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Venous thromboembolism associated with central venous catheters in patients with cancer: from pathophysiology to thromboprophylaxis, areas for future studies

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Abstract

Symptomatic catheter related thrombosis (CRT) occurs in 4%-8% of cancer patients. The mean incidence of CRT, detected either by echography or Doppler ranges between 12 and 14% with a high negative predictive value of about 95%, allowing the subsequent occurrence of CRT (symptomatic and asymptomatic) to be safely excluded. Despite its frequency and its medico-economic consequences, no thromboprophylaxis has been validated to date. In most patients, CRT occurs immediately after catheter insertion, most often within the first week and almost all within the first month after insertion. Meta analyses show a reduction of asymptomatic and symptomatic CRT incidence by about 55% to 60 % using either vitamin K antagonists or low molecular weight heparins without an increased risk of major bleeding. This pharmacological prophylaxis is only effective when started before the central venous catheter insertion at prophylactic doses and thereafter continued at subtherapeutic doses. Since no population at high risk of CRT has been identified, this review focuses on pathophysiology, epidemiology and clinical supportive data that could lead to a new CRT prophylaxis strategy.

Key words

Cancer-associated thrombosis; central venous catheter; thromboprophylaxis

49

50 Introduction

51 In the USA it is estimated that eight million central venous catheters (CVC) are inserted per
52 year even though the proportion inserted to patients with cancer is unknown [1]. The use of
53 CVC for the administration of chemotherapy, blood products and parenteral nutrition in
54 patients with malignancy is now usual daily practice. More than 15 percent of patients who
55 receive a CVC experience a complication [2]. Mechanical complications are reported in 5 to
56 19 percent of patients, infectious complications in 5 to 26 percent, and thrombotic
57 complications in 2 to 26 percent [2, 3]. Estimates of added costs from related complications
58 range from billions to tens of billions of dollars annually [1]. Complications associated with
59 catheter related thrombosis (CRT) are potential causes of morbidity and sometimes mortality
60 in patients with cancer and include pulmonary embolism (PE), infection, catheter failure and
61 potential delays in treatment [3, 4]. Furthermore, CRT may be associated with a worse
62 prognosis in cancer patients [5] while it is a leading cause of hospital-acquired deep vein
63 thromboses and represents over half of all DVTs [6]. This data highlights the need for
64 improved CRT pharmacoprophylaxis protocols that would likely benefit this population.

65

66 Definition of catheter-related deep-vein thrombosis

67 Catheter-related DVT occurs in the clinical and anatomic setting of a CVC (tunneled
68 catheters, subcutaneously implanted ports, and peripherally inserted central catheters
69 [PICC]). Catheter-related thrombosis includes upper limb, lower limb (in case of femoral
70 central catheter) and superior cava vein thromboses [7]. The pathognomonic component of
71 the catheter-related DVT is the mural thrombus extending from the catheter into the lumen
72 of a vessel, and leading to partial or total catheter occlusion with or without clinical
73 symptoms [8]. Catheter-related thrombosis must be distinguished from catheter dysfunction;
74 this latter event is generally due to the formation of a fibrin sleeve around the catheter, less
75 often to an intraluminal thrombus without mural involvement, and in some cases to the
76 compression of the catheter between the medial portion of the clavicle and the anterior face
77 of the first rib (pinch-off syndrome).

78

79 Epidemiology of Catheter-related DVT

80 The incidence of catheter-related thrombosis in cancer patients has been extensively
81 assessed in a review [4]. However, the careful definition of this incidence has been
82 hampered by some inconsistencies among studies. These include differences in study design
83 and included population, lack of standardization of the technique of CVC insertion,
84 inconsistency in the definition of venous thromboembolism (VTE) events (including the
85 difficulty in distinguishing mural thrombosis from CVC occlusion by catheter sleeve),
86 differences in the quality of inserted catheters and of patient surveillance, and different
87 accuracy of the diagnostic tests used to confirm thrombosis. This review only included
88 studies in which CRT was assessed either by venography when asymptomatic or
89 radiologically confirmed in case of clinical suggestive symptoms [4]. In this review, the
90 reported incidence of symptomatic catheter-related thrombosis in adult patients varied from
91 0.3% to 28.3%, [4]. In the last few years, a downward trend of symptomatic CRT has been
92 noted, with a reported average rate of 4%-8% (Table 1) [9]. The incidence of asymptomatic
93 CVC-related DVT assessed by venography has been reported to range from 27% to 66% [4].
94 As this review dates, back to 2003, and as phlebography is no longer a realistic option in
95 current practice, we have listed prospective studies including patients without any catheter-
96 related thrombosis prophylaxis and evaluating the rate of VTE events using US Doppler
97 and/or echography (Table 2). The incidence of all catheter-related thromboses
98 (asymptomatic and symptomatic) ranges from 1.5% to 71.9%, and, generally speaking the
99 later the screening is performed, the lower is the catheter-related thrombosis incidence.
100 Boddi et al. reported on a very low rate of asymptomatic catheter-related thrombosis using
101 US Doppler (1.5%) possibly due to an optimization of CVC implantation with the choice of
102 the best side for insertion and the checking that the distal extremity of CVC was located at
103 the junction of the superior cava vein and the right atrium [10], since CVC insertion quality
104 plays a key role in reducing the catheter-related thrombosis incidence [4, 8]. One other
105 explanation could be that this study also excluded from analysis the fibrin sleeve which can
106 easily be confused with catheter-related thrombosis [10]. In contrast, the study comparing
107 tapered and non-tapered PICC lines found a catheter-related thrombosis rate of 71.9% [11].
108 First, large-diameter CVCs and PICC lines have been found to be a predictive factor for
109 thrombosis in several studies [8, 11] and this trial only used double lumen PICC lines [12].
110 Second, although two board-certified radiologists interpreted the US scans independently,
111 the authors did not specify catheter-related thrombosis diagnostic criteria which may have

112 led to the interpretation of fibrin sheath or superficial arm thrombosis as catheter-related
113 thrombosis. Except these two extreme values, the mean incidence of doppler-detected
114 catheter-related thrombosis is between 12 and 14% (Table 2).

