Thrombosis Prophylaxis in Patient Populations With a Central Venous Catheter

A Systematic Review

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Background: Central venous catheters (CVCs) are used in a wide variety of patients. Associated complications are thrombosis and infection. It is a matter of debate whether thromboprophylaxis is beneficial.

Methods: We performed a systematic review of 3 different patient populations to render the available information in the literature more accessible to clinical practice: patients receiving parenteral nutrition (PN), patients with cancer, and patients admitted to intensive care units.

Results: Prophylaxis with heparin added to PN was found to give a nonsignificant reduction in the incidence of catheter-related thrombosis (pooled relative risk of randomized studies, 0.77; 95% confidence interval [CI], 0.11-5.48). In cancer patients, both low-dose warfarin and low-molecular-weight heparin significantly reduced the incidence of catheter-related thrombosis (relative risk of randomized studies, 0.25 [95% CI, 0.09-0.70] and 0.10 [95% CI, 0.01-0.71], respectively). So far, intensive care patients have hardly been studied with respect to thromboprophylaxis and the incidence of CVC thrombosis. Any effect of the type of catheter could not be established because of small numbers. There was no apparent increase in bleeding events with prophylactic anticoagulation in patients with CVCs.

Conclusions: In the small number of patients studied, the addition of heparin to PN did not significantly decrease the risk of catheter-related thrombosis, whereas warfarin and dalteparin did decrease the thrombosis risk in cancer patients with CVCs. There is no apparent increase in bleeding events with prophylactic anticoagulants in patients with CVCs.

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In order to render the information in the literature more accessible for clinical practice, we performed a systematic review (for a definition, see Guyatt et al) of 3 different patient populations: (1) patients receiving PN, (2) patients with cancer, and (3) critically ill patients in the intensive care unit. For each of these categories, we evaluated the incidence of both symptomatic and asymptomatic thrombosis and the effects of antithrombotic agents on this incidence.

STUDY IDENTIFICATION

A computer-assisted search was performed to identify prospective trials evaluating thrombosis related to CVCs in the specific patient populations, i.e., patients receiving PN, patients with cancer, and critically ill patients in the intensive care unit. MEDLINE was screened from 1966 to May 2002, and the following terms were used: prospective studies (Medical Subject Heading [MeSH]), catheterization (MeSH), central venous (MeSH), and thrombosis (MeSH and text word) were cross-referenced with intensive care (MeSH and text word), hematology (MeSH), hematologic diseases (MeSH), hematologic neoplasms (MeSH), hematologic (text word) or hematological (text word), medical oncology (MeSH), neoplasms (MeSH), oncologic (text word), oncological (text word) or oncology (text word), and parenteral nutrition (MeSH and text word). In EMBASE from 1988 to May 2002 the following terms were tested: central venous catheter (MeSH), indwelling catheter (MeSH), thrombosis (MeSH and text word), prospective studies (MeSH), hematologic disease (MeSH), cancer (MeSH and text word), childhood cancer (MeSH), parenteral nutrition (MeSH and text word), and intensive care (MeSH and text word).

Titles and abstracts of all publications were screened for prospective studies on the incidence of thrombosis related to CVCs. Titles and/or abstracts that seemed relevant were selected and full articles were examined. References of all articles were cross-checked to identify additional articles.

STUDY SELECTION

The following criteria were used for the selection of the trials to be included in the present analyses:

Study design: Prospective studies.

Populations: Adult and pediatric patients with a CVC in the subclavian, jugular, or femoral vein. When other localizations were used, a specification of the incidence of thrombosis in the insertion site had to be given. One specific group of patients had to be considered or described separately, i.e., patients receiving PN, patients with cancer, and patients in the intensive care unit. Patients undergoing marrow harvesting have been found to develop a hypercoagulable state; therefore, studies on patients undergoing stem cell transplantation procedures were excluded to ensure homogeneity in the malignancy group.

Intervention: When heparin flushes or antithrombotic agents in prophylactic or therapeutic doses were used, a specification of the exact amounts had to be given. When different groups of patients had different catheter regimens, the incidence of thrombosis per group had to be specified.

Outcome: Catheter-related thrombosis, being a mural thrombus, with partial or total occlusion of a vessel in which a catheter is present or had been present within the last month, as confirmed by a regular imaging technique (either ultrasound or [contrast] venography). Radionuclide venography was considered equivalent to contrast venography, since the studies that used this technique had confirmed the first 3 positive scintigrams by contrast angiography.

