Central venous catheter placement in coagulopathic patients: risk factors and incidence of bleeding complications

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BACKGROUND: Central venous catheters are frequently inserted into patients with coagulation disorders. It is unclear whether preprocedural correction of hemostasis is beneficial. We determined the incidence of bleeding complications after central venous catheter placement in patients who had severe coagulopathy and identified potential risk factors for bleeding.

STUDY DESIGN AND METHODS: The MEDLINE and Cochrane Library databases were systematically searched through November 2015. To be included, articles must have reported on hemorrhagic complications with specification of abnormal coagulation testing results. Severe coagulopathy was defined as a reduced platelet count of 50 × 10^9/L or less, and/or an elevated international normalized ratio of 1.5 or greater, and/or a partial thromboplastin time of 45 seconds or greater.

RESULTS: We included one randomized controlled trial and 21 observational studies. In total, there were 13,256 catheter insertions, including 4,213 in patients with severe coagulopathy. Before 3,150 central venous catheter placements, coagulopathy was not corrected. The bleeding incidence varied from 0 to 32%. The severity of coagulopathy did not predict the risk of bleeding. No study demonstrated a beneficial effect from the prophylactic administration of platelets or fresh-frozen plasma to prevent bleeding complications. Retrospective observational studies suggested that no preprocedural correction is required up to a platelet count of 20 × 10^9/L and an international normalized ratio of 3.0.

CONCLUSION: The incidence of major bleeding complications after central venous catheter placement is low, even in coagulopathic patients. Based on a systematic research of the literature, strong evidence supporting the correction of hemostatic defects before central venous catheter insertion is lacking. However, well-powered randomized controlled trials will be necessary to determine the minimal platelet count, the maximal international normalized ratio, and an activated partial thromboplastin time that is safe before central venous catheter insertion.
(FFP) in those with prolonged PT is potentially harmful. Transfusion products are associated with transfusion-related acute lung injury, transfusion-associated cardiac overload, allergic reactions, alloimmunization, and transfusion-related infections. Conclusive evidence of optimal platelet count and PT before CVC placement is lacking. However, current national and international guidelines support the correction of thrombocytopenia up to a platelet count of $50 \times 10^9/L$ and an international normalized ratio (INR) 1.5 or greater before (CVC) placement. The aim of this systematic review is to provide an overview of the current evidence on risk factors and incidence of bleeding complications after CVC placement in patients with severe coagulopathy.

**MATERIALS AND METHODS**

**Literature search**

The MEDLINE data was searched from January 1, 1980, through November 1, 2015, by using the following medical subject heading (MeSH) terms: complications, blood transfusion, blood plasma, fresh frozen plasma, platelets, central venous catheterization, central line, coagulopathy, and thrombocytopenia. The following text words were used: CVL (central venous line) and CVC. To identify observational studies, the MeSH terms case-control study and retrospective study were added. The Cochrane Library (2013), which contains the CENTRAL Database of Controlled Trials, the Database of Abstracts of Review Effectiveness, and the Cochrane Database of Systematic Reviews, also was searched.

In addition, we used the related articles feature of PubMed, which identifies related articles by using a hierarchical search engine that is not solely based on MeSH headings. This search was completed with articles selected by two of the authors (A.P.J.V. and B.V.). Although the search was also carried out for language citations not written in English, the resulting article review involved English-language publications only. The search strategy is detailed in Appendix 1.

**Abstract review**

After all citations based on our search strategy were identified, two of the authors (A.P.J.V. and B.B.) independently reviewed each abstract to assess its eligibility. Eligible studies were those that reported on CVC placement in patients with severe coagulopathy. To be included, studies had to report bleeding complications for a (sub)group of participants with at least one of the following characteristics: a reduced platelet count ($\leq 50 \times 10^9/L$) and an elevated INR ($\geq 1.5$) or a partial thromboplastin time (PTT) ($\geq 45$ seconds) before CVC placement. Articles were included if they were: 1) case reports, 2) had no full text available, 3) were not available in English, and 4) had Level 5 evidence according to the Oxford Centre for Evidence-based Medicine.

If an abstract was deemed eligible, then E.K.v.d.W. and A.P.J.V. independently reviewed the respective article, if available, to confirm that it met the inclusion criteria. The two reviewers either had to reach a consensus or use a fourth reviewer (J.M.B.) to resolve any discrepancies.

**Data extraction**

Data from the studies to describe study methods, study location, years of data collection, patient inclusion and exclusion criteria, patient characteristics, study findings, laboratory values, and transfusion policy were extracted using a predefined data-collection form. When available, we abstracted data on patients with and without correction of coagulopathy before CVC placement. Bleeding complications were categorized as major or minor bleeding, as reported by the article. Definitions of bleeding complications for each study were extracted and reported.

**Article review process**

One author reviewed each article (E.K.v.d.W.). Author and journal names were disclosed to the reviewer. All data were extracted by E.K.v.d.W. and were verified for accuracy by the second reviewer (A.P.J.V.).

**Quantitative pooling and presentation of findings**

Because of qualitative heterogeneity of the studies and patient heterogeneity, the results were not mathematically pooled. Since most studies lacked a comparison group, it was not possible to calculate risk differences. We assessed the risk of bias using the following criteria: 1) whether patient selection occurred randomly or consecutively versus other, 2) whether investigators excluded non-prespecified patient groups, 3) explicitness of bleeding criteria, 4) correction of hemostasis by transfusion products standardized versus left to the discretion of the physician, 5) a protocol for CVC placement, and 6) primary data collection versus data chart reports. The results of the assessment are provided in Appendix 2.

**RESULTS**

The searches of MEDLINE and the Cochrane Library yielded 302 unique articles for screening, and four additional records were identified through other sources based on the title. Subsequently, 79 articles were screened at the abstract level using the inclusion and exclusion criteria. Thirty-one full-text articles were assessed for eligibility. In total, 22 articles, including 21 observational studies and one randomized controlled trial, were reviewed for bleeding complications. All studies reported on patients who had a platelet count below $50 \times 10^9/L$, an INR greater than 1.5, and/or an activated PTT (aPTT) greater than 45 seconds.

