

10th European Haemovigilance Seminar (EHS)

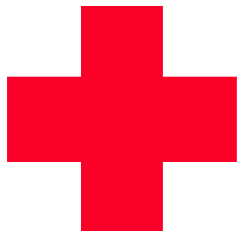
Risk of apheresis versus whole-blood donation

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Frankfurt, 29 February 2008



Risk of apheresis vs. whole-blood donation

- Whole-blood donation vs. apheresis donation -

- **Local reactions related to needle insertion**
 - vessel injuries
 - nerve injuries
 - other complications (related to needle insertion)
- **General reactions, VVR**
 - immediate
 - delayed

Risk of apheresis vs. whole-blood donation

- Whole-blood donation vs. plateletpheresis donation - What is different ?

- Extracorporeal circulation (extracorporeal volume)
- Platelets: modulation of glycoprotein expression; activation
- Increased loss of platelets → thrombocytopenia: acute/chronic
- Citrate with potential risk of citrate-related toxicity
 - hypocalcemia may cause
 - vascular smooth muscle relaxation
 - depressed myocardial function
 - arrhythmia
 - chronic metabolic (late) effects of citrate : bone demineralization
- Exposure to foreign substances with risk of allergic reactions (ethylene oxide); HES (granulocyte donors)
- Increased loss of lymphocytes ? → immune deficiency ?
- Risk of air embolism

Risk of apheresis vs. whole-blood donation

- Vasovagal reactions (VVR) -

Overall VVR incidence rate

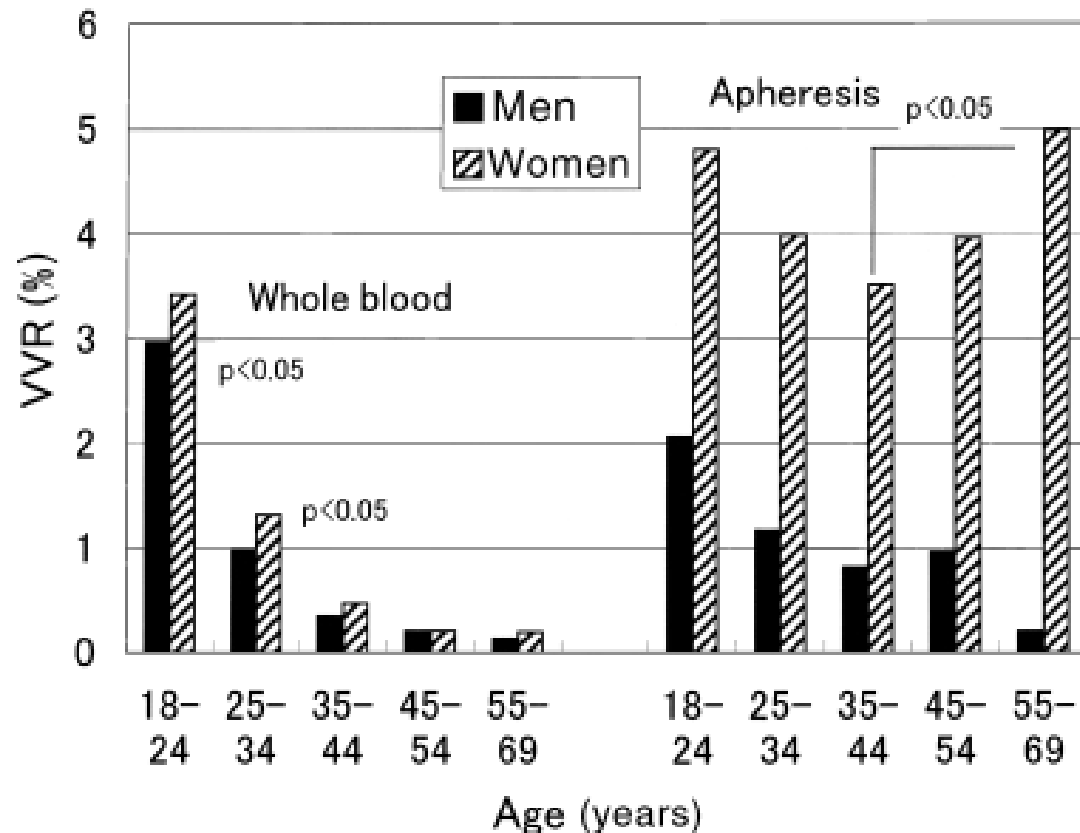
	<u>Whole blood*</u>	<u>Apheresis**</u>
Men	0.83 %	0.99 %
Women	1.25 %	4.17 %

* including 200 and 400 ml phlebotomy

** plasma (68.1 %) and platelet collection (21.9 %)
(MCS 3P)

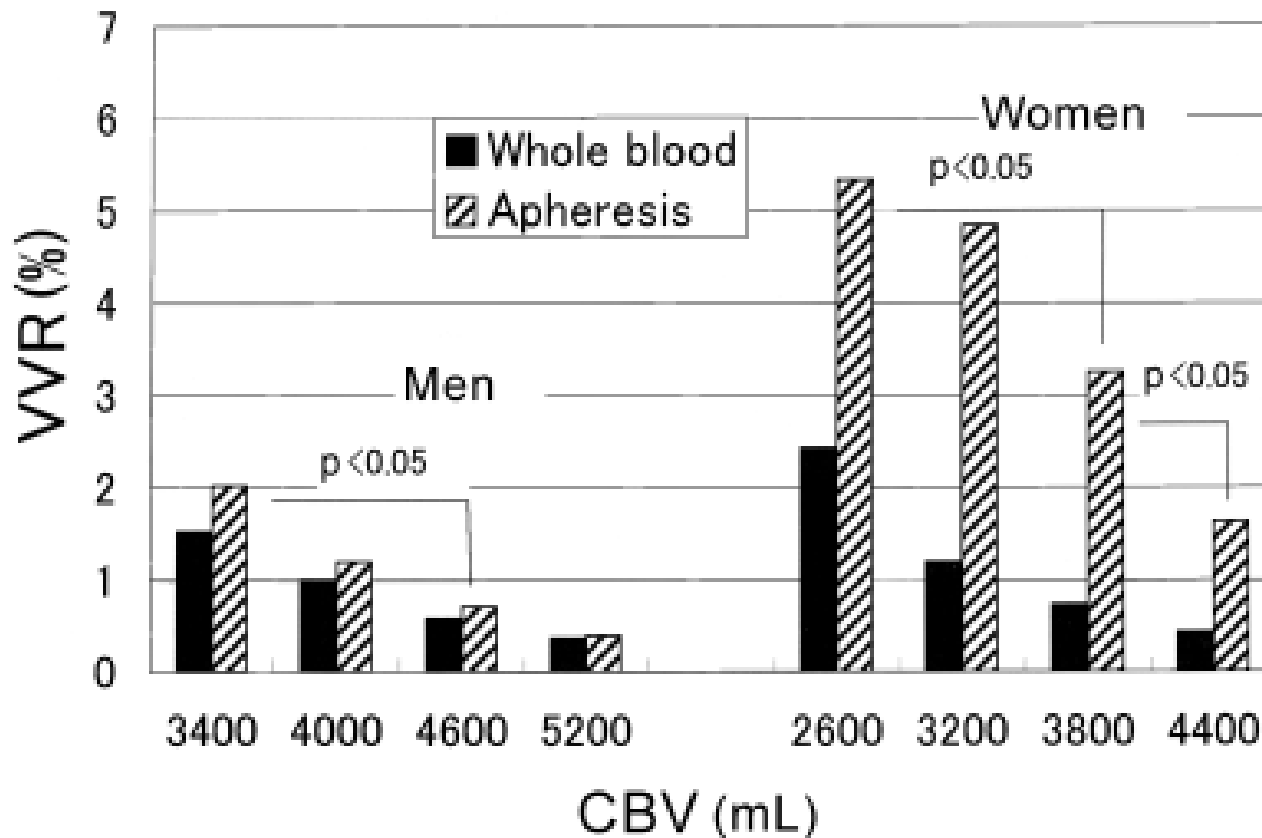
Risk of apheresis vs. whole-blood donation

