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Early detection of the existence or absence of treatment effect: a cumulative meta-analysis

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Running head (max. 65 caractères avec espaces): Cumulative meta-analysis of low-molecular-weight heparin trials in cancer patients (82 caractères)

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SUMMARY

OBJECTIVE: An unexpected promising effect of low-molecular-weight heparins (LMWHs) on survival in cancer patients was observed in early trials in post-hoc subgroup analyses but not found in more recent trials. In order to highlight a possible regression over time toward the lack of antitumoral effect of LMWHs, we performed a cumulative meta-analysis of survival data from RCTs.**STUDY DESIGN AND SETTING:** Medical databases were searched to identify randomized clinical trials comparing LMWHs to placebo or no treatment in cancer patients without VTE, or to VKA in cancer patients with VTE in overall survival. Cumulative hazard ratio (HR) was estimated after each study inclusion in chronological order.

RESULTS: Twenty-three studies (12,970 patients) were included. The cumulative meta-analysis of the earlier trials showed a significant improvement in overall survival with LMWHs. This apparent benefit then gradually regressed over time toward an absence of effect of LMWHs on survival(HR 0.98 [95% CI, 0.93; 1.03]).

CONCLUSION: Despite supportive experimental data and early clinical findings, the promising antitumor effect of LMWHs in cancer patients gradually vanished over time toward a lack of impact on overall survival. This result suggests 'p-hacking' and selective reporting of positive results from *post-hoc* subgroup analyses in the early studies.

Key words: cumulative meta-analysis; randomized clinical trial; cancer; low-molecular-weight heparin; survival; p-hacking.

198 words

INTRODUCTION

Venous thromboembolism (VTE), including deep venous thrombosis (DVT) and pulmonary embolism (PE), is a well-known complication in patients with cancer (1-3). Low-molecular-weight-heparins (LMWHs) are safe, effective and recommended by clinical practice guidelines for the treatment of VTE in cancer patients (4).

An unexpected finding of the early trials comparing LMWHs and unfractionated heparin in patients with VTE was an apparent improved survival in the subgroups of patients with cancer treated with LMWHs (5-8). This tendency was confirmed in several meta-analyses published as early as 1996 (9,10). However, these meta-analyses could only include studies that reported survival in the subgroups of cancer patients, suggesting possible selective reporting because the results were positive, otherwise known as P-hacking (11).

The first randomized clinical trial (RCT) specifically designed to confirm this possible antitumor effect of LMWHs was published in 2004 (12). Although no significant effect on survival was seen in the study population as a whole, a significant difference favouring the LMWH arm was observed in an unplanned *post-hoc* subgroup analysis of patients with a better prognosis. Similarly, in a study in cancer patients with VTE, an unplanned *post-hoc* analysis showed a significantly improved overall survival (OS) with LMWHs compared to warfarin only in the subgroup of patients with non-metastatic cancers (13,14). The only RCT that showed a significant benefit of LMWHs on OS in the entire patient population was the MALT study, published in 2005 (15). Consequently, the ensuing (positive) meta-analyses were based mainly or exclusively on data from *post-hoc* unplanned subgroup analysis that were possibly reported only in the case of positive results (16).

As the most recent trials no longer suggest any survival benefit from LMWHs in patients with cancer (17,18), we hypothesized that the “effect” observed a few years ago was fortuitous and that the only meaningful study result was a false positive (15). We had to wait for 2019 to propose strong recommendations specifying that for cancer patients without VTE, “Anticoagulant use is not recommended to improve survival in patients with cancer without VTE” (19). In order to know if the regression over time towards the lack of antitumoral effect of LMWHs on survival of cancer patients could be earlier highlighted, we performed a cumulative meta-analysis of survival data from RCTs.

METHODS

Literature search

We sought to identify all relevant published and unpublished randomized controlled trials that

compared LMWHs for at least 1 month with placebo or standard therapy in cancer patients, i.e. placebo or no treatment in cancer patients free of VTE, and VKA in cancer patients with VTE.

An exhaustive literature search, both manual and computer-assisted, was performed up to August 2019, with no restrictions on language or dates. The computer-assisted search was carried out on electronic databases (MEDLINE, Cancerlit, The Cochrane Library databases, SCOPUS, Google Scholar and the international database of clinical trials [www.clinicaltrials.gov]). In addition, the proceedings of major conferences (American Society of Clinical Oncology [ASCO], European Society for Medical Oncology [ESMO], International Society on Thrombosis and Haemostasis [ISTH], American Society of Hematology [ASH]) were searched for abstracts of relevant trials. The following keywords were used: randomized, randomized controlled trial, cancer, generic and trade names of individual preparations of LMWHs (dalteparin or Fragmin[®], enoxaparin or Lovenox[®], nadroparin or Fraxiparin[®], danaparoid or Orgaran[®], tinzaparin or Innohep[®]). We also manually searched the reference lists of journal articles reporting results from clinical trials, meta-analyses and systematic reviews to identify additional studies, and contacted manufacturers of LMWHs to learn of unpublished studies. When studies had been published as both an abstract and a full article, only the article was referenced. If more than one article was published for the same study, we extracted the relevant information from all publications as needed. A post-hoc literature search was performed to find studies that compared LMWHs versus direct oral anticoagulants (DOACs) in cancer patients with VTE, adding the following generic and trade names of individual preparations of DOACs to the search equation: dabigatran or Pradaxa[®], rivaroxaban or Xarelto[®], apixaban or Eliquis[®], edoxaban or Savaysa[®], betrixaban or Bevyxxa[®].

Study Selection

Two of the authors (SL and CC) independently assessed studies for possible inclusion and disagreements were resolved by consensus, taking into account the opinion of a third assessor (EO). To be included, studies had to be properly randomized, include cancer patients and compare LMWHs with placebo or no treatment in patients free of VTE, or VKA in VTE patients. The type of LMWHs, dose, duration of treatment, and duration of follow-up were recorded but not used to determine the eligibility of studies for inclusion.