**Included studies**

In the 22 included studies, a total of 13,256 catheter placements were performed, of which 4213 took place in
patients with severe coagulopathy. Before the placement of 1083 CVCs, coagulopathy was corrected with blood donor platelets or plasma. In 3150 coagulopathy was still present during cannulation. We retrieved only one randomized trial. This was an open-label, endpoint-blinded trial comparing prophylactic use of fresh-frozen plasma with no correction of an elevated INR in intensive care patients undergoing an invasive procedure.18 We included 13 prospective cohort studies and eight retrospective series. In the prospective studies, coagulopathy was not corrected in six studies and was corrected in all patients in one study, at various fixed thresholds in two studies (Table 1),18–26 was at the physician’s discretion in five studies. For the retrospective cohort studies, coagulopathy was corrected at a fixed threshold of 20 × 10^9/L in one study, was corrected at the physician’s discretion in six studies, and was not corrected in one study. Characteristics of studies, patients, procedures, and coagulopathies are displayed in Table 1.

The primary focus of the articles included bleeding complications, infectious complications, mechanical complications, technical success rates, method of insertion, site of insertion, the benefit of FFP transfusion, and the benefit of platelet transfusion. Endpoints were technical insertion success rates or various catheter-related complications, such as mechanical complications, bleeding, thrombosis, and infection.

Study quality
The level of quality of the studies was low. In seven of eight studies that reported major bleeding events, patient and laboratory characteristics were incompletely reported. Data were retrospectively collected by patient charts in nine studies. In five studies, patients who received preprocedural transfusions were excluded. The only randomized controlled trial that was included lacked reliability, because it included only 81 instead of the intended 400 patients.18

Coagulopathy
The definition of coagulopathy and its concomitant laboratory thresholds varied across studies. The distribution of abnormal coagulation values and the preprocedural correction of coagulopathy are displayed in Table 1. Thrombocytopenia contributed to the majority of coagulation disorders. Six studies combined the various coagulation test abnormalities into one group.21–30 Abnormal coagulation parameters were combined in groups with different terms, such as “severe abnormalities,” “high risk of bleeding,” “coagulopathy,” or “moderate-to-severe hemostatic disorders.” Three studies did not report separate coagulation parameters and also did not specify the number of patients who had more than one abnormal laboratory value. To avoid counting patients who had multiple hemostatic effects more than once, only the largest group was used.

Bleeding complications
The definitions of both minor and major bleeding varied widely across studies (Table 2).18–42 Major bleeding complications were categorized as reported by the article. We identified eight studies that reported a total of 13 major bleeding complications (Table 3).20,21,24,26,28,30,36,38 Eight major bleeding complications were observed in patients with severe coagulopathy, and five were reported in patients with mild-to-absent coagulopathy. Only one study provided detailed values of classical coagulation parameters.

Overall bleeding prevalence in the included studies varied from 0 to 32%. Notably, in the study that reported a 32% bleeding prevalence in the presence of coagulopathy, the overall bleeding incidence was not different among the patients without coagulopathy (p = 0.768).42

Platelet count
No randomized controlled trial evaluating the effect of prophylactic platelet transfusion was identified. Twenty studies reported patients or a subgroup of patients with platelet counts below 50 × 10^9/L. These single-arm studies in patients with thrombocytopenia, without a comparison group, reported a bleeding incidence that varied from 0 to 32%.

Thrombocytopenia was not corrected before cannulation in seven studies. In this uncorrected group with platelet counts below 50 × 10^9/L, no major bleeding events occurred. In three of these studies without prophylactic platelet transfusion, thrombocytopenia was identified as a risk factor for local hematoma and oozing.23,24,41 One study reported no association between thrombocytopenia and minor bleeding complications.28

In 11 studies, a small group of patients received platelet transfusion. The decision for prophylactic platelet transfusion was left to the discretion of the physician. No major hemorrhagic events occurred in the patients with platelet counts below 50 × 10^9/L. Two studies identified thrombocytopenia as a risk factor for local hematoma and oozing.20,42 All of these hematomas were self-limiting, and oozing could be managed by prolonged manual compression or bandage changes in most cases. Mumtaz and colleagues reported that over-sewing of the catheter site was an effective solution in case of prolonged bleeding.28 One study by Kander and coworkers revealed no association between thrombocytopenia and minor bleeding complications.26 Zieidler and colleagues demonstrated no association between platelet count (down to a count of 20 × 10^9/L) and bleeding risk.42 Of note, all physicians were experienced, and CVC placement was ultrasound guided.

