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1 **Title**

2 Variation in blood transfusion and coagulation management in Traumatic Brain Injury at the Intensive  
3 Care Unit: A survey in 66 neurotrauma centers participating in the Collaborative European  
4 NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) study.

5 **Running title**

6 Transfusion and coagulation management

7 **Table of contents title**

8 Variation in transfusion and coagulation management in European neurotrauma centers

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3 123 Abstract  
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6 124 Our aim was to describe current approaches and to quantify variability between European intensive care  
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8 125 units (ICU)s in patients with TBI. Therefore, we conducted a provider profiling survey as part of the  
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10 126 'Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury' (CENTER-TBI)  
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12 127 study. The ICU Questionnaire was sent to 68 centers from 20 countries across Europe and Israel. For this  
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14 128 study, we used ICU questions focused on 1) hemoglobin target level (Hb-TL), 2) coagulation  
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16 129 management, and 3) deep venous thromboembolism (DVT) prophylaxis. **Seventy-eight participants,**  
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18 130 **mostly intensivists and neurosurgeons of 66** centers completed the ICU questionnaire. For ICU-patients,  
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20 131 half of the centers (N=34; 52%) had a defined Hb-TL in their protocol. For patients with TBI, 26 centers  
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22 132 (41%) indicated a Hb-TL between 70 and 90 g/l and 38 centers (59%) above 90 g/l. To treat **trauma**  
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24 133 **related** hemostatic abnormalities the use of fresh frozen plasma (N=48; 73%) or platelets (N=34; 52%)  
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26 134 was most often reported, followed by the supplementation of vitamin K (N=26; 39%). Most centers  
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28 135 reported using DVT prophylaxis with anticoagulants frequently or always (N=62; 94%). In the absence of  
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30 136 hemorrhagic brain lesions, 14 centers (21%) delayed DVT prophylaxis until 72 hours after trauma. If  
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32 137 hemorrhagic brain lesions were present, the number of centers delaying DVT prophylaxis for 72 hours  
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34 138 increased to 29 (46%). Overall, a lack of consensus exists between European ICUs on blood transfusion  
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36 139 and coagulation management. The results provide a baseline for the CENTER-TBI study and the large  
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38 140 between-center variation indicates multiple opportunities for comparative effectiveness research.  
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46 141 **Keywords:** intensive care unit; traumatic brain injury; coagulopathy; transfusion; Europe  
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## 144 Introduction

145 The management of hemorrhage and disordered coagulation is a common and critically  
146 important challenge in trauma patients. This is particularly the case for patients with severe traumatic  
147 brain injury (TBI) where physicians have to balance the risks of progressive hemorrhage in the brain  
148 against secondary thrombotic complications including deep venous thrombosis (DVT). Many  
149 controversies continue to exist regarding the appropriate management for optimizing blood and  
150 coagulation status.

151 Transfusion thresholds for anaemia are a particularly controversial area in TBI. According to the  
152 guidelines<sup>1, 2</sup>, transfusion in general critically ill patients is recommended at a restrictive hemoglobin  
153 target level (Hb-TL) of 70 g/l rather than a liberal Hb-TL of 90 g/l or 100g/l. Whether such target levels  
154 also apply to patients with TBI is unclear.<sup>3, 4</sup> Inappropriate use of blood products exposes patients to a  
155 number of systemic risks and may even lead to progressive hemorrhagic injury following TBI.<sup>3</sup> However,  
156 cerebral oxygenation may be improved with higher hemoglobin concentrations<sup>5, 6</sup> whereas restrictive  
157 transfusion thresholds may predispose to brain tissue hypoxia and may increase the risk of early  
158 mortality.<sup>7</sup> On the other hand, a recent large retrospective cohort study indicated that a restrictive  
159 blood transfusion policy was not associated with increased mortality and can be cost-effective in  
160 patients with TBI.<sup>8</sup> An additional challenge for the management of both blood - and coagulation status  
161 is the presence of coagulopathy.<sup>9</sup> Both pro- and anticoagulatory abnormalities can be observed after TBI  
162 in around one out of three patients.<sup>10-12</sup> Coagulopathy at admission is associated with increased  
163 mortality and poor neurological outcome.<sup>12-14</sup> Coagulopathy may result from defective clot initiation,  
164 poor clot formation or hyper fibrinolysis. Acidosis, hypothermia, coagulation factor consumption or  
165 dilution, and the more recently described acute coagulopathy of trauma-shock which results from  
166 widespread endothelial activation after hypoperfusion may contribute to coagulopathy.<sup>15</sup> Finally,  
167 patients with TBI are at increased risk of venous thromboembolism (VTE) (around 20%)<sup>16</sup> compared



