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# Transition from fresh frozen plasma to solvent/detergent plasma in the Netherlands: comparing clinical use and transfusion reaction risks

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## ABSTRACT

Plasma transfusion is indicated for replenishment of coagulative proteins to stop or prevent bleeding. In 2014, the Netherlands switched from using ~300mL fresh frozen plasma (FFP) units to using 200mL Omniplasma, a solvent/detergent treated pooled plasma (SD plasma), units. We evaluated the effect of the introduction of SD plasma on clinical plasma use, associated bleeding, and transfusion reaction incidences. Using diagnostic data from six Dutch hospitals, national blood bank data, and national hemovigilance data for 2011 to 2017, we compared the plasma/red blood cell (RBC) units ratio ( $f$ ) and the mean number of plasma and RBC units transfused for FFP (~300mL) and SD plasma (200mL) for various patient groups, and calculated odds ratios comparing their associated transfusion reaction risks. Analyzing 13,910 transfusion episodes, the difference ( $\Delta f = f_{SD} - f_{FFP}$ ) in mean plasma/RBC ratio ( $f$ ) was negligible ( $\Delta f_{entire\_cohort} = 0.01$  [95% confidence interval (CI): -0.02 - 0.05];  $P=0.48$ ). SD plasma was associated with fewer RBC units transfused per episode in gynecological (difference of mean number of units -1.66 [95% CI: -2.72, -0.61]) and aneurysm (-0.97 [-1.59, -0.35]) patients. SD plasma was further associated with fewer anaphylactic reactions than FFP (odds ratio 0.37 [0.18, 0.77;  $P<0.01$ ]) while the differences for most transfusion reactions were not statistically significant. SD plasma units, despite being one third smaller in volume than FFP units, are not associated with a higher plasma/RBC ratio. SD plasma is associated with fewer anaphylactic reactions than FFP plasma/RBC units ratio.

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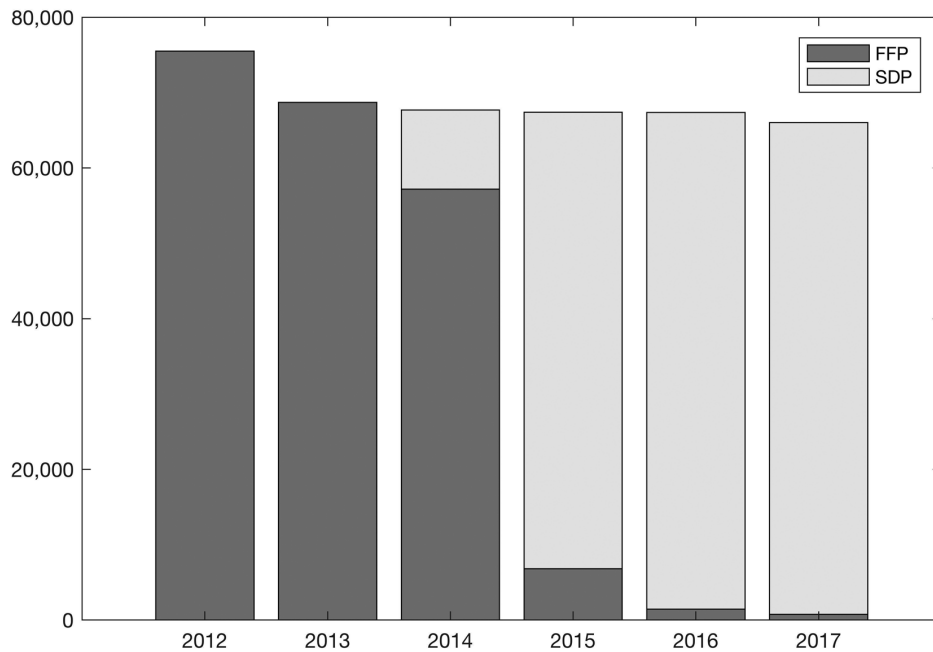
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## Introduction

Plasma transfusion is indicated in a range of medical situations involving replenishment of coagulative proteins to stop or prevent bleeding (e.g. surgery, liver disease), or removal of an insulting entity via plasma exchange (e.g. thrombotic thrombocytopenic purpura, hemolytic-uremic syndrome [TTP/HUS]).<sup>1,2</sup> On January 1, 2014, Sanquin Blood Bank, the National Blood Bank of the Netherlands, replaced quarantined FFP units, with a volume of ~300mL, with SD plasma Omniplasma made by Octapharma from a pool of either ~600 or ~1200 apheresis plasma donations, whose units are exactly 200mL in volume. Omniplasma is made



**Figure 1. Number and type of plasma units distributed to all Dutch hospitals between 2012 and 2017.** The national switch from FFP to SD plasma occurred on January 1, 2014, but FFP units can be stored for up to two years prior to use, hence a gradual transition to SD plasma is observed. Residual amounts of FFP are still transfused in 2016 and 2017 for those few patient groups for which SD plasma is counter-indicated (see background). FFP: fresh frozen plasma; SD plasma: solvent/detergent treated pooled plasma.

from plasma donations of non-remunerated Dutch donors, the same pool as that of FFP, and is functionally equivalent to OctaplasLG.<sup>3</sup> As FFP can be stored for up to 2 years, FFP distribution and use continued in a decreasing fashion during the period from 2014 to 2015. As of 2016, with the exception of a patient groups for which FFP remains indicated (e.g. IgA-deficient patients, protein S deficient patients), SD plasma is the only plasma type available for transfusion in the Netherlands.<sup>4</sup>