In three studies all patients with a low platelet count received prophylactic platelet concentrate, based on a threshold, varying from 10 to 50 × 10^9/L. All patients had a platelet count of 30 × 10^9/mL or less and received prophylactic platelet transfusion in one study.33 Another
| Study                  | Design, country                  | Population              | Period       | CVCs in patients with abnormal test results (N) | Correction of hemostasis                  | Additional patient data and procedural details |
|-----------------------|----------------------------------|--------------------------|--------------|------------------------------------------------|-------------------------------------------|-------------------------------------------------|
| Barrera, 1996<sup>19</sup> | Single center, Prospective cohort, USA | Oncohematologic patients | 1990-1993   | PLT ≤ 20 (N) = 115 INR > 1.5 (N) = 8          | 107/115 patients received a median of 6 units of platelet transfusion prior to CVC placement, with a mean post-transfusion platelet count of 24 ± 14. 4/8 patients with prolonged PT received FFP transfusion. | Total cohort: 115 CVCs in 115 patients (60 males, 52%); landmark method, 18-gauge inducer needle, SCV 55%, UV 45%, proceduralists had various levels of experience. |
| Carino, 2012<sup>20</sup> | Single center, retrospective cohort study, USA | Intensive Care patients | 2008-2008   | INR > 1.5 (N) = 100                           | The use of FFP was generally discouraged but left to the discretion of the operator. 27/100 patients received FFP. | Total cohort: 287 CVCs, in 281 patients, (130 males, 45%), mean age 66 years; Both US-guidance and landmark method, 18-gauge inducer needle, 57% IJV, 43% SCV; Proceduralists had varying levels of experience. |
| DeLoughery, 1996<sup>21</sup> | Single center, Retrospective cohort study, USA | Intensive Care patients | NR          | Severe abnormalities (N) = 253 PLT ≤ 50 (N) = 65 INR > 1.5 (N) = 9 PTT > 45 (N) = 94 | An attempt to correct hemostasis was made in 144 patients, of which 57 specifically for CVC placement. | Total cohort: 938 Catheters (including CVC, pulmonary artery and arterial lines) in 490 patients; no procedural details on CVC placement. |
| Della Vigna, 2009<sup>22</sup> | Single center, Retrospective cohort, Italy | Oncologic patients       | 2001-2008   | High bleeding risk: (N) = 45 Definition: INR and PTT > 2.2 and/or PLT < 50 | No correction of hemostasis prior to CVC. | Total cohort: 239 CVCs in 157 patients (93 males, 59%), mean age 49 years, US-guidance, 22-gauge inducer needle, SCV 97%, IJV 3%, Experienced operators. |
| Doerfler, 1996<sup>23</sup> | Single center, prospective cohort study, USA | All patients with an indication for CVC | 1992-1993   | Total (N) = 50 PLT ≤ 50 (N) = 41 INR > 1.5 (N) = 6 PTT ≥ 1.5 x control (N) = 6 | No correction of hemostasis prior to CVC. | Total cohort: 104 CVCs in 76 patients (43 males, 56%), mean age 57 years, Landmark method, 18-gauge inducer needle, SCV 80%, IJV 12%, EJV 6%, FV 3%, CVCs placed under direct supervision or by intensivist. |
| Fisher, 1999<sup>24</sup> | Single center, prospective observational study, UK | Liver disease, liver transplantation | 1996-1997   | PLT 10-50 (N) = 146 INR > 1.5 (N) = 580 | FFP and platelets were not routinely given for correction of coagulopathy and were normally only given in other interventional procedures. | Total cohort: 658 CVCs in 283 patients, Landmark method, 18-gauge inducer needle, 53% SCV, 47% IJV; CVCs placed by attending clinician, usually registrar. The number of patients with a combination of platelet count < 10 and INR > 1.5 not reported in the article. |
| Haas, 2010<sup>25</sup> | Single center retrospective cohort study, USA | All CVC indications, except ICU | 2001-2008   | Total (N) = 626 PLT ≤ 50 (N) = 300 INR > 1.5 (N) = 828 PTT ≤ 50 and INR ≥ 1.5 (N) = 44 | After exclusion of intercurrent blood product transfusion, 626 CVCs placed in 567 patients with PLT ≤ 50 and/or INR ≥ 1.5. | Total cohort: 3170 CVCs in 2514 patients, (1783 males, 56%), mean age 54 years; US guidance, 21-gauge inducer needle; IJV 96%, FV1%, EJV 1%; CVCs placed by interventional radiologists. |
| Kander, 2013<sup>26</sup> | Single center retrospective cohort study, Sweden | All patients with an indication for a CVC | 2009-2010   | Coagulopathy: (N) = 283 PLT < 50 = 79 APTT > 45 sec = 168 PT > 1.8 = 36 | 70 patients received prophylactic platelet concentrate, 14 patients received plasma transfusion | Total cohort: 1737 CVCs in 1444 patients, 49% US-guidance; IJV 68%, EJV 8%, SCV 15%, FV 1%, Placed by anaesthesiology residents and specialists; Inducer needle size not reported. |
| Mey, 2002<sup>27</sup> | Single center, prospective cohort study, Germany | Hematology-oncology       | 1994-1998   | PLT ≤ 50 (N) = 116 | Thrombocytopenic patients had a platelet count of <20, and received platelet concentrate. | Total cohort: 490 CVCs in 490 patients, (287 male, 59%) mean age 57 years; US-guidance, 14-G needle; 95% IJV. |
| Study          | Design, country                     | Population                                      | Period    | CVCs in patients with abnormal test results (N) | Correction of hemostasis                                                                 | Additional patient data and procedural details                                      |
|---------------|------------------------------------|-------------------------------------------------|-----------|-----------------------------------------------|----------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|
| Müller, 2015  | Multicenter randomized open -label trial, Netherlands | Intensive Care patients                          | 2010-2013 | INR ≥ 1.5 (N) = 58                           | Patients with an INR of 1.5-3 were randomized to receiving FFP transfusion (N = 29)   | Total cohort: 76 invasive procedures, of which 58 CVCs, both US-guided and landmark technique; Proceduralist, site of placement and inducer needle size not reported. |
| Mumtaz, 2000  | Single center retrospective cohort study, USA | All patients with an indication for a CVC       | 1997-1999 | Coagulopathy: (N) = 330                        | In 242/330 patients, disorders of hemostasis were corrected prior to CVC placement.   | Total cohort: 2010 CVCs in 1825 patients, of which 330 in patients with any disorder of hemostasis; 96% SV, 4% UV; Proceduralist was mostly a surgical intern supervised by an attending; Use of Ultrasound and inducer needle size not reported. |
| Nosari, 2008  | Single center, prospective cohort study, Italy | Oncohematologic patients                        | 2003-2004 | PLT ≤ 50 (N) = 77                            | All 36 patients with a platelet count < 30 received prophylactic platelet concentrate. | Total cohort: 388 CVCs in 279 patients (148 males, 53%), mean age 50; UV 86%, EJV 3%, SCV 1%, FV 9%; Proceduralist, inducer needle size and the use of ultrasound not reported. |
| Ong, 2012     | Single center, prospective cohort study, USA | TTP                                             | 2008-2010 | PLT ≤ 50 (N) = 10                            | 2/11 patients received prophylactic platelet concentrate.                             | Total cohort: 11 CVCs in 11 patients, (5 males, 45%), median age 58 years; Site of placement, use of US-guidance, inducer needle size and proceduralists not reported. |
| Oguzkurt, 2005| Single center, prospective cohort study, Turkey | Hemodialysis patients                            | 2002-2004 | Coagulopathy: (N) = 61                        | No correction of hemostasis prior to CVC.                                              | Total cohort: 220 CVC in 172 patients (93 males, 54%), mean age 56 years; US-guidance, 18-gauge inducer needle; 100% IJV; Experience of proceduralists not reported. |
| Ray, 1997     | Single center, Prospective outcomes study, USA | All patients with an indication for a CVC       | 1995-1996 | PLT ≤ 50 (N) = 37                            | All patients received platelet transfusion during implementation.                      | Total cohort: 87 CVCs in 105 patients (60 males, 57%) mean age 50; landmark method, 21-Gauge needle; Placed by interventional radiologists. |
| Rizvi, 2000   | Single center, prospective cohort study, USA | TTP-HUS                                         | 1996-1999 | PLT ≤ 50 (N) = 49                            | 7/18 catheter insertions that had took place in patients with a platelet count of <20x10^9 received prophylactic platelet concentrate. | Total cohort: 92 CVCs in 88 patients (20 males, 30%), mean age 50; 71% UV/SCV, 29% FV; No standard protocol for CVC-placement. |
| Singh, 2015   | Single center, prospective cohort study, India | Liver disease                                    | 2011-2012 | PLT < 30 (N) = 111                           | No correction of hemostasis prior to CVC.                                              | Total cohort: 699 CVCs in 421 patients (238 males, 57%), mean age 42; US-guided, IJV 100%; Elective setting by trained anesthesiologists; Inducer needle size not reported. |
| Tercan, 2008  | Single center, prospective observational study, Turkey | Patients with bleeding disorders                 | 2002-2006 | Total (N) = 133                              | No correction of hemostasis prior to CVC.                                              | Total cohort: 133 CVCs in 119 patients (51 males, 49%), age range 18-95 years; US guidance, 18-G inducer needle; IJV 97%, SCV 1.5%, FV 1.5%; Experienced interventional radiologists placed the CVC. |
| Tomoyose, 2009| Single center, retrospective, observational, Japan | Thrombocytopenic patients with hematological malignancies | 2007-2009 | PLT ≤ 50 (N) = 67                            | 42/67 thrombocytopenic patients received prophylactic platelet concentrate.           | Total cohort: 108 CVCs in 72 patients (38 males, 52%) 44 CVCs US-guided, 49 CVCs landmark, 22-G inducer needle; All central veins; The decision of platelet transfusion was left to the discretion of the individual physicians. |
Table 1: Continued