Data Extraction and Quality Assessment

Data were independently extracted by two of the authors. In the event of discrepancies between reviewers, a consensus was reached. For each clinical trial, we extracted details on

study characteristics (author names; year of publication; number of randomized patients in each group); study design (double-blind or open); methodological quality of the study; patient characteristics. The methodological quality of each trial was evaluated using the Cochrane Collaboration tool for assessing risk of bias in randomized trials, taking into account random sequence generation, concealment of the allocation sequence, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data and selective reporting (20).

Endpoint

The endpoint of the meta-analysis was overall survival at the end of the treatment period if available, if not at the end of the follow-up period. The hazard ratio (HR) for overall survival and its 95% confidence interval (95% CI) were either computed (when individual patient data were available), extracted from the corresponding publication, or derived from the number of deaths in each treatment group and the log-rank *P* value reported in the publication, as described by Parmar et al. (21). When statistical information was missing, data were requested from the investigators or the sponsor. Finally, if data remained unavailable after several contacts, HRs were derived from the survival curves (21) or estimated according to the corresponding relative risk (RR).

Statistical Analysis

We used a fixed-effects model based on the logarithm of the HR weighted by the inverse of the variance for combining results from the individual trials. Statistical heterogeneity among studies was explored using Cochran's *Q* statistic and study consistency was quantified with the *I*² statistic (22). In the event of significant heterogeneity (*p*-value less than 0.10) and in the absence of any clear explanation for this heterogeneity, a random-effects model was used (23).

We performed a cumulative meta-analysis with all indications combined (including both cancer patients free of VTE and cancer patients with VTE). The cumulative meta-analysis was performed by updating the pooled estimate of the treatment effect each time the results of trials with a more recent publication date were added. A *p*-value for the association of less than 0.05 was considered statistically significant. The results of the meta-analysis are presented graphically with forest plots representing the effect size expressed as the HR with the corresponding 95% CI. An HR equal to 1 indicates no difference between the treatments, less than 1 indicates superiority of the LMWHs and greater than 1 indicates superiority of the control (i.e. placebo, no treatment, or long-term VKA in VTE patients). We explored the publication biases of the studies included in the final analysis using Begg's funnel plot and

Egger's test to help to determine whether additional small studies might have been conducted but not published because of unfavourable or negative results (24,25).

The meta-analysis was performed with R software version 3.5.1 (meta package, downloaded from www.r-project.org).

Consistency of results

Consistency of the results was verified across the subgroups of trials according to the priority of the overall survival endpoint in the study (primary or secondary outcome). Subgroups analyses took into account the type of patients (patients free of VTE and patients with VTE), the dosing of LMWHs (prophylaxis, intermediate, therapeutic) and the type of cancer. A posthoc analysis was performed by including the recent trials having compared LMWHs and direct oral anticoagulants in cancer patients with VTE.

RESULTS

Study Selection

The search procedure identified 385 potentially eligible references, of which 363 were excluded after a scan of their titles and abstracts (Fig 1). After assessment of the fulltexts, seven additional references were excluded. Finally, 25 references, reporting the results of 26 trials, were included in the meta-analysis (12,13,15,17,18,26-45). The search procedure of the post-hoc analysis is given in Appendix 2.

Study description

Table 1 shows the design of the 26 studies included in the meta-analysis. Twenty-one studies included patients free of VTE and compared LMWHs to a control group, while five studies included patients with symptomatic VTE and compared LMWHs to a long-term VKA group. Seven studies were double-blind, one study was single-blind and one study was originally designed as double-blind but was subsequently converted to open-label with the aim of improving recruitment. Information regarding the potential biases of the studies included is provided in Appendix 3.

Cumulative meta-analysis of overall survival

Only 23 studies reported overall survival data, concerning a total of 12,625 patients. The cumulative meta-analysis of studies reported since 2002 shows the expected progressive

precision of the confidence interval with the accrual of the new studies (Fig 2). After inclusion of the first studies, the cumulative meta-analysis showed a significant improvement in overall survival with LMWHs. With the inclusion of further studies reported from about 2005 onward, there was a gradual regression of the results over time toward the absence of an antitumor effect of LMWHs, culminating in a non-significant difference between the treatment groups after inclusion of the studies reported in 2019 (HR 0.98, [95%CI, 0.93 to 1.03], $p = 0.38$, $I^2 = 5\%$).

The funnel plot reveals a potential publication bias, with a lack of studies on the lower left side of the summary treatment effect (Appendix 4), but this apparent publication bias was not statistically significant (Egger's test; $p = 0.47$).

Consistency of results

This trend is especially apparent when considering only studies that defined overall survival as the primary endpoint (Fig 3). When the cumulative meta-analysis is performed according to the type of patients (patients with or without VTE) or the dosing of LMWHs (prophylaxis, intermediate, therapeutic), the trend toward the lack of antitumoral effect is the same in each category (Fig 4 and 5 respectively). Finally, no heterogeneity of the trend is observed across types of cancer (Appendix 5). A trend toward a lack of antitumoral effect of LMWHs is still observed when adding the recent studies of LMWHs versus direct oral anticoagulants: (HR 0.96, [95%CI, 0.86 to 1.07], Appendix 6).

DISCUSSION

This meta-analysis did not reveal any significant decrease in the mortality of cancer patients treated with LMWHs, whether compared to placebo or no treatment in patients without VTE, or compared to VKA treatment in patients with VTE (HR = 0.98 [95% CI, 0.93 to 1.03], 12,625 patients). After the promising results obtained in the earlier studies, there was a regression of the results over time toward the absence of antitumor effect of LMWHs since 2005. Despite the accumulation of available data from RCTs and the statistical power gain, this meta-analysis did not allow detection of a significant treatment effect.

Several meta-analyses have been performed in cancer patients to assess the effect of LMWHs on overall mortality, either comparing LMWHs with VKA in cancer patients with VTE (16,46-51), or comparing LMWH with standard care (placebo or no treatment) in cancer

patients without thrombosis (52-56). The first originality of this meta-analysis is that we pooled all these trials on the grounds that an antitumor effect of LMWHs on mortality was expected in patients both with and without VTE. No heterogeneity of treatment effect was seen across these two groups of trials, as well as the groups of dosing, pleading for the absence of any apparent dose-effect relationship of LMWHs over the range of doses studied. We therefore believe that the pooling of data across these trials is a valid approach.