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3 168 with general ICU patients (around 6-8%).<sup>17</sup> Here, the balance between the prevention of VTE and the  
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5 169 risk of (progressive) hemorrhage of the brain depends largely on the timing of thromboprophylaxis with  
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7 170 anticoagulants. However, current Brain Trauma Foundation guidelines do not make clear  
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9 171 recommendations on coagulation management.<sup>18</sup>  
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13 172 In summary, no definitive evidence exists to guide physicians in determining the transfusion and  
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15 173 coagulation management in patients with (severe) TBI. This will likely lead to variations in management.  
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17 174 Our aim was to describe and quantify variability in European ICUs for blood transfusion and coagulation  
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19 175 management in patients with TBI, using a survey among European neurotrauma centers participating in  
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21 176 the Collaborative European Neurotrauma Effectiveness Research in TBI (CENTER-TBI) study.<sup>19, 20</sup>  
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3 179 Material and Methods  
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6 180 *Participating centers*  
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10 181 This study is part of the prospective, longitudinal ‘Collaborative European NeuroTrauma  
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12 182 Effectiveness Research in Traumatic Brain Injury’ (CENTER-TBI) study in 68 centers from 20 countries  
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14 183 across Europe and Israel. The CENTER-TBI investigators and participants are listed in Supplemental Data  
15  
16 184 1. In 2014, before the start of inclusion of patients, the principle investigators of each center were asked  
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18 185 to complete a set of questionnaires on structure and process of care: ‘the Provider Profiling  
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20 186 Questionnaires’.<sup>19, 20</sup> The questionnaires were about TBI management irrespective of systemic injuries.  
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23 187 One of these questionnaires concerned ICU management.  
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28 189 *Provider Profiling Questionnaire*  
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31 190 The provider profiling questionnaire was developed in a systematic manner. The literature  
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33 191 (including guidelines and available surveys) was reviewed and experts of various disciplines  
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35 192 (neurosurgeons, (neuro)intensivists, neurologists, emergency department physicians, rehabilitation  
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37 193 physicians, medical ethicists, health care economists and epidemiologists) were consulted throughout  
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39 194 the different phases in the development process. Preliminary questionnaires were pilot-tested in 16 of  
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41 195 the participating centers for unexpected or missing values and ambiguity, and received feedback was  
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43 196 incorporated. For more information about the development, administration and content of the total set  
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45 197 of provider profiling questionnaires, see Clossen et al., 2016.<sup>19</sup> In this study, we focus on 10 questions  
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47 198 (with additional sub questions) on hemoglobin target levels, trauma related coagulation management,  
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49 199 and use and timing of thromboprophylaxis (Supplemental Data 2).  
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56 201 *Hemoglobin target level and coagulation management*  
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3 202 Participants were explicitly asked for their general policy rather than for individual treatment  
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6 203 preferences. General policy was defined as ‘the way the large majority of patients (>75%) with a certain  
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8 204 indication would be treated’. The ICU questionnaire consisted mostly of multiple-choice questions and  
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10 205 one open question; the Hb-TL in the protocol at the ICU for the general ICU population. For the  
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12 206 hemoglobin unit conversion from mmol/L towards g/L we multiplied with the factor 1.6 and then  
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14 207 rounded up to tens.  
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19 209 *Statistical analysis*  
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24 211 Descriptive statistics (frequencies and percentages) were used to describe the treatment  
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26 212 policies reported by the participating centers. For some questions in which centers had to indicate how  
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28 213 often a certain approach was taken by choosing ‘never’ (in 0-10% of cases), ‘rarely’ (in 10-30% of cases),  
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30 214 ‘sometimes’ (in 30-70% of cases), ‘frequently’ (in 70-90% of cases) and ‘always’ (90-100% of cases),  
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32 215 categories were combined (e.g. combining ‘always’ and ‘frequently’) because of low numbers in these  
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34 216 categories.  
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38 217 To gain more insight into characteristics that determine treatment policies we divided centers in  
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40 218 relatively high- and middle-income countries versus lower-income countries, and in countries from  
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42 219 different geographic locations (North and West Europe versus South and East Europe and Israel). The  
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44 220 designation into relatively lower-income countries was based on a 2007 report by the European  
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46 221 Commission <sup>21</sup>, and the designation into geographic location was based on the classification by the  
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48 222 United Nations. Analyses were performed using the Statistical Package for Social Sciences (SPSS) version  
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51 223 21. <sup>22</sup>  
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226 Results

227 *Participating centers*

228 Sixty-six centers of the 68 centers completed the ICU questionnaire (response rate= 97%). The  
229 questionnaire was completed by intensivists (N=33; 50%), neurosurgeons (N=23; 35%), administrative  
230 staff (N=11; 17%), neurologists (N=5, 8%), anesthetists (N=5, 8%) and a trauma surgeon (N=1; 2%).

231 Almost all the centers had an academic affiliation (N=60; 91%) and most centers were designated as a  
232 level I trauma center (N=44; 67%). Centers had a median of 33 (interquartile range 22-44) beds for  
233 general ICU patients and treated a median of 92 (interquartile range 52-160) patients with TBI, of all  
234 severities, annually. An extensive overview of all the center characteristics is described in a previous  
235 publication.<sup>19</sup>

236 For the management of TBI at the ICU, most centers indicated to follow the 2007 Brain Trauma  
237 Foundation (BTF) guidelines (N=28; 42%) or institutional guidelines (N=21; 32%), which were broadly  
238 based on BTF and/or national guidelines. Some centers indicated they did not have specific guidelines  
239 for management of TBI (N=11; 17%) or that they developed a guideline independently from available  
240 guidelines (N=2; 3%).

241 *Hemoglobin target level*

242 Half of the centers (N=34; 52%) reported to have hemoglobin target levels (Hb-TL) described in  
243 their protocol for general/non-TBI ICU patients. The reported Hb-TL varied (open question): 110 g/l  
244 (N=1; 3%), 100 g/L (N=8; 28%), 90 g/L (N=4; 14%), 80 g/L (N=9; 31%), 70 g/L (N=5; 18%), 80-100 g/L (N=1;  
245 3%) and 70-80 g/L (N=1, 3%). In non-neurological critically ill patients, 35 of the centers (56%) reported a  
246 Hb-TL between 70 g/L and 80 g/L. In patient with TBI, 10 of the centers (16%) indicated to use a Hb-TL  
247 between 70 and 80 g/L. The remainder of the centers used higher Hb-TL: between 80 g/L and 90 g/L (N=  
248 16; 25%), between 90g/L and 100 g/L (N=20; 31%), and above 100 g/L (N=18; 28%). (Table 1)