| Study                  | Design, country                  | Population                  | Period         | CVCs in patients with abnormal test results (N) | Correction of hemostasis | Additional patient data and procedural details |
|------------------------|----------------------------------|-----------------------------|----------------|-----------------------------------------------|--------------------------|-----------------------------------------------|
| Vinson, 2014          | Multicenter retrospective cohort study, USA | Sepsis                      | 2010-2012      | Moderate to severe: (N) = 300                  | 20 patients received transfusion: FFP N = 17, Platelets N = 3. Inducer needle size not reported. | Total cohort: 936 CVCs in 936 patients, (535 males, 57%), mean age 68 years; Both US-guided and Landmark method; IJV 86%, SCV 13%, FV 1.4%. Proceduralists were predominately attendings (84%). |
| Weigand, 2009         | Multi center open prospective trial, Germany | Intensive Care & hematologic patients | 2005-2007      | Total cohort: 604 CVCs in 193 patients, (114 males, 59%), median age 49 years; SVC 85%, IJV 15%; Experienced staff from the anesthesiology or intensive care unit. Inducer needle size not reported. | No correction of hemostasis prior to CVC. | 196 CVCs in 196 patients, (132 males, 68%), mean age 62 years; US-guidance, 18G inducer needle; IJV 88%, FV 10%, SCV 2%; Number of previous insertions per physician 2-29. |
| Zeidler, 2011         | Single center, retrospective cohort study, Switzerland | Acute leukemia patients     | 2001-2007      | All patients with a platelet count below 20 (N=2) received platelet transfusion, between 20-50 it was left to the physician's discretion. 138/234 thrombocytopenic patients received transfusion. | Total cohort: 936 CVCs in 936 patients, (535 males, 57%), mean age 68 years; Both US-guided and Landmark method; IJV 86%, SCV 13%, FV 1.4%. Proceduralists were predominately attendings (84%). |

CVC = Central Venous catheter; EJV = external jugular vein; FV = femoral vein; IJV = internal jugular vein; INR = international normalized ratio; N = number of procedures; PLT = Platelet count \( \times 10^9/L \); PTT = activated partial thromboplastin time in seconds; SCV = subclavian vein; US = Ultrasound.

Other risk factors

Several procedural factors were associated with bleeding complications. An analysis of the influence of catheter site produced conflicting results, which varied from no effect to favoring the internal jugular or subclavian site.19,23,24,42 More than one needle pass into the vein was associated with bleeding complications.13,33,40 Other mechanical factors reported no association with bleeding.24,30 Several studies failed to report any guide wire and documented arterial puncture.24,30

Partial thromboplastin time

Four studies reported CVC placements in patients or a subgroup of patients with a PTT of 45 seconds or more in the absence of correction. No association between prolonged PTT and major/minor bleeding was observed (p = 0.6).

International normalized ratio

Eight studies reported patients or a subgroup of patients with an INR of 1.5 or greater. One randomized controlled trial evaluated the effect of prophylactic transfusion on bleeding complications.17,18,25,30,31 Notably, patients in the first group received a transfusion of FFP on day 1. There were no major bleeding complications.41