The second originality is the use of cumulative meta-analysis to highlight the trend of the treatment effect with the accumulation of data over time. Cumulative meta-analyses may reveal that numerous RCTs have been conducted to address efficacy questions that prior trials had already definitively answered, as noted, for example, in 2005 with respect to the use of aprotinin in cardiac surgery (57). As regards our meta-analysis, the earlier promising results were based either on the analysis of subgroups defined *a posteriori*, or on meta-analyses of subgroups or of a secondary endpoint. Only one large-scale double-blind study found an improvement in overall survival in cancer patients treated with LMWHs (15); this result was widely highlighted but never reproduced. As the published clinical research literature may be distorted by the pursuit of statistically significant results, it cannot be excluded that the effect of LMWHs on overall mortality in cancer patients was related to publication biases and p-hacking, which inflate the risk of false positive results when these are derived from analyses of subgroups or secondary outcomes.

Its potential limitation is the differences in design of the studies included, which are inevitable given that the individual trials used different treatment protocols. However, differences in the design of individual trials do not necessarily preclude pooling of their results, as in a meta-analysis, individual patients are directly compared only with other patients within the same trial rather than across the various trials included.

Despite supportive experimental data and promising early clinical findings, the supposed antitumor effect of LMWHs in cancer patients gradually vanished over time toward their true impact on overall survival, i.e., none. This result suggest that we should beware of early enthusiasm when a study reports a result that may seem revolutionary, especially if this is based on an unplanned subgroup analysis or concerns a secondary outcome.

CONCLUSION

The cumulative meta-analysis tool allows to early highlight the lack of antitumoral effect of

LMWHs on the survival of cancer patients and the stability of this result for several years.

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Table 1. Characteristics of the studies included (ordered by DVT at inclusion and year of publication)

Author, Year	Study acronym	NCT	Design	No. of patients	Type of cancer	Known metastases (%)
VTE at inclusion (LMWHs compared to VKA)						
Meyer, 2002 (26)	CANTHANOX	-	Open	146	Various	53
Lee, 2003 (13)	CLOT	-	Open	676	Solid tumor or hematologic cancer	67
Deitcher, 2006 (29)	ONCENOX	-	Open	102	Various	58
Hull, 2006 (30)	MAIN LITE	NCT00689520	Open	200	Solid tumor	41
Lee, 2015 (17)	CATCH	NCT01130025	Open	900	Solid tumor or hematologic cancer	55
No VTE at inclusion (LMWHs compared to placebo or no treatment)						
Kakkar, 2004 (12)	FAMOUS	-	DB	374	Solid tumor	86
Altinbas, 2004 (27)	SCLC	-	Open	84	Small cell lung cancer	43
Klerk, 2005 (15)	MALT	-	DB	302	Solid tumor	91
Sideras, 2006 (28)	-	NCT00003674	DB then open	141	Various solid tumor	100*
Agnelli, 2009 (31)	PROTECHT	NCT00951574	DB	1166	Solid tumor	NA
Perry, 2010 (32)	PRODIGE	NCT00135876	DB	186	Brain tumor	NA
van Doormaal, 2011 (33)	INPACT	NCT00312013	Open	503	Solid tumor	NA
Agnelli, 2012 (34)	SAVE-ONCO	NCT00694382	DB	3212	Solid tumor	68
Haas, 2012 (35)	TOPIC 1	-	DB	353	Breast cancer	100
Haas, 2012 (35)	TOPIC 2	-	DB	547	Lung cancer	53
Maraveyas, 2012 (36)	FRAGEM	NCT00462852	Open	123	Pancreatic cancer	54
Zwicker, 2013 (37)	MICROTEC	-	Open	34	Solid tumor	79
Lecumberri, 2013 (38)	ABEL	NCT00324558	Open	38	Small cell lung cancer	NA
Vadhan-Raj, 2013 (39)	-	NCT00966277	Open	75	Pancreatic cancer	NA
Pelzer, 2015 (40)	CONKO-004	ISRCTN02140505	Open	312	Pancreatic cancer	76
Macbeth, 2016 (41)	FRAGMATIC	ISRCTN80812769	Open	2202	Lung cancer	61
Groen, 2016 (42)	NVALT-8	NTR1250	Open	201	Non-small cell lung cancer	0
Khorana, 2017 (43)	PHACS	NCT00876915	Open	98	Various	NA
Ek, 2018 (44)	RASTEN	NCT00717938	Open	377	Small cell lung cancer	NA
Meyer, 2018 (18)	TILT	NCT00475098	Open	549	Non-small cell lung cancer	0
Taghizadeh Kermani, 2019 (45)	-	NCT03254511	SB	69	Esophageal cancer	0

DB: double-blind; NA: not available; SB: single-blind; VTE: venous thromboembolic event

* advanced solid cancer, the proportion of locally-advanced and metastatic tumors is unavailable.