Since the purpose of plasma in the surgical setting is to stop active bleeding, the number of RBC units transfused alongside the plasma serves as a measure of effectiveness of plasma transfusion at the population level. Plasma and RBC units are often transfused in fixed ratios in the surgical setting (e.g. two units of plasma for every RBC), however SD plasma units are smaller than FFP units (200 mL vs. ~300mL, respectively). Of interest was thus whether this ratio of blood product use changed with the switch from FFP to SD plasma. Further, the switch to SD plasma was expected to result in a reduced risk of TRALI and allergic reactions as well as (theoretically) viral and prion transmission<sup>5</sup> as observed in other countries switching to SD plasma.<sup>6-14</sup>

### Analysis objectives

A comparison of the plasma/RBC units ratio, the number of RBC units concurrently transfused, and the transfusion reaction risks for SD plasma and FFP in the Netherlands in the period before and after the national switch to SD plasma on January 1, 2014.

## Methods

### Data Sources

With approval from the medical ethical committee of the Leiden University Medical Centre (protocol number P13.251), we submitted our study plan to the Dutch National Blood Bank (Sanquin), six Dutch hospitals (which altogether account for

roughly 20% of the plasma transfused per annum in the Netherlands), and the Dutch National Hemovigilance and Biovigilance Office (TRIP: Transfusie-en transplantatie Reacties In Patiënten). Data from these sources were used to examine change in blood product use (blood bank data and hospital data) and transfusion reaction risk (hemovigilance data) in the years before and after the national switch to SD plasma in 2014. A more detailed description of our methodology and the data collected from each source is found in the *Online Supplementary Materials and Methods*.

### Grouping of transfusions into transfusion episodes and patient subpopulations

Transfusions were grouped into transfusion episodes, with a transfusion episode defined as a series of consecutive transfusions for which the time interval between transfusions did not exceed 72 hours. In order to be able to perform the comparisons in relatively homogeneous patient groups, transfusion episodes were subdivided based on the ward specified by their diagnostic code(s), the four analyzed wards being (1) cardiothoracic surgery + cardiology (CTsurg+cardio); (2) general surgery (gs); (3) gynaecology (gyn); (4) all others (oth), with this last group including TTP/HUS patients. To create further homogenous groups, within each of the analyzed wards we selected transfusion episodes coded with the most commonly occurring diagnostic codes. Within the cardiothoracic surgery + cardiology group, we selected episodes involving patients undergoing cardio arterial bypass grafting (CABG), valve replacement (VR), or maze procedure. Within the general surgery group, we selected episodes involving patients with any type of aneurysm. Within the gynecological group, we selected obstetric episodes. We analyzed episodes involving plasma exchange for TTP/HUS patients separately.

### Blood product use analysis

#### National plasma use during study period

For visualization of blood product use at the national level, we plotted the number of FFP and SD plasma units distributed by the Dutch Blood Bank (Sanquin) to all hospitals for the period between 2011 and 2017.

**Table 1.** Blood product details for the different cohorts (episodes involving plasma transfusion).

Episode characteristics	CT surg. + cardiology		general surgery		gynecology		other	TTP/HUS	entire cohort
	all	CABG, VR, maze	all	non-elective aneurysm	all	labor			
transfusion episodes	9,420	4,334	4,249	534	652	478	3,540	79	17,861
median age in years (IQR)	62 (35-73)	68 (57-75)	58 (36-70)	74 (67-79)	34 (29-39)	33 (29-36)	46 (11-65)	53 (43-60)	58 (27-71)
proportion male	0.64	0.68	0.58	0.79	0	0	0.54	0.18	0.59
Transfused blood products:									
FFP									
episodes:	7,232	3,267	3,332	390	506	362	2,917	67	13,987
total units transfused:	31,073	12,156	16,985	2,364	1,795	1,384	14,707	3,211	64,560
mean units per episode (sd):	4.30 (8.0)	3.72 (5.2)	5.10 (9.7)	6.06 (6.2)	3.55 (5.1)	3.82 (5.8)	5.04 (14.0)	47.9 (69.3)	4.62 (9.8)
SD plasma									
episodes:	2,188	1,067	917	144	146	116	623	12	3,874
total units transfused:	10,704	4,256	4,652	748	395	325	3,155	979	18,906
mean units per episode (sd):	4.89 (5.2)	3.99 (3.2)	5.07 (5.0)	5.19 (3.9)	2.71 (1.5)	2.80 (1.6)	5.06 (6.4)	81.6 (37.6)	4.88 (5.3)
RBC									
episodes:	8,115	3,603	3,426	510	603	448	2,181	23	14,325
total units transfused:	50,066	20,229	25,356	4,719	3,094	2,261	10,815	57	89,331
mean units per episode (sd):	6.17 (8.1)	5.61 (6.7)	7.40 (7.5)	9.25 (8.2)	5.13 (4.4)	5.05 (4.2)	4.96 (5.0)	2.48 (1.3)	6.24 (7.4)
Platelets									
episodes:	6,153	3,137	1,634	294	198	155	1,073	3	9,058
total units transfused:	15,489	6,395	5,135	653	549	290	4,521	3	25,694
mean units per episode (sd):	2.52 (4.4)	2.04 (2.1)	3.14 (4.3)	2.22 (1.8)	2.77 (3.6)	1.87 (1.2)	4.21 (6.5)	1.00 (0.2)	2.84 (4.9)