Follow-up: As proposed by Randolph et al, the percentage of patients who are not analyzed after inclusion should not exceed 40%. In the case of prospective imaging, this also means that at least 60% of the patients included should have had an imaging study performed that was evaluable.

RECORDED DATA

Of all studies, the following data were extracted: whether the study was a randomized or prospective cohort study, which patient group was studied, the number of cases (either patients or catheters), the type of catheter (tunneled, not tunneled, or port), the use of anticoagulants and/or heparin flush and dosage, the duration of observation, the imaging technique used to detect thrombosis, the total number of cases of thrombosis (when imaging was performed prospectively), and the number of cases of symptomatic thrombosis.

COMPARISONS

Studies were divided according to patient population studied (patients receiving PN, patients with cancer, and patients in the intensive care unit). The included studies were further classified on the basis of their methodological strength. Studies in which the patients were randomized to different anticoagulation regimens, intervention vs placebo, or intervention vs no intervention, were considered to represent the most convincing studies (level 1). Prospective cohort studies and studies that were randomized for possible prognostic factors other than anticoagulant therapy, for example, the type of CVC, were considered level 2 studies, since this forms a higher potential for bias in antithrombotic regimen.

The level 2 studies were subsequently subdivided into (1) cohorts receiving no anticoagulant therapy, (2) cohorts receiving heparin flushing, and (3) cohorts receiving another form of antithrombotic therapy in either a prophylactic or therapeutic dose. Patients receiving heparin locks were considered to receive no anticoagulant therapy, since a lock implicates that the fluid present in the catheter is taken out before a new infusion is started, whereas flushing implicates (heparinized) fluid entering the body. Heparin-bonded catheters were considered as a form of anticoagulant treatment and were therefore included in the third group. Studies that included different catheter regimens or both heparin-bonded catheters and standard catheters were considered to be different cohorts.

Within these groups, we also analyzed the effects of the different types of catheters. We divided the wide array of devices that are available into 3 groups: the totally implanted subcutaneous port, and 2 external forms, the tunneled catheter, where a part of the catheter is positioned underneath the skin; and the catheter that is not tunneled but goes directly through the skin into the vein.

STATISTICAL ANALYSIS

When the level 1 studies compared the effects of similar anticoagulant treatment, the data were pooled and analyzed with a statistical software package (Review Manager version 4.1; The Cochrane Collaboration 2000). For each study the relative risk (RR) with 95% confidence interval (CI) for dichotomous data was calculated. Since the studies were found to be rather heterogeneous, we used the DerSimonian-Laird method for random effects.14 P < .05 was considered to be statistically significant.
Sixty-three prospective studies were found in which one of our predefined populations was studied. Of these 63 studies, 42 were excluded because of the reasons specified below, thus leaving 21 studies: 6 on patients receiving PN, 11 on patients with cancer, and 4 on patients in the intensive care unit.

**PARENTERAL NUTRITION**

Thirteen studies were identified in which data on patients receiving PN were reported. Six of these were eligible for this analysis and included five level 1 studies and one level 2 study. All 6 studies were performed in adults. No eligible studies on pediatric patients were identified. The details of the included studies are listed in Table 1. Seven studies were excluded because of the following reasons: the predefined locations of interest were not reported separately; distinction was not possible between thrombosis and thrombophlebitis or catheter obstruction; patients received other anticoagulant treatment, but separate analysis was not feasible; no objective tests were used to confirm the clinically suspected deep vein thrombosis; and the catheter was removed more than 1 month before imaging.

**Level 1 Studies**

In the level 1 studies, a total of 204 patients were studied with prospective imaging of the relevant veins. One hundred patients received heparin infusions and the other 104 patients served as a control group.

Macoviak et al15 studied 37 surgical patients who were randomized to receive either heparin or a saline solution added to their PN. In patients undergoing surgery, the PN and its additions were temporarily stopped and instead a 10% dextrose solution was given via the catheter. Venography was performed in all patients after 2 weeks, and 2 cases of thrombosis were found in the 17 heparin-treated patients compared with 1 in the 20 controls. Four weeks after catheter insertion, venography was repeated in 5 patients of both study arms and 2 new cases of occlusion were found in the heparin group and none in the control group. The authors concluded that heparin (in the dosage of 1 IU/mL PN) had no effect on the prevention of catheter-related thrombosis in surgical patients who received PN.

