li>• Excluding anticoagulant, must not exceed 16% of TBV</li><li>• Should not exceed 750 mL <u>unless fluid replacement is undertaken</u></li></ul> |

For donors weighing 50-65 kg, the total blood volume should be estimated.

Current recommendations are made in the **absence of conclusive studies of outcomes** from different regimes of volumes and frequencies of plasmapheresis. Despite some data being available from studies with several years of follow-up, further short- and long-term prospective studies are needed and should be undertaken.

# Intermittent flow plasmapheresis (IFP) and Extra-corporeal volume (ECV)

- ECV(max) during donation **does not reliably predict the degree of hypovolemic stress**, as long as it remains below 20 % TBV (14,0 ml per Kg body weight).
- Plasmapheresis donors need not be deferred if ECV exceeds 16% TBV (10,5 ml per Kg body weight).

Karger 2006

- Hemodynamic response to intravascular volume changes of up to  $\approx$  20% of TBV in the setting of IFP **is sufficient to maintain cardiac function**.
- Administration of **volume replacement** as part of the source plasmapheresis donation process, using procedural saline or oral fluids, **results in a net end-ECV well below any** of the presented single unit whole blood or source plasma collection volume **guidelines**.

Becker 2015

**Table 1. Blood volume of women in mL**  
as calculated according to the ICSH formula<sup>1</sup>

The weights and heights corresponding to the minimum acceptable blood volumes of 3 233 mL, 3 400 mL and 3 567 mL are indicated with grey backgrounds.

| kg     | 50    | 51    | 52    | 53    | 54    | 55    | 56    | 57    | 58    | 59    |
|--------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
| 145 cm | 3 141 | 3 167 | 3 193 | 3 219 | 3 244 | 3 269 | 3 294 | 3 319 | 3 343 | 3 367 |
| 146 cm | 3 157 | 3 183 | 3 209 | 3 235 | 3 260 | 3 285 | 3 310 | 3 335 | 3 359 | 3 384 |
| 147 cm | 3 172 | 3 199 | 3 225 | 3 251 | 3 276 | 3 301 | 3 327 | 3 351 | 3 376 | 3 400 |
| 148 cm | 3 187 | 3 214 | 3 240 | 3 266 | 3 292 | 3 318 | 3 343 | 3 368 | 3 392 | 3 417 |
| 149 cm | 3 203 | 3 230 | 3 256 | 3 282 | 3 308 | 3 334 | 3 359 | 3 384 | 3 409 | 3 433 |
| 150 cm | 3 218 | 3 245 | 3 272 | 3 298 | 3 324 | 3 350 | 3 375 | 3 400 | 3 425 | 3 450 |
| 151 cm | 3 234 | 3 261 | 3 287 | 3 314 | 3 340 | 3 366 | 3 391 | 3 416 | 3 441 | 3 466 |
| 152 cm | 3 249 | 3 276 | 3 303 | 3 329 | 3 356 | 3 381 | 3 407 | 3 433 | 3 458 | 3 483 |
| 153 cm | 3 264 | 3 291 | 3 318 | 3 345 | 3 371 | 3 397 | 3 423 | 3 449 | 3 474 | 3 499 |
| 154 cm | 3 279 | 3 307 | 3 334 | 3 361 | 3 387 | 3 413 | 3 439 | 3 465 | 3 490 | 3 515 |
| 155 cm | 3 295 | 3 322 | 3 349 | 3 376 | 3 403 | 3 429 | 3 455 | 3 481 | 3 506 | 3 532 |
| 156 cm | 3 310 | 3 337 | 3 365 | 3 392 | 3 418 | 3 445 | 3 471 | 3 497 | 3 523 | 3 548 |
| 157 cm | 3 325 | 3 353 | 3 380 | 3 407 | 3 434 | 3 461 | 3 487 | 3 513 | 3 539 | 3 564 |
| 158 cm | 3 340 | 3 368 | 3 396 | 3 423 | 3 450 | 3 476 | 3 503 | 3 529 | 3 555 | 3 581 |
| 159 cm | 3 355 | 3 383 | 3 411 | 3 438 | 3 465 | 3 492 | 3 519 | 3 545 | 3 571 | 3 597 |
| 160 cm | 3 370 | 3 399 | 3 426 | 3 454 | 3 481 | 3 508 | 3 535 | 3 561 | 3 587 | 3 613 |
| 161 cm | 3 385 | 3 414 | 3 442 | 3 469 | 3 497 | 3 524 | 3 550 | 3 577 | 3 603 | 3 629 |
| 162 cm | 3 400 | 3 429 | 3 457 | 3 485 | 3 512 | 3 539 | 3 566 | 3 593 | 3 619 | 3 645 |
| 163 cm | 3 416 | 3 444 | 3 472 | 3 500 | 3 528 | 3 555 | 3 582 | 3 609 | 3 635 | 3 661 |
| 164 cm | 3 430 | 3 459 | 3 487 | 3 515 | 3 543 | 3 571 | 3 598 | 3 625 | 3 651 | 3 677 |
| 165 cm | 3 445 | 3 474 | 3 503 | 3 531 | 3 559 | 3 586 | 3 613 | 3 640 | 3 667 | 3 693 |
| 166 cm | 3 460 | 3 489 | 3 518 | 3 546 | 3 574 | 3 602 | 3 629 | 3 656 | 3 683 | 3 709 |
| 167 cm | 3 475 | 3 504 | 3 533 | 3 561 | 3 589 | 3 617 | 3 645 | 3 672 | 3 699 | 3 726 |
| 168 cm | 3 490 | 3 519 | 3 548 | 3 577 | 3 605 | 3 633 | 3 660 | 3 688 | 3 715 | 3 741 |