- VVR incidence rate -
in relation to age in whole blood and apheresis donors



Risk of apheresis vs. whole-blood donation

- VVR incidence in relation to circulatory blood volume (CBV)* -

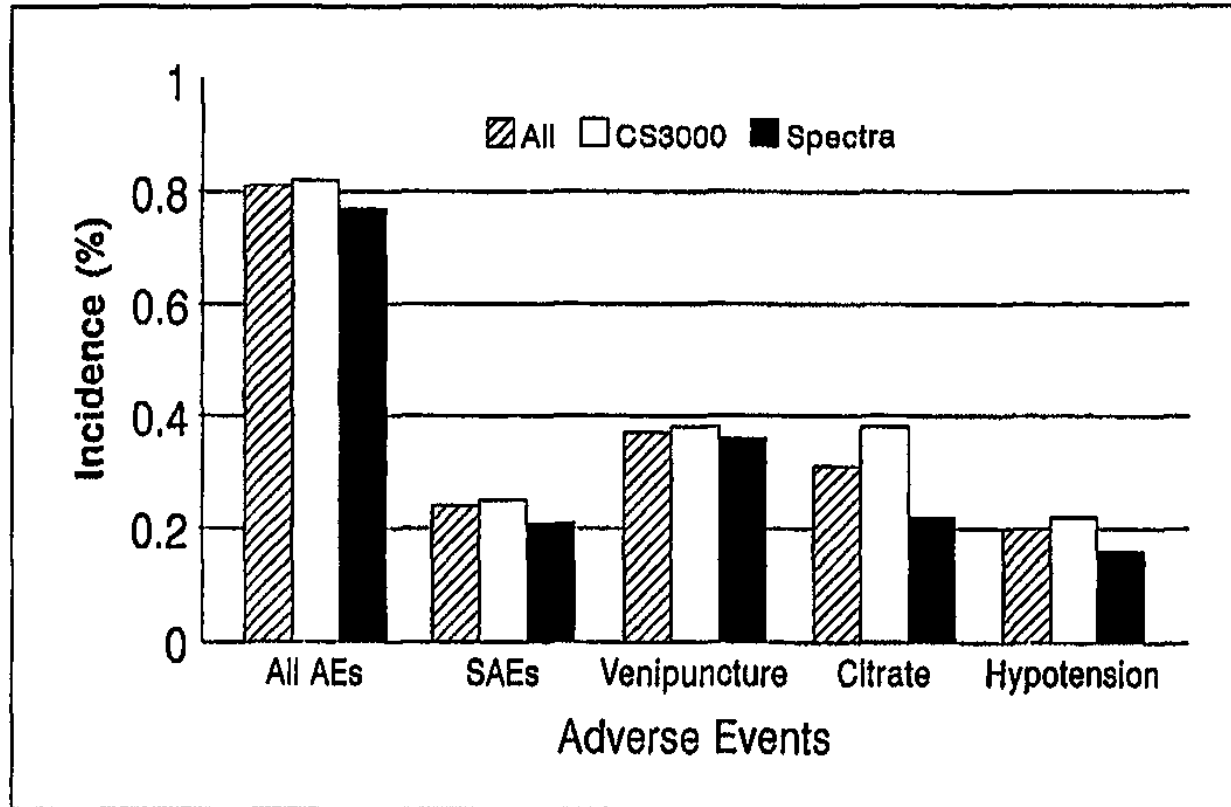


CBV significantly less (4 %; $p < 0.01$) in VVR donors for WB and apheresis donation of both sexes.

* CBV men: $168 \times \text{height}^3 + 50 \times \text{weight} + 444$
women: $250 \times \text{height}^3 + 63 \times \text{weight} + 662$

Risk of apheresis vs. whole-blood donation

Adverse Events in Platelet Apheresis Donors: A Multivariate Analysis in a Hospital-Based Program - Incidence of All Adverse Events and Various Categories -



n = 19,736 platelet apheresis procedures
159 (0.8%) associated with adverse events

Risk of apheresis vs. whole-blood donation

- Adverse events in platelet apheresis donors -

n = 19.736 apheresis procedure (platelet [98.5 %] or leukocyte donation [1.5 %])

n = 2.386 donors (average of 24 donations)

159	donations with adverse events	(0,81 %)	
26	in 2.376 first-time donors	(1.09 %)	
133	in 17.360 repeat procedures	(0.77 %)	p = 0.1
47	serious adverse events	(0.24 %)	240 / 10 ⁵
	- 7 emergency room evaluation		
	- 2 hospitalization: myocardial ischemia		
39	hypotensive SAE		
	- 35 citrate toxicity / hypovolemia		
	29 / 35 preceded by citrate-related symptoms		
	(most significant independent predictor of hypotension)		
	- 4 VVR		

Conclusion: Apheresis procedures have a 150-fold higher incidence of SAE requiring hospitalization compared to whole-blood donation

1 hospitalization per 198.000 donations (Popovsky et al., 1995) **(1999 – still true in 2008 ?)**

Risk of apheresis vs. whole-blood donation

- Whole-blood donation vs. apheresis donation - What is different ?

- Extracorporeal volume
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- Citrate with potential risk of citrate-related toxicity
 - hypocalcemia may cause
 - vascular smooth muscle relaxation
 - depressed myocardial function
 - arrhythmia
 - chronic metabolic effects of citrate anticoagulation: bone demineralization
- Exposure to foreign substances with risk of allergic reactions (ethylene oxide); HES (granulocyte donors)
- [Risk of air embolism]
- [Increased loss of lymphocytes → immune deficiency?]