**Table 1. Characteristics of Level 1 and Level 2 Studies on the Incidence of Catheter-Related Thrombosis in Patients Receiving Parenteral Nutrition (PN)**

<table>
<thead>
<tr>
<th>Source</th>
<th>Intervention</th>
<th>Incidence of Asymptomatic + Symptomatic Thrombosis, No. (%)</th>
<th>Incidence of Symptomatic Thrombosis, No. (%)</th>
<th>Duration of Observation</th>
<th>Investigation</th>
<th>Catheter</th>
<th>Localization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macoviak et al,15 1984</td>
<td>1 U heparin per 1 mL PN; 10% dextrose when operation was needed</td>
<td>4/17 (23.5)</td>
<td>. . .</td>
<td>Catheter duration &lt;6 wk</td>
<td>Venography at 2-wk interval</td>
<td>Not specified</td>
<td>Subclavian</td>
</tr>
<tr>
<td>Brismar et al,16 1982</td>
<td>5000 IU heparin every 6 h; 250-500 U heparin after use</td>
<td>0/23</td>
<td>. . .</td>
<td>Catheter duration 7-94 d</td>
<td>Catheter venography</td>
<td>Not tunneled</td>
<td>Jugular</td>
</tr>
<tr>
<td>Fabri et al,7 1984</td>
<td>3000 U heparin per liter PN</td>
<td>1/26 (3.8)</td>
<td>0/20</td>
<td>Catheter duration 19.6 ± 2.4 d&lt;sup&gt;*&lt;/sup&gt;</td>
<td>Radionuclide venography</td>
<td>Not tunneled</td>
<td>Subclavian</td>
</tr>
<tr>
<td>Fabri et al,12 1982</td>
<td>3000 USP U heparin per liter PN</td>
<td>2/24 (8.3)</td>
<td>. . .</td>
<td>Catheter duration 22.1 ± 3.2 d&lt;sup&gt;*&lt;/sup&gt;</td>
<td>Radionuclide venography</td>
<td>Not tunneled</td>
<td>Subclavian</td>
</tr>
<tr>
<td>Ruggiero and Aisenstein,17 1983</td>
<td>No heparin, different catheter material</td>
<td>0/20</td>
<td>0/20</td>
<td>Catheter duration 19.6 ± 2.4 d&lt;sup&gt;*&lt;/sup&gt;</td>
<td>Radionuclide venography</td>
<td>Not tunneled</td>
<td>Subclavian</td>
</tr>
<tr>
<td>Valerio et al,18 1981</td>
<td>No heparin</td>
<td>6/18 (33)</td>
<td>1/30 (3)</td>
<td>Therapy duration 18 (7-43) d†</td>
<td>Venography</td>
<td>Not tunneled</td>
<td>Subclavian and jugular</td>
</tr>
</tbody>
</table>

*Period is given as mean ± SE.
†Period is given as mean (range).
In the 2 studies performed by Fabri et al.\textsuperscript{7,12} and in the study by Ruggiero and Aisenstein,\textsuperscript{7} randomization was performed between addition of heparin to the PN or no form of prophylaxis (ie, no heparin flushes either). One of these studies indicated a decrease in thrombosis in the heparin group (32% and 8%, respectively, \(P < .05\))\textsuperscript{12} yet the other 2 studies found no thrombosis in either study arm.\textsuperscript{7,17}

Of the 206 cases studied (204 patients with 206 catheter periods), imaging showed thrombosis related to 6 (6%) of 101 catheters of heparin recipients and 9 (9%) of 105 catheters in the controls, resulting in a weighted RR of 0.77 (95% CI, 0.11-5.48). If one excludes the study in which both treated patients and controls received additional heparin flushes,\textsuperscript{16} the mean thrombosis incidence was slightly higher (8% [6/78] and 10% [8/79], respectively), resulting in a weighted RR of 1.00 (95% CI, 0.06-17.09). However, surprisingly, the exclusion of this study resulted in a significant test for heterogeneity (\(P = .026\)). Taken together, the analysis shows a nonsignificant trend in favor of the addition of heparin to PN, but this trend disappears when the study with additional heparin flushing is left out of the analysis.

**Level 2 Studies**

The single level 2 study studied a total of 30 patients, 16 of whom had cancer and none of whom received anticoagulation.\textsuperscript{18} Venography was performed in the 24-hour period prior to catheter removal. The percentage of thrombosis found (33%) is similar to that in the untreated group of three level 1 studies.\textsuperscript{12,15,16}

**Bleeding**

In the 5 studies on patients receiving heparin added to their PN, 1 does not report bleeding complications,\textsuperscript{17} 3 mention specifically that no bleeding complications were detected,\textsuperscript{7,12,11} and 1 reports 3 episodes of mild hemorrhage.\textsuperscript{16} In the latter study, patients were randomized to receive or not receive 5000 IU of heparin every 6 hours in addition to the standard protocol, which consisted of heparin flushes after each use. In the heparin group, 3 bleeding episodes were reported in 3 different catheter periods in 2 patients. One patient with a preexistent colitis ulcerosa had melena and the other with a preexistent Crohn disease had bleeding in a fistula. Both hemorrhages were mild and transfusions were not necessary.\textsuperscript{16} All 3 catheter episodes were excluded from further analyses by the original investigators, and are therefore not included in Table 1.