| kg     | 50    | 51    | 52    | 53    | 54    | 55    | 56    | 57    | 58    | 59    |
|--------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
| 169 cm | 3 505 | 3 534 | 3 563 | 3 592 | 3 620 | 3 648 | 3 676 | 3 703 | 3 731 | 3 757 |
| 170 cm | 3 520 | 3 549 | 3 578 | 3 607 | 3 636 | 3 664 | 3 692 | 3 719 | 3 746 | 3 773 |
| 171 cm | 3 535 | 3 564 | 3 593 | 3 622 | 3 651 | 3 679 | 3 707 | 3 735 | 3 762 | 3 789 |
| 172 cm | 3 550 | 3 579 | 3 608 | 3 637 | 3 666 | 3 695 | 3 723 | 3 750 | 3 778 | 3 805 |
| 173 cm | 3 564 | 3 594 | 3 624 | 3 653 | 3 681 | 3 710 | 3 738 | 3 766 | 3 794 | 3 821 |
| 174 cm | 3 579 | 3 609 | 3 638 | 3 668 | 3 697 | 3 725 | 3 754 | 3 782 | 3 809 | 3 837 |
| 175 cm | 3 594 | 3 624 | 3 653 | 3 683 | 3 712 | 3 741 | 3 769 | 3 797 | 3 825 | 3 853 |
| 176 cm | 3 608 | 3 639 | 3 668 | 3 698 | 3 727 | 3 756 | 3 784 | 3 813 | 3 841 | 3 868 |
| 177 cm | 3 623 | 3 653 | 3 683 | 3 713 | 3 742 | 3 771 | 3 800 | 3 828 | 3 856 | 3 884 |
| 178 cm | 3 638 | 3 668 | 3 698 | 3 728 | 3 757 | 3 786 | 3 815 | 3 844 | 3 872 | 3 900 |
| 179 cm | 3 652 | 3 683 | 3 713 | 3 743 | 3 772 | 3 801 | 3 830 | 3 859 | 3 887 | 3 916 |
| 180 cm | 3 667 | 3 698 | 3 728 | 3 758 | 3 787 | 3 816 | 3 845 | 3 875 | 3 903 | 3 931 |
| 181 cm | 3 682 | 3 712 | 3 743 | 3 773 | 3 803 | 3 832 | 3 861 | 3 890 | 3 919 | 3 947 |
| 182 cm | 3 696 | 3 727 | 3 758 | 3 788 | 3 818 | 3 847 | 3 876 | 3 905 | 3 934 | 3 962 |
| 183 cm | 3 711 | 3 742 | 3 772 | 3 803 | 3 833 | 3 862 | 3 892 | 3 921 | 3 950 | 3 978 |
| 184 cm | 3 725 | 3 756 | 3 787 | 3 818 | 3 848 | 3 878 | 3 907 | 3 936 | 3 965 | 3 994 |
| 185 cm | 3 740 | 3 771 | 3 802 | 3 832 | 3 863 | 3 893 | 3 922 | 3 952 | 3 981 | 4 009 |

% ml  
 $16 : 100 = 600 : X \text{ (TBV)}$   
 $X \text{ (TBV)} = 3750 \text{ ml}$   
 $20\% = 750 \text{ ml}$