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3 249 [Insert HuijbenTable1]  
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5 250 *Coagulation management*  
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9 251 Transfusion with fresh frozen plasma was most often reported for correction of trauma related  
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11 252 coagulopathy (N= 48; 73%), followed by the use of platelets (N=34; 52%). Coagulopathy was most often  
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13 253 managed with vitamin K (N=26; 39%), fibrinogen (N=19; 29%), Prothrombin Complex Concentrate (N=  
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15 254 17; 26%), Tranexamic acid (N=7; 11%) or recombinant factor VIIa (N=3; 5%). One center reported to use  
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17 255 Desmopressin, in addition to Tranexamic Acid. (Figure 1)  
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20 256 [Insert HuijbenFig 1]  
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22 257 Most centers indicated that they use deep venous thrombosis (DVT) prophylaxis with  
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24 258 anticoagulants frequently (N=18; 27%) or always (N=44; 67%) in patients with TBI. Fourteen centers  
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26 259 (21%) indicated they generally wait 72 hours after trauma before commencing DVT prophylaxis in the  
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28 260 absence of hemorrhagic brain lesions. However, twice that number of centers (N=29; 46%) indicated to  
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30 261 wait 72 hours after trauma in the presence of hemorrhagic brain lesions. Low molecular weight heparin  
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32 262 was most commonly indicated as the prophylactic drug of choice (N=54; 82%), followed by  
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34 263 subcutaneous unfractionated heparin (N=7; 11%) and intravenous heparin (N=1; 2%). (Table 2)  
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39 264 [Insert HuijbenTable2]  
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41 265 Most centers indicated that they would always test a coagulation panel prior to the insertion of  
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43 266 a parenchymal sensor (N=45; 69%) or a ventricular catheter (N=46; 71%). The reported minimum  
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45 267 platelet count for the insertion of a ventricular catheter was variable:  $>100 \times 10^9/L$  (N=30; 46%),  $>80$   
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47 268  $\times 10^9/L$  (N=9; 14%) or  $>50 \times 10^9/L$  (N=9; 14%). In most of the remaining centers the minimum platelet  
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49 269 count depended on the surgeon (N=13; 20%). Also, the reported minimum International Normalized  
50  
51 270 Ratio (INR) considered safe for placement of a ventricular catheter was variable:  $<1.4$  (N=21; 33%),  $<1.3$   
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53 271 (N=17; 26%) or  $<1.2$  (N=8; 12%). Again, in most of the remaining centers the minimum INR was indicated  
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3 272 to depend on surgeon’s individual preferences (N=15; 23%). There were no centers that answered  
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6 273 ‘never’ on all questions. (Table 3)  
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8 274 [Insert HuijbenTable3]  
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10 275 Twenty-nine centers indicated identical policies for coagulation management (always using DVT  
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12 276 prophylaxis, and always obtaining a coagulation panel prior to insertion of a parenchymal or ventricular  
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14 277 catheter). The majority of these centers are located in South and East Europe and Israel (N=13, 56%)  
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16 278 versus (N=16, 37%) in North and West Europe and the majority are located in high income countries  
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18 279 (N=26, 47%), versus (N=3, 27%) in lower income countries.  
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3 292 Discussion  
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6 293 This study shows large between-center variation in blood transfusion and coagulation-directed  
7 policies in critically ill patients with TBI. More centers indicated a restrictive Hb-TL (between 70 g/l and  
8 294 80 g/L) in general ICU patients compared to patients with TBI. Reported coagulation management was  
9 295 variable regarding timing of deep venous thrombosis (DVT) prophylaxis with anticoagulants, minimum  
10 296 platelet count and INR values prior to ICP probe insertion, and correction of trauma related  
11 297 coagulopathy.  
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13 299 The large between-center differences are likely in part explained by a lack of evidence on  
14 300 optimal management of patients with TBI. A majority of centers in our study reported to adhere to the  
15 301 2007 Brain Trauma Foundation (BTF) guidelines for the treatment of patients with TBI, but this guideline  
16 302 does not provide specific recommendations on red blood cell transfusion or coagulopathy management.  
17 303 Equally, some trauma guidelines have stated policies on blood transfusion and coagulation in trauma  
18 304 patients of which some pertain to patients with TBI, but recommendations are still scarce.<sup>1, 2, 23</sup> A recent  
19 305 update of the Cochrane Review of all Red Cell Transfusion trials reported on 12587 patients identified in  
20 306 31 randomized trials and suggested that a restrictive rather than liberal transfusion practice improves  
21 307 outcomes, but noted the data was very limited for neurocritical care.<sup>24</sup> Regarding patients with TBI,  
22 308 several trials have been conducted on blood transfusion management<sup>25, 26</sup>, and the reversal of  
23 309 coagulopathy<sup>27, 28</sup>, but these all had a limited power. A recent large retrospective single-center study in  
24 310 TBI patients admitted to the intensive care<sup>8</sup> found that transfusion guided by a restrictive Hb-TL was  
25 311 associated with significantly less time with fever, higher cost-effectiveness and had the same risk of  
26 312 mortality compared with a liberal Hb-TL. Another explanation for the variation in management would be  
27 313 the between-center variation in the content of available protocols. E.g. we found that even between  
28 314 centers that do have a protocol on red blood cell transfusion policy, the reported Hb-TL still varied  
29 315 substantially. Overall in patients with TBI, there is no conclusive evidence or clear guidance in guidelines  
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3 316 and protocols on blood transfusion and coagulopathy treatment. Still, with an aging TBI demographic  
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5 317 with an increased prevalence of comorbidity, coagulation management might even become more  
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7 318 complex. Concurrent use of anticoagulant and antiplatelet medication is a growing concern, prior  
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9 319 warfarin treatment for example is associated with an increased risk of poor outcome.<sup>29</sup> In addition,  
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11 320 coagulation management in TBI is further complicated by the recent introduction of newer  
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13 321 anticoagulants, such as direct thrombin inhibitors (dabigatran, argatroban).<sup>30</sup>  
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19 323 For DVT prophylaxis the BTF guidelines do provide a recommendation, which was formulated  
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21 324 quite broadly: DVT prophylaxis with anticoagulants can be started if the brain injury is stable and the  
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23 325 benefit is considered to outweigh the risk of increased intracranial hemorrhage. Recommendations on  
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25 326 the preferred agent, dose, or timing are lacking.<sup>18</sup> In our study only 65% of centers indicated that they  
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27 327 always would implement DVT prophylaxis. A review including 15 studies and 4,491 patients on DVT  
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29 328 occurrence in TBI published in 2015 showed that DVT incidence is significantly increased (18% versus  
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31 329 approximately 2%) when pharmaceutical prophylaxis is not given in the first 8 days.<sup>31</sup> For the timing  
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33 330 issue in DVT prophylaxis a novel theoretical prophylaxis protocol, 'the Parkland Protocol' has been  
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35 331 recently described.<sup>32</sup> The protocol takes into account the likelihood of natural progression of brain  
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37 332 hemorrhage and in that way determines the timing of anticoagulation. The risk classification is based on  
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39 333 the stability of the brain hemorrhage at a computed tomography (CT) scan, the modified Berne  
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41 334 Norwood criteria (subdural hematoma >8 mm, epidural hematoma >8 mm, contusion or intraventricular  
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43 335 hemorrhage >2 cm, multiple contusions per lobe, subarachnoid hemorrhage with abnormal CT  
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45 336 angiography), and the presence of an ICP monitor or craniectomy. A randomized controlled trial (RCT)  
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47 337 including 62 low risk patients showed the safety of this protocol for this group: no progression of brain  
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49 338 hemorrhage with the use of low molecular weight heparin at 24 hours post injury and one DVT with the  
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3 339 use of placebo at 24 hours post injury.<sup>33</sup> However, more evidence is needed before this protocol can be  
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6 340 widely accepted for the guidelines.

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8 341 The large between center-variation we found is in line with previous studies. For critically ill  
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10 342 trauma patients, several surveys have been conducted to study the management of trauma related  
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12 343 hemorrhage and coagulopathy.<sup>34-36</sup> These studies also found large differences in clinical practices, even  
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14 344 among level 1 trauma centers, for example in the use of viscoelastic testing. In the survey of Hamada et  
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16 345 al. the reported Hb-TLs in critically ill trauma patients were compared with patients with TBI, and were  
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18 346 significantly higher in patients with TBI, like in our study.<sup>37</sup> In addition, two previous surveys were  
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20 347 conducted that report the percentage respondents that chose specific Hb-TLs and the rationale for  
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22 348 blood transfusion in patients with TBI (coagulation management was not assessed). In the study of Sena  
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24 349 et al. a newly developed multiple-choice survey was completed by 312 physicians of the trauma surgery  
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26 350 -, neurosurgery -, and ICU department of level I trauma centers in the United States.<sup>38</sup> In the study of  
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28 351 Badenes et al. a newly developed multiple-choice survey was used as well, but was completed by 868  
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30 352 respondents, mostly specialists in anesthesiology and intensive care, worldwide.<sup>39</sup> In the study of Sena  
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32 353 et al. 55% of respondents chose a restrictive policy of 70 g/l or less. Likewise, in the study of Badenes et  
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34 354 al. 50% of respondents chose a low Hb-TL of 70 or 80 g/l, while in our study 16% chose a Hb-TL between  
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36 355 70 and 80 g/l. The difference could either be explained by a difference in patient population (severely  
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38 356 injured patients with TBI in the study of Sena et al.), by a difference in answer options (we did not have  
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40 357 an answer option below 70 g/l), or by a difference in policy between Europe and other continents.