**MALIGNANCIES**

Thirty-five studies were identified on CVC-related thrombosis in patients with hematological malignancies or solid tumors. Eleven studies were included in the analysis, two level 1 studies and nine level 2 studies. Two of the latter studies included patients with different anticoagulation regimens. Therefore, these different groups were regarded as cohorts.\textsuperscript{26,27} Another study reported both on retrospective and prospective data.\textsuperscript{28} Only the prospective study has been included. One study dealt with pediatric patients,\textsuperscript{29} the others all studied adults. Details of the studies are presented in Table 2. The other 24 studies were excluded because of the following reasons: no specification of the catheter location,\textsuperscript{8,38-43} other locations than the predefined locations were used,\textsuperscript{44,45} the predefined locations of interest were not reported separately,\textsuperscript{46-51} objective tests had not been used to confirm clinically suspected deep vein thrombosis,\textsuperscript{52,53} a separate specification of thrombosis incidence in patients receiving additional anticoagulants was not presented,\textsuperscript{54} the heparin dose was not specified,\textsuperscript{55} or patients undergoing stem cell transplantation procedures were included.\textsuperscript{56,57} Finally, 2 studies reported on different aspects of the same study population.\textsuperscript{58,59} The most recent of them, covering the largest time scale, was selected to be included in the present systematic review.\textsuperscript{32}

**Level 1 Studies**

In the study of Bern et al.,\textsuperscript{30} 121 patients receiving chemotherapy for either hematological malignancies or solid tumors were prospectively randomized to no therapy or 1 mg/d of warfarin or less to keep the prothrombin time within the reference range (11.5-13.5 seconds). Medication was started 3 days before catheter insertion and was continued for 90 days. In addition, patients of both groups received a maximum of 500 U of heparin for catheter flush. In 82 patients venography was performed at day 90 or earlier in case of clinical indications of thrombosis.

The second level 1 study\textsuperscript{31} reports on 29 patients with solid tumors randomized to no therapy or 2500 IU of dalteparin once daily, starting 2 hours before catheter insertion. Venography was performed at day 90 or earlier when thrombosis was suspected.

Both studies found an important and statistically significant reduction in thrombosis when prophylaxis was used in addition to standard catheter care by heparin flushing in both groups (ie, from 37.5% to 9.5% and from 61.5% to 6.3%, respectively, resulting in RRs of 0.25 [95% CI, 0.09-0.70] and 0.10 [95% CI, 0.01-0.71], respectively). Since these 2 studies used different forms of prophylaxis (warfarin in one and dalteparin in the other), the data were not pooled.

**Level 2 Studies**

In the level 2 studies, 7 cohorts were described in which no anticoagulation was used,\textsuperscript{26,28,32-34} 2 in which heparin flushing was used,\textsuperscript{27,35} 2 in which low-dose warfarin was given,\textsuperscript{36,37} and 1 in which heparin was infused.\textsuperscript{26}

In the studies in which no anticoagulant treatment was reported, the incidences of thrombosis varied considerably (incidences between 27% and 90%, symptomatic thrombosis between 0% and 20%), possibly reflecting a time-incidence correlation. For example, in the study with a mean duration of observation of 12.8 days, the incidence of thrombosis was 27%,\textsuperscript{26} whereas in the study in which the observation lasted for a median of 105 days the incidence was 66.3%.\textsuperscript{33}

In the true anticoagulation group, in which either heparin was added to the infusion fluids or warfarin was administered, a longer duration of catheterization (a mean of 121.8 days vs 12.8 days) is also associated with a higher
incidence (4.4% vs 0%\textsuperscript{26,37}). When the range of incidences in the 3 different treatment groups is considered (Table 3), a trend toward a decrease in especially asymptomatic thrombosis is found in the studies in which some kind of prophylactic regimen was used (either flushing or true anticoagulation). However, whether there is an additional decrease in incidence when anticoagulant treatment (heparin addition or warfarin) is used instead of (only) flushing with heparin cannot yet be concluded with certainty.