# Extra-corporeal volume (ECV) during apheresis

Woman, kg 51, cm 165

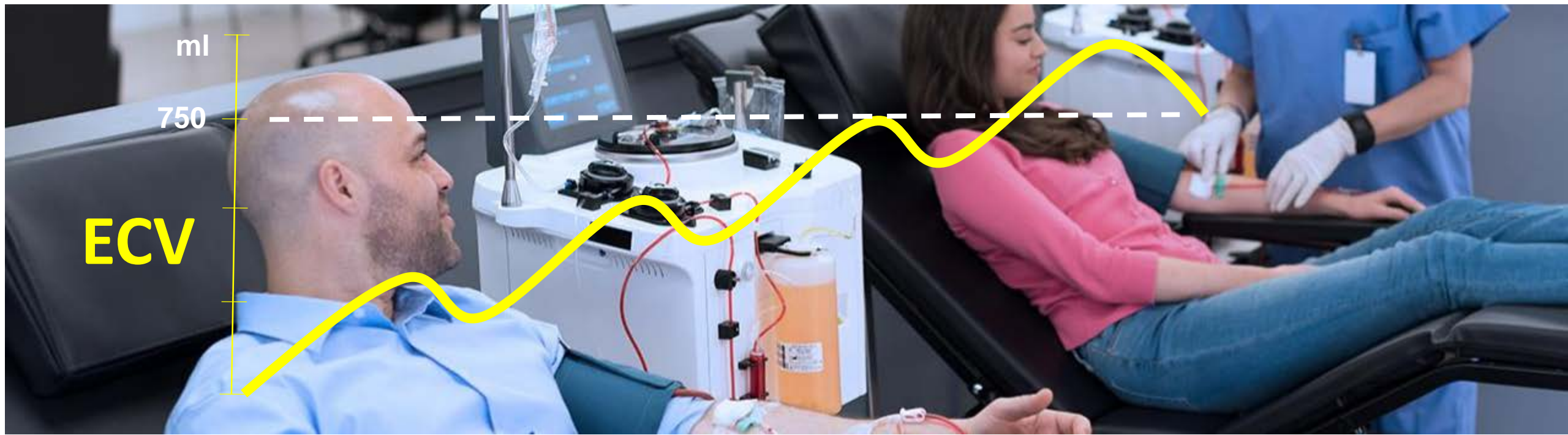
ml                      %  
600 : TBV 3474 = X : 100  
**X (%) = 17.3**  
16% = 556 ml  
20% = 695 ml

Woman, kg 55, cm 165

ml                      %  
600 : TBV 3586 = X : 100  
**X (%) = 16.7**  
16% = 574 ml  
20% = 717 ml

Woman, kg 59, h 165

ml                      %  
600 : TBV 3693 = X : 100  
**X (%) = 16.2**  
16% = 591 ml  
20% = 739 ml





# Pre-donation water-loading and VVR risk

| Pre-donation loading                       | Immediate VVR<br>RR or OR (95% CI) | Off site VVR<br>RR or OR (95% CI) | Ref         |
|--|------------------------------------|-----------------------------------|-------------|
| 500 mL of water within 30 min              | RR, 0.79 (0.70–0.89)               |                                   | Fisher 2016 |
| 500 mL of water 9 min before phlebotomy    | OR, 0.74 (0.55–0.99)               |                                   | Morand 2016 |
| 500 mL of isotonic drink before phlebotomy |                                    | OR, 0.62 (0.40–0.98)              | Morand 2016 |

# Hypotension during plasma donation

Severe acute hypotension  
(young women at first/second donation)