Note that for each blood product, the denominator used for calculation of the average units per episode is the number of episodes involving transfusion of that blood product (indicated). RBC: red blood cells; avg per ep: average units/episode of given blood product for episodes involving transfusion of that product; CABG: coronary arterial bypass graft; CT surgery: cardiothoracic surgery; FFP: fresh frozen plasma; IQR: interquartile range; maze: maze procedure; sd: standard deviation; SD plasma: solvent/detergent treated pooled plasma; TTP/HUS: thrombocytopenic thrombotic purpura/hemolytic uremic syndrome; VR: valve replacement.

### Patient-level blood product use

For each of the analyzed groups, we selected episodes involving transfusion of both plasma and RBC units and calculated the mean plasma units per episode, the mean RBC units per episode, and the mean ratio thereof (plasma/RBC units).

### Sensitivity analyses

As a first sensitivity analysis, we repeated the patient-level blood product use analysis described above using only those patients in each analysis cohort receiving  $\geq 5$  RBC units during the transfusion episode to additionally compare use in patients experiencing heavy bleeding. As a second sensitivity analysis, to ensure the chosen hierarchy did not affect our results, we re-ran this analysis using two other hierarchies for group selection (see the *Online Supplement Materials and Methods* for the hierarchy description).

### Comparison of transfusion reaction risk for FFP and SD plasma

We compared the risk of non-infectious transfusion reactions between the two plasma types. Infectious transfusion reactions are rarely attributed to plasma transfusion, with the few cases reported involving infection with bacteria present in the water baths used to thaw the plasma units.<sup>15</sup>

## Results

### Comparison of blood product use

#### National plasma use during the study period

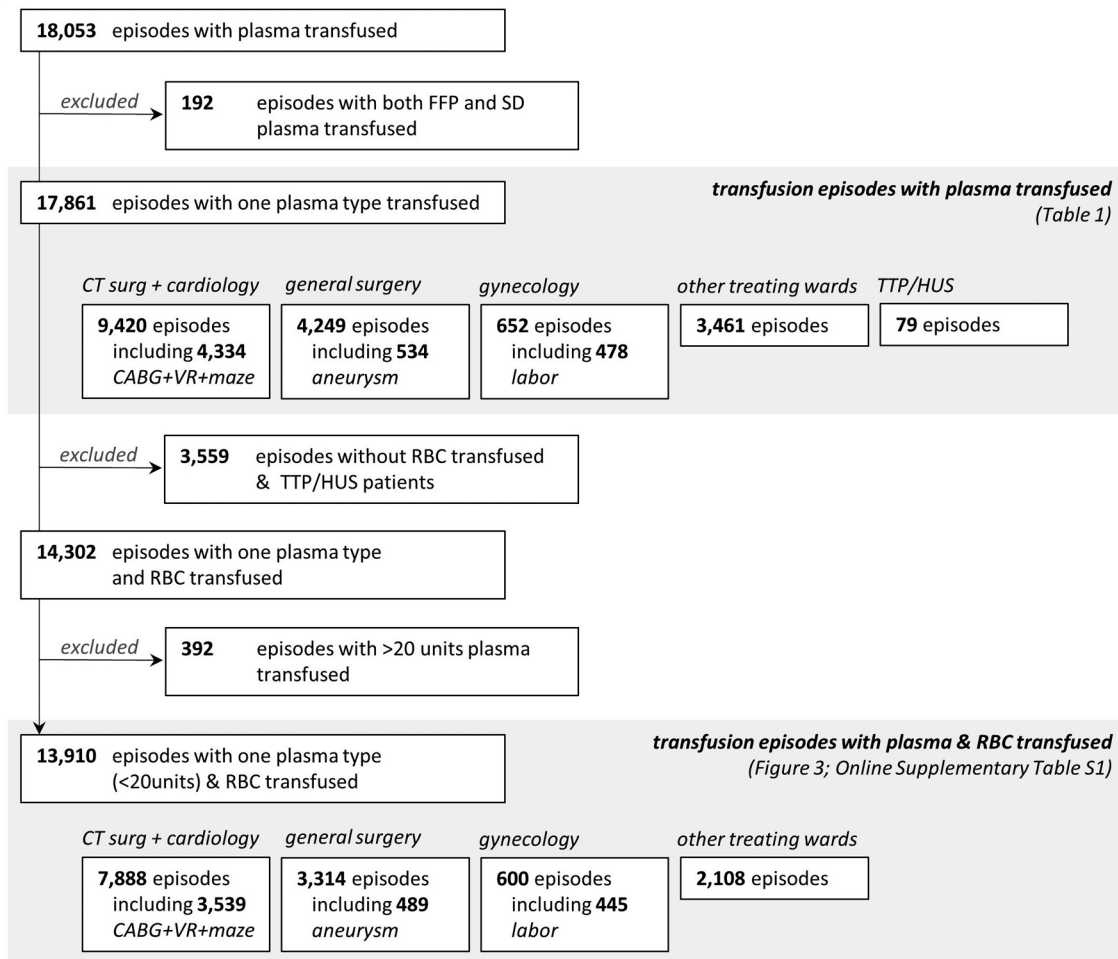
Figure 1 shows plasma use in the Netherlands of the

period from 2012 to 2017, with the national switch to SD plasma occurring on January 1, 2014 (the date as of which Sanquin began distributing SD plasma to hospitals as the standard plasma product). As FFP can be stored for up to two years, stocks continued to be distributed and transfused in the Netherlands until the end of 2015. Total plasma units used decreased by 13% in the course of the 6-year study period. This trend was not reversed by the switch to the smaller SD plasma units.