Risk of apheresis vs. whole-blood donation

Nonvenipuncture Adverse-Effect Rates for Different Donation Procedures

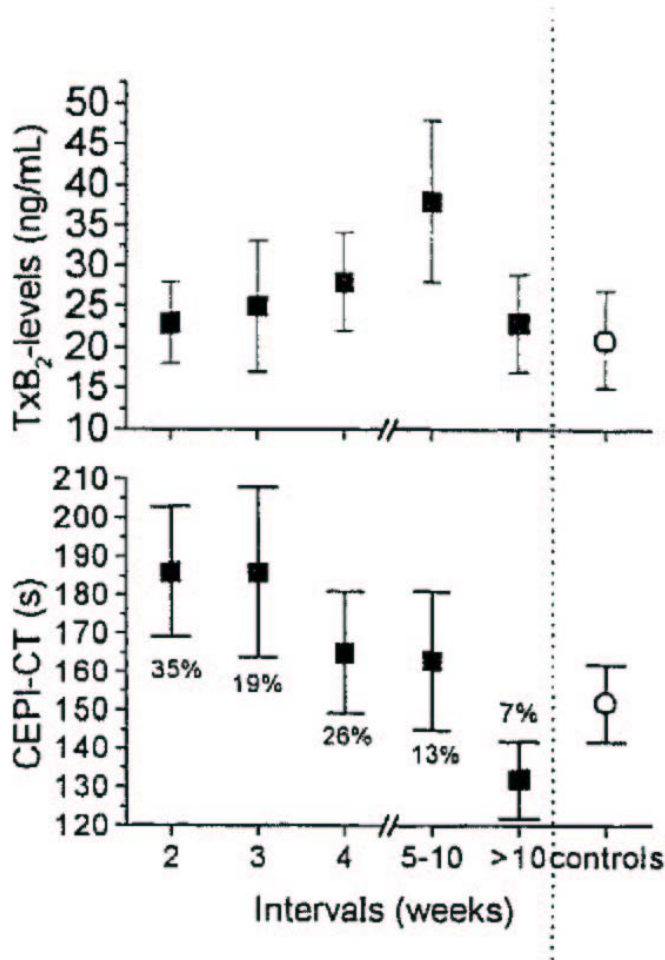
Donation procedure	Reactions	
	Number	Percentage
Platelet (n = 17,584*)	185	1.05
Granulocyte (n = 594*)	4	0.67
Plasma (n = 1,359*)	5	0.37

* 74 donations either did not specify a donation type or specified more than one.

Citrate effects: 0.96% in first time, 0.32% in repeat donors
VVR: 3.13% in first time, 0.54% in repeat donors

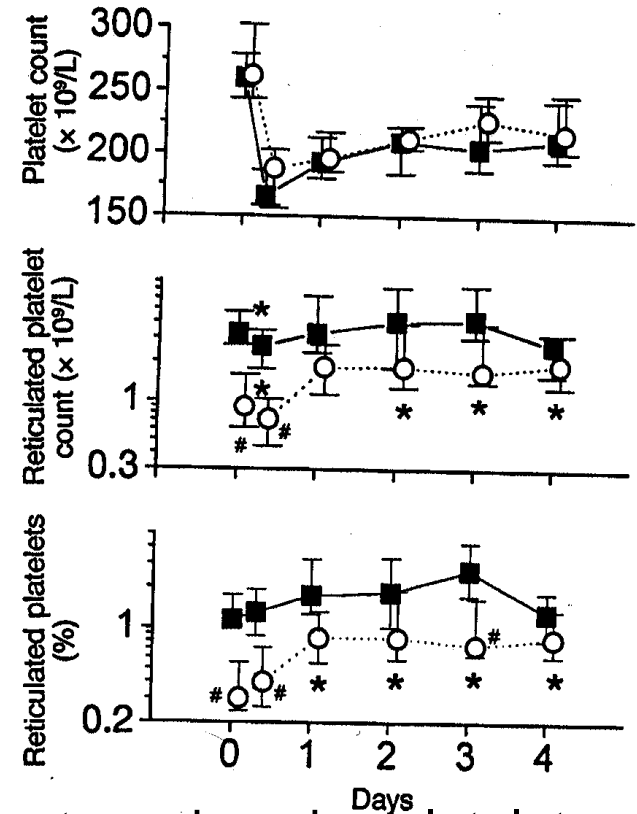
McLeod et al., Transfusion 38: 938-943 (1998)

Frequent platelet apheresis is associated with reduced platelet aggregation under shear stress



Jilma-Stohlawetz et al,
Thromb Haemost 2001; 86: 880-886

Time Course of Peripheral Blood Platelet Counts and Reticulated Counts



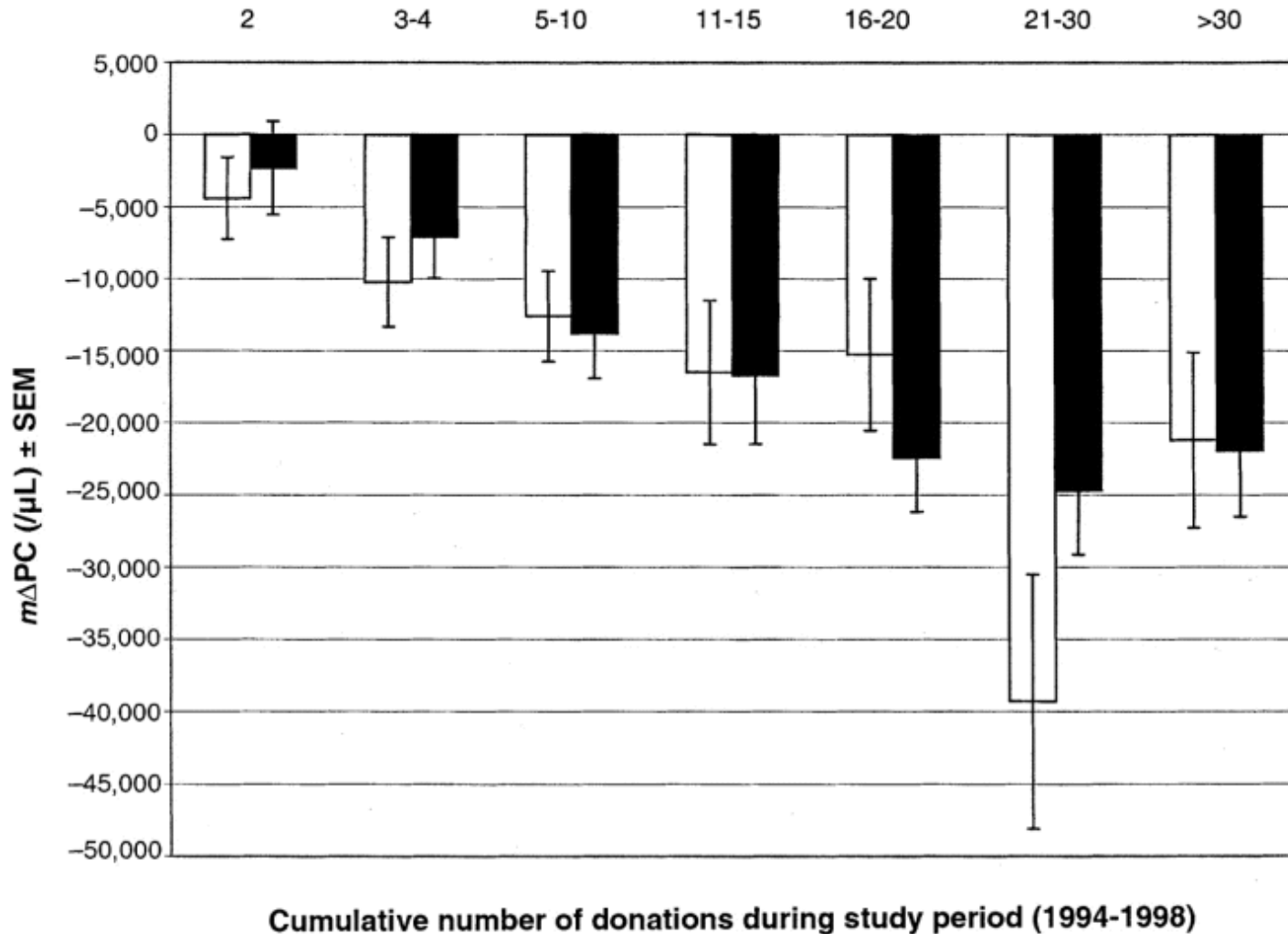
- subjects undergoing platelet apheresis for the first time
- subjects who donate platelets every 2nd week for > 18 months