115

116 Pathogenesis of catheter-related thrombosis

117 The pathogenesis of upper limb DVT in patients with CVC is probably multifactorial.
118 Vessel injury caused by the procedure of CVC insertion, venous stasis caused by indwelling
119 CVC, and cancer-related hypercoagulability contribute to the development of catheter-
120 related thrombosis [4]. The loss of vessel integrity caused by the procedure of CVC insertion
121 is probably the most important factor by determining changes in the endothelial cells with
122 production of procoagulant factors and activation of platelets and blood coagulation. These
123 events could cause, usually within 24 hours from CVC insertion, the formation of a fresh
124 thrombus [4]. That is the reason why catheter-related thrombosis occurs very quickly after
125 insertion, within the first eight days in some studies [13], but generally within the first two
126 months as showed in Table 2. Two large prospective studies confirmed these data. In the
127 first one, a total of 4920 central lines were inserted into 3130 patients with solid tumor or
128 hematologic malignancy [14]. Catheter-related thrombosis developed at a median of 12 days
129 (range 1- 266 days), with 75% occurring within the first 26 days and 95% occurring within
130 104 days of insertion [14]. The study conducted by Decousus et al. included 3032 cancer
131 patients, the median time to any symptomatic catheter-related thrombosis was 45 days [15].

132

133 Diagnosis of catheter related DVT

134 Although venography is considered the gold standard for the diagnosis of catheter-related
135 thrombosis, Doppler ultrasound is usually carried out [9]. Reasons for the limited use of
136 phlebography include concerns over contrast toxicity and radiation exposure, as well as the
137 low availability of this invasive imaging. Furthermore, upper limb phlebography is not
138 possible in about 25% of cancer patients [16].

139 Two meta-analyses attempted to better characterize ultrasound test features for upper
140 extremity thrombosis [17, 18]. The accuracy of different ultrasound techniques
141 (compression, Doppler, and combined) did not differ significantly. The summary estimates
142 of sensitivity and specificity were 97% (95% CI, 90–100) and 96% (95% CI, 87–100) for
143 compression ultrasonography, 84% (95% CI, 72–97%) and 94% (95% CI, 86–100) for

144 Doppler ultrasonography, and 91% (95% CI, 85–97) and 93% (95% CI, 80–100) for
145 Doppler ultrasonography with compression, respectively.

146 Direct features suggestive of thrombosis are a partially compressible or totally non-
147 compressible lumen, hypoechoic, homogeneous appearance of clots, and presence of free-
148 floating thrombi [17-19]. At subclavian vein, the decrease or lack in cardiac and respiratory
149 modulation of Doppler flow signal, always compared with data obtained on the opposite
150 corresponding veins, can be considered as an indirect sign of central veins occlusion
151 (innominate trunks / superior vena cava) that cannot not be directly visualized because of
152 bone and air barrier [17-20] .

153 As demonstrated in the table 2, the negative predictive value of US doppler +/- echography
154 is very high for CRT screening (> 95% in most studies), allowing the subsequent occurrence
155 of catheter related thrombosis (symptomatic and asymptomatic) to be safely excluded. In
156 selected patients presenting with central occlusion of superior vena cava or its tributaries
157 [21], CT phlebography [22] can accurately depict the degree and location of central vein
158 obstruction, presence of collaterals (internal thoracic veins, azygos network) and of extrinsic
159 compression, the nature of thrombus (clot or tumoral), and the precise course and length of
160 the indwelling catheter [23].

161

162 Prophylaxis of catheter related DVT

163 Large number of investigators have attempted to identify an effective catheter-related
164 thrombosis prophylaxis regimen (Table 1). An open randomized study by Bern and
165 colleagues initially suggested that low dose warfarin (1 mg daily) could significantly reduce
166 the incidence of catheter-related thrombosis in cancer patients (37.5% vs. 9.5%) [24].
167 However, several subsequent randomized clinical trials (RCT) have failed to demonstrate
168 any protective effect with fixed low dose warfarin [25-28]. RCT with low-molecular-weight
169 heparins (LMWH) evolved in a similar fashion. A small open RCT conducted by Monreal et
170 al. demonstrated that dalteparin 2500 IU once daily significantly reduced CVC-related DVT
171 compared with no treatment (1/16, 6.2% versus 8/13, 61.5%, p=0.002) [29]. However
172 subsequent larger RCT with prophylactic regimens of dalteparin, nadroparin and enoxaparin
173 have been unable to demonstrate reductions in catheter-related thrombosis [13, 30-32]. A
174 small open label trial of continuous infusion UFH (100 units/kg/day) performed in adult and
175 pediatric bone marrow transplant patients noted a significant reduction in catheter-related

176 thrombosis (1/65 1.5% versus 8/63 12.6%, $p=0.03$) [33]. However, this regimen has not
177 been replicated perhaps because it is rather cumbersome and labor intensive to administer.
178 The study conducted by Lavau-Denes et al. included 420 patients and found a lower rate of
179 catheter-related thrombosis in patients treated with prophylactic dose of vitamin K
180 antagonists (VKA) or LMWH (8.1%) when compared with patients without any
181 anticoagulation (14.8%) [34].

182 Seven meta-analyses of anticoagulant CVC thromboprophylaxis have been performed
183 (Table 3) [35-41]. Carrier et al. and Kirkpatrick et al. did not note a reduction in
184 symptomatic CVC-associated DVT, while Akl et al. noted a 44% relative risk reduction in
185 symptomatic CVC-associated DVT episodes when the results of all anticoagulant modalities
186 were combined [35, 37, 38]. Kirkpatrick et al. noted that VKA and LMWH were associated
187 with a 63% and 28% relative risk reduction in all asymptomatic and symptomatic CRT
188 respectively [38] whereas Chaukiyal et al. and D'Ambrosio et al. did not, likely due to
189 differences in study inclusion criteria [39, 40]. The relative reduction in the risk of catheter-
190 related thrombosis was found only with LMWH for symptomatic events (- 52%) and only
191 with VKA for asymptomatic events (-57%) in the meta-analysis performed by Akl and al.
192 [41]. No meta-analysis demonstrated superiority for any anti-thrombotic regimen (i.e.,
193 Vitamin K antagonists vs. LMWH, etc.). No differences in major bleeding or mortality
194 between control patients and patients receiving anticoagulants were noted.