#### Patient-level plasma use

Figure 2 shows our data flow. From the six participating hospitals, we collected data on 18,053 transfusion episodes involving plasma transfusion. Together, these episodes involved transfusion of 85,768 plasma units (65,160 FFP; 20,608 SD plasma), 91,318 red cell units, and 26,290 platelet units, and were coded by 891 unique diagnostic codes. Following exclusion of 192 episodes involving transfusion of both SD plasma and FFP, blood product details for the remaining 17,861 episodes are provided in Table 1. Comparing average plasma units per episode for FFP and SD plasma across the cohorts shows no systematic increase in plasma units transfused with the switch to SD plasma, excepting for the TTP/HUS cohort where the average number of plasma units transfused was higher for SD plasma than for FFP (81 vs. 48 plasma units/episode).

Figure 3 shows the results of our comparison of SD plasma and FFP with regard to (a) mean plasma units transfused, (b) mean RBC units transfused and (c) mean plasma/RBC units ratio for episodes involving transfusion of both RBC and plasma units (13,910 episodes), with



**Figure 2.** Data flow diagram showing categorization of episodes into sub-cohorts for patients receiving plasma transfusion in (all or part of) 2010 to 2016. CABG+VR+maze: cardio arterial bypass graft + valve replacement + maze procedure; CT surgery: cardiothoracic surgery; FFP: fresh frozen plasma; maze: maze procedure; RBC: red blood cells; SD plasma: solvent/detergent treated pooled plasma; TTP/HUS: thrombotic thrombocytopenic purpura/hemolytic uremic syndrome.

numeric results presented in the *Online Supplementary Table S1*. For all three outcomes (mean plasma units/episode; mean RBC units/episode; mean plasma/RBC units ratio), a positive difference in means indicates a higher mean value for SD plasma. Changes in mean plasma ( $\Delta\mu_{PI} = \mu_{FFP} - \mu_{SD}$ ) and RBC ( $\Delta\mu_{RBCs} = \mu_{RBCs\_pre-switch} - \mu_{RBCs\_post-switch}$ ) units transfused per episode with the switch were negative for some groups, indicating a decrease with the switch to SD plasma (aneurysm:  $\Delta\mu_{PI(an)} = -1.06$  [-1.71, -0.41],  $\Delta\mu_{RBCs(an)} = -1.66$  [-2.72, -0.61]; gynecology:  $\Delta\mu_{PI(gyn)} = -0.52$  [-0.95, -0.08],  $\Delta\mu_{RBCs(gyn)} = -0.97$  [-1.59, -0.35]) and positive for others, indicating an increase (cardiothoracic surgery + cardiology:  $\Delta\mu_{PI(cts)} = 0.33$  [0.15, 0.51],  $\Delta\mu_{RBCs(cts)} = 0.36$  [0.08, 0.64]). For the group as a whole, the mean number of plasma units transfused per episode increased slightly with the switch to SD plasma ( $\Delta\mu_{PI(cohort)} = 0.19$  [0.06, 0.32]).

The mean plasma/RBC units ratio ( $f$ ) for the group as a whole (13,910 episodes) involving transfusion of both plasma and RBC units was 0.86 (95% CI: 0.84 - 0.88) for FFP and 0.87 (0.85-0.91) for SD plasma. The difference in means ( $f_{SD} - f_{FFP}$ ) was 0.01 [-0.02- 0.05];  $P=0.48$  indicating no significant change in the number of plasma units transfused per unit of RBC when SD plasma is transfused. For

all wards (cardiothoracic surgery + cardiology, general surgery, gynecology) and diagnoses (CABG+valve replacement+maze procedure, aneurysm, labor),  $f_{SD} - f_{FFP}$  remained consistently close to zero with none of the differences being statistically significant at the  $\alpha=0.05$  level.

### Sensitivity analyses

The *Online Supplementary Figure S1* shows the results of our first sensitivity analysis, the plasma/RBC units ratio ( $f$ ) comparison for those episodes involving transfusion of plasma and five or more RBC units. The ratios for both plasma types were lower in this group of massive transfusion patients compared to the patient cohort as a whole:  $f_{FFP} = 0.56$  (0.55 - 0.57); the *Online Supplementary Figure S1* shows the results of our first sensitivity analysis, the plasma/RBC units ratio ( $f$ ) comparison for those episodes involving transfusion of plasma and five or more RBC units. The ratios for both plasma types were lower in this group of massive transfusion patients compared to the patient cohort as a whole:  $f_{FFP} = 0.56$  (0.55 - 0.57);  $f_{SD} = 0.57$  (0.55 - 0.59);  $f_{SD} - f_{FFP} = 0.02$  (-0.01-0.04);  $P=0.19$ . Here too none of the ward or diagnostic based sub-cohorts returned a statistically significant result for the difference in means



**Table 2.** Comparison of the number of transfusion reactions and transfusion reaction risk for fresh frozen plasma and solvent/detergent plasma using national hemovigilance data.