Stohlawetz et al., *Transfusion* 38: 454-458 (1998)

Risk of apheresis vs. whole-blood donation

Platelet donors:

Reduction of platelet numbers in
female (n=447) and male (n=486) donors
stratified by number of donations



Lazarus et al.
Transfusion
41: 757, 2001

Risk of apheresis vs. whole-blood donation

- Plateletpheresis: Loss of leukocytes -

Immunodeficiency is unlikely unless
loss $> 1 \times 10^{11}$ lymphocytes within few weeks
lymphocyte count $< 0.5 \times 10^9/L$

Loss by plateletpheresis: $1 \times 10^6 - 5 \times 10^7$
→ annual loss (even with 24 donations) $< 10^{11}$

Strauss; J.Clin.Apheresis 9:130, 1994

non-donor
control
(n = 27)

long-term
whole-blood donors
(n = 29)
42 life-time
donations

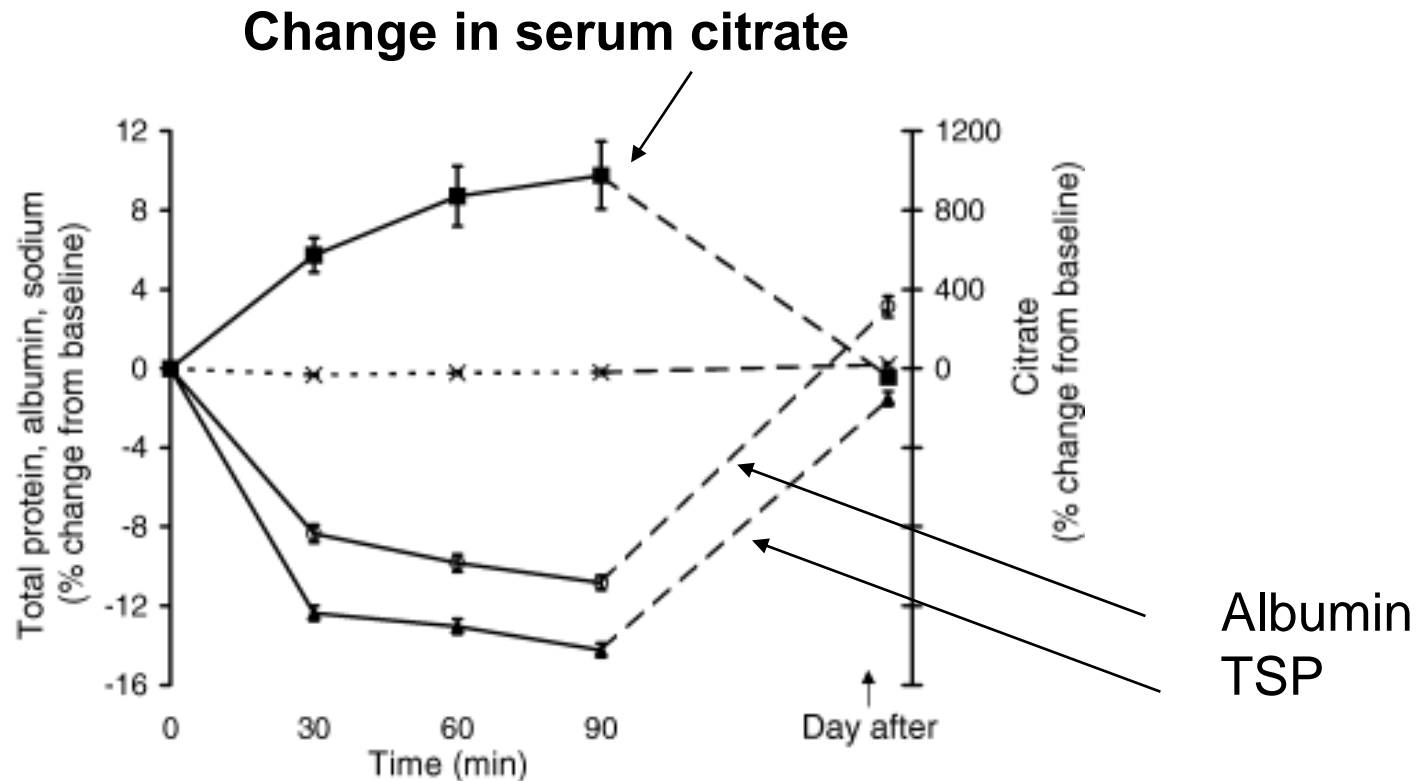
long-term
platelet donors
(n = 20)
45 life-time
donations

WBC count and lymphocyte subpopulations (CD3⁺, CD4⁺, CD19⁺, CD3⁻CD56⁺, CD8⁻/CD11b⁻, CD8⁺/CD11b⁻, CD3⁺DR⁺) not significantly different

S.L.Lewis et al., Transf. Sci. 18: 205; 1997

Risk of apheresis vs. whole-blood donation

- Plateletpheresis - Metabolic effects of citrate anticoagulant and oral calcium-carbonate supplementation

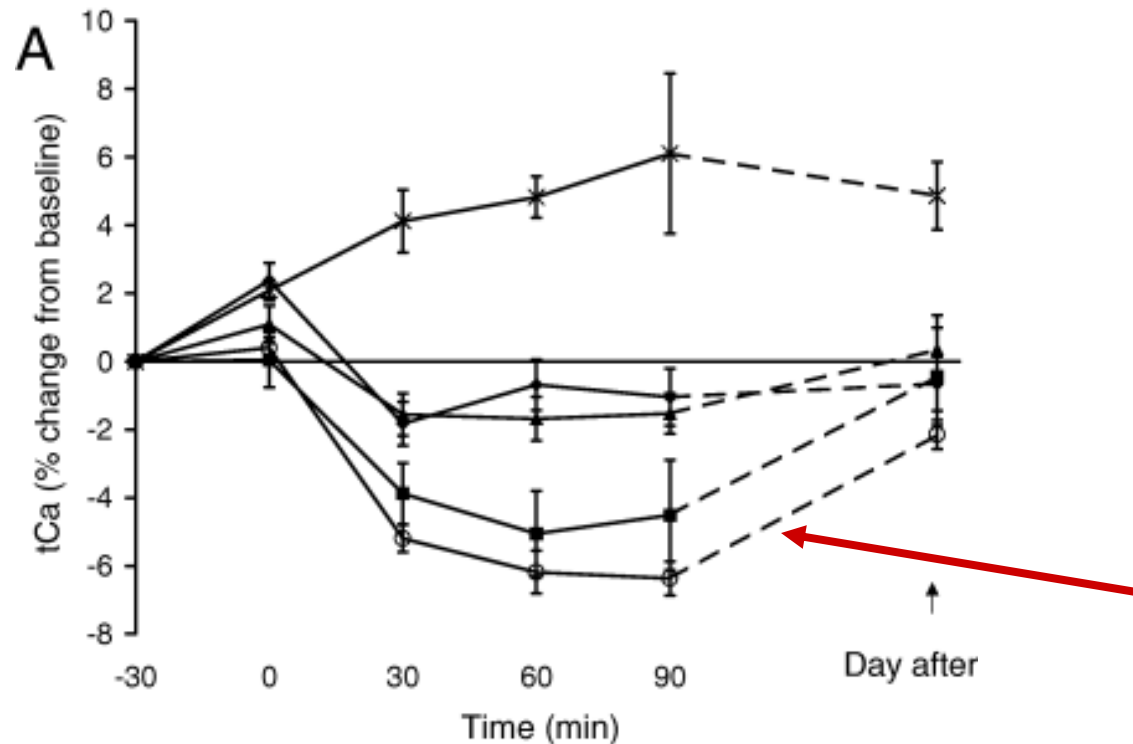


Risk of apheresis vs. whole-blood donation

- Plateletpheresis -

Metabolic effects of citrate anticoagulant and oral calcium-carbonate supplementation