195 Consequently, guidelines recommend against the routine administration of pharmacologic
196 prophylaxis [7-9, 42] to prevent catheter-associated DVT. But there are some conflicting
197 data since most meta-analyses found a benefit of prophylactic anticoagulation whereas a
198 lower rate of catheter-related thrombosis was noticed in a few clinical trials (Tables 1 and 3).
199 Unfortunately, results of most large, randomized studies carried out to date might have two
200 important limitations. The first limitation is the anticoagulant dosage. The WARP trial, a
201 multicenter open label randomized trial compared no warfarin, fixed-dose warfarin (1 mg
202 daily) and dose-adjusted warfarin (INR 1.5–2.0), in 1590 cancer patients with CVC [28].
203 Fixed- dose warfarin did not reduce the incidence of symptomatic radiographically
204 confirmed catheter-associated thrombosis compared with no treatment (7% vs. 6%; $P =$
205 0.98), but dose-adjusted warfarin did significantly decrease the incidence of symptomatic
206 catheter-associated thrombosis (2.7% vs. 7.2%; $RR=0.38$; $P = 0.002$) at the expense of
207 increased major bleeding complications (3.4% vs. 1.5%; $P = 0.04$). The second limitation is

208 the late and quite heterogeneous initiation of antithrombotic prophylaxis following catheter
209 insertion. Thus, authors may not have observed a benefit of prophylaxis because medication
210 was started after the initiation of the pathophysiologic events leading to thrombosis. There is
211 no specific data about catheter-related thrombosis pathogeny, but it has been emphasized
212 that during the first hours or days after CVC insertion, cancer patients are at particularly
213 high risk for catheter-related thrombosis [13, 43, 44]. This fact is indirectly confirmed by the
214 rapid onset of catheter-related thrombosis after CVC insertion (Table 2). Catheter insertion
215 itself seems to be the most important catheter-related thrombosis risk factor [4, 8] probably
216 because of direct vessel wall trauma or endothelial injury which predisposes to thrombosis,
217 in particular during the first hours or days after CVC insertion when the repair processes are
218 not yet concluded [13, 45]. This evidence underlines the importance of starting
219 antithrombotic prophylaxis before CVC insertion as showed by De Cicco and al. [13]. In this
220 prospective clinical study, 348 cancer patients were prescribed either acenocumarine 1 mg
221 daily or dalteparin 5000 IU respectively 3 days and 2 h before CVC insertion or no
222 anticoagulant treatment. The duration of VKA and LMWH treatment was 8 days after
223 catheter insertion [13]. The incidence of catheter-related thrombosis assessed by mandatory
224 phlebography on days 8 and 30 after CVC insertion, was lower in the anticoagulant group:
225 21.9% and 40.0% for VKA and LMWH vs. 52.6% for observation, $p < 0.01$.
226 Acenocumarine was more effective than dalteparin (OR 0.4, $P = 0.01$) [13] possibly due to
227 an excessive dosage of VKA since 10% of patients in the acenocumarine group experienced
228 an INR value > 1.5 . The doses of the prophylactic agents used in this study proved to be safe
229 with no major bleeding. In the same way, two studies found a benefit in initiating
230 antiplatelet agents or anticoagulant before catheter insertion [15, 28]. The WARP study
231 allowed start of warfarin from 3 days before CVC insertion to enable sufficient exposure to
232 warfarin for the immediate postinsertion period which may partly explain the positive results
233 of this trial [28]. In the prospective survey ONCOCIP, 3032 cancer patients were included
234 and followed up for 12 months [15]. Ongoing treatment with an antiplatelet agent at baseline
235 was found to be associated with a lower rate of catheter-related thrombosis (HR = 0.44; 95%
236 CI, 0.21- 0.90; $p=0.024$).

237
238 Areas for future studies

239 Considering the above data, a three-step catheter-related thrombosis prophylaxis strategy
240 (prophylactic dosage of anticoagulants before catheter insertion, short subtherapeutic dosage
241 of anticoagulants after CRT insertion and US Doppler before anticoagulants cessation) could
242 be effective.

243 First, analysis of studies included in meta-analyses shows a reduction of asymptomatic and
244 symptomatic catheter-related thrombosis incidence by about 55% to 60 % using either VKA
245 or LMWH without an increased risk of bleeding (Table 3). This decrease in the incidence of
246 catheter-related thrombosis is only significant when pharmacological prophylaxis is started
247 before CVC insertion at preventive dosage and thereafter continued at subtherapeutic doses.
248 In this regard, we must keep in mind that in the post-surgical prevention of lower limbs VTE
249 and PE in cancer patients, almost all the performed studies included a prevention that began
250 prior to surgery, i.e. before the occurrence of the thrombogenic event [46]. Furthermore,
251 thrombosis occurs immediately after catheter insertion, most in the first week and almost all
252 in the first month. So, a new catheter-related thrombosis prophylaxis strategy using
253 anticoagulant at a preventive dosage before insertion and then at a subtherapeutic dosage for
254 a limited time only, could be considered. In this option, VKA have some limitations. VKA
255 are difficult to use in cancer patients even at low dose and clinical practice revealed a high
256 incidence of INR elevation (> 2) when minidose warfarin was given alone or along with
257 chemotherapy [13], especially 5-FU infusion [47]. The other two treatment options are
258 LMWH and direct oral anticoagulants (DOAC). As showed in The Catheter Studies (1 and
259 2), LMWH and DOAC are safe in CRT patients with cancer [48,49]. Potential LMWH
260 limitations include the fear of heparin-induced thrombocytopenia and the need of daily
261 subcutaneous injections [50]. But despite the negative emotional impact for patients and
262 physicians' reluctance to prescribe long-term LMWH, the perception of the anticoagulant
263 treatment is usually good among patients with catheter-related thrombosis [50] because
264 patients perceived themselves as cancer patients first and as VTE patients second [51].
265 Guidelines recommend LMWH as the first line treatment of catheter-related thrombosis and
266 LMWH have been extensively used in this indication [8]. A metanalysis found that LMWH
267 reduces catheter related VTE compared to no LMWH without any excess of minor or major
268 bleeding [52]. DOACs, which are given in fixed oral doses, are a potential alternative to
269 VKA or LMWH [53] but data on the use of DOACs in CRT are scarce. In a prospective
270 study which compared rivaroxaban 10 mg/d, enoxaparin 4000IU Anti-Xa/d and observation