Figure 1. Selection of the studies

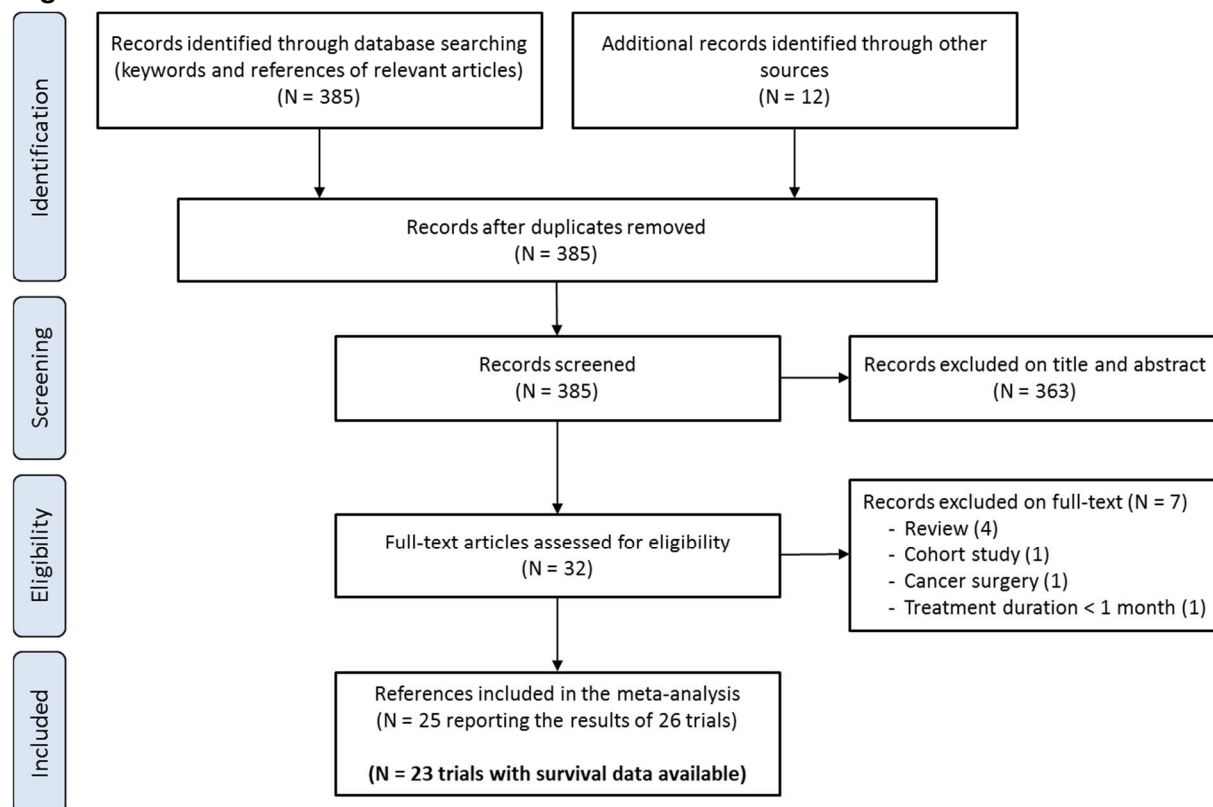