Seven observational studies, of which six were prospective, reported a subgroup of patients with an INR of 1.5 or greater. Two studies found an association between INR exceeding 1.5 and bleeding complications.22,23 One retrospective study included 100 patients with an INR between 10 and 50, with a bleeding group of 27 patients, and no benefit of prophylactic plasma was observed (p = 0.6).
| Study                  | Major bleeding, definition, and no. of patients                                                                 | Minor bleeding, definition, and no. of patients                                                                                                                                                                                                 | Relevant results                                                                                                                                                                                                 |
|-----------------------|------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Barrera 1996<sup>19</sup> | Bleeding from the site requiring blood transfusion or mediastinal hematomas                                      | Oozing of blood and/or hematomas ≤ 5 cm at the CVC site not requiring therapy (total N = 23; 19 in patients with a normal coagulation pattern, 4 in patients with elevated PT and PTT)                                                                 | The mean PLT count (× 10<sup>3</sup>/L) associated with minor bleeding was 15 ± 5 (range, 6-20) pretransfusion and 25 ± 16 (range, 2-59) posttransfusion; for the group without complications, the PLT count was 15 (range, 3-20) pretransfusion and 23 ± 13 (range, 2-73) posttransfusion |
| Carino 2012<sup>20</sup> | Clinically evident bleeding: documented hematoma at the insertion site, line-related blood transfusion, any need for an intervention beyond local manual pressure, or any new radiographic opacity in the hemithorax (N = 1) (Table 3) | No specific definition (no. not reported)                                                                                                                                                                                                 | The overall occurrence of bleeding was 0.3% (95% CI, 0%-2%); no bleeding occurred in patients without prophylactic plasma, (n = 0/73); one case of bleeding occurred in the group of patients that had received plasma (n = 1/27); no benefit of prophylactic plasma was observed (p = 0.6) |
| DeLoughery 1996<sup>21</sup> | No specific definition (N = 2) (Table 3)                                                                        | Oozing of blood, manageable with dressing changes (N = 10)                                                                                                                                                                                                                                      | By combining coagulation test, a group at high risk for bleeding could be identified                                                                                                                                  |
| Della Vigna 2009<sup>22</sup> | Major bleeding (N = 0)                                                                                             | Oozing, requiring compression (N = 1)                                                                                                                                                                                                                                                            | Patients (N = 45) with a high risk of bleeding did not experience any bleeding complications                                                                                                                        |
| Doerfler 1996<sup>23</sup>  | Intrathoracic bleeding seen on x-ray or unexpected decrease in hematocrit (N = 0)                                | Bleeding that requires direct pressure for 10-20 min; 5 patients had bleeding from the skin, 2 small periosteal hematomas (N = 7; 6.5%)                                                                                                     | PLT count was the only risk factor statistically associated with minor bleeding; the PLT count associated with this risk in this series was <38,000/mL (in all but one patient, it was 25,000/mL) |
| Fisher 1999<sup>24</sup>   | Any hemodynamically significant hemorrhage (N = 1) (Table 3)                                                       | Superficial oozing or hematoma PPT ratio ≥ 2 (4/80; 5%); PTT ≤ 2 sec (N = 6/146; 4%)                                                                                                                                                  | Low PLT independent risk factor for persistent oozing; high INR (p < 0.01) and low PLTs (p < 0.05) were independent risk factors for hematoma formation, whereas regional anticoagulation with heparin (p < 0.01) and low PLTs (p < 0.05) were independent risk factors for persistent oozing |
| Haas 2010<sup>26</sup>     | Bleeding defined according to the Society of Interventional Radiology Technology Assessment Committee reporting standards<sup>31</sup> (N = 3; 0.095%): oozing at catheter exit site requiring treatment, hematoma, and hematoma | Minor oozing at the exit site not requiring any intervention other than brief manual compression was not considered a complication                                                                                                           | No bleeding complications in coagulopathic patients; image-guided placement of CVCs in patients with PLT counts between 25,000/dL and 50,000/ dL and/or an INR between 1.5 and 2.0 is safe when performed by an experienced physician |
| Kander 2013<sup>26</sup>    | World Health Organization (WHO) grade 3 or 4 bleeding (N = 0)                                                      | Bleeding requiring prolonged compression at the insertion site, grade 2 bleeding (N = 16; 9%)                                                                                                                                              | Fisher's exact test revealed that coagulation independent variables alone yielded no significant differences as risk factor for bleeding observations (896 missing observations; p = 0.47). |
| Mey 2002<sup>27</sup>      | No specific definition (N = 0)                                                                                     | Local hematomas in 4.3% of patients, 10.2% in thrombocytopenic patients                                                                                                                                                                   | Complications were significantly more frequent in thrombocytopenic patients (p = 0.02), primarily due to an increased incidence of local hematomas                                                                     |
| Müller 2015<sup>18</sup>   | According to HEME score<sup>32</sup> (N = 0)                                                                      | Prolonged bleeding at the site of insertion or increase in size of subcutaneous hematoma (no. not reported for CVC group)                                                                                                                   | Preprocedural omission of FFP was not associated with increased occurrence of bleeding (relative risk, 1.17; 95% CI, 0.62-2.19; p = 0.78)                                                                                 |
### Table 2: Continued

| Study               | Major bleeding, definition, and no. of patients                                                                 | Minor bleeding, definition, and no. of patients                                      | Relevant results                                                                                                                                 |
|---------------------|-------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------|
| Mumtaz 2000        | Significant bleeding: when an intervention other than digital pressure was necessary to secure hemostasis (N = 4; 0.2%) | Occurrence of minor bleeding was not recorded                                         | A PLT count <50 \times 10^9 was the only significant predictor of bleeding complication in patients with abnormal hemostasis                      |
| Nosari 2008        | No specific definition, no hemothorax (N = 0)                                                                      | Hemorrhage and/or hematoma, without major sequelae (N = 5; 14%)                      | All patients with hemorrhage and/or hematomas were severely thrombocytopenic (5/36; 13.8%) and received transfusion before placement             |
| Oguzkurt 2004      | No specific definition (N = 0)                                                                                     | Oozing of blood (N = 3; 1.4%); small hematoma (N = 1; 0.4%)                         | Oozing of blood was seen only in patients with disorders of hemostasis                                                                       |
| Ong 2012           | Significant bleeding, HCT after line placement (N = 0)                                                            | Oozing (N = 0)                                                                        | No relevant postprocedural oozing in 8 patients with a platelet count of 8-34 \times 10^9/L                                                   |
| Ray 1997           | Bleeding complications that necessitate intervention (N = 0)                                                      | No specific definition (no. not reported)                                             | No bleeding complications                                                                                                                     |
| Rizvi 2000         | Criteria similar to Ziselman (N = 2; 2%)                                                                           | Complications that did not meet the criteria by Ziselman; minor hemorrhage at the insertion site (N = 2; 2%) | N = 11 CVCs were inserted when the platelet count was <20 \times 10^9/L without PLT transfusions and without bleeding complications           |
| Tercan 2008        | Major complication like hemothorax (N = 0)                                                                          | Oozing of blood (N = 5; 3.8%); small hematoma (N = 2; 1.5%)                         | There were significant association between high INR and the development of hemotoma (p < 0.05); PLT count and aPTT were not associated with bleeding complications (p > 0.05) |
| Tomoyose           | No hemothorax (N = 0)                                                                                               | Subcutaneous hematomas: 0.0% in US group, 7.8% in landmark group                    | PLT transfusion rate in thrombocytopenic patients with PLT counts >20 \times 10^9/L was 28.6% (2 of 7 patients) in the US group and 100% in the landmark group (p = 0.002) |
| Singh 2015         | A vascular complication for which active medical intervention required like blood transfusion, chest drain insertion (N = 0) | Hematoma, development of swelling of >2 cm at site of skin puncture, 10%; persistence of ooze even after 15 min of digital compression or requiring change in dressing for >3 times in 24 hours, 13%; both hematoma and ooze: 4.7% | Hematoma: INR >3 (12%); <3 (10%); PLT (in \times 10^9/L) <3 (10%), >30 (12%); ooze: INR >3 (12%); <3 (13%); PLT <30 (23%); >30 (11%); PLT count <30 (OR, 2.29) was an independent risk factor for oozing |
| Vinson 2014        | Major hemorrhage or minor hemorrhage with procedural intervention: mild coagulopathy group (N = 6), moderate-to-severe coagulopathy group (N = 3; 0.3%) | Mild coagulopathy group N = 23 (3.6%); moderate-to-severe coagulopathy group (N = 15; 5%) | The difference in the incidence of hemorrhagic complications between mild and moderate-to-severe laboratory abnormalities was not significant (p = 0.32), nor was the difference in the incidence of major hemorrhage combined with minor hemorrhage requiring procedural intervention (p = 1.0); 8 patients with minor bleeding received a post-hemorrhagic intervention |
| Weigand 2009       | A drop of hemoglobin >1.5 g/dL within 24-36 hours after catheter placement; one patient required a suture (N = 5; 1.5%) | Subcutaneous hematoma and/or strong bleeding at the puncture site (N = 5; 3%)         | RR for bleeding compared with the study population without hematostatic disorders is not significant for PLTs <50 \times 10^9/L (N = 19; RR, 0.28; p = 0.25), INR >1.5 (N = 39; RR, 0.86; p = 0.90), combined PLTs and INR 1.5 (N = 7; RR, 0.695; p = 0.94); the study did not report laboratory values of the patients who had major complications |
Various patient characteristics were associated with hemorrhagic complications. One study reported more bleeding complications in medical patients compared with surgical or trauma patients.\textsuperscript{21} The presence of ascites was also identified as an independent risk factor for post-procedural bleeding.\textsuperscript{40} In another study, fibrinogen levels was also identified as an independent risk factor for post-procedural bleeding complications.\textsuperscript{42} Fibrinogen levels were significantly lower in the bleeding group (4.1 g/dL; range, 1.0-14.4 g/dL) compared with the nonbleeding group (4.8 g/dL; range, 0.7-14.7 g/dL).\textsuperscript{42}