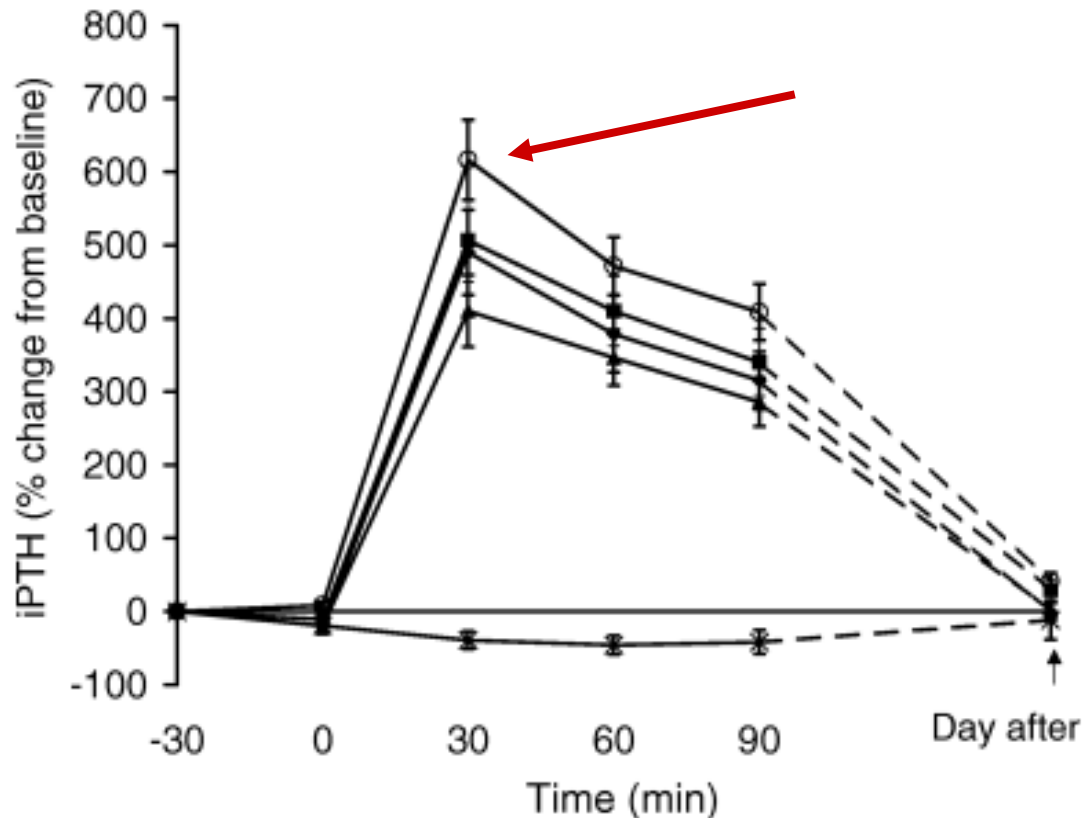
Changes in total Ca^{2+} levels during plateletpheresis



Risk of apheresis vs. whole-blood donation

- Plateletpheresis - Metabolic effects of citrate anticoagulant and oral calcium-carbonate supplementation

Changes in iPTH levels during plateletpheresis



Risk of apheresis vs. whole-blood donation

Long-term effects of citrate on bone metabolism and bone density in health plateletpheresis donors

1. Markers of bone metabolism

n = 77

ctelopeptide of type I collagen (CLX) and
osteocalcin measurement (OCL)

CLX ↑ (p = 0.001) → increased bone resorption

2. Bone mineral density measurement

n = 45

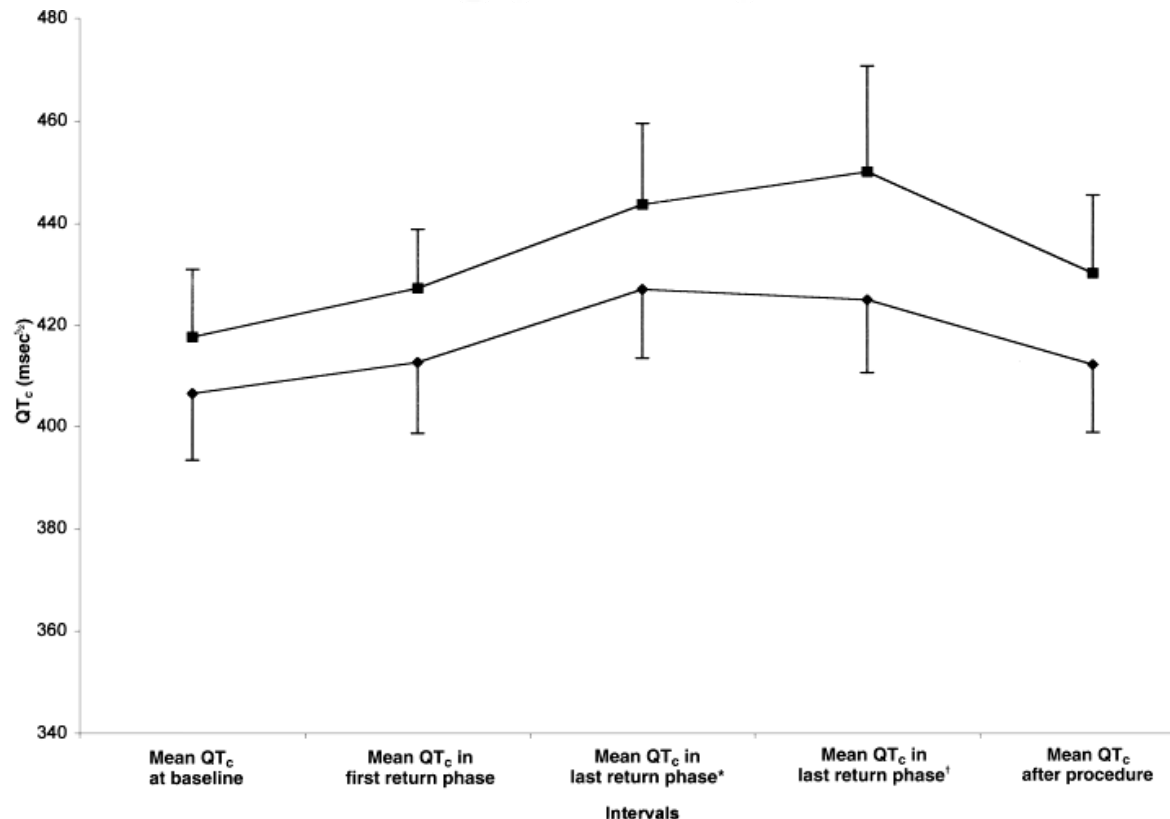
multi-time apheresis donors (> 100 donations)

35 % osteopenia (lumbar or femoral score < -1)

not detected in a control group (n = 40) of sporadic donors
(< 50 donations)

Risk of apheresis vs. whole-blood donation

- QT_c values of men (▲) and women (■) during plateletpheresis -



QTc prolongation: general finding during plateletpheresis.