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47 358 Strengths of our study include the comprehensive development process of the questionnaires  
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49 359 and the high response rate of 97%. Limitations include the survey-design, resulting in perceived  
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51 360 practices rather than actual practices. Although we explicitly asked for general policy and data were  
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53 361 anonymously collected, we cannot exclude differences between current findings and actual treatment in  
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55 362 the participating centers. In addition, questions were aimed to assess general policy and contained no  
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3 363 specific details on patient characteristics. This is not representative for clinical practice (possibly making  
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5 364 the questions more difficult to answer). In addition, we could not make a distinction between  
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7 365 pharmaceutical versus mechanical DVT prophylaxis. A further limitation comprises the  
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9 366 representativeness of our sample. The majority of centers were Academic level I trauma centers with a  
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11 367 special interest in neurotrauma. Findings are therefore not generalizable to non-specialized centers. In  
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13 368 addition, differences between centers could represent differences in case-mix instead of true practice.  
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17 369 The practice variability we report supports that evidence on optimal treatment approaches is  
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19 370 needed. Such evidence can potentially be obtained in a non-randomized design by comparing outcomes  
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21 371 between centers with different treatment policies. Such a Comparative Effectiveness Research approach  
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23 372 exploits the existing between-center variation. Data on real time patient management and clinically  
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25 373 relevant outcomes in the CENTER-TBI study are now being collected.<sup>20</sup> Future research on blood  
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27 374 transfusion and coagulation management in patients with TBI could lead to prevention of progressive  
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29 375 brain hemorrhage and secondary problems like coagulopathy and VTE. For now, the optimal transfusion  
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31 376 strategies to correct coagulopathy in terms of the ratio of packed blood cells, fresh frozen plasma (or  
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33 377 similar products) and platelets are still being debated.<sup>40</sup> This debate pertains both to optimal strategies  
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35 378 with regard to reversal of trauma related coagulopathy and management of coagulopathy induced by  
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37 379 conventional agents (such as vitamin K antagonists) and newer ones such as direct thrombin inhibitors.<sup>9</sup>  
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40 380<sup>30, 41</sup> Still, others warn for the use of transfusion considering the possibility of complications of  
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43 381 transfusion and unknown effects on (functional) outcome.<sup>42</sup> Also for coagulation (enhancing) products  
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45 382 larger studies are needed to prove a positive balance between the beneficial effects in terms of patient  
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47 383 outcome and adverse effects on (thromboembolic) complications.<sup>27, 28, 42-45</sup> New evidence is clearly  
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49 384 needed on these topics, since control of blood and coagulation status could have a large impact on  
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51 385 patient outcome, especially in patients with TBI.  
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387 Conclusions

388 In conclusion, we showed substantial variation in blood and coagulation management of  
389 patients with TBI at the ICUs in 66 centers in Europe and Israel participating in the CENTER-TBI study.  
390 This variation may be largely attributable to the lack of guidelines and high quality evidence on these  
391 topics. The large practice variation provides an opportunity to study the effectiveness of different  
392 policies in comparative effectiveness research.

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414 **References**

- 415 1. Carson, J.L., Guyatt, G., Heddle, N.M., Grossman, B.J., Cohn, C.S., Fung, M.K., Gernsheimer, T.,  
416 Holcomb, J.B., Kaplan, L.J., Katz, L.M., Peterson, N., Ramsey, G., Rao, S.V., Roback, J.D., Shander, A. and  
417 Tobian, A.A. (2016). Clinical Practice Guidelines From the AABB: Red Blood Cell Transfusion Thresholds  
418 and Storage. *JAMA* 316, 2025-2035.
- 419 2. Rossaint, R., Bouillon, B., Cerny, V., Coats, T.J., Duranteau, J., Fernandez-Mondejar, E., Filipescu, D.,  
420 Hunt, B.J., Komadina, R., Nardi, G., Neugebauer, E.A., Ozier, Y., Riddez, L., Schultz, A., Vincent, J.L. and  
421 Spahn, D.R. (2016). The European guideline on management of major bleeding and coagulopathy  
422 following trauma: fourth edition. *Crit Care* 20, 100.
- 423 3. Vedantam, A., Yamal, J.M., Rubin, M.L., Robertson, C.S. and Gopinath, S.P. (2016). Progressive  
424 hemorrhagic injury after severe traumatic brain injury: effect of hemoglobin transfusion thresholds. *J*  
425 *Neurosurg* 125, 1229-1234.
- 426 4. Lelubre, C. and Taccone, F.S. (2016). Transfusion strategies in patients with traumatic brain injury:  
427 which is the optimal hemoglobin target? *Minerva Anestesiol* 82, 112-116.
- 428 5. Smith, M.J., Stiefel, M.F., Magge, S., Frangos, S., Bloom, S., Gracias, V. and Le Roux, P.D. (2005).  
429 Packed red blood cell transfusion increases local cerebral oxygenation. *Crit Care Med* 33, 1104-1108.
- 430 6. Zygun, D.A., Nortje, J., Hutchinson, P.J., Timofeev, I., Menon, D.K. and Gupta, A.K. (2009). The effect of  
431 red blood cell transfusion on cerebral oxygenation and metabolism after severe traumatic brain injury.  
432 *Crit Care Med* 37, 1074-1078.
- 433 7. Yamal, J.M., Benoit, J.S., Doshi, P., Rubin, M.L., Tilley, B.C., Hannay, H.J. and Robertson, C.S. (2015).  
434 Association of transfusion red blood cell storage age and blood oxygenation, long-term neurologic  
435 outcome, and mortality in traumatic brain injury. *J Trauma Acute Care Surg* 79, 843-849.
- 436 8. Ngwenya, L.B., Suen, C.G., Tarapore, P.E., Manley, G.T. and Huang, M.C. (2017). Safety and cost  
437 efficiency of a restrictive transfusion protocol in patients with traumatic brain injury. *J Neurosurg*, 1-8.
- 438 9. Maegele, M., Schöchl, H., Menovsky, T., Maréchal, H., Marklund, N., Buki, A. and Stanworth, S.J.  
439 (2017). Coagulopathy and haemorrhagic progression in traumatic brain injury: advances in mechanisms,  
440 diagnosis, and management. *Lancet Neurol* 16, 630-647.
- 441 10. Laroche, M., Kutcher, M.E., Huang, M.C., Cohen, M.J. and Manley, G.T. (2012). Coagulopathy after  
442 traumatic brain injury. *Neurosurgery* 70, 1334-1345.
- 443 11. Maegele, M. (2013). Coagulopathy after traumatic brain injury: incidence, pathogenesis, and  
444 treatment options. *Transfusion* 53 Suppl 1, 28S-37S.
- 445 12. Harhangi, B.S., Kompanje, E.J., Leebeek, F.W. and Maas, A.I. (2008). Coagulation disorders after  
446 traumatic brain injury. *Acta Neurochir (Wien)* 150, 165-175; discussion 175.
- 447 13. Wafaisade, A., Lefering, R., Tjardes, T., Wutzler, S., Simanski, C., Paffrath, T., Fischer, P., Bouillon, B.,  
448 Maegele, M. and Trauma Registry of DGU. (2010). Acute coagulopathy in isolated blunt traumatic brain  
449 injury. *Neurocrit Care* 12, 211-219.
- 450 14. Greuters, S., van den Berg, A., Franschman, G., Viersen, V.A., Beishuizen, A., Peerdeman, S.M., Boer,  
451 C. and ALARM-BLEEDING investigators. (2011). Acute and delayed mild coagulopathy are related to  
452 outcome in patients with isolated traumatic brain injury. *Crit Care* 15, R2.
- 453 15. Brohi, K., Cohen, M.J., Ganter, M.T., Schultz, M.J., Levi, M., Mackersie, R.C. and Pittet, J.F. (2008).  
454 Acute coagulopathy of trauma: hypoperfusion induces systemic anticoagulation and hyperfibrinolysis. *J*  
455 *Trauma* 64, 1211-1217; discussion 1217.
- 456 16. Skrifvars, M.B., Bailey, M., Presneill, J., French, C., Nichol, A., Little, L., Duranteau, J., Huet, O.,  
457 Haddad, S., Arabi, Y., McArthur, C., Cooper, D.J., Bellomo, R., EPO-TBI investigators and the ANZICS  
458 Clinical Trials Group (2016). Venous thromboembolic events in critically ill traumatic brain injury  
459 patients. *Intensive Care Med.* 43, 419-428