271 for catheter-related thrombosis primary prophylaxis in 423 cancer patients treated with
272 chemotherapy, the rate of catheter-related thrombosis was lower in the anticoagulation
273 groups (factor Xa antagonist: 3.8%, LMWH: 3.0%) when compared with no treatment
274 (12.4%). However, this trial had an important limitation which is the lack of randomization
275 because treatment was decided by the physicians [54]. Recently, an open blinded end trial
276 compared standard care and a primary prophylaxis with rivaroxaban 10 mg daily for 3
277 months [55]. Thrombotic events occurred in 3 patients in the rivaroxaban group (5.8% n =
278 52) compared with 5 patients in the control group (9.4% n = 53) without an excess of
279 bleeding [56]. In a curative setting, anticoagulant treatment of pediatric central venous
280 catheter-related venous thromboembolism has been specifically evaluated in the
281 EINSTEIN-Jr study [57]. Children with catheter-related thrombosis were administered
282 rivaroxaban (n = 96) or standard anticoagulants (n = 30) [55]. Complete or partial vein
283 recanalization occurred in 57 (55%) and 38 (37%) of 103 evaluable children, 3 children
284 experienced clinically relevant nonmajor bleeding (2.4%; 95% CI, 0.7%-6.5%), all in the
285 rivaroxaban arm. There were no major bleedings in this study, but DOAC hemorrhagic
286 complications are an issue of concern in cancer patients. In the treatment of DVT/PE in
287 cancer patients and at therapeutic dosage, the excess of major bleeding with DOAC was
288 confined to patients with gastrointestinal and urinary tract cancer in the SELECT-D and
289 HOKUSAI CANCER trials [57]. For lower limbs VTE and PE prophylaxis and at
290 preventive dosage, hemorrhagic complications were not increased in the CASSINI study
291 [58]. In the AVERT trial, major bleeding excess was only statically significantly higher in
292 the apixaban group in the modified intention-to-treat analysis, but not during the treatment
293 period (2.1% vs.1.1%, HR = 1.89; 95% CI, 0.39 to 9.24) [59]. So, it makes sense to assess
294 the efficacy and safety of LMWH or DOAC for thrombo-prophylaxis in cancer patients with
295 a CVC.

296 Second, as previously demonstrated, the negative predictive value of US doppler is about
297 95%. Catheter insertion itself appears to be the most important catheter-related thrombosis
298 risk factor as thrombosis occurs immediately after catheter insertion, most in the first week
299 and almost all in the first month. CVC-related DVT is more frequently asymptomatic than
300 upper limbs DVT not associated with CVC, probably because thrombosis is less acute and
301 less commonly occlusive [4]. Asymptomatic DVT identified by screening represents a sub-
302 clinical manifestation of disease, and recommendations for prophylaxis are largely based on

303 studies that used such routine screening approaches. Both European regulatory agencies and
304 the FDA accept this approach in evaluating registration trials. As showed in table 2,
305 compression ultrasonography is regarded as the standard method for the diagnosis of
306 symptomatic catheter-related thrombosis because of its low level of invasiveness and high
307 sensitivity and specificity [7]. So, after a negative US Doppler performed between day 8 and
308 day 10, the risk of catheter-related thrombosis (symptomatic and asymptomatic) is very low,
309 and the duration of anticoagulation could be restricted to 8-10 days as in the study conducted
310 by De Cicco et al. [13]. For safety purposes, an US Doppler examination could be scheduled
311 at D30.

312

313 Conclusions

314 Up to now, catheter-related thrombosis prophylaxis has not been proven effective in cancer
315 patients, but probably due to inappropriate timing and dosage of anticoagulants but a three-
316 step catheter-related thrombosis prophylaxis strategy could be effective. These three steps
317 are: prophylactic doses of LMWH or DOAC before insertion, short-term subtherapeutic
318 doses of the same anticoagulant after catheter placement and then echography Doppler
319 before stopping anticoagulants, all of this with a sufficient margin of safety because of the
320 limited duration of prophylaxis and therefore a low bleeding risk and because of the very
321 low risk of catheter-related thrombosis following a negative echography Doppler.
322 Unfortunately, catheter-related thrombosis prophylaxis trials remain unattractive to both
323 pharmaceutical industry and academia as evidenced by the lack of randomized trials
324 conducted in the treatment of symptomatic catheter related thrombosis.

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329 Conflict of interest

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331 Author's contribution

332 PD conceived and designed the study. PD drafted the manuscript. AL, TD, LV and PYM
333 critically revised the manuscript for important intellectual content. All authors read and
334 approved the final manuscript version.

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Accepted Article

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Table 1 Clinical studies on catheter related thrombosis prophylaxis 1

References	Patients n = included /evaluated	Features of included patients	Intervention	End point	Arm A	Arm B	p
MONREAL 1996[29] Prospective open study Mar 1993– Mar1995	32/29 pts 90 days	Solid tumors; CVC (Port-a-cath) platelets count > 100 G/L no previous DVT	Arm A (n=16): dalteparin 2500 IU 1/day, started 2h before catheter insertion Arm B (n=13): no treatment For 90 days or up to symptomatic CRT confirmed by phlebography	Asymptomatic CRT (venography)	1/16 (6.2%)	8/13 (61.5%)	p = 0.002 RR = 6.75 95% CI [1.05 - 43.58]
HEATON 2002[25] Randomized controlled trial Not specified	NS/88 3 months	88 patients Hematologic cancers	Am A n=45 warfarin 1 mg/day, 90 days Arm B n=43 no intervention	Symptomatic CRT + asymptomatic CRT D90 Phlebography	8/45 (17.8%)	5/43 (11.2%)	p = 0.42
ABDELKEFI 2004[33] Randomized controlled trial May 2002–Sep 2003	108/108 pts 128 CVC pts/128 17 months	Adults < 60 years Children > 4 years Bone marrow transplant	Arm A (pts = 55, CVC = 65): UFH (continuous IV perfusion 100 IU/kg/d), maximum = 10000 IU/d) Arm B (pts = 53, CVC = 63): saline 50 mL/d	Symptomatic CRT + asymptomatic CRT (Ultrasound Doppler at catheter removal) Major bleeding	1/65 (1.5%)	8/63 (12.6%)	p = 0.03
MISMETTI 2003[60] Randomized controlled trial May 1998– Mar2000	59/45 pts 6 months	Adults Solid tumors CVC	Arm A (29 included / 21 evaluated): nadroparin SC. 2850 IU, 1/day, started 2h before catheter insertion Arm B (30 included / 24	Asymptomatic and symptomatic CRT (venography) at 90 days All VTE events At 6 months	6/21 (28.6%)	4/24 (16.7%)	p = 0.48
					8/22 (36.4%)	4/24 (16.7%)	p = 0.13