Prolongation in females > men.

Ask for family history of sudden death (asymptomatic carrier of long QT-gene)

Risk of apheresis vs. whole-blood donation

- Complications related to blood donation -

*Data from a regional survey in the county of Aarhus, Denmark
(41,274 donations)*

	Number ^a		%	Rate ^b	
Needle injuries					
Injury of a vessel (haematoma)	113		33	274	(228 - 329)
Injury of a vessel (arterial puncture)	1		0	2	(0.5 - 1.4)
Injury of a nerve	29	(8)	9	70	(49 - 101)
Total	143	(8)	42	346	(294 - 408)
Vasovagal reactions					
Vasovagal reaction	165	(3)	49	400	(343 - 465)
Vasovagal reaction with loss of consciousness	32	(1)	9	78	(55 - 109)
Total	197	(4)	58	478	(415 - 549)
Total (needle injuries <u>and</u> vasovagal reactions)	340	(12)	100	824	(741 - 916)

^a Number in parenthesis indicates number of complications reported to the Danish Register of Complications Related to Blood Donation. All other complications were considered mild.

^b Number per 100,000 donations (95 % CI).

Risk of apheresis vs. whole-blood donation

- Moderate and severe complications related to blood donation -

Data from a regional survey from Aarhus County and the Danish Register of Complications Related to Blood Donation

	Regional survey ^a			National survey ^b		
	No.	%	Rate ^c	No.	%	Rate ^c
Needle injuries	8	67	19 (10 - 38)	559	74	22 (20 - 24)
Vasovagal reactions	4	33	10 (4 - 25)	193	26	7 (7 - 9)
Total	12	100	29 (17 - 51)	752	100	29 (27 - 31)

a) Based on 41,274 donations.

b) Based on 2,575,264 donations.

c) Number per 100,000 donations (95 % CI).

Risk of apheresis vs. whole-blood donation

- Complications related to whole-blood donation -

Mobile blood collection teams, Institute Ulm, Year 2007

n = **176,668** whole-blood donations [14,399 first-time donations]
(73,556 females; 103,112 males)

n = **146** donors with complications

- required immediate medical treatment
- categorized as event with at least one of the following:
 - possibly will require treatment after leaving session
 - prolonged persistence of symptoms and possibly disability to work
 - possibly long-term disability

146 in 176,668 donations: $83 / 10^5$ (1 / 1,210)

91 in female donors: $124 / 10^5$ (1 / 808)

55 in male donors: $53 / 10^5$ (1 / 1,875)

33 in 14,399 first-time donations: $229 / 10^5$ (1 / 436)

113 in 162,269 repeat donations: $70 / 10^5$ (1 / 1,436)

Risk of apheresis vs. whole-blood donation

- Complications related to whole-blood donation -

Mobile blood collection teams, Institute Ulm, Year 2007

Categorization according ISBT / EHN standards

100	Local reactions related to needle insertion		
110	Vessel injuries	31	(18 / 10⁵; 1 / 5,599)
111	Haematoma	18	
112	Arterial puncture	13	
113	Thrombophlebitis	0	
112	Nerve injuries	40	(23 / 10⁵; 1 / 4,417)
121	Injury of a nerve	32	
122	Injury of a nerve by a haematoma	3	
[Paraesthesia]	5	
130	Other complications	0	
200	General reactions		
211	Immediate	83	(47 / 10⁵; 1 / 2,129)
		33	subjective symptoms only
		4	vomiting
		41	lost consciousness (no injury)
		5	lost consciousness (injury)
	212	Delayed type	0
322	Accidents not related to donation	2	