- 1  
2  
3 460 17. PROTECT Investigators for the Canadian Critical Care Trials Group and the Australian and New  
4 461 Zealand Intensive Care Society Clinical Trials Group., Cook, D., Meade, M., Guyatt, G., Walter, S., Heels-  
5 462 Ansdell, D., Warkentin, T.E., Zytaruk, N., Crowther, M., Geerts, W., Cooper, D.J., Vallance, S., Qushmaq,  
6 463 I., Rocha, M., Berwanger, O. and Vlahakis, N.E. (2011). Dalteparin versus unfractionated heparin in  
7 464 critically ill patients. *N Engl J Med* 364, 1305-1314.
- 8 465 18. Carney, N., Totten, A.M., O'Reilly, C., Ullman, J.S., Hawryluk, G.W., Bell, M.J., Bratton, S.L., Chesnut,  
9 466 R., Harris, O.A., Kisson, N., Rubiano, A.M., Shutter, L., Tasker, R.C., Vavilala, M.S., Wilberger, J., Wright,  
10 467 D.W. and Ghajar, J. (2016). Guidelines for the Management of Severe Traumatic Brain Injury, Fourth  
11 468 Edition. *Neurosurgery*.
- 12 469 19. Clossen, M.C., Polinder, S., Lingsma, H.F., Maas, A.I., Menon, D., Steyerberg, E.W., CENTER-TBI  
13 470 Investigators and Participants. (2016). Variation in Structure and Process of Care in Traumatic Brain  
14 471 Injury: Provider Profiles of European Neurotrauma Centers Participating in the CENTER-TBI Study. *PLoS*  
15 472 *One* 11, e0161367.
- 16 473 20. Maas, A.I., Menon, D.K., Steyerberg, E.W., Citerio, G., Lecky, F., Manley, G.T., Hill, S., Legrand, V.,  
17 474 Sorgner, A., Participants, CENTER-TBI Investigators and Participants. (2015). Collaborative European  
18 475 NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI): a prospective longitudinal  
19 476 observational study. *Neurosurgery* 76, 67-80.
- 20 477 21. European Commission. Remuneration of researchers in the public and private sectors Brussels:  
21 478 European Communities; 2007.
- 22 479 22. IBM Corp. Released 2012. IBM SPSS Statistics for Windows [OR Macintosh], Version 21.0. Armonk,  
23 480 NY: IBM Corp.
- 24 481 23. Nyquist, P., Jichici, D., Bautista, C., Burns, J., Chhangani, S., DeFilippis, M., Goldenberg, F.D., Kim, K.,  
25 482 Liu-DeRyke, X., Mack, W. and Meyer, K. (2017). Prophylaxis of Venous Thrombosis in Neurocritical Care  
26 483 Patients: An Executive Summary of Evidence-Based Guidelines: A Statement for Healthcare Professionals  
27 484 From the Neurocritical Care Society and Society of Critical Care Medicine. *Crit Care Med* 45, 476-479.
- 28 485 24. Carson, J.L., Stanworth, S.J., Roubinian, N., Fergusson, D.A., Triulzi, D., Doree, C. and Hebert, P.C.  
29 486 (2016). Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion.  
30 487 *Cochrane Database Syst Rev* 10, CD002042.
- 31 488 25. Robertson, C.S., Hannay, H.J., Yamal, J.M., Gopinath, S., Goodman, J.C., Tilley, B.C., Epo Severe TBI  
32 489 Trial Investigators, Baldwin, A., Rivera Lara, L., Saucedo-Crespo, H., Ahmed, O., Sadasivan, S., Ponce, L.,  
33 490 Cruz-Navarro, J., Shahin, H., Aisiku, I.P., Doshi, P., Valadka, A., Neipert, L., Waguspack, J.M., Rubin, M.L.,  
34 491 Benoit, J.S. and Swank, P. (2014). Effect of erythropoietin and transfusion threshold on neurological  
35 492 recovery after traumatic brain injury: a randomized clinical trial. *JAMA* 312, 36-47.
- 36 493 26. McIntyre, L.A., Fergusson, D.A., Hutchison, J.S., Pagliarello, G., Marshall, J.C., Yetisir, E., Hare, G.M.  
37 494 and Hebert, P.C. (2006). Effect of a liberal versus restrictive transfusion strategy on mortality in patients  
38 495 with moderate to severe head injury. *Neurocrit Care* 5, 4-9.
- 39 496 27. Yuan, Q., Wu, X., Du, Z.Y., Sun, Y.R., Yu, J., Li, Z.Q., Wu, X.H., Mao, Y., Zhou, L.F. and Hu, J. (2015).  
40 497 Low-dose recombinant factor VIIa for reversing coagulopathy in patients with isolated traumatic brain  
41 498 injury. *J Crit Care* 30, 116-120.
- 42 499 28. Etemadrezai, H., Baharvahdat, H., Shariati, Z., Lari, S.M., Shakeri, M.T. and Ganjeifar, B. (2007). The  
43 500 effect of fresh frozen plasma in severe closed head injury. *Clin Neurol Neurosurg* 109, 166-171.
- 44 501 29. Batchelor, J.S. and Grayson, A. (2013). A meta-analysis to determine the effect of preinjury  
45 502 antiplatelet agents on mortality in patients with blunt head trauma. *Br J Neurosurg* 77, 12-18.
- 46 503 30. Pakraftar, S., Atencio, D., English, J., Corcos, A., Altschuler, E.M. and Stahlfeld, K. (2014). Dabigatran  
47 504 etixilate and traumatic brain injury: Evolving anticoagulants require evolving care plans. *World J Clin*  
48 505 *Cases* 2, 362-366.
- 49 506 31. Abdel-Aziz, H., Dunham, C.M., Malik, R.J. and Hileman, B.M. (2015). Timing for deep vein thrombosis  
50 507 chemoprophylaxis in traumatic brain injury: an evidence-based review. *Crit Care* 19, 96.
- 51  
52  
53  
54  
55  
56  
57  
58  
59  
60