	evaluated); warfarin 1 mg/day, started 3 days before catheter insertion for 90±5 days or up to symptomatic CRT	Major bleeding	1 patient	0 patient	p not specified
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Table 1 Clinical studies on catheter related thrombosis prophylaxis 2

References	Patients n = included /evaluated	Features of included patients	Intervention	End point	Arm A	Arm B	P [95% CI]
VERSO 2005[30] Randomized double blind study Mar 2000–Mar 2003	385/310 pts 3 months	Cancer CVC	Arm A (n=191 included / 155 evaluated): Enoxaparin 40 mg, SC, 1/day started 2h before catheter insertion Arm B (n=194 included / 155 evaluated): placebo 6 weeks	Asymptomatic + symptomatic CRT (venography at D42) or symptomatic PE Symptomatic catheter thrombosis Major bleeding Death	22/155 (14.1%)	28/155 (18.0%)	p = 0.35 RR = 0.78 [0.4 - 1.31] p NS RR = 0.32 [0.07-1.66]
COUBAN 2005[26] Randomized controlled trial	255/255 pts Median = 25 weeks	Solid tumors: 20 % Hematological malignancies	Arm A (n=130): warfarin 1 mg/day (72h after catheter insertion), median	Symptomatic CRT Major bleeding	6/130 (4.6%) 0/130 (0%)	5/125 (4.0%) 3 / 125 (2%)	HR = 1.20 [0.37-3.94] p = 0.07 [-5.1 - 0.31]

Mar 1999–Jul 2002	(1 -184)		duration: 8 weeks Arm B (n=125): placebo, median duration: 9 weeks				
KARTHAUS 2006[31]	439/425 pts	Cancer Chemotherapy	Arm A (294 included / 285 treated): Dalteparin 5000 IU SC 1/day x 16 weeks Arm B (145 included / 140 treated) : placebo SC 1/day x 16 weeks	Symptomatic CRT Asymptomatic CRT (phlebography or echography Doppler W16)	11/285: 3.7%	5/140: 3.4%	RR = 1,08 [0.37-3.19]
Randomized double blind study Aug 1999-Jun 2001	16 weeks	CVC inserted 5 to 7 days before randomization A/B: 2/1 Solid tumors 271/125 Hematological tumors: 23/20		Major Bleeding	1/285 (0.35%)	1/140 (0.7%)	OR = 0.81 [0.29 - 2.29]
				Major and minor bleeding	50/285 (17.5) %	21/140 (15.0) %	RR = 1.20 [0.69 - 2.10]
RUUD 2006[27]	73/62 pts	Children with cancer	Arm A (n = 29): warfarin 0.1 mg/kg started on the day of catheter insertion, 1.3 < INR < 1.9 Arm B (n = 33): no warfarin Frequency of INR in target range 64%	Asymptomatic CRT US Doppler M1, M3, M6 Symptomatic CRT	PP: 14/29 (48%) ITT: 15/31 (48%)	PP: 12/33 (36%) ITT: 17/42 (40%)	PP: p = 0.44 ITT: p = 0.63
Randomized controlled trial Jan 2002-Oct 2003	6 months	Catheter inserted in the jugular vein		Major bleeding	1/29 (3.5%)	1/33 (3.0%)	NS
				Major bleeding	2/29 (6.9%)	0/33 (0%)	NS
NIERS 2007[32]	113/87 pts	Hematologic malignancies: CVC (chemotherapy and stem-cell transplantation)	Arm A : (41 evaluated /56 nadroparin (2850IU/day) Arm B : (46 evaluated /57 placebo 3 weeks	Asymptomatic CRT (venography D21) Major bleeding Minor bleeding Major bleeding	7/41 (17%)	4/46 (9%)	p = 0.49
Randomized controlled trial Not specified				Major bleeding	0	0	p not specified
				Major bleeding	5/56 (9%)	2/57 (4%)	
				Major bleeding PE	no major bleeding no PE		

Table 1 Clinical studies on catheter related thrombosis prophylaxis 3

References	Patients n = included /evaluated Follow-up	Features of included patients	Intervention	End point	Arm A	Arm B	p Confidence interval
DE CICC0 2009[13] Randomized controlled trial Not specified	450/348 pts Not specified	Cancer CVC	Arm A: n=120 Acenocoumarol 1 mg/day started 3 days before CVC insertion x 8 d Arm B: n=114 Dalteparin 5000 IU/day, 2h before CVC insertion x 8 d	Asymptomatic CRT (venography D2, D8, D30 and every 2 months)	A vs. C 25/120 (21.9 %) vs. 60/114 (55.3 %) OR = 4.35; 95%CI [2.43 – 7.69] B vs. C 48/114 (40 %) vs. 60/114 (55.3 %) OR = 1.85; 95% CI [1.10 – 3.13] A vs. B 25/120 (21.9%) vs. 48/114 (40%) OR = 2.37; 95% CI [1.34 – 4.22]		p<0.001 p = 0.02 p = 0.003
YOUNG 2009[28] Randomized controlled trial Oct 1999-Dec 2004	1590/1590	Cancer All types of CVC	Arm A: n=713 Warfarin 1mg/day Arm B: n=471 Warfarin INR = 1.5 - 1.9 Arm C: n=404 Observation Start of warfarin allowed from 3 days before CVC insertion	Symptomatic CRT Major bleeding Minor bleeding	Warfarin any dose vs. observation 24/404 (4%) vs. 24/408 (6%) RR = 0.99; 95CI: [0.57–1.72] Warfarin 1 mg vs INR 1.5 – 1.9 34/471 (7%) vs. 13/473 (3%) RR = 0.38; 95CI: [0.20–0.71] Warfarin any dose vs. observation 1/404 (<1%) vs. 7/408 (2%); RR = 6.93; 95CI: [0.86–56.08] Warfarin 1 mg vs INR 1.5 – 1.9 7/471 (<%) vs. 16/473 (3%); RR = 2.28; 95CI: [0.95–5.48]		0.98 0.002 0.07 0.09 0.07
					Warfarin any dose vs. observation 1/404 (<1%) vs. 14/408 (3%); RR = 6.93; 95CI: [0.86–56.08] Warfarin 1 mg vs INR 1.5 – 1.9 21/471 (<4%) vs. 24/473 (5%); RR = 2.28; 95CI: [0.95–5.48]		0.09 0.07