**DISCUSSION**

Our goal was to identify the incidence and risk factors of bleeding complications after central venous catheterization in patients with severe hemostatic defects. The 22 included studies indicated that major bleeding complications are rare in patients with thrombocytopenia and/or prolonged bleeding time. However, the exact values of platelet count, INR, and PTT in which central venous catheterization can safely be performed remain unclear.

A major shortcoming of the current literature on bleeding complications after CVC placement in the presence of coagulopathy is study design. Except for one, all included studies had an observational cohort design. The rationale for correction of coagulopathy was often incompletely reported.

Furthermore, the definition of bleeding complications varied widely across studies. The reporting of minor bleeding complications varied from no reporting to the reporting of hematomas, prolonged oozing, and small interventions, such as the placement of a suture, bandage dressing, or prolonged manual compression. The lack of consistency in definitions of bleeding complications is a serious problem. A uniform definition should be used in studies that investigate bleeding complications. In addition, outcomes should be scored on clinically relevant bleeding, because the clinical relevance of a minor bleeding complication may be questionable.

Abnormal coagulation parameters are observed more frequently in patients who have bleeding complications compared with those without bleeding complications after CVC placement. However, the severity of coagulopathy does not correspond with the bleeding risk. In various invasive procedures, there is insufficient evidence that coagulation test results predict bleeding.\textsuperscript{14,44} DeLoughery and coworkers stated that a group at high risk for bleeding could be identified. Unfortunately, the predictive value of the combination of coagulation abnormalities could not be proven. Other authors found no difference in the incidence of hemorrhagic complications for independent coagulation variables alone.\textsuperscript{21,30} The association between severe thrombocytopenia and minor bleeding complications is consistent for the included studies: seven studies reported evidence supporting this result, whereas only two found no association.

The correction of hemostatic defects before CVC placement remains a matter of debate. The introduction of ultrasound guidance for CVC placement led to a decrease in the number of puncture attempts and complication rates.\textsuperscript{15-49} Current national and international guidelines are based on the landmark technique and subsequently still support correction of thrombocytopenia up to a platelet count of 50 × 10\(^9\)/L and an INR of 1.5 or greater before CVC placement.\textsuperscript{15-17} Various authors advise transfusing platelets below a platelet count of 20 × 10\(^9\)/L.\textsuperscript{18,39,42} However, there is no profound evidence to support this threshold. The minimum platelet count at which central cannulation can safely be performed without prophylactic platelet transfusion may be less than 20 × 10\(^9\)/L. Several studies revealed no significant difference in the outcome of bleeding complications in patients who attained precatheter correction of hemoestasis.\textsuperscript{18,28}

Two studies reported no positive effect of prophylactic FFP administration on bleeding complications in patients with prolonged PT.\textsuperscript{16,35} In one observational cohort study, patients who received FFP had a higher baseline INR.\textsuperscript{35} This may have reduced the positive effect of prophylactic FFP. That study had a high risk of selection bias. FFP transfusion was left to the discretion of the operator, and no clear rationale for FFP could be identified in a substantial amount of patients. The mere preprocedural measurement of PT was a risk factor for FFP transfusion.

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**Table 2: Continued**

| Study | Major bleeding, definition, and no. of patients | Minor bleeding, definition, and no. of patients | Relevant results |
|-------|-----------------------------------------------|-----------------------------------------------|-----------------|
| Zeidler 2011\textsuperscript{52} | WHO grade 3 to 4 bleeding (N = 0) | WHO grade 1 and grade 2 bleeding requiring prolonged local compression; incidence, 32% (96% grade 1, 4% grade 2) | Bleeding incidence was 33% in patients with laboratory hemostatic dysfunction, vs. 32% without (p = 0.768); only patients with a PLT count <20 × 10\(^9\)/L were at higher risk for bleeding both before transfusion (OR, 2.88; p = 0.015) and after pre-procedural platelet transfusions (OR, 2.84; p = 0.006) compared with those who had PLT counts ≥100 × 10\(^9\)/L |
The other study was a moderate to high-quality, randomized controlled trial that lacked statistical power because of a low inclusion rate. The prevalence of hematoma has also been associated with insertion technique. In an observational study, 1584 placements by the landmark method were compared with 2367 catheter placements after the introduction of ultrasound guidance. The incidence of hematoma decreased from 8.2% in the landmark group to 1.6% after the introduction of ultrasound guidance. Our study included studies that used both insertion methods.