- 1  
2  
3 508 32. Phelan, H.A., Eastman, A.L., Madden, C.J., Aldy, K., Berne, J.D., Norwood, S.H., Scott, W.W.,  
4 509 Bernstein, I.H., Pruitt, J., Butler, G., Rogers, L. and Minei, J.P. (2012). TBI risk stratification at  
5 510 presentation: a prospective study of the incidence and timing of radiographic worsening in the Parkland  
6 511 Protocol. *J Trauma Acute Care Surg* 73, S122-127.
- 7 512 33. Phelan, H.A., Wolf, S.E., Norwood, S.H., Aldy, K., Brakenridge, S.C., Eastman, A.L., Madden, C.J.,  
8 513 Nakonezny, P.A., Yang, L., Chason, D.P., Arbique, G.M., Berne, J. and Minei, J.P. (2012). A randomized,  
9 514 double-blinded, placebo-controlled pilot trial of anticoagulation in low-risk traumatic brain injury: The  
10 515 Delayed Versus Early Enoxaparin Prophylaxis I (DEEP I) study. *J Trauma Acute Care Surg* 73, 1434-1441.
- 11 516 34. Schafer, N., Driessen, A., Frohlich, M., Sturmer, E.K., Maegele, M. and TACTIC partners (2015).  
12 517 Diversity in clinical management and protocols for the treatment of major bleeding trauma patients  
13 518 across European level I Trauma Centres. *Scand J Trauma Resusc Emerg Med* 23, 74.
- 14 519 35. Albrecht, V., Schafer, N., Sturmer, E.K., Driessen, A., Betsche, L., Schenk, M. and Maegele, M. (2015).  
15 520 Practice management of acute trauma haemorrhage and haemostatic disorders across German trauma  
16 521 centres. *Eur J Trauma Emerg Surg*.
- 17 522 36. Driessen, A., Schafer, N., Albrecht, V., Schenk, M., Frohlich, M., Sturmer, E.K., Maegele, M. and  
18 523 TACTIC partners. (2015). Infrastructure and clinical practice for the detection and management of  
19 524 trauma-associated haemorrhage and coagulopathy. *Eur J Trauma Emerg Surg* 41, 413-420.
- 20 525 37. Hamada, S.R., Gauss, T., Pann, J., Dunser, M., Leone, M. and Duranteau, J. (2015). European trauma  
21 526 guideline compliance assessment: the ETRAUSS study. *Crit Care* 19, 423.
- 22 527 38. Sena, M.J., Rivers, R.M., Muizelaar, J.P., Battistella, F.D. and Utter, G.H. (2009). Transfusion practices  
23 528 for acute traumatic brain injury: a survey of physicians at US trauma centers. *Intensive Care Med* 35,  
24 529 480-488.
- 25 530 39. Badenes, R., Oddo, M., Suarez, J.I., Antonelli, M., Lipman, J., Citerio, G. and Taccone, F.S. (2017).  
26 531 Hemoglobin concentrations and RBC transfusion thresholds in patients with acute brain injury: an  
27 532 international survey. *Crit Care* 21, 159.
- 28 533 40. Hallet, J., Lauzier, F., Mailloux, O., Trottier, V., Archambault, P., Zarychanski, R. and Turgeon, A.F.  
29 534 (2013). The use of higher platelet: RBC transfusion ratio in the acute phase of trauma resuscitation: a  
30 535 systematic review. *Crit Care Med* 41, 2800-2811.
- 31 536 41. Gaist, D., Garcia Rodriguez, L.A., Hellfritsch, M., Poulsen, F.R., Halle, B., Hallas, J. and Pottegard, A.  
32 537 (2017). Association of Antithrombotic Drug Use With Subdural Hematoma Risk. *JAMA* 317, 836-846.
- 33 538 42. Reddy, G.D., Gopinath, S. and Robertson, C.S. (2015). Transfusion in Traumatic Brain Injury. *Curr*  
34 539 *Treat Options Neurol* 17, 46.
- 35 540 43. Joseph, B., Hadjizacharia, P., Aziz, H., Kulvatunyou, N., Tang, A., Pandit, V., Wynne, J., O'Keeffe, T.,  
36 541 Friese, R.S. and Rhee, P. (2013). Prothrombin complex concentrate: an effective therapy in reversing the  
37 542 coagulopathy of traumatic brain injury. *J Trauma Acute Care Surg* 74, 248-253.
- 38 543 44. Schochl, H., Schlimp, C.J. and Maegele, M. (2014). Tranexamic acid, fibrinogen concentrate, and  
39 544 prothrombin complex concentrate: data to support prehospital use? *Shock* 41 Suppl 1, 44-46.
- 40 545 45. Schochl, H., Voelckel, W., Maegele, M., Kirchmair, L. and Schlimp, C.J. (2014). Endogenous thrombin  
41 546 potential following hemostatic therapy with 4-factor prothrombin complex concentrate: a 7-day  
42 547 observational study of trauma patients. *Crit Care* 18, R147.
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Table 1. Red blood cell transfusion policy <sup>a</sup>