LAVAU DENES 2013[34] Prospective randomized trial Sep 1999-Jun 2009	420/407	Subclavian CVC inserted for < 7 days Solid invasive cancer First-line chemotherapy	Arm A: anticoagulation Warfarin 1 mg/day n = 134 LMWH prophylactic dosage N = 138 within the 1 st 6 days after insertion for 90 days Arm : Observation 135 evaluated / 140	Asymptomatic + symptomatic CRT (venography + Doppler ultrasound at D1 - D90) Symptomatic CRT	Anticoagulation 22/272 (8.1%) VKA 8/134 (5.9%) LMWH 14/138 (10.1%) Anticoagulation 2/272 (0.7%) VKA 1/134 (0.7%) LMWH 1/138 (0.7%)	20/135 (14.8%) 6/135 (4.4%)	Anticoagulation vs. observation p = 0.0357 Anticoagulation vs. observation p = 0.018
LV 2019[54] Prospective open study Jan 2014 – Jun 2015	423/394	Single lumen PICC 4 Fr Oeso-gastric, lung, breast, colorectal, or ovarian cancer Chemotherapy	Arm A: n = 138 rivaroxaban 10 mg /day Arm B: n = 144 enoxaparin 4000 IU / day Arm C: n=131 observation Duration NS	Asymptomatic + symptomatic CRT Doppler US D1, D3, D7, D14 + each chemotherapy Bleeding	Arm A: 5/132 (3.8%) Arm B: 4/144 (3.0%) Arm A: 0/132 (3.8%) Arm B: 1/144 (0.8%)	Arm C: 16/141 (12.4%)	p = 0.003 NS
EINSTEIN-Jr CVC-VTE 2020 [56] Multicenter, open-label, randomized trial March 2015- January 2019	126/126	Children with CVC-VTE	Arm A: n=90 Rivaroxaban body weight-adjusted 20-mg equivalent doses, given once daily, twice daily, or thrice daily for body weights ≥ 30, 12 to <30, and <12 kg, respectively Arm B: n=36 Standard anticoagulation	Recurrent VTE Other clinically relevant venous thrombosis Major bleeding Clinically relevant nonmajor bleeding	Arm A: 0/90 (0%) Arm A: 1/90 (1.1%) Arm A: 0/90 (0%) Arm A: 3/90 (3.3%)	Arm B: 0/36 (0%) Arm B: 1/36 (2.8%) Arm B: 0/36 (0%) Arm B: 0/36 (0%)	NS NS NS

TRIM-Line 2021 [55]	105/105	Cancer CVC inserted within 72hours of enrollement	Arm A: n= 52 Rivaroxaban 10mg/day Arm B: n=53 Standard of care	Symptomatic thrombotic complications Major VTE events Major bleeding episodes CVC-related complications within 90 ±3 days of randomization.	Arm A: 3/52 (5.8%) Arm A: 2/52 (3.9%) Arm A: 1/52 (1.9%) Arm A: 0/52 (0%)	Arm B: 5/53 (9.4%) Arm B: 3/53 (5.7%) Arm B: 0/53 (0%) Arm B: 5/53 (9.4%)	NS NS NS
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Table 2 Clinical studies using US Doppler for CRT incidence evaluation

References	Study design	Diagnosis methodology	Catheter type	CRT incidence in cancer patients without prophylaxis	Time to CRT onset
Study design	Features of included patients				Negative predictive value
Inclusion period					
BONFELS 1996[60]	Prospective observational study ENT cancer	US Doppler Timing NS	Subclavian CVC	Symptomatic + asymptomatic CRT 11/78 (14.1%) Symptomatic CRT 4/78 (5.1%)	91% < 2 months VPN: NS
LUCCIANI 2001[61]	Prospective observational study Localized ENT cancer	US Doppler M1, M2, M3, M4, M5, M6	Port Subclavian vein contralateral to the tumor	Symptomatic + asymptomatic CRT 17/145 (11.7%)	82% < 2 months VPN: NS
VAN ROODEN 2003[62]	Prospective observational study Hematological cancer Intensive chemotherapy	US Doppler Once a week until CVC removal	CVC double or triple lumen	Symptomatic + asymptomatic CRT 26/105 (24.8%) Symptomatic CRT 13/105 (12.4%)	100% < 2 months VPN = 94.9% (75/79)
ABDELKEFI 2004[34]	Randomized controlled trial Bone marrow transplant	Ultrasound Doppler at catheter removal	Externalized, non-tunneled, polyurethane double-lumen catheters	Symptomatic + asymptomatic CRT 8/63 (12.6%)	Median: 21 days VPN: NS
KARTHAUS 2006[32]	Cancer Randomized double blind study	Phlebography or echography Doppler W16	NS	Symptomatic + asymptomatic CRT 10/140 (7.1%)	Median 70 days VPN: NS
RUUD 2006[28]	Randomized controlled trial Children with cancer	US Doppler M1, M3, M6	Single and double lumen CVC Port	Symptomatic + asymptomatic CRT 13/33 (39%)	61% < 1 month VPN = 82.6% (38/46)
ITKIN 2014[13]	Prospective randomized study Population NS	US Doppler at removal or between D14-D28	Double lumen PICC Tapered vs. non-tapered	Symptomatic + asymptomatic CRT 197/274 (71.9%) Symptomatic CRT 13/331 (3.9%)	NS
BODDI 2014[11]	Prospective observational study Cancer	US Doppler M1, M6, M12	Port	Symptomatic + asymptomatic CRT 6/400 (1.5%)	83% < 1 month VPN: 99.7% (395/396)
MARCV 2014[63]	Prospective observational study Solid tumors	US Doppler M1, M3, M6, M12	Port	Symptomatic + asymptomatic CRT 34/215 (15.8%)	Median 82 days 100% < 4 months