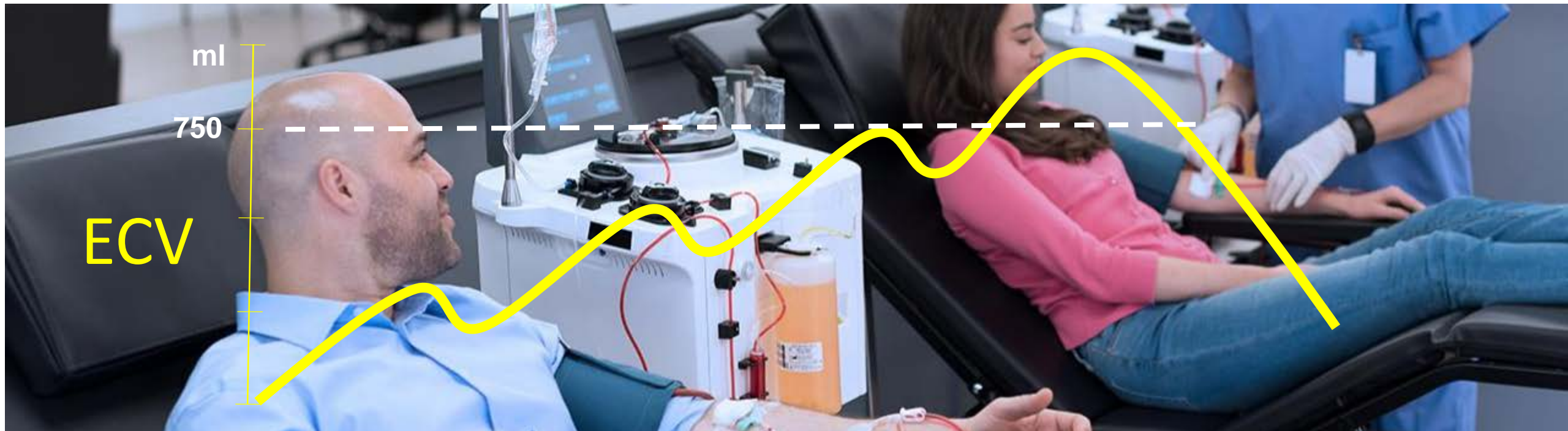
45 ± 20 min

602 ± 240 ml collected plasma  
≈ 1000 ml ECV

NaCl 0,9%  
2 x 500 ml

Recovery  
49 ± 18 min

Donation Start



# Plasma collection, PDMP yield and AE

Target 750 ml  
No saline infusion

Target 840 ml  
Saline infusion  
250+250 ml

Target 800 ml  
Saline infusion  
500 ml

| Plasma characteristics      | Method 1<br>(n = 85)* | Method 2<br>(n = 88)* | Method 3<br>(n = 82)* |
|-----------------------------|-----------------------|-----------------------|-----------------------|
| Number of donations         | 271                   | 292                   | 259                   |
| Mean volume collected (mL)† | 657 ± 96.21 (182-753) | 822 ± 79.45 (240-935) | 730 ± 138.64 (0-840)  |
| Mean collection time (min)† | 40.3 ± 9.83 (14-101)  | 53.6 ± 9.81 (6-111)   | 49.2 ± 11.61 (6-144)  |
| Total protein (g/L)‡        | 57.99 (57.11-58.87)   | 51.82 (51.06-52.59)§  | 53.9 (53.09-54.72)§   |
| Average protein yield (g)¶  | 38.1                  | 42.6                  | 39.3                  |
| IgG (g/L)‡                  | 6.14 (5.87-6.41)      | 5.79 (5.54-6.05)§     | 5.97 (5.71-6.23)§     |
| Average IgG yield (g)¶      | 4.03                  | 4.76                  | 4.36                  |
| FVIII (IU/L)‡               | 1.14 (1.07-1.22)      | 1.03 (0.96-1.11)§     | 1.08 (1.00-1.15)§     |
| Average FVIII yield (IU)¶   | 0.75                  | 0.85                  | 0.79                  |

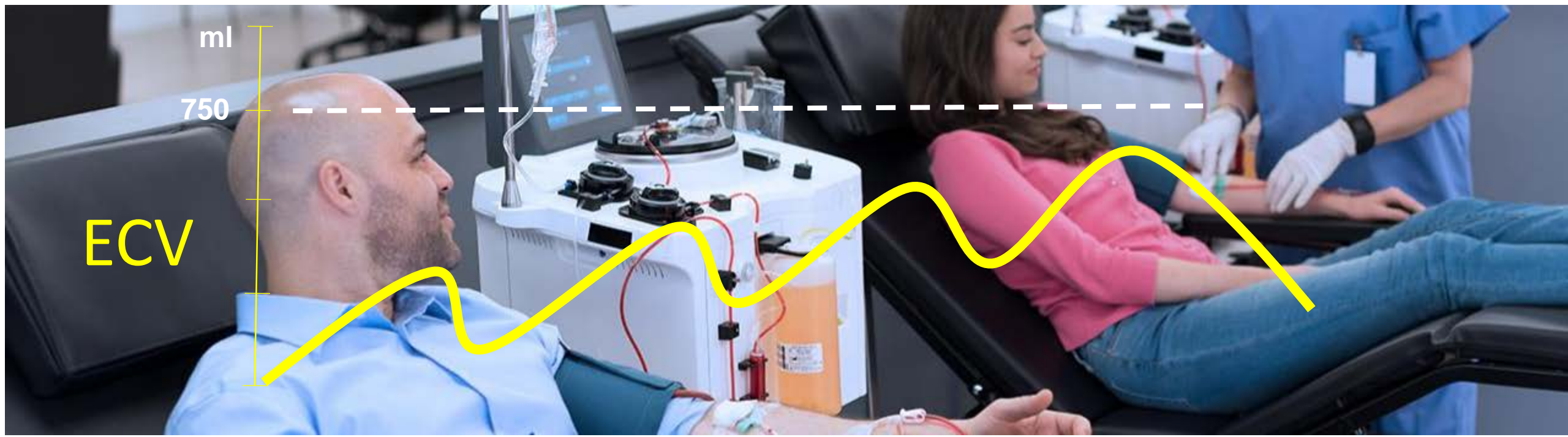
\* The number of participants donating at least once under each method.