Transfusion reaction	FFP (209,681 units)	SD plasma (137,028 units)	Risk Ratio (95% CI) $\text{risk}_{\text{SD}}/\text{risk}_{\text{FFP}}$	Significance
allergic (other) reaction	114	14	0.19 [0.11 to 0.33]	$P < 0.01$
allergic (anaphylactic) reaction	37	9	0.37 [0.18 to 0.77]	$P < 0.01$
non-hemolytic transfusion reaction	9	1	0.17 [0.02 to 1.34]	$P = 0.10$
febrile non-hemolytic transfusion reaction	8	1	0.19 [0.02 to 1.53]	$P = 0.10$
transfusion associated circulatory overload	2	2	1.53 [0.22 to 10.86]	$P = 0.65$
transfusion related acute lung injury	1	1*	1.53 [0.10 to 24.46]	$P = 0.71$
other	24	5	0.32 [0.12 to 0.84]	$P = 0.01$

\*Upon review, the expert panel tasked with evaluating debatable cases could not rule out TACO. TACO: transfusion associated circulatory overload; FFP: fresh frozen plasma; SD plasma: solvent/detergent treated pooled plasma.

$f_{\text{SD}} - f_{\text{FFP}}$ . In the *Online Supplementary Table S1*, the numeric results of our entire blood product use analysis are shown.

In our second sensitivity analysis, involving use of varying hierarchies for cohort selection, we found changing the hierarchy yielded nearly identical results as only a few transfusion episodes were coded with diagnostic codes from two different treatment wards (*data not shown*).

### Comparison of plasma transfusion reaction risk

During the period from 2012 to 2016, Sanquin distributed 209,681 units of FFP and 137,028 units of SD plasma. During the same period, the National Hemovigilance Office received reports of 46 allergic (anaphylactic) reactions, 128 allergic (other) reactions, 10 mild non-hemolytic febrile reactions (mild NHFR), nine non-hemolytic transfusion reactions (NHTR), four cases of transfusion associated circulatory overload (TACO), two cases of transfusion related acute lung injury (TRALI), and 29 'other' plasma transfusion reactions in association with transfusion of one or more plasma units. Table 2 shows risk ratios comparing SD plasma and FFP for the seven plasma transfusion reaction types reported during the study period with an imputability of 'certain', 'probable', or 'possible'. SD plasma was associated with fewer allergic (other) reactions (RR=0.19 [95% CI: 0.11 - 0.34];  $P < 0.01$ ) and allergic (anaphylactic) reactions (RR=0.38 [0.18 - 0.79];  $P < 0.01$ ), as well as fewer 'other' plasma transfusion reactions (RR=0.33 [0.13 - 0.86];  $P = 0.02$ ) than FFP. No bacterial transfusion reactions were attributed to transfusion of either plasma during the study period.

### Discussion

We compared the plasma/RBC units ratio, number of RBC units concurrently transfused, and transfusion reaction risks for SD plasma (200 mL) and FFP (~300mL) units in the Netherlands in the years surrounding the Dutch switch to SD plasma in 2014 and compared plasma unit use for transfusion episodes involving the two plasma types for the same period. The mean number of plasma and RBC units transfused per episode decreased significantly in the aneurysm and gynecological groups, and the decrease in overall plasma use continued despite the switch to the smaller SD plasma units. Despite the significantly (one third) smaller volume of SD plasma units, the plasma/RBC units ratio remained constant across all