Risk of apheresis vs. whole-blood donation

- Complications related to whole-blood donation -

Mobile blood collection teams, Institute Ulm, Year 2007

Categorization according ISBT / EHN standards

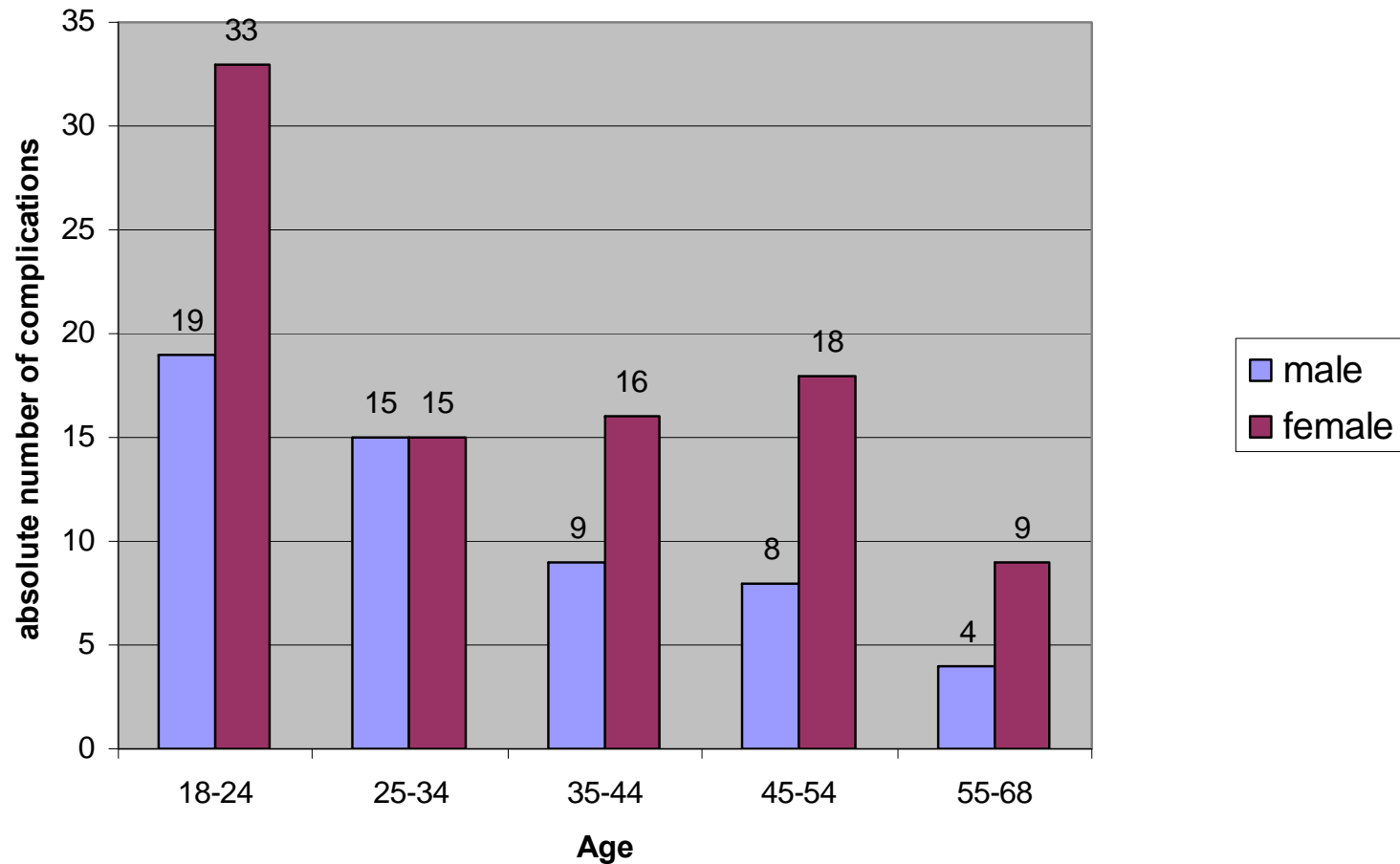
210 Vasovagal reactions

n = 83		47 / 10 ⁵	(1 / 2,128)
27	first-time donors	188 / 10 ⁵	(1 / 533)
56	repeat donors	34 / 10 ⁵	(1 / 2,950)
51 occurred in first three donations			
53	female donors	72 / 10 ⁵	(1 / 1,388)
30	male donors	29 / 10 ⁵	(1 / 3,437)

Risk of apheresis vs. whole-blood donation

- Gender and age distribution -

Mobile blood collection teams, Institute Ulm, Year 2007



Risk of apheresis vs. whole-blood donation

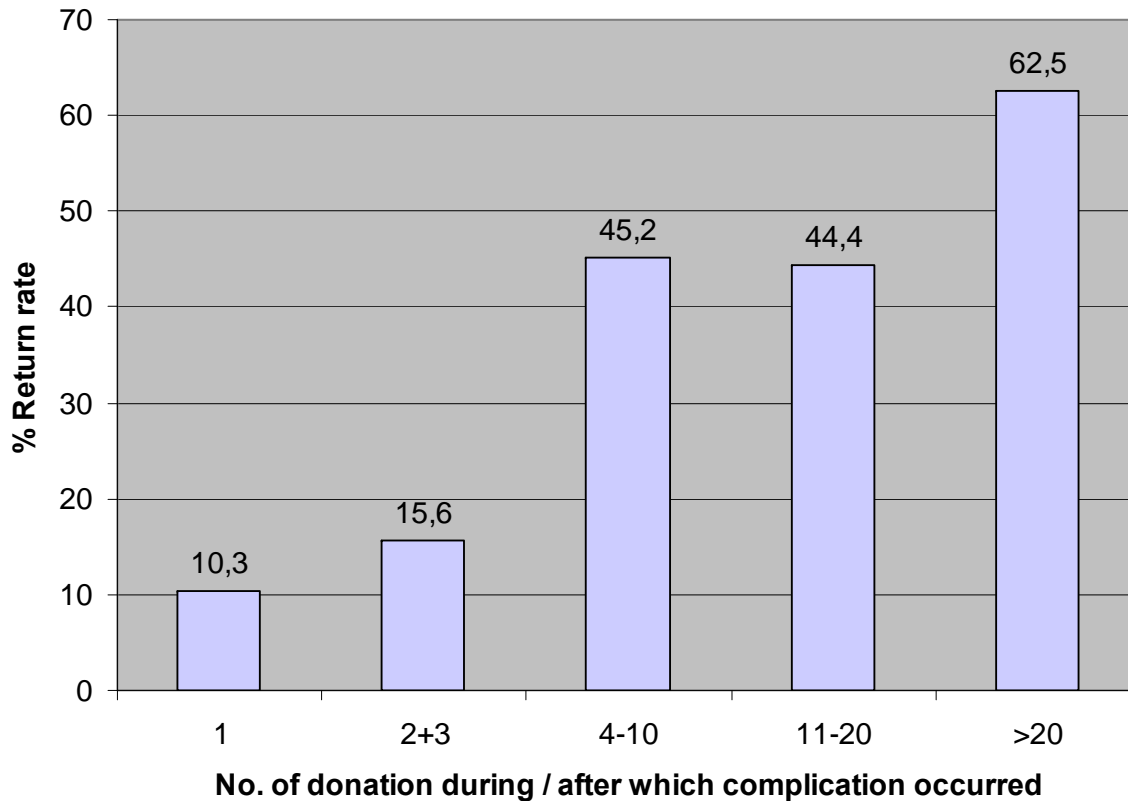
- Complications related to whole-blood donation -

Mobile blood collection teams, Institute Ulm, Year 2007

Effect of complication in whole-blood donation on return rate

n = 146 donors with complications in 2007

n = 126 before 31.10.2007, i.e. interval until analysis > 84 days



Return rate of donors with complications:

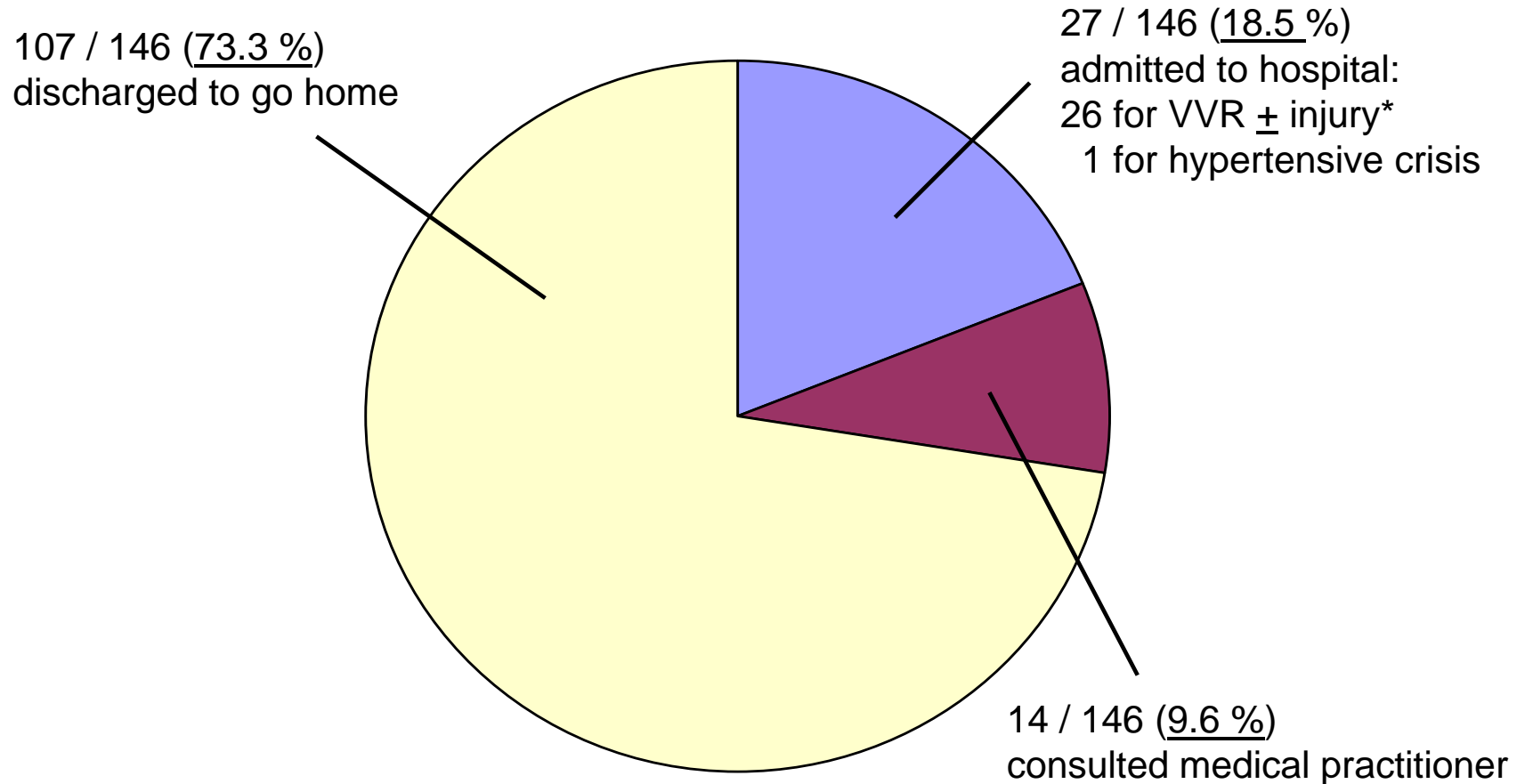
Code 110: Vessel injury	51.8 %
Code 120: Nerve injury	45.5 %
Code 210: VVR	17.8 %