§ Indicates significant difference (p > 0.05) in comparison to Method 1.

| Systemic Adverse Event | Severity        | Method 1<br>Incidence N (%) | Method 2<br>Incidence (%) | Method 3<br>Incidence (%) |
|------------------------|-----------------|-----------------------------|---------------------------|---------------------------|
| VVR                    | Moderate-severe | 1 (0.4)                     | 0                         | 0                         |
|                        | Mild            | 1 (0.4)                     | 2 (0.7)                   | 2 (0.8)                   |
| Citrate                | Moderate-severe | 0                           | 2 (0.7)                   | 0                         |
| Nausea                 | Mild            | 0                           | 1 (0.3)                   | 2 (0.8)                   |

# Saline infusion during apheresis

Donation Start 





# Adverse events and safety issues in blood donation—A comprehensive review

Karin Amrein <sup>a,\*</sup>, Angelika Valentin <sup>a,1</sup>, Gerhard Lanzer <sup>b,2</sup>, Camilla Drexler <sup>b,2</sup>

## Apheresis donation

| Adverse event  | Frequency  |
|--|--|
| Citrate effects (lab): hypocalcaemia, hypomagnesaemia hypercalciuria, metabolic alkalosis, secondary hyperparathyroidism <sup>77–80,82</sup> | Obligatory   |
| Citrate effects (symptoms): perioral paraesthesia, malaise, nausea, chest tightness, paresthesias and nausea <sup>4,81</sup>                 | Mild: up to 80%, severe: 0.4%                                  |
| Elevated bone turnover markers <sup>77,82</sup>  | Regular  |
| QTc prolongation <sup>83</sup>   | Regular, greater prolongation in women than in men             |
| Arrhythmia <sup>4</sup>  | Rare   |
| Vasovagal reactions <sup>4,85,86</sup>   | 0.1–0.7%, men: 1.0%, women: 4.2%                               |
| Exposure to endocrine disruptors <sup>94,95</sup>  | Regular  |
| Protein depletion in high-intensity plasmapheresis <sup>101–104,208</sup>  | Depending on donation frequency, up to 16% temporary deferrals |
| Myocardial infarction, stroke, death <sup>75,90,109,110</sup>  | Anecdotal  |



# SIPLA study: 65 (6-180) donations in 475 (39-1093) days

## Dropout reasons

| Subgroup, <i>n</i> (%)   | All<br><i>n</i> = 3783 | Arm I<br><i>n</i> = 2402 | Arm II<br><i>n</i> = 1381 | Females<br><i>n</i> = 897 | Males<br><i>n</i> = 2886 | Arm I vs.<br>arm II | <i>P</i> -value<br>F vs. M |
|--|------------------------|--------------------------|---------------------------|---------------------------|--------------------------|---------------------|----------------------------|
| Donors completing the study  | 923 (24.4)             | 587 (24.4)               | 336 (24.3)                | 193 (21.5)                | 730 (25.3)               | 0.97                | 0.023                      |
| Total number of dropouts   | 2860 (75.6)            | 1815 (75.6)              | 1045 (75.7)               | 704 (78.5)                | 2156 (74.7)              |                     |                            |
| Socioeconomic reasons  | 1860 (49.2)            | 1159 (48.3)              | 701 (50.8)                | 396 (44.1)                | 1464 (50.7)              | 0.14                | 0.0007                     |
| Lack of time or work schedule conflicts  | 686 (18.1)             | 416 (17.3)               | 270 (19.6)                | 114 (12.7)                | 572 (19.8)               | 0.090               | < 0.0001                   |
| Moving from the area   | 121 (3.2)              | 81 (3.4)                 | 40 (2.9)                  | 31 (3.5)                  | 90 (3.1)                 | 0.48                | 0.69                       |
| Other personal reasons   | 1053 (27.8)            | 662 (27.6)               | 391 (28.3)                | 251 (28)                  | 802 (27.8)               | 0.64                | 0.94                       |
| Medical reasons unrelated to plasmapheresis  | 393 (10.4)             | 247 (10.3)               | 146 (10.6)                | 122 (13.6)                | 271 (9.4)                | 0.82                | 0.0004                     |
| Medical diseases   | 138 (3.6)              | 85 (3.5)                 | 53 (3.8)                  | 43 (4.8)                  | 95 (3.3)                 | 0.70                | 0.056                      |
| Surgery, accidents, injuries   | 88 (2.3)               | 54 (2.2)                 | 34 (2.5)                  | 23 (2.6)                  | 65 (2.3)                 | 0.75                | 0.67                       |
| Malaise, disturbed well-being  | 65 (1.7)               | 46 (1.9)                 | 19 (1.4)                  | 24 (2.7)                  | 41 (1.4)                 | 0.27                | 0.024                      |
| Pregnancy  | 16 (0.4)               | 10 (0.4)                 | 6 (0.4)                   | 16 (1.8)                  |                          | 0.93                |                            |
| Diagnostic endoscopy   | 11 (0.3)               | 9 (0.4)                  | 2 (0.1)                   | 5 (0.6)                   | 6 (0.2)                  | 0.34                | 0.17                       |
| Laboratory findings not related to plasmapheresis  | 75 (2)                 | 43 (1.8)                 | 32 (2.3)                  | 11 (1.2)                  | 64 (2.2)                 | 0.31                | 0.083                      |
| Dropouts because of low IgG, TSP or Hb/Hct and clinical events related to plasmapheresis | 607 (16)               | 409 (17.0)               | 198 (14.3)                | 186 (20.7)                | 421 (14.6)               | 0.031               | < 0.0001                   |
| Low IgG  | 468 (12.4)             | 300 (12.5)               | 168 (12.2)                | 99 (11.0)                 | 369 (12.8)               | 0.80                | 0.18                       |
| Low total serum protein  | 77 (2.0)               | 58 (2.4)                 | 19 (1.4)                  | 38 (4.2)                  | 39 (1.4)                 | 0.039               | < 0.0001                   |
| Low Hb or Hct  | 56 (1.5)               | 46 (1.9)                 | 10 (0.7)                  | 48 (5.4)                  | 8 (0.3)                  | 0.005               | < 0.0001                   |
| Others <sup>a</sup>  | 5 (0.1)                | 5 (0.2)                  | (0.0)                     | 1 (0.1)                   | 4 (0.1)                  | 0.21                | 0.84                       |