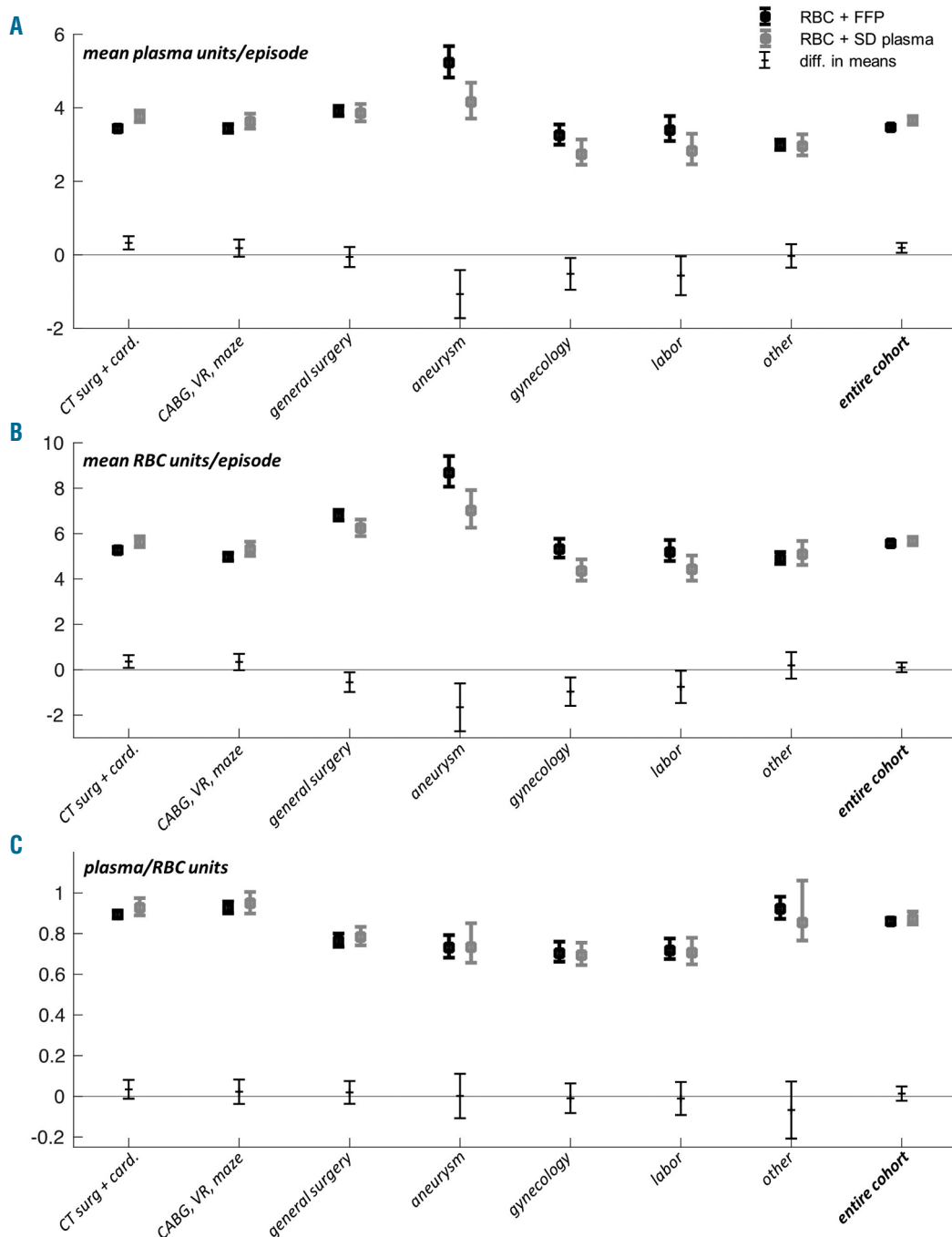
patient cohorts with the switch from FFP to SD plasma units. The risk of most plasma transfusion reactions decreased.

The SD process involves pooling FFP, treating the pool to disrupt lipid-coated viruses, and running the pool through a filter designed to remove prions. This process normalizes coagulation factor levels and dilutes proteins/cytokines from the individual donations, and is thus expected to reduce the incidence of some transfusion reactions (e.g. allergic, FNHTR). However, no aspect of the SD process is expected to increase the product efficiency, suggesting equal volumes of the two would be needed to affect the same reduction in active bleeding. In the Netherlands, a 200 mL unit of SD plasma is smaller than a unit of FFP which typically contains between 300 and 330 mL of plasma,<sup>3</sup> meaning transfusing equal volumes of the two plasma products requires transfusing more units of SD plasma.

At the national level, we observed no such increase in units issued, with the switch to SD plasma not interrupting the downward trend in plasma use over the period. At the transfusion episode level, we observed only a small increase in mean plasma units transfused per episode for the cohort as a whole. Rather than a large increase of SD plasma being transfused – an increase of 50% in the number of transfused units could have been expected – this small increase is likely due to plasma exchange patients who, being exchanged with a specific volume, were transfused with more units of SD plasma (Table 1). The changes in the plasma use for the ward-based patient groups and diagnosis-based sub-cohorts varied, but did not show the trend we expected to see were the number of plasma units transfused systematically different for FFP versus SD plasma. When the changes in mean plasma units per episode did reach the level of statistical significance (e.g. cardiothoracic surgery + cardiology group), the effect sizes were in line with those of the other cohorts and the statistical significance resembles the result of the larger size of these cohorts. Given that the change in plasma/RBC ratio ( $f$ ) was not significant for any of the cohorts, we interpret these results as showing continued transfusion of SD plasma units in the same proportion to RBC units as FFP plasma. We have found no previous studies comparing the plasma/RBC units ratio for FFP and SD plasma. In broad terms, plasma is transfused to replenish plasma proteins during active bleeding (e.g. during surgery) or to remove a harmful entity/constituent *via* plasma

exchange (e.g. in TTP/HUS patients). By creating cohorts of transfusion episodes involving transfusion of both RBC and plasma units, we aimed to capture episodes where plasma was used in cases of active bleeding. The further stratification of these episodes by ward and diagnosis was intended to create progressively more homogeneous cohorts for comparison. If one plasma type more effectively stopped active bleeding than the other, we might

expect to observe a change in the mean number of RBC units transfused per episode with the switch to SD plasma.<sup>16</sup> We observed such a change in the general surgery and gynecological groups, where the number of RBC units transfused alongside plasma was around half a unit (general surgery) and one unit (gynecology) lower for SD plasma than for FFP. Confounding our results, however, is the trend of decreased RBC transfusion within the



**Figure 3. Blood product use prior to versus after the switch from fresh frozen plasma to solvent/detergent treated pooled plasma.** (A) mean plasma units, (B) mean RBC units, and (C) mean plasma/RBC units ratio for FFP (thick black) and SD plasma (thick grey) along with mean differences (thin black) for all three values. Note that mean differences are calculated as  $\text{mean}_{\text{SD}} - \text{mean}_{\text{FFP}}$  such that a positive value indicates a higher value for SD plasma, and vice versa. CABG, VR, maze: coronary artery bypass graft, valve replacement, maze procedure; CT surg + card.: cardiothoracic surgery + cardiology; FFP: fresh frozen plasma; RBC: red blood cell; SD plasma: solvent/detergent treated pooled plasma.