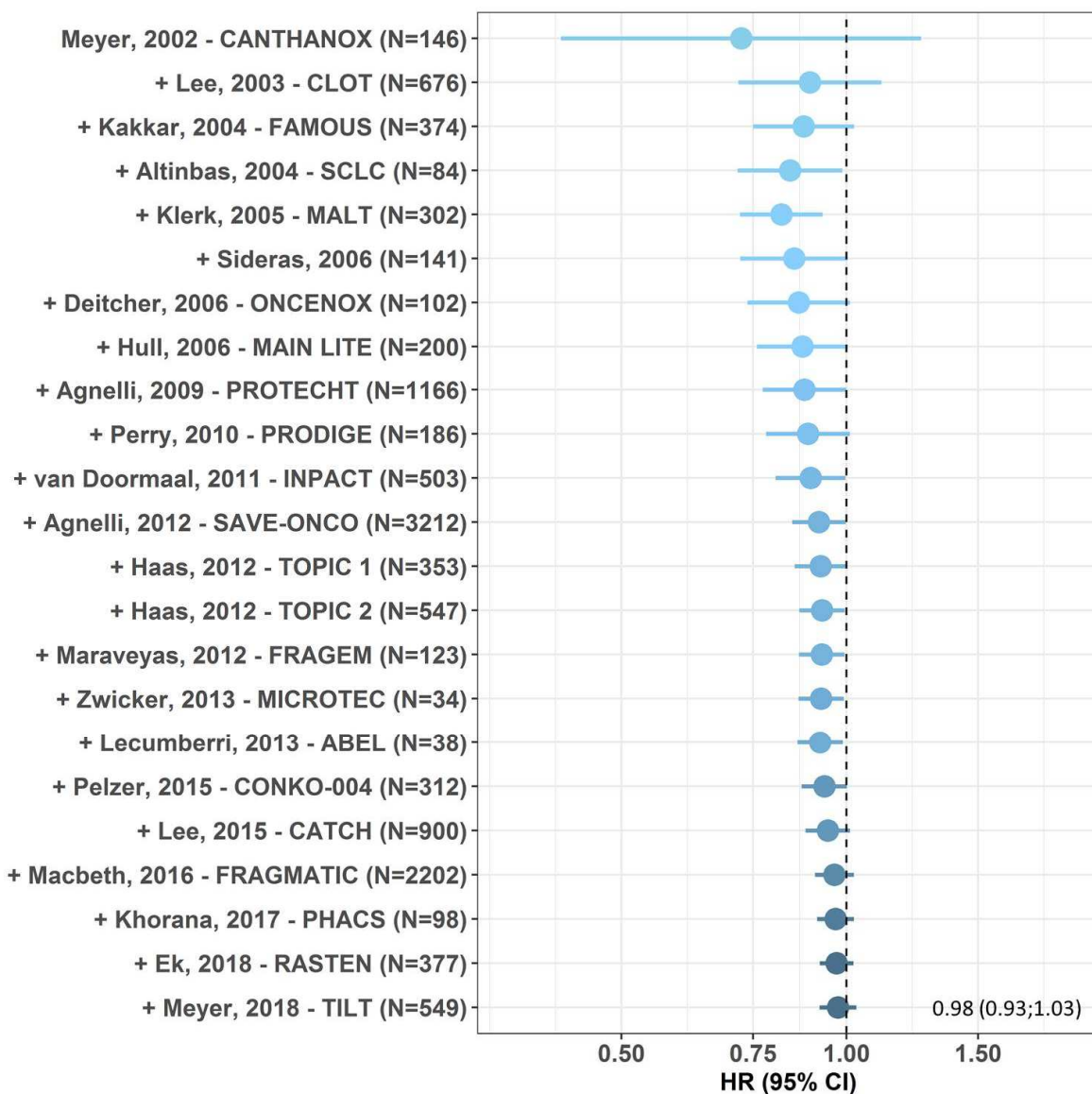
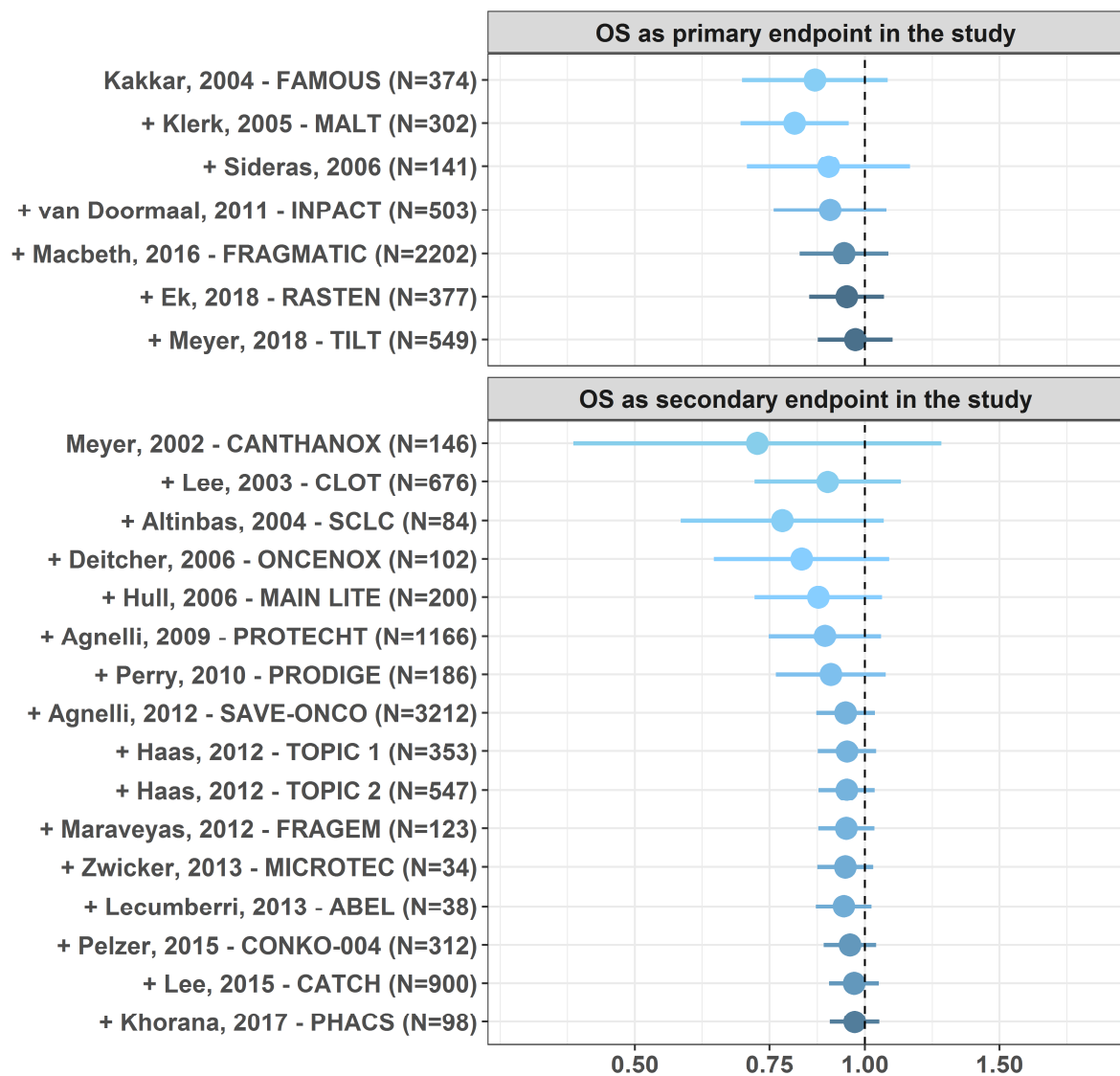