Items	Number	N	(%)
questionnaire	completed		
<b>Protocol at the ICU</b>			
Protocol	65		
- Presence of a protocol with a Hb-TL		34	(52%)
- Absence of a protocol with a Hb-TL		31	(48%)
<b>Transfusion at Hb-TL in protocol (open question)</b>			
	29		
- 110 g/L		1	(3%)
- 100g/L		8	(28%)
- 90 g/L		4	(14%)
- 80 g/L		9	(31%)
- 70 g/L		5	(18%)
- 80-100 g/L		1	(3%)
- 70-80 g/L		1	(3%)
<b>In non-neurological critically ill patients</b>			
Transfusion at Hb-TL	63		
- > 100 g/L		1	(2%)
- Between 90 g/l and 100g/L		6	(9%)
- Between 80 g/l and 90 g/L		21	(33%)
- Between 70 g/l and 80 g/L		35	(56%)
<b>In patients with TBI <sup>b</sup></b>			
Transfusion at Hb-TL	64		
- > 100 g/L		18	(28%)
- Between 90 g/l and 100g/L		20	(31%)
- Between 80 g/l and 90 g/L		16	(25%)
- Between 70 g/l and 80 g/L		10	(16%)
Frequencies and percentage of centers with corresponding answers, ICU: Intensive Care Unit, Hb-TL: hemoglobin			

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target levels, TBI: traumatic brain injury, g/L: grams per liter

a) General policy: the way the large majority of patients (>75%) with a certain indication would be treated at the intensive care b) Policy in the acute phase

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Table 2. Coagulation policies, deep venous thrombosis <sup>a</sup>

Items	Number	N	(%)
questionnaire	completed		
<b>DVT prophylaxis</b>			
Frequency of DVT prophylaxis	66		
- Never (0-10%)		1	(2%)
- Rarely (10-30%)		0	(0%)
- Sometimes (30-70%)		3	(4%)
- Frequently (70-90%)		18	(27%)
- Always (90-100%)		44	(67%)
Start in the absence of hemorrhagic lesions	65		
- < 24 hours		26	(40%)
- 24-72 hours		24	(37%)
- > 72 hours		14	(21%)
- Never		1	(2%)
Start in the presence of hemorrhagic lesions	63		
- < 24 hours		5	(8%)
- 24-72 hours		25	(40%)
- > 72 hours		29	(46%)
- Never		4	(6%)
Start after intracranial surgery	64		
- < 24 hours		10	(16%)
- 24-72 hours		31	(48%)
- > 72 hours		21	(33%)
- Never		2	(3%)
Pharmacological DVT prophylaxis	66		
- Subcutaneous unfractionated heparin		7	(11%)
- Intravenous heparin		1	(2%)

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- Low-molecular weight heparin	54	(82%)
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Frequencies and percentage of centers with corresponding answers

DVT: deep venous thrombosis

a) General policy: the way the large majority of patients >75% with a certain indication would be treated at the intensive care

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For Peer Review Only/Not for Distribution

Table 3. Coagulation policies, ICP monitoring<sup>a</sup>

Items	Number	N	(%)
questionnaire	completed		
Checks prior to insertion of parenchymal sensor for ICP monitoring			
Coagulation panel	65		
- Never (0-10%)		4	(6%)
- Rarely (10-30%)		2	(3%)
- Sometimes (30-70%)		5	(8%)
- Frequently (70-90%)		5	(8%)
- Always (90-100%)		45	(69%)
- Not available <sup>b</sup>		4	(6%)
Checks prior to insertion ventricular catheter for ICP monitoring			
Coagulation panel	65		
- Never (0-10%)		3	(4%)
- Rarely (10-30%)		2	(3%)
- Sometimes (30-70%)		5	(8%)
- Frequently (70-90%)		4	(6%)
- Always (90-100%)		46	(71%)
- Not available <sup>b</sup>		5	(8%)
Minimum platelet count	65		
- >150 x10 <sup>9</sup> /L		1	(2%)
- >100 x10 <sup>9</sup> /L		30	(46%)
- > 80 x10 <sup>9</sup> /L		9	(14%)
- > 50 x10 <sup>9</sup> /L		9	(14%)
- Depending on the surgeon		13	(20%)
- No minimum		0	(0%)
- Other		3	(4%)
Minimum INR	65		

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- <1.4	21	(33%)
- <1.3	17	(26%)
- <1.2	8	(12%)
- Depending on the surgeon	15	(23%)
- No minimum	0	(0%)
- Other	4	(6%)

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Frequencies and percentage of centers with corresponding answers

DVT: deep venous thrombosis, ICP: intracranial pressure, INR: International Normalized Ratio, L: Liter

a) General policy: the way the large majority of patients >75% with a certain indication would be treated at the intensive care b) Centers that did not have this technique

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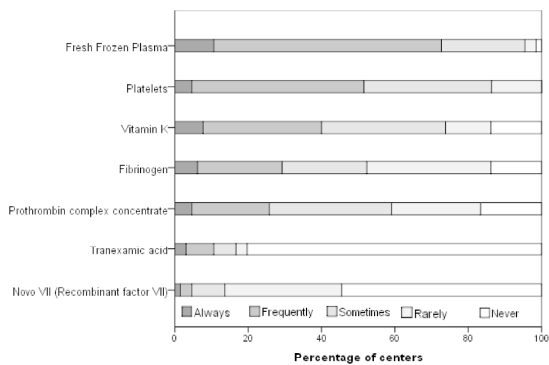


Figure 1. Trauma related coagulopathy treatment

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**Figure title**

Figure 1. Trauma related coagulopathy treatment

**Figure legend**

Bars represent the percentage of centers that indicated to use this treatment as general policy (the way the large majority of patients >75% with a certain indication would be treated). In order of always and frequently summed. Always: in 90-100% of cases; Frequently: in 70-90% of cases; Sometimes: in 30-70% of cases; Rarely: in 10-30% of cases; Never: in 0-10% of cases