Netherlands.<sup>17</sup> Within our analysis, the mean number of concurrently transfused RBC units was generally similar to or lower for SD plasma, transfused after 2014, than for FFP, transfused before 2016 (Figure 3). While we cannot separate the effects of plasma efficiency from those of this trend, our data suggest no differences in effectiveness of stoppage of bleeding between the two plasma types, despite a one third reduction of plasma volume being transfused following the switch to SD plasma.

The results of our transfusion reaction risk analysis, showing a lower incidence of allergic reactions, both anaphylactic and 'other', for SD plasma as compared to FFP, are in line with those of several other studies in which SD plasma was consistently found to lead to fewer transfusion reactions in general.<sup>6-14</sup> While transfusion reaction reporting practices likely changed during the seven years of data collection, the number of transfusion reactions reported to the National Haemovigilance Office has remained fairly constant across all categories in the last five years of FFP use (*data not shown*). This suggests the reporting procedures in use have reached steady-state, meaning a low risk of bias in our comparison due to differences in reporting processes between the periods in which two plasma products were used.

Given the rarity with which they are ascribed to plasma transfusion, our study did not observe enough TACO or TRALI cases to make meaningful conclusions with regards to their relative risks following FFP versus SD plasma transfusion, despite other studies noting a decreased incidence of TRALI with SD plasma.<sup>18</sup> Of note, thus, is the TRALI case associated with transfusion of SD plasma in 2016. The patient, a pediatric stem-cell transplant recipient, was already at an increased risk for respiratory transfusion reactions and had received transfusions of RBC and platelets, in addition to plasma.<sup>19</sup> As a debatable case, this was further evaluated by an expert panel which agreed TRALI was a possibility but could not rule out TACO. As such, it was recorded in the TRIP database as a TRALI with a low imputability of 'possible.'

### Relevance and future research

Our study shows that in the Netherlands, reducing the size of plasma units by one third resulted in no change in the number of transfused plasma units. This suggests clinicians continued to transfuse the same number of plasma units, despite the decrease in volume, resulting in a reduction of around one third in the country's total transfused plasma volume. Given the SD process is not reported to increase product efficiency, the fact that the number of transfused RBC units did not concurrently increase at a population level serves as a suggestion, though not the first,<sup>20</sup> that the clinical evidence base for the volume ratio of plasma to RBC transfused to stop bleeding needs re-evaluation. A logical next step would be an observational study exploring mortality in matched patients receiving different plasma/RBC volume ratios, or a trial exploring the effect on mortality of a reduction in transfused plasma volume. A potential general decrease in demand of plasma for transfusion would have obvious benefits to a country's donor population and healthcare costs.

### Limitations

In our analysis of blood product use and plasma transfusion safety, around 20% (3,559 of 17,861 episodes – see Figure 1) of the transfusion episodes involved transfusion of only plasma, without concurrent RBC units. This is not in line with current evidence-based indications for plasma transfusion which (if followed) would lead to plasma always being transfused with RBC units except in cases of plasma exchange (plasma exchange episodes comprise less than 1% of the transfusion episodes analyzed in our study).<sup>21</sup> After review of a sample of these patients' transfusion data we confirmed that data were not missing (*i.e.* that only plasma was transfused during these episodes). Previous studies have likewise pointed out a high rate of plasma transfusion outside the context of evidence-based indications.<sup>2,22,23</sup> As an example, in some of the reporting hospitals, plasma is transfused prophylactically prior to biopsy procedures.

The large standard deviations in mean plasma and RBC units transfused (Table 1) demonstrate the extent to which transfusion practice varied among the patients in our study. Further, we matched patients only on ward or diagnosis without correcting for other predictors, as this was not the goal of our analysis. The conclusions are thus to be interpreted at a population level, and not at the level of the individual patient. Finally, given the rare nature of many of the transfusion reactions analyzed, even 6 years of data from a country performing only 60,000 plasma transfusions per year yields datasets too small for solid hemovigilance comparisons. Meta-analyses, large-scale observational trials, or active hemovigilance studies are better equipped to address comparative safety of blood products with regard to rare adverse events.

### Conclusions

Using national blood bank and hemovigilance data, as well as transfusion data from six large hospitals in the Netherlands, we compared FFP and SD plasma with regard to blood product use and transfusion reaction risk in the period surrounding the national switch from FFP to SD plasma in 2014. We found some small differences in the average number of RBC units transfused alongside SD plasma *versus* FFP, but no systemic changes in mean RBC transfused or the mean plasma/RBC units ratio when comparing the two products. This suggests the two plasmas were transfused in the same ratio (by units) to RBC and that they do not differ significantly in their effectiveness at stopping bleeding at a unit level, despite the significantly (one third) smaller volume of SD plasma units and their chemical similarity to FFP. SD plasma is associated with fewer allergic (other) and allergic (anaphylactic) transfusion reactions.