Our review comes with several limitations. The retrospective and/or observational nature of most of the studies we included is a disadvantage. Because of the observational design, patient selection may have occurred. In a study by Mey and colleagues, puncture teams in which both the sonographer and the puncturing physician were experienced produced more complications compared with teams in which only the sonographer was experienced. This was explained as a result of bias, which made experienced physicians more likely to perform the procedure in clinical situations that made puncture difficult. Important

| Study       | PLT, ×10^9/L | INR | PTT, sec | CVC | Correction                  | Complication, comments                                                                 |
|-------------|--------------|-----|----------|-----|-----------------------------|----------------------------------------------------------------------------------------|
| Carino20    | 118          | 3.9 | NR       | IJV | Patient received 5 units of FFP preprocedure | Postprocedure, a large hematoma was noted, and both local compression and an additional 5 units of FFP were used to stop the bleeding technical difficulties with placing the line and multiple cannulation attempts were documented; ultimately, placement of the line failed |
| Deloughery21| —*           | —* | —*       | NR  | Not specified               | CVC placement during trauma resuscitation; patient developed a hemothorax that required chest tube drainage |
| Deloughery21| —*           | —* | —*       | NR  | Not specified               | Woman developed a hemothorax                                                                 |
| Doerfler26  | 6            | NR  | NR       | SCV | No correction               | Postprocedural transfusion of 5 units of platelet concentrates; one patient with Kaposis’s sarcoma of the skin required 1 hour of direct pressure to stop the bleeding from the skin |
| Fisher24    | 68           | <1.5| NR       | SCV | Patient received massive blood transfusion for variceal hemorrhage | Hemothorax after accidental subclavian artery puncture in a patient who received prostacyclin therapy for hemofiltration; the hemothorax caused respiratory embarrassment and required evacuation at thoracotomy, but the patient died of multiorgan failure 2 days later |
| Rizvi36     | 83           | NR  | NR       | SCV/IJV | Not specified | Death, 28-year-old woman, hemorrhage related in part to systemic lupus erythematosus with recurrent pleuritic and pericarditis that had been treated continually with glucocorticoids for 9 years |
| Rizvi36     | 75           | NR  | NR       | SCV/IJV | Not specified | Major hemorrhage, that prevented plasma exchange treatment |
| Tercan38    | NR           | 4   | NR       | IJV | No correction               | The catheter had to be removed, because oozing around the catheter could not be stopped; every attempt to stop bleeding, including manual compression and pressure dressing and 3 units of FFP, failed; manual compression after removal of the catheter stopped the bleeding |
| Vinson30    | 207          | 1.4 | NR       | SCV | Not specified               | Hemothorax in a critically ill emergency department patient who had a refractory septic shock |
| Mumtaz28    | 12           | 1.2 | 24       | NR  | No correction               | In a patient with multiple myeloma, manual compression was not sufficient to stop bleeding; hemostasis was obtained by placing a string suture around the catheter entry site |
| Mumtaz28    | 31           | 1.5 | 34       | NR  | No correction               | In a patient with septic shock, manual compression was not sufficient to stop bleeding; hemostasis was obtained by placing a string suture around the catheter entry site |
| Mumtaz28    | 46           | 1.1 | 42       | NR  | No correction               | In a patient with renal failure, manual compression was not sufficient; hemostasis was obtained by placing a string suture around the catheter entry site |
| Mumtaz28    | 154          | 1.1 | 35       | NR  | Abnormal hemostasis corrected, type and amount of units not specified | In a patient with multiple myeloma, abnormal hemostasis was corrected before cannulation; manual compression was not sufficient to stop bleeding; hemostasis was obtained by placing a string suture around the catheter entry site |

* Multiple hemostatic defects were reported.
gaps in methodological reporting and the acknowledge-
ment of bias and confounders have been described previ-
ously in clinical platelet transfusion studies.\textsuperscript{51} Therefore,
the low occurrence of bleeding in severely coagulopathic
patients may be confounded by more precarious mea-
sures before cannulation, such as placement by more
experienced staff members or the selective use of ultra-
sound for high-risk patients.

The positive effect of ultrasound guidance and the
effect of experience with the procedure on complication
rates have previously been demonstrated.\textsuperscript{46,52-54} Hence, it
is suggested that the risk of bleeding after central venous
catheterization is multifactorial and includes procedural,
patient, and physician characteristics. The number of
attempts, inadvertent arterial puncture, vein size, vein
lesion, patient compliance, obesity, and hyperinflation
have been associated with bleeding risk.\textsuperscript{37,55} Echo guid-
ance can be used to identify the vessel or to advance the
needle under real-time ultrasound guidance.\textsuperscript{56} The use of
real-time ultrasound and experience with the procedure
reduce the complication rate.\textsuperscript{46,52,54} Real-time ultrasound
guidance was not yet available at the time of all studies
we included, and this may have caused bias between
studies. Therefore, it is difficult to assess the sole effect of
cogulopathy in current observational cohort studies.

In conclusion, our systematic review of the published
literature demonstrates that major bleeding after CVS
placement is rare in patients with severe coagulopathy.
The severity of coagulopathy does not correspond with
the bleeding risk. Well-powered randomized controlled
trials are necessary to determine the minimal platelet
count and the maximal, safe INR and PTT values before
CVC insertion. In these trials, the definition of bleeding
complications should be uniform, the physicians involved
should be experienced, and standard use of ultrasound
should be compulsory.

\textbf{CONFLICT OF INTEREST}

The authors have no conflicts of interest to declare.

\textbf{APPENDIX 1: SEARCH STRATEGY}

- We searched allowing any study design, except for
case report. Controlled trials, retrospective or pro-
spective cohort study, case-control study, case-
control study, case series. Bleeding complications
related to CVC placement had to be reported as an
outcome. The subgroup of patients with coagulop-
athy should be defined, and the bleeding complica-
tions should be reported for this subgroup.
- We only included studies in adults. In order not to
miss any relevant publication, no filter was used
and pediatric records were excluded manually.
- Patients must have received a central venous catheter.
- We performed four searches, with the search terms
as described below. An initial search was performed
on 01-01-2015, after which the selection of eligible
articles took place. The search was repeated on
01-11-2015, to include recent articles.
- The first three searches were performed in MED-
LINE using PUBMED with the search terms as
described below. This resulted in a total of 338 hits,
302 after removal of duplicates. A search in the
Cochrane library added 16 titles, of which 15 were
unique.
- 34 pediatric studies were excluded.
- 3 studies were excluded for not being available in
the English language.
- 3 studies were excluded for not being available in
full-text.
- 83 abstract were checked for suitability using a pre-
deﬁned form. Of all the 83 articles that were
screened on abstract level, we performed a “related articles” search. Relevant articles were checked for duplicates, after which four articles were identified for abstract review.