					Symptomatic CRT 19/135 (4.4%)	VPN: NS
SCHOOT 2016[64]	Prospective randomized study Pediatric patients, solid tumors Hematological malignancies	US Doppler within 6 months	Tunneled CVC	Asymptomatic CRT 11/185 (5.9%)	NS	VPN: NS
LUO 2016[65]	Prospective observational study Solid tumors	Weekly US Doppler	Single lumen PICC	Asymptomatic CRT 27/128 (21%)	Median 3 days 85% < 1 week	VPN: NS
DEBOURDEAU 2017[66]	Prospective observational study Breast cancers	Doppler US D7, D30, D90	Port	Symptomatic + asymptomatic CRT 6/524 (1.5%) Symptomatic CRT 14/524 (2.6%)	65% < 1 month	VPN = 99.1% (464/468)
LV 2019[53]	Prospective open study Solid tumors	Doppler US D1, D3, D7, D14 + each chemotherapy	Single lumen PICC	Symptomatic + asymptomatic CRT 16/141 (12.4%)	Median 15 days	VPN: NS

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Table 3 Metanalyses on catheter related thrombosis prophylaxis

References	Bibliographic search Number of studies analyzed Period of study selection	No. of patients Treatment	Thrombosis	Bleeding	Other outcomes
CARRIER 2007[36]	Medline® (1950 – 2007) Embase® (1980 – 2007) CCTR (first semester 2007) Seven studies; 1950–2007	2131 patients; VKA (warfarin 1 mg) or LMWH	Symptomatic CRT (defined as upper extremity DVT or CVC occlusion) VKA vs. control: NS RR = 0.82 ; 95% CI [0.46–1.47] LMWH vs. control: NS RR = 0.473 ; 95% CI [0.120–1.560] VKA or LMWH vs. control: 52/1145 (4.6%) vs. 65/986 (6.6%) RR = 0.71 ; 95% CI [0.42–1.20]	Major Bleeding NS Minor Bleeding VKA vs. control: RR = 0.93 ; 95% CI [0.31-2.77] LMWH vs. Control: RR = 1.32 ; 95% CI [0.87-2.02]	Mortality VKA vs. control RR = 0.95 ; 95% CI [0.62-1.46] LMWH vs. control RR = 1.51 ; 95% CI [0.49-4.70]
RAWSON 2007[37]	Medline® (1966 – 2007) Embase® (1988 – 2007) Cancerlit (1975 – 2007) Cinahl (1982 – 2007) ASCO, abstracts (1999 – 2007) ASH, abstracts (2001 – 2007) Four studies 1966–2007	1236 patients Warfarin 1 mg or INR > 1.5	Symptomatic and asymptomatic CRT VKA vs. control: 40/625 (6.4%) vs. 46/611 (7.5%) Risk difference = 5.0%, 95% CI [-9.0% to +5.0%]		
KIRKPATRICK 2007[38]	Medline® (1964– 2006) Embase® (2002 – 2005) ASCO, abstracts (1999 – 2006) ISTH, abstracts (2001 – 2005) Fifteen studies (10 studies on only cancer patients)	1714 patients VKA (fixed low dose) or LMWH	CRT (symptomatic and asymptomatic) VKA vs. control: 30/162 (18.5%) vs. 78/154 (50.6%) RR = 0.37 ; 95%CI [0.26–0.52] LMWH vs. control: 93/617 (15.1%) vs. 113/447 (25.3%) RR = 0.72 ; 95% CI [0.57–0.90] LMWH vs. VKA: 46/114 (40.4%) vs. 26/120 (21.7%) RR = 1.88 ; 95% CI [1.28–2.75]	Major bleeding VKA vs. control: 0/175 (0%) vs. 3/168 (1.8%) RR = 0.24 ; 95% CI [0.03–2.13] LMWH vs. control: 1/529 (0.2%) vs. 1/368 (0.3%) RR = 0.66 ; 95% CI [0.12–3.68]	All Cause Mortality: VKA vs. control RR = 0.95 ; 95% CI [0.62-1.46] LMWH vs. control: RR = 1.57 ; 95% CI [0.54-4.58]