<sup>a</sup>Four haematomas, one metacarpal fracture.

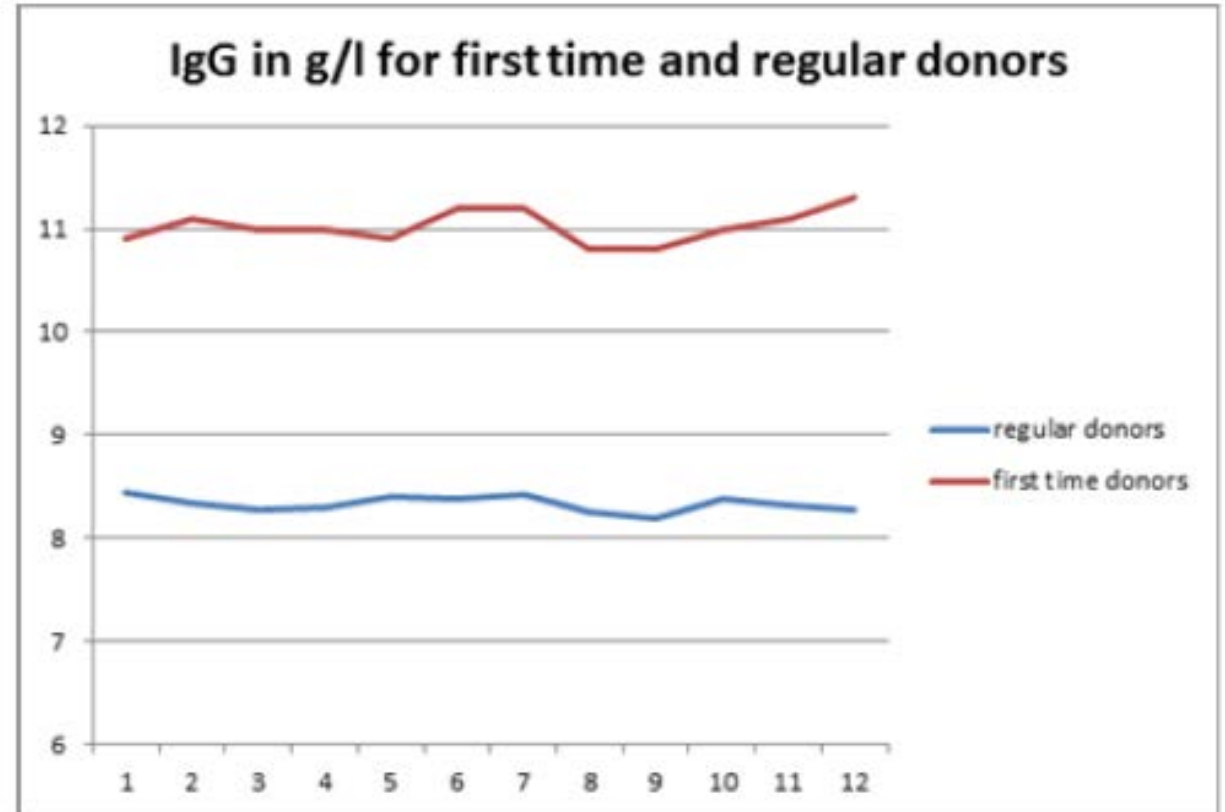
# Practice versus standards: donations per donor LFY