### Table 2. Characteristics of Level 1 and Level 2 Studies on the Incidence of Catheter-Related Thrombosis in Patients With Cancer

<table>
<thead>
<tr>
<th>Source</th>
<th>Intervention</th>
<th>Incidence of Asymptomatic + Symptomatic Thrombosis, No. (%)</th>
<th>Incidence of Symptomatic Thrombosis, No. (%)</th>
<th>Duration of Observation(^*)</th>
<th>Investigation</th>
<th>Catheter</th>
<th>Localization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bern et al,\textsuperscript{26} 1990</td>
<td>Warfarin, 1 mg/d; maximum 500 U heparin per week</td>
<td>4/42 (9.5)</td>
<td>4/42 (9.5)</td>
<td>90 d</td>
<td>Venography</td>
<td>Ports</td>
<td>Subclavian</td>
</tr>
<tr>
<td>Monreal et al,\textsuperscript{21} 1996</td>
<td>2500 IU low-molecular-weight heparin daily and 10 mL heparin/saline mixture once per week</td>
<td>1/16 (6.3)</td>
<td></td>
<td>90 d</td>
<td>Venography</td>
<td>Ports</td>
<td>Subclavian</td>
</tr>
</tbody>
</table>

**Level 2 Studies: Incidence Without Anticoagulation**

<table>
<thead>
<tr>
<th>Source</th>
<th>Intervention</th>
<th>Incidence of Asymptomatic + Symptomatic Thrombosis, No. (%)</th>
<th>Incidence of Symptomatic Thrombosis, No. (%)</th>
<th>Duration of Observation(^*)</th>
<th>Investigation</th>
<th>Catheter</th>
<th>Localization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bozzetti et al,\textsuperscript{26} 1983</td>
<td>No heparin</td>
<td>10/37 (27)</td>
<td>0/37</td>
<td>12.8 (6-38) d</td>
<td>Venography</td>
<td>Not specified</td>
<td>Subclavian</td>
</tr>
<tr>
<td>Horne et al,\textsuperscript{27} 1995</td>
<td>Only saline flush</td>
<td>5/13 (38)</td>
<td></td>
<td>40 ± 8.6 d</td>
<td>Venography</td>
<td>Tunneled and 1 port</td>
<td>Subclavian</td>
</tr>
<tr>
<td>Lokich et al,\textsuperscript{28} 1983</td>
<td>None reported</td>
<td>12/26 (46.2)</td>
<td>5/26 (19.2)</td>
<td>Therapy duration (5 d-7 mo); asymptomatic maximum 30 d</td>
<td>Venography</td>
<td>Tunneled</td>
<td>Subclavian</td>
</tr>
<tr>
<td>Knöfler et al,\textsuperscript{29} 1999</td>
<td>Heparin lock every 7 d when not in use</td>
<td>...</td>
<td>9/77 (11.7)</td>
<td>Not specified</td>
<td>Sonography, sometimes with venography</td>
<td>76 Tunneled and 1 subcutaneous</td>
<td>Jugular</td>
</tr>
<tr>
<td>Tolar and Gould,\textsuperscript{29} 1996</td>
<td>Saline flush</td>
<td>...</td>
<td>66/324 (20)</td>
<td>168.1 (0-952) d</td>
<td>Venography</td>
<td>Tunneled</td>
<td>Subclavian</td>
</tr>
<tr>
<td>De Cicco et al,\textsuperscript{30} 1997</td>
<td>Heparin lock at least once per 3 wk</td>
<td>63/95 (66.3)</td>
<td>4/95 (4.2)</td>
<td>Median 105 d</td>
<td>Venography</td>
<td>Ports and Groshong catheter</td>
<td>Subclavian</td>
</tr>
<tr>
<td>De Cicco et al,\textsuperscript{31} 1995</td>
<td>None</td>
<td>36/40 (90)</td>
<td>...</td>
<td>19.4 (8-40) d</td>
<td>Venography</td>
<td>Not tunneled</td>
<td>Subclavian</td>
</tr>
</tbody>
</table>

**Level 2 Studies: Incidence With Heparin Flushing**

<table>
<thead>
<tr>
<th>Source</th>
<th>Intervention</th>
<th>Incidence of Asymptomatic + Symptomatic Thrombosis, No. (%)</th>
<th>Incidence of Symptomatic Thrombosis, No. (%)</th>
<th>Duration of Observation(^*)</th>
<th>Investigation</th>
<th>Catheter</th>
<th>Localization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Horne et al,\textsuperscript{27} 1995</td>
<td>Tunneled: 200 U heparin daily; port: 200 U heparin per month</td>
<td>13/37 (35)</td>
<td>...</td>
<td>40 ± 8.6 d</td>
<td>Venography</td>
<td>Tunneled and 1 port</td>
<td>Subclavian</td>
</tr>
<tr>
<td>Brown-Smith et al,\textsuperscript{32} 1990</td>
<td>5 mL of 10 U/mL heparin daily and/or 10 mL of 100 U/mL heparin daily</td>
<td>...</td>
<td>50/294 (17)</td>
<td>Maximum 12 mo</td>
<td>Venography or autopsy after clinical suspicion</td>
<td>Tunneled</td>
<td>Subclavian</td>
</tr>
</tbody>
</table>