AKL 2007[39]	Medline® (1966– NS) Embase® (1980 – NS) ASCO, abstracts (1982 – NS) ASH, abstracts (2003 – NS) Nine studies	852 pts asymptomatic CRT 1859 pts symptomatic CRT VKA or heparin (UFH or LMWH)	<p><i>Asymptomatic DVT</i></p> <p>LMWH vs. control: 30/465 (6.5%) vs. 31/313 (9.9%) RR = 0.84; 95% CI [0.52–1.36]</p> <p>Heparin vs. control: 0/38 (0%) vs. 1/36 (2.8%) RR = 0.82 ; 95% CI [0.51–1.32]</p> <p>VKA or heparin vs. control: 30/503 (6%) vs. 32/349 (9.2%) RR = 0.82; 95% CI [0.73–1.68]</p> <p><i>Symptomatic DVT:</i></p> <p>VKA vs. control: 31/507 (6.1%) vs. 47/500 (9.4%) RR = 0.62; 95% CI [0.30–1.27]</p> <p>LMWH vs. control: 13/465 (2.8%) vs. 16/313 (5.1%) RR = 0.49; 95% CI [0.17–1.39]</p> <p>Heparin vs. control: 1/38 (2.6%) vs. 5/36 (13.9%) RR = 0.43; 95% CI [0.18–1.06]</p> <p>VKA or heparin vs. control: 45/1010 (4.5%) vs. 89/849 (10.5%) RR = 0.56; 95% CI [0.34–0.92] p=0.02</p>	<p><i>Major bleeding</i></p> <p>Heparin vs. control: 2/223 (0.62%) vs. 2/176 (1.1%) RR = 0.68; 95% CI [0.10–4.78]</p> <p>VKA or heparin vs. control: 9/731 (1.2%) vs. 3/579 (0.52%) RR = 1.83 ; 95% CI [0.34–9.87]</p>	<p><i>Death</i></p> <p>LMWH vs. control: 18/492 (3.7%) vs. 22/347 (6.3%) RR = 0.73; 95% CI [0.39–1.36]</p> <p>Heparin vs. control: 1/38 (2.6%) vs. 1/36 (2.8%) RR = 0.74 ; 95% CI [0.40–1.36]</p> <p>VKA or heparin vs. control: 19/530 (3.6%) vs. 23/383 (6%) RR = 0.74; 95% CI [0.40–1.36]</p>
CHAJUKYAL 2008 [40]	Medline® (1966– 2006) CTR (June 2006) Eight studies	1428 patients VKA (warfarin 1 mg) or heparin (UFH or LMWH)	<p><i>CRT (symptomatic and asymptomatic)</i></p> <p>VKA vs. control: 18/217 (8.3%) vs. 25/208 (12%) RR = 0.75 ; 95% CI [0.24–2.35] p=0.63</p> <p>Heparin vs. control: 34/520 (6.5%) vs. 49/366 (13.4%) RR = 0.46; 95% CI [0.18–1.20] p= 0.06</p> <p>VKA or heparin vs. control: 52/737 (7.1%) vs. 74/574 (12.9%) RR = 0.59; 95% CI [0.31–1.13] p= 0.11</p> <p>VKA vs. LMWH: 6/21 (28.6%) vs. 4/24 (16.7%) RR = 1.71; 95% CI [0.56–5.26]</p>	<p><i>Major bleeding</i></p> <p>VKA vs. control: 6/175 (3.4%) vs. 6/168 (3.6%) RR = 0.14; 95% CI [0.01–2.63]</p> <p>Heparin vs. control: 63/499 (12.6%) vs. 28/351 (8%) RR = 0.41 ; 95% CI [0.05–3.30] ;</p> <p>VKA or heparin vs. control: 69/674 (10.2%) vs. 34/519 (6.6%) RR = 0.44; 95% CI [0.12–1.67]</p>	
D'AMBROSIO 2014[41]	NS Twelve studies	3018 patients symptomatic CRT VKA or heparin (UFH or LMWH)	<p><i>Symptomatic CRT</i></p> <p>Anticoagulant vs. control: 63/1716 (3.7%) vs. 89/1302 (6.8%) RR=0.62; 95%CI: [0.30–1.27]</p>	NS	NS

AML 2014[42]	Medline® (NS - 2013) Embase® (NS - 2013) Twelve studies	2823 patients VKA or LMWH	Symptomatic CRT	Major bleeding	Death
			<p>LMWH vs. control: 20/726 (2.8%) vs. 35/591 (5.9%) RR=0.48; 95CI: [0.72-0.86]</p> <p>VKA vs. control: 44/712 (6.2%) vs. 74/739 (10.0%) RR=0.51; 95CI: [0.21-1.22]</p> <p>LMWH vs. VKA: 9/279 (3.2%) vs. 4/272 (1.5%) RR=2.15; 95CI: [0.65-7.14]</p> <p><i>Asymptomatic CRT</i></p> <p>LMWH vs. control: 93/726 (12.8%) vs. 104/593 (17.5%) RR=0.82; 95CI: [0.65-1.03]</p> <p>VKA vs. control: 39/313 (12.5%) vs. 71/305 (23.2%) RR=0.43; 95CI: [0.30-0.62]</p> <p>LMWH vs. VKA: 61/279 (21.8%) vs. 34/272 (12.5%) RR=1.74; 95CI: [1.2-2.52]</p>	<p>LMWH vs. control: 1/571 (0.2%) vs. 1/441 (0.3%) RR=0.49; 95CI: [0.03-7.84]</p> <p>VKA vs. control: 7/474 (1.5%) vs. 1/505 (0.2%) RR=7.6; 95CI: [0.94-61.49]</p> <p>LMWH vs. VKA: 1/141 (0.7%) vs. 0/138 (0%) RR=3.41; 95CI: [0.15-79.47]</p> <p><i>Minor bleeding</i></p> <p>LMWH vs. control: 15/275 (5.5%) vs. 11/269 (4.1%) RR=1.35; 95CI: [0.62-2.92]</p> <p>VKA vs. control: 17/473 (3.6%) vs. 5/505 (0.1%) RR=3.14; 95CI: [0.14-71.51]</p> <p>LMWH vs. VKA: 3/120 (2.5%) vs. 3/114 (2.6%) RR=0.95; 95CI: [0.20-4.61]</p>	<p>LMWH vs. Control: 37/689 (5.4%) vs. 42/547 (7.7%) RR=0.82; 95CI: [0.53-1.26]</p> <p>VKA vs. control: 186/712 (26.1%) vs. 191/733 (25.8%) RR=0.99; 95CI: [0.64-1.55]</p> <p>LMWH vs. VKA: 29/279 (10.4%) vs. 27/272 (9.9%) RR=1.14; 95CI: [0.59-2.21]</p> <p><i>Catheter related infection</i></p> <p>LMWH vs. Control: 20/296 (6.8%) vs. 16/172 (9.3%) RR=1.00; 95CI: [0.54-1.85]</p> <p>VKA vs. control: 22/45 (48.9%) vs. 18/43 (41.9%) RR=1.17; 95CI: [0.74-1.85]</p> <p><i>Thrombocytopenia</i></p> <p>LMWH vs. Control: 87/569 (15.3%) vs. 76/433 (17.6%) RR=1.03; 95CI: [0.80-1.33]</p> <p>LMWH vs. VKA: 61/159 (36.9%) vs. 16/158 (12.6%) RR=3.73; 95CI: [2.26-6.16]</p>