Figure 2. Cumulative meta-analysis.



CI, confidence interval; HR, hazard ratio.

Figure 3. Cumulative meta-analysis according to the priority of the overall survival endpoint in the study.



OS, overall survival.

Figure 4. Cumulative meta-analysis according to the type of patients (patients with or without VTE).

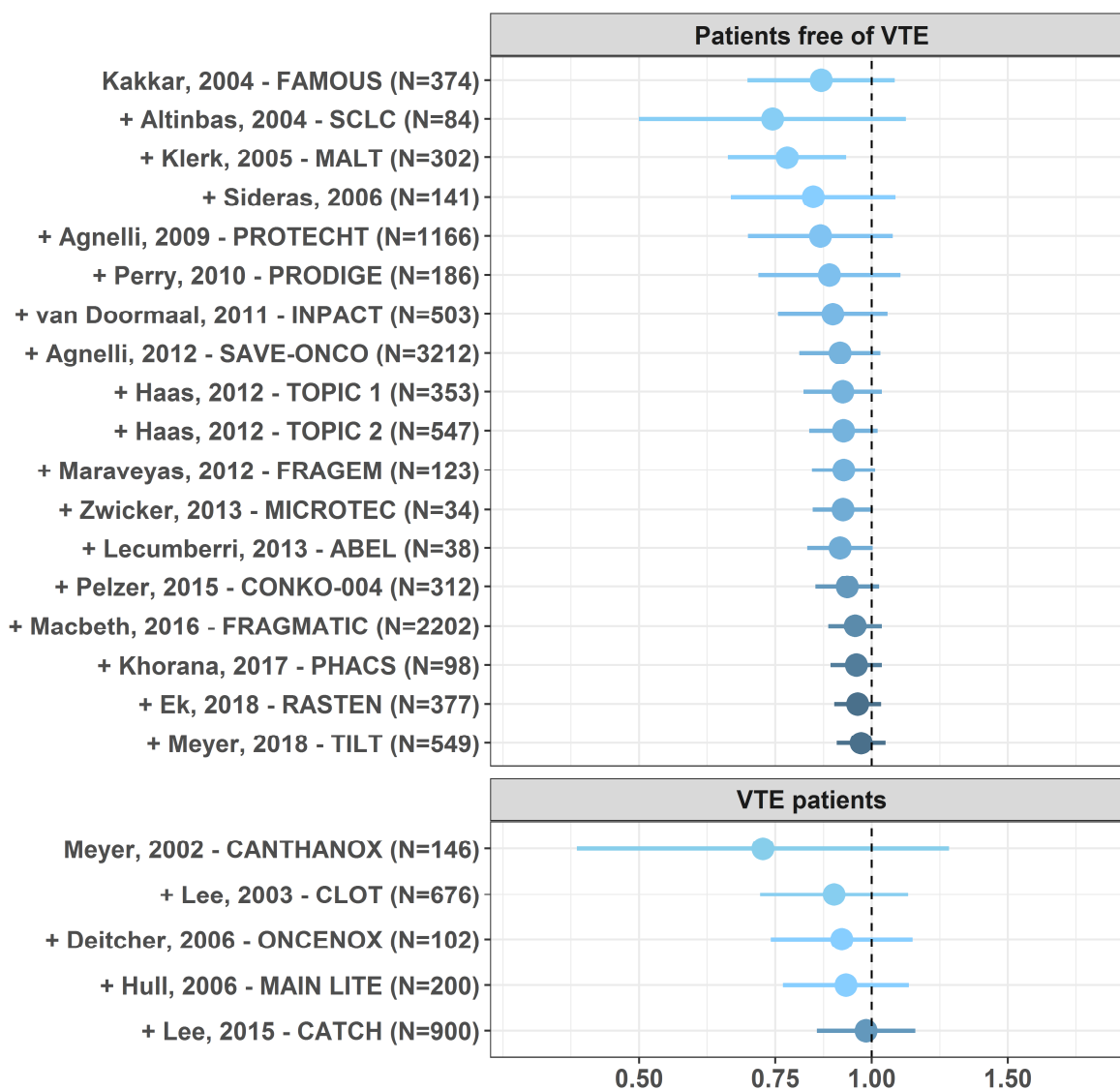
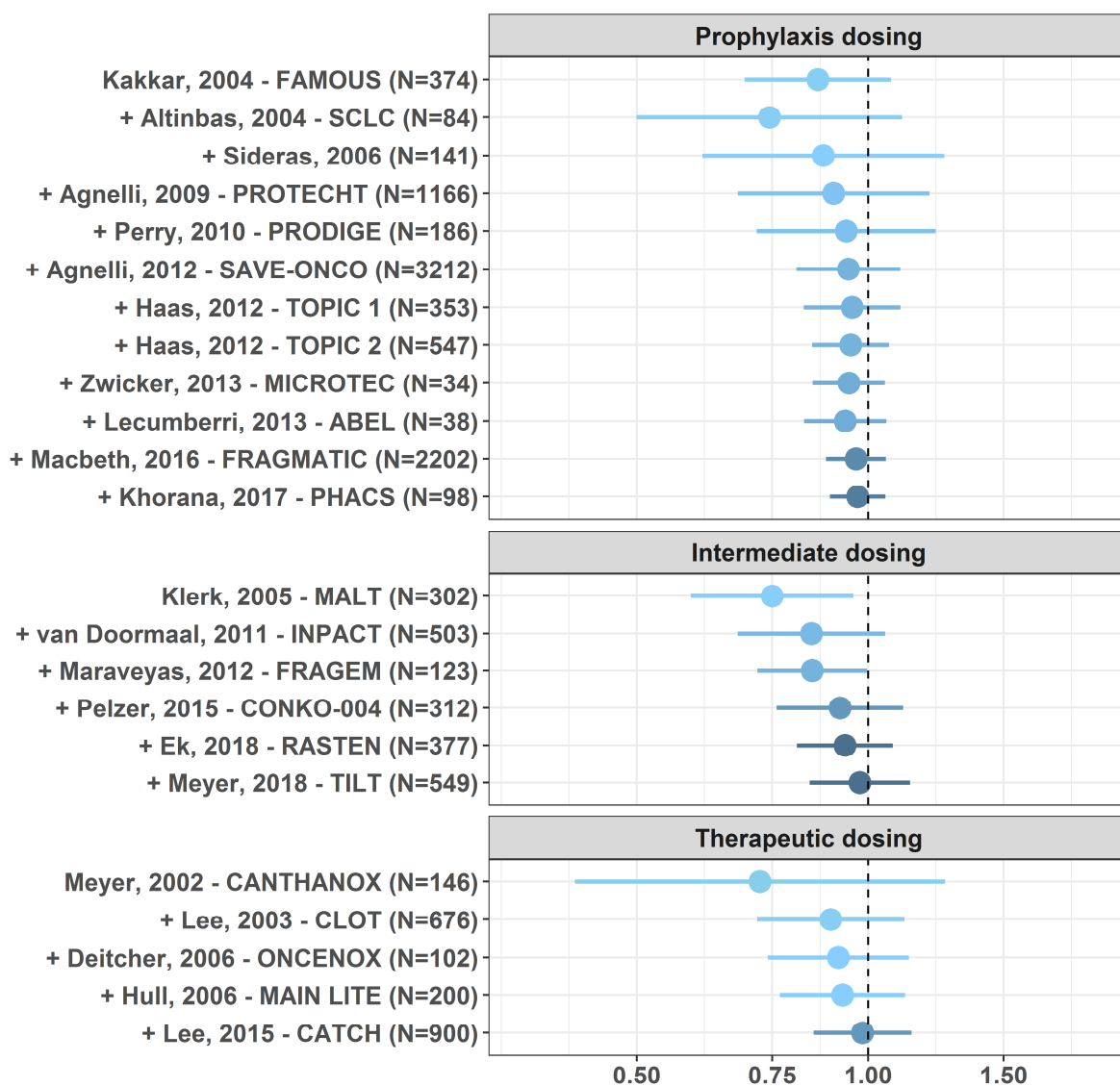