CoE Guide standard: max 33 donations per year

| Number of donations per donor and per 12-month period                        | 1-5 | 6-10 | 11-15 | 16-20 | 21-25 | > 25 |
|--|-----|------|-------|-------|-------|------|
| Aligned/lower than Guide<br>11 BE: 611 833 donors and<br>2 062 034 donations | 82% | 16%  | 4%    | 1%    | 1%    | 0%   |
| Higher than Guide<br>5 BE: 40 456 donors and<br>561 622 donations            | 39% | 15%  | 11%   | 7%    | 7%    | 21%  |

# The art of keeping donors above IgG level = 6 g/L

- 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.



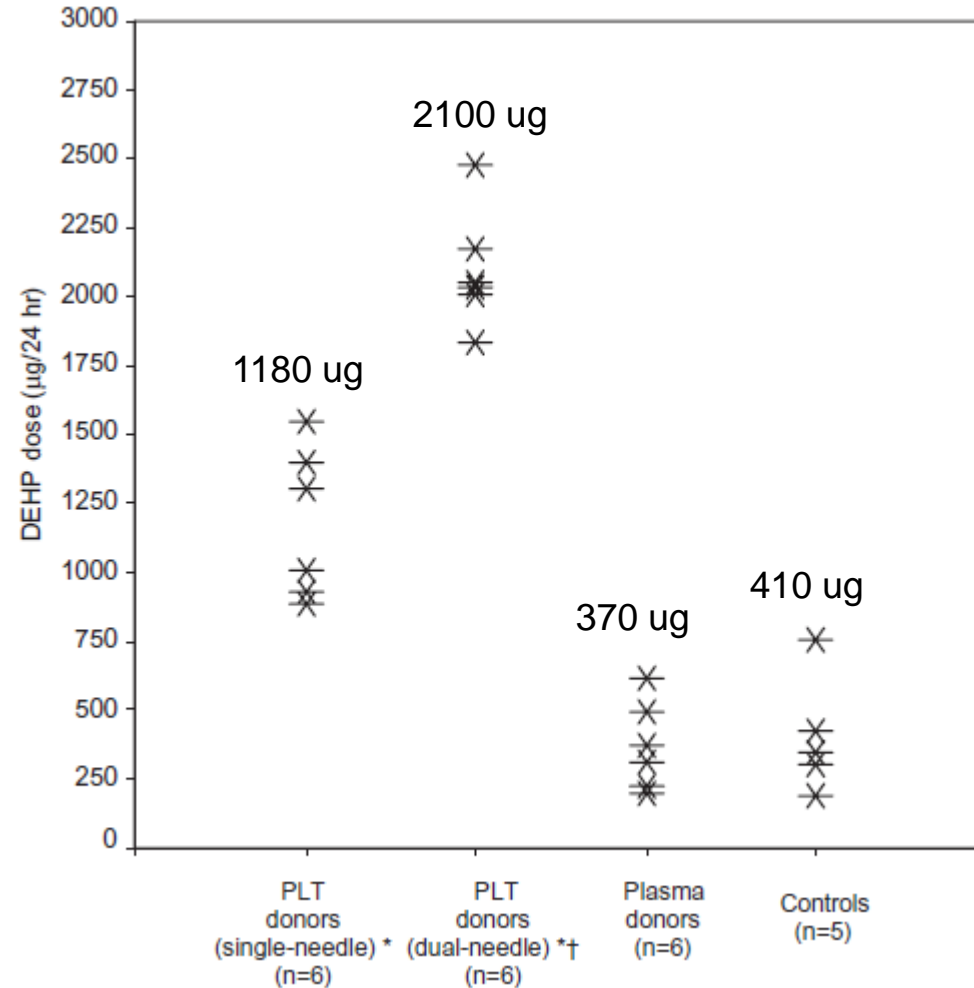
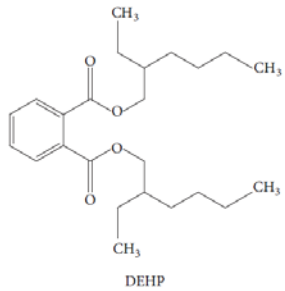