**Level 2 Studies: Incidence With Anticoagulation**

<table>
<thead>
<tr>
<th>Source</th>
<th>Intervention</th>
<th>Incidence of Asymptomatic + Symptomatic Thrombosis, No. (%)</th>
<th>Incidence of Symptomatic Thrombosis, No. (%)</th>
<th>Duration of Observation(^*)</th>
<th>Investigation</th>
<th>Catheter</th>
<th>Localization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bozzetti et al,\textsuperscript{26} 1983</td>
<td>Heparin, 1 U/mL infusion (2500-3100 mL/d)</td>
<td>5/15 (33)</td>
<td>0/15</td>
<td>12.8 (6-38) d</td>
<td>Venography</td>
<td>Not specified</td>
<td>Subclavian</td>
</tr>
<tr>
<td>Boraks et al,\textsuperscript{36} 1998</td>
<td>Warfarin, 1 mg/d; when not in use, 20 mL heparin twice per week</td>
<td>...</td>
<td>5/108 (4.6)</td>
<td>Catheter duration</td>
<td>Venography or ultrasound</td>
<td>External both tunneled and not</td>
<td>Subclavian</td>
</tr>
<tr>
<td>Nightingale et al,\textsuperscript{37} 1997</td>
<td>Warfarin, 1 mg/d; twice per week heparin flush</td>
<td>...</td>
<td>42/949 (4.4)</td>
<td>Mean 121.8 d</td>
<td>Venography or ultrasound</td>
<td>Tunneled</td>
<td>Subclavian, jugular, and femoral</td>
</tr>
</tbody>
</table>

\(^*\)Unless otherwise indicated the period is given as mean ± SD or mean (range).
Interestingly, the incidences found in patients treated with heparin flushes in the level 1 study by Bern et al are comparable to those found in the level 2 studies (37.5% vs 35% overall incidence\(^27\) and 25% vs 17% for symptomatic thrombosis\(^35\)), but are rather low compared with the incidence of 61.5% found in the control group of the other level 1 study.\(^31\) Conversely, both level 1 studies reported a lower overall incidence in the treatment group than the level 2 studies (6.3%\(^30\) and 9.5%\(^31\) vs 33% in the level 2 study by Bozzetti et al\(^26\)).

### Bleeding

In both level 1 studies on patients with cancer who were randomized to receive or not receive anticoagulant treatment in addition to heparin flushes, bleeding did not occur.\(^30,31\) Of the level 2 studies on cancer patients only 1 reported on bleeding complications: Boraks et al\(^30\) stated specifically that no episodes of fatal, life-threatening, intracranial, or intraocular bleeding had occurred in the 108 patients who received warfarin.

### INTENSIVE CARE

Fifteen studies were identified on thrombosis associated with CVCs in patients in the intensive care unit. Four of these were included in our analysis. All were level 2 studies, 1 on adults\(^60\) and 3 on pediatric patients.\(^61-63\) The details of these studies are given in Table 4. The other 11 studies were excluded for the following reasons: the location of the catheter studied,\(^64-68\) or a separate specification of thrombosis incidence in patients receiving (additional) anticoagulants was not presented.\(^69-74\)

#### Level 1 Studies

Level 1 studies on catheter-related thrombosis in this patient population were not identified.

#### Level 2 Studies

The study of Durbec et al\(^60\) appeared to be the only one on adults admitted to the intensive care unit that was eligible for inclusion in our systematic review. Venography was performed on removal of the (femoral) catheters of 70 patients and the authors concluded that the complication rates of the femoral catheters (8.5% femoral vein thrombosis) were similar to those reported in jugular and subclavian catheters.