1.8 donations/year
before complication →
0.7 donation/year
after complication

Risk of apheresis vs. whole-blood donation

- Need for monitoring and medical care after donation session -

Mobile blood collection teams, Institute Ulm, Year 2007



*monitoring (+ X-ray to exclude bone fractures, n = 4)

Risk of apheresis vs. whole-blood donation

- Drug treatment of complications -

Mobile blood collection teams, Institute Ulm, Year 2007

n	% of all donors with complication	Treatment
Systemic		
	67.4%	
52	35	Dihydroergotamin p.o.
34	23	Infusion (RINGER -LACTAT solution n=33)
9	6	Metoclopramide (7 p.o.; 2 i.v.)
3	2	Cafedrinhydrochlorid / Theodrenalin i.v.
1	0.7	Ibuprofen
1	0.7	Dimenhydrat
Local		
26	18	Dressing cubital vein (heparin n = 14; hirudoid n = 12)

Risk of apheresis vs. whole-blood donation

- Donor complications in plateletpheresis donors -

Institute Ulm, 2007

52 events / 1,181 plateletpheresis sessions

- 28 venipuncture related: swelling / haematoma
 - 11 citrate effects: hypocalcaemic symptoms 931 /10⁵
 - 11 VVR (mild) (2 also with hypocalcaemia) 931 /10⁵
 - 4 malfunctions:
 - leak (n = 1) or inability to return (1) or insufficient flow (2)
-
- 18 early termination of apheresis

all donors discharged to go home, no hospitalization, no outside medical treatment

79 % return rate of donors after complication

Treatment:

- 13 calcium gluconat p.o.; no further drug treatment

Risk of apheresis vs. whole-blood donation

- Frequency of donor complications (per 10⁵) -

Reactions	Whole blood	Apheresis	Reference
Moderate	377.5	116.2	Wiltbank & Giordano, 2007
Severe	93.5	32.2	Wiltbank & Giordano, 2007
All adverse reactions	1761	1073	Franchini et al., 2002
VVR (moderate /severe)	125	46	
Local injury	381	358	
Citrate toxicity	-	77	
Moderate	80		Bianco & Robins, 1994
Severe	120		Bianco & Robins, 1994
Moderate	226		Shehata et al., 2004
Severe	46		Shehata et al., 2004
Venipuncture related		1,117	McLeod et al., 1998
Non-venipuncture related		1,020	McLeod et al., 1998
Venipuncture related		530	Despotis et al., 1999
Hemodynamic/citrate related		350	Despotis et al., 1999
Very severe complication (requiring hospitalization)		35	Despotis et al., 1999
Very severe complication (requiring hospitalization)	0.2		Popovsky et al., 1995
All adverse reactions	1761	1073	Red Cross Blood Donor Service, Institute Ulm, unpublished
VVR (all)	47	931	
VVR (severe)	15	0	
Citrate reactions	-	931	

Risk of apheresis vs. whole-blood donation

- Safety profile of blood collection -

Procedure	Number of units collected	Moderate reactions			Severe reactions		
		Number	Rate per 10,000 donations	Percent	Number	Rate per 10,000 donations	Percent
Whole blood	1,023,682	3864	37.75	0.38	957	9.35	0.09
Automated double RBC	249,154	317	12.72	0.13	73	2.93	0.03
Automated single RBC	40,870	121	29.61	0.30	32	7.83	0.08
Plateletpheresis with or without concurrent plasma	90,082	105	11.62	0.12	29	3.22	0.03*

*p < 0.005 compared to whole-blood collection

Added safety of 2-unit automated collections due to donor selection, saline replacement, smaller volume removed (400 ml RBC vs. 500 ml whole-blood).

Risk of apheresis vs. whole-blood donation

- Why are results on donor complications that heterogeneous? -

- Heterogeneous definitions of type and severity of complications.
- Different donation volumes (200 / 400 / 500 / 550).
- Different donor selection criteria.
- In case of apheresis: different devices.
- Reporting bias.

Adverse effects in blood donors after whole-blood donation: a study of 1000 blood donors interviewed 3 weeks after whole-blood donation

- Donor AEs (%): solicited versus reported rates -

	Systemic reactions			Arm injuries			
	Fatigue	Vasovagal	Nausea and vomiting	Bruise	Sore arm	Hematoma	Sensory changes
Solicited rate	7.8	5.3*	1.1	22.7	10.0	1.7*	0.9*
Reported rate	No studies	2.1 (212 / 10,090)	No studies	No studies	No studies	0.32* (55 / 17,000)	0.016* (66 / 419,000)
Underreported		60 %				82	98

* p = 0.0001

Risk of apheresis vs. whole-blood donation

- Profile of complications is different -

	Whole-blood donation	Plateletpheresis
Venipuncture complications	+	+
VVR	+	+
Citrate-related toxicity		
- immediate	-	+
- long-term metabolic effects	-	+
Loss of		
- iron	+	(+)
- platelets	(+)	+
- lymphocytes	(+)	(+)
Allergic reactions	-	(+)

Risk of apheresis vs. whole-blood donation

- Safety profile of blood collection -

- Standards for classification and severity assessment of adverse events
- Further studies required to assess the risk of type of donation, taking into account
 - donor selection
 - collection volume
 - apheresis device
- Long-term effects need to be ascertained
(long-term apheresis donation, late effects of donation)

Observation programs like in G-CSF treated stem cell donors also after other types of apheresis.

- Consider different risk profile

Risk of apheresis vs. whole-blood donation

Many thanks to

... **all blood donors**

- ... Professor Dr. H. Klüter, Mannheim
Director, Donation Service
German Red Cross Blood Donor Service Baden-Württemberg - Hessen
- ... Blood collection teams
of the German Red Cross, Blood Donor Service Baden-Württemberg -
Hessen
- ... Dr. M. Wiesneth
Head, Blood collection teams, Production and Stem Cell Unit, Institute Ulm
- ... Dr.P.Reinhardt,
Head, Apheresis Unit, Institute Ulm

Thank you for your attention