# Protein content in plasma pools (mean $\pm$ SD)

| Group            | Remuneration | Method<br>collection<br>plasma | Number<br>batches | Mean plasma<br>volume per<br>donation (ml) |
|------------------|--------------|--------------------------------|-------------------|--|
| <b>Group I</b>   |              |                                |                   |  |
| Finland          | Unpaid       | Recovered                      | 6                 | 288 $\pm$ 1 <sup>a</sup>                   |
| France           | Unpaid       | Recovered                      | 3                 | 320 $\pm$ 7                                |
| Germany          | Unpaid       | Recovered                      | 2                 | 306 $\pm$ 1                                |
| The Netherlands  | Unpaid       | Recovered                      | 10                | 318 $\pm$ 2                                |
|                  | Unpaid       | Source                         | 10                | 634 $\pm$ 5                                |
| Belgium          | Unpaid       | Recovered                      | 10                | 280 $\pm$ 2                                |
|                  |              | Source                         | 10                | 581 $\pm$ 7                                |
| <b>Group II</b>  |              |                                |                   |  |
| United States    | Unpaid       | Recovered                      | 5                 | 317 $\pm$ 14                               |
| <b>Group III</b> |              |                                |                   |  |
| Germany          | Compensated  | Source                         | 8                 | 657 $\pm$ 95                               |
| <b>Group IV</b>  |              |                                |                   |  |
| United States    | Paid         | Source                         | 41                | 814 $\pm$ 13                               |

| Protein (g/l)              | Content in g/l in donations   |                         | %<br>Variation <sup>a</sup> | P-value  |
|----------------------------|-------------------------------|-------------------------|-----------------------------|----------|
|                            | Group I<br>n = 51<br>A        | Group IV<br>n = 41<br>B |                             |          |
| Total protein              | 60.46 $\pm$ 3.46 <sup>b</sup> | 55.20 $\pm$ 2.60        | -9                          | < 0.0001 |
| Albumin                    | 34.05 $\pm$ 2.24              | 29.05 $\pm$ 3.08        | -15                         | < 0.0001 |
| Total IgG                  | 8.48 $\pm$ 0.61               | 6.49 $\pm$ 0.51         | -24                         | < 0.0001 |
| IgM                        | 0.96 $\pm$ 0.13               | 0.69 $\pm$ 0.09         | -28                         | < 0.0001 |
| IgA                        | 1.64 $\pm$ 0.22               | 1.54 $\pm$ 0.18         | -6                          | < 0.05   |
| Transferrin                | 2.23 $\pm$ 0.18               | 2.06 $\pm$ 0.15         | -7                          | < 0.0001 |
| Haemopexin                 | 0.70 $\pm$ 0.05               | 0.62 $\pm$ 0.06         | -11                         | < 0.0001 |
| $\alpha_1$ glycoprotein    | 0.67 $\pm$ 0.04               | 0.65 $\pm$ 0.07         | -2                          | > 0.05   |
| Retinol-binding<br>protein | 0.03 $\pm$ 0.01               | 0.03 $\pm$ 0.01         | -10                         | < 0.05   |
| C <sub>1</sub> inhibitor   | 0.21 $\pm$ 0.01               | 0.232 $\pm$ 0.02        | +12                         | < 0.0001 |
| Prealbumin                 | 0.19 $\pm$ 0.03               | 0.21 $\pm$ 0.02         | +9                          | < 0.0001 |
| C-reactive<br>protein      | 1.72 $\pm$ 0.29               | 2.08 $\pm$ 0.67         | +21                         | < 0.05   |

# Total DEHP dose ( $\mu\text{g}/24\text{ h}$ ) in controls and apheresis donors



# Conclusions

1. In the near future, an **increase in plasmapheresis donations** is predictable and desirable.
2. In order to increase the donor safety, specific interventions are required focusing on:
  - donor information and support, aimed to **improve his/her global donation experience, minimize adverse reaction incidence** and increase intention to donate;
  - **identification of donors at major risk** of citrate reaction (high Ht, low EBV, Albumin, Mg, Vit. D, hyperventilation) or VVR (young, first time, low BMI-EBV, fear/anxiety).
3. Excluding a few **Adverse Events**, reported in the context of intensive apheresis programmes, the main AE are VVRs, vessel injuries, citrate reactions: all of them are foreseeable and mostly **preventable or manageable** since the early symptoms/signs. Severe events are rare, particularly in plasmapheresis procedures.
4. The **standards (about volume and donation frequency)** ratified by the Italian Decree november 2<sup>nd</sup> 2015 **look adequate** to guarantee donor safety, PDMP quality and system sustainability.
5. Yet **donor safety must be constantly pursued and improved**, emphasizing the available scientific evidences.
6. In particular, water loading and saline infusion intra and/or at the end of procedure allow to **better control extracorporeal volume, within safety thresholds**, even in donors at major risk.