- Of the 83 abstract screened, 31 full-text articles were carefully read to obtain relevant information.
- A total of 22 articles were included in the current review.

The specific search terms were as follows:

- In MEDLINE: (“Catheterization, Central Venous”[Mesh] OR “Central Catheterization”[tiab] OR “Central Catheterizations”[tiab] OR “Central Venous Catheterization”[tiab] OR “Central Venous Catheterizations”[tiab] OR CV[tiab] OR CVL[tiab] OR CVCs[tiab] OR “Central Vein Catheterization”[tiab] OR “Central Vein Catheterizations”[tiab] AND (“Platelet Count”[Mesh] OR “Platelet Count”[tiab] OR “Platelet Counts”[tiab] OR “Platelet Count” OR “Platelet Number”[tiab] OR “Platelet Numbers”[tiab] OR “Blood Platelet Disorders”[Mesh] OR “Blood Platelet Disorders”[tiab] OR “Blood Platelet Disorder”[tiab] OR Thrombocytopenia[tiab] OR “Platelet Storage Pool Deficiency”[tiab]) AND (“Hemorrhage”[Mesh] OR “Hemorrhage”[tiab] OR bleeding*[tiab] OR Hematom*[tiab] OR Hemotaxon*[tiab] OR Haematom*[tiab])
- In MEDLINE: (“Catheterization, Central Venous”[Mesh] OR “Central Catheterization”[tiab] OR “Central Catheterizations”[tiab] OR “Central Venous Catheterization”[tiab] OR “Central Vein Catheterization”[tiab] OR “Central Vein Catheterizations”[tiab] OR CV[tiab] OR CVL[tiab] OR CVCs[tiab] OR “Central Venous Catheterization”[tiab] OR “Central Vein Catheterization”[tiab] OR “Central Vein Catheterizations”[tiab] AND (“Platelet Transfusion”[Mesh] OR “Platelet Transfusion”[tiab] OR “PLT transfusion”[tiab] OR “fresh frozen plasma”[tiab]) AND (“Hemorrhage”[Mesh] OR “Hemorrhage”[tiab] OR bleeding*[tiab] OR Hematom*[tiab] OR Hemotaxon*[tiab] OR Haematom*[tiab]) AND (complication*[ti] OR “Risk Factors”[Mesh] OR “risk factor”[ti]))
- In the COCHRANE library: (Central Catheterization* OR Central Catheterization* OR Central Vein Catheterization* OR CVC OR CVL OR CVCs) AND (Hemorrhage OR bleeding* OR Hematoma* OR Hemotaxon* OR Haematom*) AND (complication*)

**APPENDIX 2: RISK OF BIAS**

| Study       | Consecutive or random | No exclusions | Explicit bleeding criteria | Correction of hemostasis standardized | CVC placement standardized | Primary data collection | Criteria met | Oxford CEBM level of evidence |
|-------------|-----------------------|---------------|----------------------------|---------------------------------------|---------------------------|-------------------------|--------------|--------------------------------|
| Barrera 1996 | ✓                     | ✓             | ✓                          | X                                     | X                         | ✓                       | 4            | 3b                             |
| Carino 2012  | ✓                     | ✓             | ✓                          | X                                     | X                         | X                      | 3            | 4                             |
| Della Vigna 2009 | ✓                | ✓             | ✓                          | X                                     | X                         | X                      | 2            | 4                             |
| Doerfler 1996 | ✓                     | ✓             | ✓                          | X                                     | X                         | X                      | 4            | 3b                             |
| Fisher 1999  | ✓                     | ✓             | ✓                          | X                                     | X                         | X                      | 5            | 2c                             |
| Haas 2010    | ✓                     | ✓             | ✓                          | X                                     | X                         | X                      | 2            | 4                             |
| Kander 2013  | ✓                     | ✓             | ✓                          | X                                     | X                         | X                      | 3            | 4                             |
| Mey 2002     | ✓                     | ✓             | ✓                          | X                                     | x                         | x                      | 4            | 3b                             |
| Müller 2015  | ✓                     | ✓             | ✓                          | X                                     | ✓                         | X                      | 4            | 2b                             |
| Mumtaz 2000  | ✓                     | ✓             | ✓                          | X                                     | ✓                         | X                      | 4            | 3b                             |
| Nosari 2008  | ✓                     | ✓             | ✓                          | X                                     | ✓                         | X                      | 5            | 2c                             |
| Ong 2012     | ✓                     | ✓             | ✓                          | X                                     | x                         | X                      | 3            | 4                             |
| Oguzkurt 2005 | ✓                | ✓             | ✓                          | X                                     | X                         | X                      | 3            | 4                             |
| Ray 1997     | ✓                     | ✓             | ✓                          | X                                     | X                         | X                      | 3            | 4                             |
| Rizvi 2000   | ✓                     | ✓             | ✓                          | X                                     | X                         | X                      | 3            | 4                             |
| Singh, 2015  | ✓                     | ✓             | ✓                          | X                                     | X                         | X                      | 3            | 4                             |
| Tercan 2008  | ✓                     | ✓             | ✓                          | X                                     | X                         | X                      | 4            | 2c                             |
| Tomoyose 2003 | ✓                     | ✓             | ✓                          | X                                     | X                         | X                      | 4            | 2c                             |
| Vinson 2014  | ✓                     | ✓             | ✓                          | X                                     | X                         | X                      | 3            | 4                             |
| Weigand 2009 | ✓                     | ✓             | ✓                          | X                                     | X                         | X                      | 4            | 2c                             |

We assessed the risk of bias using the following criteria: 1) patient selection (random or consecutive vs. other), 2) whether investigators excluded non-prespecified patient groups, 3) explicitness of bleeding criteria, 4) correction of hemostasis by transfusion products (standardized vs. left to the discretion of the physician), 5) a protocol for CVC placement, and 6) primary data collection versus data chart reports. CEBM = Oxford Centre for Evidence-based Medicine.
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