The other 3 studies were performed on pediatric patients. Krafte-Jacobs et al\(^61\) described a population of 50 patients in whom both standard and heparin-bonded cath-

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**Table 3. Ranges of Incidence of Catheter-Related Thrombosis in Patients With Cancer, Subdivided by Intervention Into Those Receiving No Anticoagulation, Those Receiving Heparin Flushes, and Those Receiving True Anticoagulation**

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Incidence of Asymptomatic + Symptomatic Thrombosis, %</th>
<th>Incidence of Symptomatic Thrombosis, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>No anticoagulation</td>
<td>27-90</td>
<td>0-20</td>
</tr>
<tr>
<td>Heparin flushes</td>
<td>35</td>
<td>17</td>
</tr>
<tr>
<td>True anticoagulation</td>
<td>33</td>
<td>0-4.6</td>
</tr>
</tbody>
</table>

**Table 4. Characteristics of the Level 2 Studies on the Incidence of Catheter-Related Thrombosis in Critically Ill Patients in the Intensive Care Unit**

<table>
<thead>
<tr>
<th>Source</th>
<th>Intervention</th>
<th>Incidence of Asymptomatic + Symptomatic Thrombosis, No. (%)</th>
<th>Incidence of Symptomatic Thrombosis, No. (%)</th>
<th>Duration of Observation</th>
<th>Investigation</th>
<th>Catheter Localization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Durbec et al,(^60) 1997</td>
<td>None mentioned</td>
<td>8/70 (11.4)</td>
<td>0/70</td>
<td>Catheter duration, 8.8 ± 4.4 d(^*)</td>
<td>Venography</td>
<td>Tunneled Femoral</td>
</tr>
<tr>
<td>Krafte-Jacobs et al,(^61) 1995</td>
<td>None mentioned†</td>
<td>11/25 (44.0)</td>
<td>11/25 (44.0)</td>
<td>Catheter duration</td>
<td>Ultrasound</td>
<td>Not tunneled Femoral</td>
</tr>
<tr>
<td>Beck et al,(^62) 1998</td>
<td>100 IU/mL heparin every 6 h when not in use</td>
<td>17/93 (18.3)</td>
<td>7/93 (7.5)</td>
<td>Catheter duration</td>
<td>Ultrasound</td>
<td>Not specified Subclavian, jugular, and femoral</td>
</tr>
<tr>
<td>Krafte-Jacobs et al,(^61) 1995</td>
<td>Heparin-bonded catheter</td>
<td>2/25 (8.0)</td>
<td>2/25 (8.0)</td>
<td>Catheter duration</td>
<td>Ultrasound</td>
<td>Not tunneled Femoral</td>
</tr>
<tr>
<td>Talbott et al,(^63) 1995</td>
<td>10 U heparin every 6 h when not in use; heparin-bonded catheter</td>
<td>7/20 (35.0)</td>
<td>1/20 (5.0)</td>
<td>Up to 10 d after placement (catheter duration; mean 5 d)</td>
<td>Ultrasound</td>
<td>Not specified Femoral</td>
</tr>
</tbody>
</table>

*Period is given as mean ± SD.
†Standard catheter.
eters were used in a nonrandomized manner. A similar percentage of patients in each catheter group received PN. The incidence of cancer was not reported. Ultrasonography was performed weekly and the authors found a significant decrease in thrombosis in the patients with a heparin-bonded catheter (8% vs 44%, \(P = .004\)). Beck et al\(^\text{62}\) reported on 93 pediatric patients. An ultrasound was performed on these patients in the first week after CVC placement and weekly thereafter. They found that 15 of the 17 cases of thrombosis that had been detected were diagnosed within 4 days of CVC placement. Young age and the presence of cancer were found to be risk factors in this study (odds ratio for age, 0.72 [95% CI, 0.54-0.96] and for cancer 17.23 [95% CI, 1.5-194]). Talbott et al\(^\text{63}\) described a population of 20 patients with heparin-bonded catheters. Six of these patients received PN, 2 of whom developed thrombosis. Imaging in this study was performed within 48 hours of placement, on days 3 to 5 and days 7 to 10. In this study, 5 of the 7 cases of thrombosis were found during initial evaluation. Thus, formation of thrombus in the punctured vessel seems to be an early event in these children. However, the reported incidences of thrombosis in the different studies were very divergent, and surprisingly the patients with heparin-bonded catheters who also received heparin infusion have a similar risk of thrombosis as those who do not receive any anticoagulation.

### Bleeding

In the studies that were included on catheter-related thrombosis in patients in the intensive care unit, none reported on bleeding complications.

### COMMENT

In this review, we studied the incidence of catheter-related thrombosis, the effect of anticoagulant treatment on this incidence, and the incidence of bleeding associated with anticoagulant treatment in 3 separate patient populations: patients receiving PN, patients with cancer, and patients in the intensive care unit. We considered these populations separately as much as possible since each is associated with its own profile both with respect to the risk of thrombosis and the risk of anticoagulant-related bleeding risk. However, in clinical practice there is often overlap, for example, cancer patients receiving PN.