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 13 Menon David<sup>65</sup>, Menovsky Tomas<sup>58</sup>, Morganti-Kossmann Cristina<sup>109</sup>, Mulazzi Davide<sup>38</sup>, Mutschler Manuel<sup>102</sup>,  
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 15 Mühlan Holger<sup>110</sup>, Negru Ancuta<sup>111</sup>, Nelson David<sup>82</sup>, Neugebauer Eddy<sup>102</sup>, Newcombe Virginia<sup>65</sup>,  
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 17 Noirhomme Quentin<sup>95</sup>, Nyirádi József<sup>4</sup>, Oddo Mauro<sup>112</sup>, Oldenbeuving Annemarie<sup>113</sup>, Oresic Matej<sup>114</sup>,  
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 19 Ortolano Fabrizio<sup>38</sup>, Palotie Aarno<sup>91,115,116</sup>, Parizel Paul M.<sup>117</sup>, Patruno Adriana<sup>118</sup>, Payen Jean-François<sup>31</sup>,  
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 21 Perera Natascha<sup>119</sup>, Perlberg Vincent<sup>25</sup>, Persona Paolo<sup>120</sup>, Peul Wilco<sup>121</sup>, Pichon Nicolas<sup>122</sup>, Piilgaard Henning<sup>67</sup>,  
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 23 Piippo Anna<sup>90</sup>, Pili Floury Sébastien<sup>123</sup>, Pirinen Matti<sup>91</sup>, Ples Horia<sup>111</sup>, Polinder Suzanne<sup>46</sup>, Pomposo Inigo<sup>40</sup>,  
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 25 Psota Marek<sup>33</sup>, Pullens Pim<sup>117</sup>, Puybasset Louis<sup>124</sup>, Ragauskas Arminas<sup>125</sup>, Raj Rahul<sup>90</sup>, Rambadagalla Malinka<sup>126</sup>,  
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 37 Sandor Janos<sup>137</sup>, Santos Edgar<sup>28</sup>, Sasse Nadine<sup>51</sup>, Sasu Luminita<sup>59</sup>, Savo Davide<sup>118</sup>, Schipper Inger<sup>138</sup>,  
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 41 Schou Rico Frederik<sup>140</sup>, Schwendenwein Elisabeth<sup>9</sup>, Schöll Michael<sup>28</sup>, Sir Özcan<sup>141</sup>, Skandsen Toril<sup>142</sup>,  
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 45 Stanworth Simon<sup>52</sup>, Stegemann Katrin<sup>110</sup>, Steinbüchel Nicole<sup>145</sup>, Stevens Robert<sup>146</sup>, Stewart William<sup>147</sup>,  
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 47 Steyerberg Ewout W.<sup>46</sup>, Stocchetti Nino<sup>148</sup>, Sundström Nina<sup>35</sup>, Synnot Anneliese<sup>149,150</sup>, Szabó József<sup>94</sup>,  
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 53 Tibboel Dick<sup>41</sup>, Toliás Christos<sup>152</sup>, Tshibanda Jean-Flory Luaba<sup>153</sup>, Tudora Cristina Maria<sup>111</sup>, Vajkoczy Peter<sup>154</sup>,  
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5 Vespa Paul M. <sup>157</sup>, Vik Anne <sup>158</sup>, Vilcinis Rimantas <sup>159</sup>, Vizzino Giacinta <sup>14</sup>, Vleggeert-Lankamp Carmen <sup>143</sup>,  
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9 Wildschut Eno <sup>41</sup>, Williams Guy <sup>65</sup>, Willumsen Lisette <sup>67</sup>, Wilson Adam <sup>5</sup>, Wilson Lindsay <sup>161</sup>, Winkler Maren K.L. <sup>103</sup>,  
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11 Ylén Peter <sup>162</sup>, Younsi Alexander <sup>28</sup>, Zaaroor Menashe <sup>99</sup>, Zhang Zhiqun <sup>163</sup>, Zheng Zelong <sup>28</sup>, Zumbo Fabrizio <sup>2</sup>,  
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15 van Heugten Caroline <sup>57</sup>, van der Jagt Mathieu <sup>165</sup>, van der Naalt Joukje <sup>85</sup>  
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**Supplemental data 2. Provider Profiling Questionnaire (ICU part)**

The following questions about ICU policies are included in the manuscript

**Information about the completer of the questionnaire**

Other than the CENTER-TBI investigator, which of the following individuals was involved in completion of this questionnaire?

*Select all that apply*

- Neurologist
- Neurosurgeon
- Trauma Surgeon
- ED physician
- Administrative staff member / data manager / financial department
- Other, please specify.....
- NA. The questionnaire is solely completed by the CENTER TBI local investigator

The Local investigator is the senior clinician(s) at your hospital involved in supervision of CENTER TBI

**General patient statistics**

What is the number of patients treated in your Intensive Care Unit (ICU) annually?

1. 2012: .....
2. 2013: .....

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What is the number of Traumatic Brain Injury (TBI) patients treated in your Intensive Care Unit (ICU) annually?

3. 2012: .....

4. 2013: .....

With reference to guidelines for Intensive Care Unit (ICU) management of Traumatic Brain Injury (TBI), does your ICU:

- Not have specific guidelines for management
- Follow the Brain Trauma Foundation Guidelines
- Follow National Guidelines (Please specify: .....)
- Have institutional guidelines which are broadly based on BTF and/or National Guidelines
- Have separate guidelines which you have developed independently

**Intensive Care Unit (ICU) practice around ICP monitoring**

	Never (0-10%)	Rarely (10-30%)	Sometimes (30-70%)	Frequently (70-90%)	Always (90-100%)	N/A, we do not have this technique
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23. Is a coagulation panel assessed prior to insertion of an ICP monitoring device?	Ventricular catheter:					
	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
	Parenchymal sensor					
	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

24. What is considered a minimum platelet count for insertion of a ventricular catheter in your Intensive Care Unit (ICU)?

- >150K
- >100K
- > 80 K
- >50K
- Variable, depends on surgeon
- No minimum

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- Other, please specify .....

25. What is consider the minimum INR for safe placement of a ventricular catheter in your Intensive Care Unit (ICU)?

- <1.4
- <1.3
- <1.2
- Variable, depending on surgeon
- No minimum
- Other, please specify.....

Deep venous thrombosis (DVT) prophylaxis

The responses to the following questions should represent, as best as practicable, a general consensus on treatment at your centre, rather than individual management preferences.

Never (0-10%)	Rarely (10-30%)	Sometimes (30-70%)	Frequently (70-90%)	Always (90-100%)
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53. How often is DVT prophylaxis used?

54. If you use DVT prophylaxis, when is DVT prophylaxis initiated?

< 24 hrs	24-72 hrs	< 72 hrs	Never
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In the absence of hemorrhagic lesions

In the presence of hemorrhagic lesion

After intracranial surgery

55. In patients who receive DVT prophylaxis, what medication is given?

Subcutaneous unfractionated heparin



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- Low-molecular weight heparin
- Other, please specify.....

56. Coagulopathy related to the trauma is treated with :

	Never (0-10%)	Rarely (10-30%)	Sometimes (30-70%)	Frequently (70-90%)	Always (90-100%)
Fresh Frozen plasma (FFP)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Platelets	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Fibrinogen	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Novo 7 ( recombinant factor VII)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Vitamin K	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
PCC (Prothrombin Complex Concentrate)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>