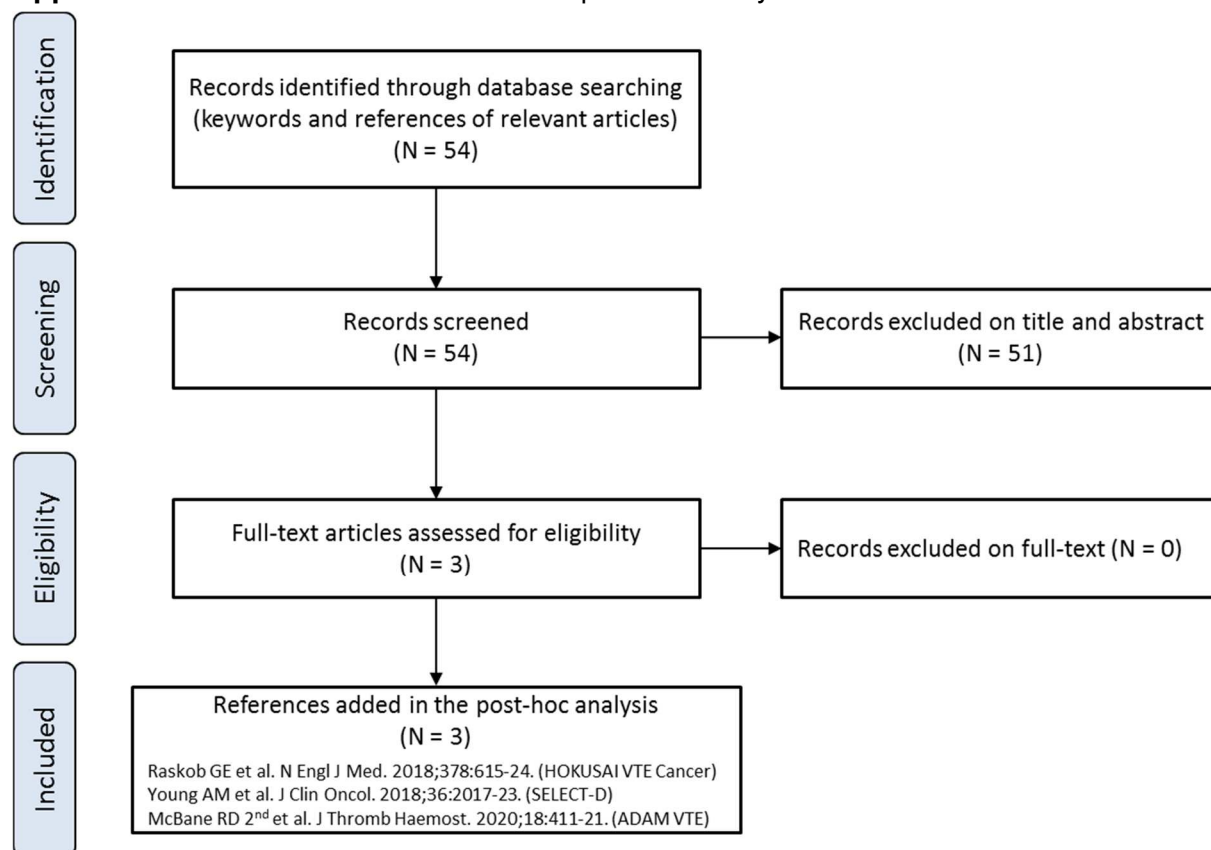
Figure 5. Cumulative meta-analysis according to the dosing of LMWHs.



Appendix 1. META-EMBOL study group

S. Laporte (chair), P. Mismetti, P. Zufferey, *Saint-Etienne*; F. Couturaud, *Brest*; M. Cucherat, F. Gueyffier, A. Leizorovicz, *Lyon*; G. Meyer, C. M. Samama, G. Steg, *Paris*.
Members: P. Albaladejo, *Grenoble*; L. Bertoletti, C. Chapelle, P. Garnier, C. Labruyère, N. Mottet, *Saint-Etienne*; Ph. Girard, E. Marret, F. Parent, N. Rosencher, *Paris*; J. C. Lega, P. Nony, *Lyon*; D. Wahl, *Nancy*.

Appendix 2. Selection of the studies of the post-hoc analysis

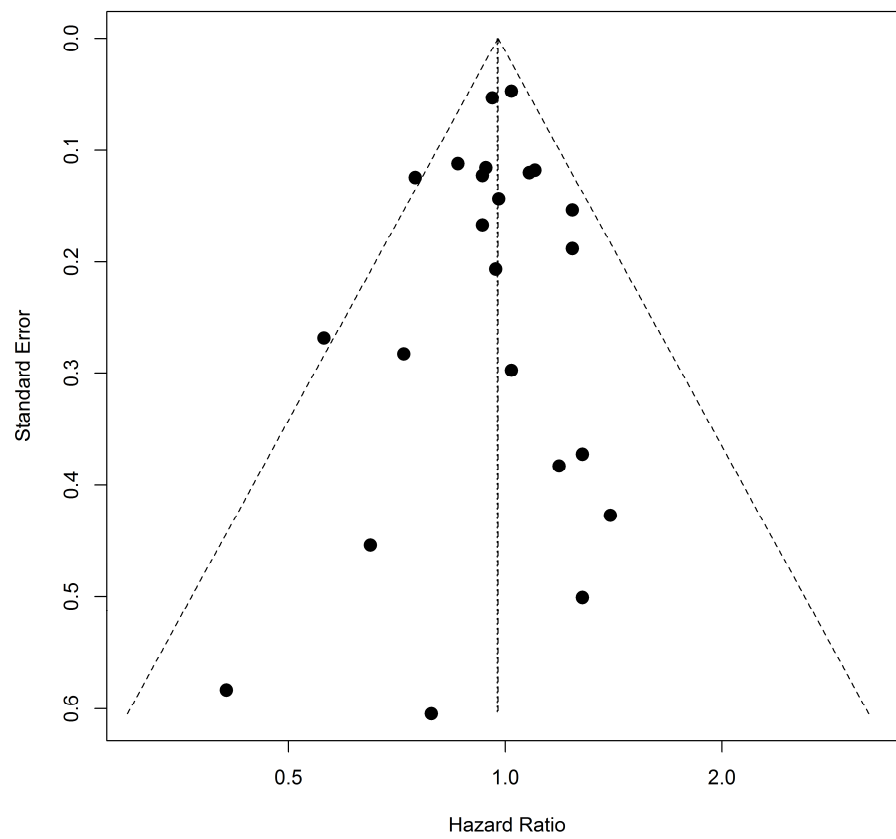


Appendix 3. Assessment of the risk of bias according to the Cochrane collaboration tool (ordered by VTE at inclusion and year of publication)