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## References

- Wong MP, Droubatchevskaia N, Chipperfield KM, Wadsworth LD, Ferguson DJ. Guidelines for frozen plasma transfusion. *B C Med J*. 2007;49(6):311-319.
- Tinmouth A, Thompson T, Arnold DM, et al. Utilization of frozen plasma in Ontario: a provincewide audit reveals a high rate of inappropriate transfusions. *Transfusion*. 2013;53(10):2222-2229.
- Sanquin Bloed Supply. Vergelijking Q-plasma Omniplasma. [https://www.sanquin.org/binaries/content/assets/nl/producten-en-diensten/plasmaproducten/vergelijking\\_q-plasma-omniplasma.pdf](https://www.sanquin.org/binaries/content/assets/nl/producten-en-diensten/plasmaproducten/vergelijking_q-plasma-omniplasma.pdf) (2014, accessed May 23, 2019).
- Wiersum-Osselton JC, Middelburg RA, van der Bom JG, Van TA, Zijlker-Jansen PY, Schipperus MR. Effect of using male-only fresh frozen plasma for TRALI prevention in the Netherlands. *Vox Sang*. 2010;99(S):457.
- Wiersum-Osselton JC, Schipperus MR. Transfusiereacties bij patiënten: hemovigilantiemeldingen aan het Landelijk Hemovigilantie-bureau over 2003. *Ned Tijdschrift voor Geneeskde*. 2005;149(47):2622-2627.
- Edel E, Al-Ali HK, Seeger S, Kauschat D, Matthes G. Efficacy and Safety Profile of Solvent/Detergent Plasma in the Treatment of Acute Thrombotic Thrombocytopenic Purpura: A Single-Center Experience. *Transfus Med Hemother*. 2010;37(1):13-19.
- Solheim BG, Seghatchian J. Update on pathogen reduction technology for therapeutic plasma: an overview. *Transfus Apher Sci*. 2006;35(1):83-90.
- Saadah NH, van der Bom JG, Wiersum-Osselton JC, et al. Comparing transfusion reaction risks for various plasma products - an analysis of 7 years of ISTARE haemovigilance data. *Br J Haematol*. 2018;180(5):727-734.
- Scully M, Longair I, Flynn M, Berryman J, Machin SJ. Cryosupernatant and solvent detergent fresh-frozen plasma (Octaplas) usage at a single centre in acute thrombotic thrombocytopenic purpura. *Vox Sang*. 2007;93(2):154-158.
- Mayr WR. Haemovigilance: are there significant differences among plasma products? *Transfus Apher Sci*. 2010;43(3):407-409.
- Riedler GF, Haycox R, Duggan K, Dakin H. Cost-effectiveness of solvent/detergent-treated fresh-frozen plasma. *Vox Sang*. 2003;85(2):88-95.
- Klein HG, Dodd RY, Dzik WH, et al. Current status of solvent/detergent-treated frozen plasma. *Transfusion*. 1998;38(1):102-107.
- Baudoux E, Margraff U, Coenen A, et al. Hemovigilance: clinical tolerance of solvent-detergent treated plasma. *Vox Sang*. 1998;74(S1):237-239.
- Hellstern P, Solheim BG. The Use of Solvent/Detergent Treatment in Pathogen Reduction of Plasma. *Transfus Med Hemother*. 2011;38(1):65-70.
- Pandey S, Vyas GN. Adverse effects of plasma transfusion. *Transfusion*. 2012;52(Suppl 1):65S-79S.
- Cinqualbre J, Kientz D, Remy E, Huang N, Corash L, Cazenave JP. Comparative effectiveness of plasma prepared with amotosalen-UVA pathogen inactivation and conventional plasma for support of liver transplantation. *Transfusion*. 2015;55(7):1710-1720.
- van Hoeven LR, Koopman MM, Koffijberg H, Roes KC, Janssen MP. Historical time trends in red blood cell usage in the Netherlands. *Int J Clin Transfus Med*. 2016;4(4):67-77.
- Marietta M, Franchini M, Bindi ML, Picardi F, Ruggeri M, De Silvestro G. Is solvent/detergent plasma better than standard fresh-frozen plasma? A systematic review and an expert consensus document. *Blood Transfus*. 2016;14(4):277-286.
- TRIP National Hemovigilance and Biovigilance Office. Transfusie- en transplantatiereacties in Patiënten annual report (2016). 10-11. <https://www.tripnet.nl/publicaties/rapporten/> (accessed May 23, 2019).
- Holcomb JB, Tilley BC, Baraniuk S, et al. Transfusion of plasma, platelets, and red blood cells in a 1:1:1 vs a 1:1:2 ratio and mortality in patients with severe trauma: the PROPPR randomized clinical trial. *JAMA*. 2015;313(5):471-482.
- Liunbruno GM, Catalano L, Piccinini V, Pupella S, Grazzini G. Reduction of the risk of bacterial contamination of blood components through diversion of the first part of the donation of blood and blood components. *Blood Transfus*. 2009;7(2):86-93.
- Iorio A, Basileo M, Marchesini E, et al. Audit of the clinical use of fresh-frozen plasma in Umbria: Study design and results of the pilot phase. *Blood Transfus*. 2008;6211-6219.
- Pahuja S, Sethi N, Singh S, Sharma S, Jain M, Kushwaha S. Concurrent audit of fresh frozen plasma: experience of a tertiary care hospital. *Hematology*. 2012;17(5):306-310.