In all 3 study groups the incidences of thrombosis varied considerably, ranging from 0% to 33% in patients receiving PN, 0% to 90% in patients with cancer, and 0% to 44% in patients in the intensive care unit.

In patients receiving PN, prospective imaging found an overall reduction in thrombosis of 10% to 7% in patients receiving heparin added to their PN regimen. However, this difference was not statistically significant. The studies reviewed concerned short- to intermediate-term treatment with PN (4-94 days). Prospective studies on long-term treatment with PN are not available. However, a cross-sectional study by Andrew et al\(^\text{75}\) in pediatric patients receiving PN at home showed a high incidence of thrombosis (6 bilateral and 2 unilateral cases of thrombosis in 12 patients) even though the catheters were flushed with heparin after each use. The authors suggested that this group of patients should receive more intense anticoagulant treatment than heparin flushing alone.

It is still unknown what the implications of asymptomatic thrombosis are. Yet, it is conceivable that the presence of a thrombus in a vein is problematic for the future access of that vein, which is an aspect that must be taken into consideration in patients who are dependent on that access, such as patients receiving long-term or even lifelong PN. Moreover, thrombosis has been associated with infection. In a recent meta-analysis, which did not make a distinction between different patient populations, it was found that heparin treatment not only decreased catheter-related thrombosis, but was also associated with a smaller risk of catheter-related bacteremia (RR, 0.26; 95% CI, 0.07-1.03).\(^\text{13}\) Although the reduction in bacteremia was not statistically significant, it may be of importance, especially in immunocompromised patients, such as those receiving chemotherapy.

The two level 1 studies on patients with cancer reported a considerable reduction in overall incidence of thrombosis when anticoagulant therapy was used (ie, from 37.5% to 9.5% \([P < .001]\) and from 61.5% to 6.3% \([P = .002]\), respectively).\(^\text{30, 31}\) Since these studies analyzed 2 different forms of anticoagulant therapy (1 mg of warfarin\(^\text{30}\) vs therapeutic low-molecular-weight heparin\(^\text{31}\)), a conclusion cannot be drawn as to which agent should be administered. Yet, some form of prophylaxis seems to be indicated, especially since none of the included studies reported any bleeding in patients in the treatment arm of the study.

The third population that was studied was that of patients in the intensive care unit. Only a small number of studies on these patients could be identified and no definite conclusions can be drawn. The incidence of overall thrombosis reported varied between 8% and 70%. For symptomatic thrombosis this incidence was 0% to 44%.

In this review we have only included studies in which the location of the catheter studied was the subclavian, jugular, or femoral vein. However, if we look at the studies in which the site of the catheter was not given or in which the incidence of catheter-related thrombosis was not specified for our predefined catheter sites of interest, the conclusions for the different populations do not change. The only possible exception is the study by Pierce and colleagues,\(^\text{57}\) who compared heparin-bonded catheters with non–heparin-bonded ones in pediatric intensive care patients and found a significant decrease in CVC thrombosis incidence in favor of the coated CVC. Whether these findings are relevant for more CVCs needs confirmation.

Another important discussion is whether femoral catheters are associated with a higher incidence of complications than those located in the subclavian or jugular vein in critically ill patients. Since the only study that included subclavian and jugular catheters analyzed a different form of prophylaxis than the other studies that were included on femoral catheters, a conclusion could not be drawn with respect to this issue. However, in a recent study by Merrer et al,\(^\text{14}\) a significantly higher risk of...
thrombosis was found in patients with a femoral catheter (21.5% vs 1.9%) in subclavian catheters). Most of these patients who were examined with ultrasound received prophylactic anticoagulation (87% and 91% in those with a catheter in the femoral and the subclavian vein, respectively); however, the type of anticoagulation is not specified. The incidences of thrombosis found are comparable to the incidences found in this review.

In conclusion, different types of patients may have a different need for anticoagulant treatment while their CVC is in situ. Despite the small number of patients studied, it seems clear that patients with cancer should receive some form of prophylaxis, although more research is needed as to which drug should be preferred. Again, although only 206 cases were properly studied, it appears that patients with PN do not seem to benefit significantly from adding heparin to their PN. No methodologically strong studies have been performed in the intensive care setting that allow a conclusion on thromboprophylaxis of CVCs in this population. Finally, anticoagulation prophylaxis does not seem to increase the risk of bleeding in patients with CVC in general.

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