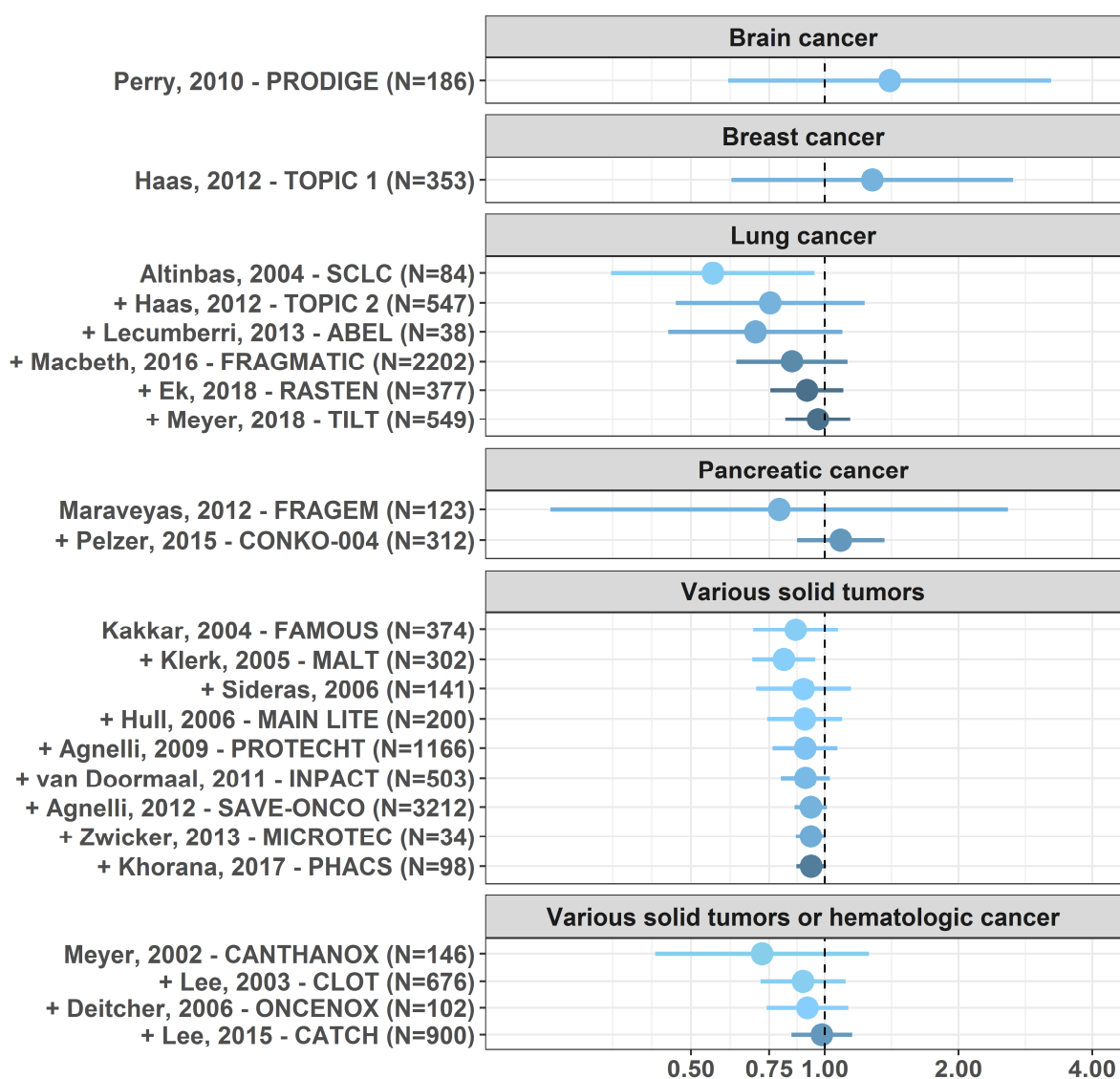
Author, Year	Study acronym	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting
VTE at inclusion							
Meyer, 2002 (26)	CANTHANOX	+	+	-	-	+	-
Lee, 2003 (13)	CLOT	+	+	-	-	+	-
Deitcher, 2006 (29)	ONCENOX	+	+	-	-	+	-
Hull, 2006 (30)	MAIN LITE	?	?	-	-	+	-
Lee, 2015 (17)	CATCH	+	+	-	+	+	-
No VTE at inclusion							
Kakkar, 2004 (12)	FAMOUS	+	+	+	+	+	+
Altinbas, 2004 (27)	SCLC	?	?	-	-	+	-
Klerk, 2005 (15)	MALT	+	+	+	+	+	+
Sideras, 2006 (28)	-	+	+	-	-	+	+
Agnelli, 2009 (31)	PROTECHT	+	+	+	+	+	-
Perry, 2010 (32)	PRODIGE	+	+	+	+	+	-
van Doormaal, 2011 (33)	INPACT	+	+	-	-	+	+
Agnelli, 2012 (34)	SAVE-ONCO	+	+	+	+	+	-
Haas, 2012 (35)	TOPIC 1	+	+	+	+	+	-
Haas, 2012 (35)	TOPIC 2	+	+	+	+	+	-
Maraveyas, 2012 (36)	FRAGEM	+	+	-	-	+	-
Zwicker, 2013 (37)	MICROTEC	?	?	-	-	?	-
Lecumberri, 2013 (38)	ABEL	+	+	-	-	+	-
Vadhan-Raj, 2013 (39)	-	?	?	-	-	?	-
Pelzer, 2015 (40)	CONKO-004	+	+	-	-	+	-
Macbeth, 2016 (41)	FRAGMATIC	+	+	-	-	+	+
Groen, 2016 (42)	NVALT-8	?	?	-	-	+	-
Khorana, 2017 (43)	PHACS	?	?	-	-	+	-
Ek, 2018 (44)	RASTEN	+	+	-	-	-	+
Meyer, 2018 (18)	TILT	+	+	-	+	+	+
Taghizadeh Kermani, 2019 (45)	-	?	?	-	-	-	+

VTE: venous thromboembolic event

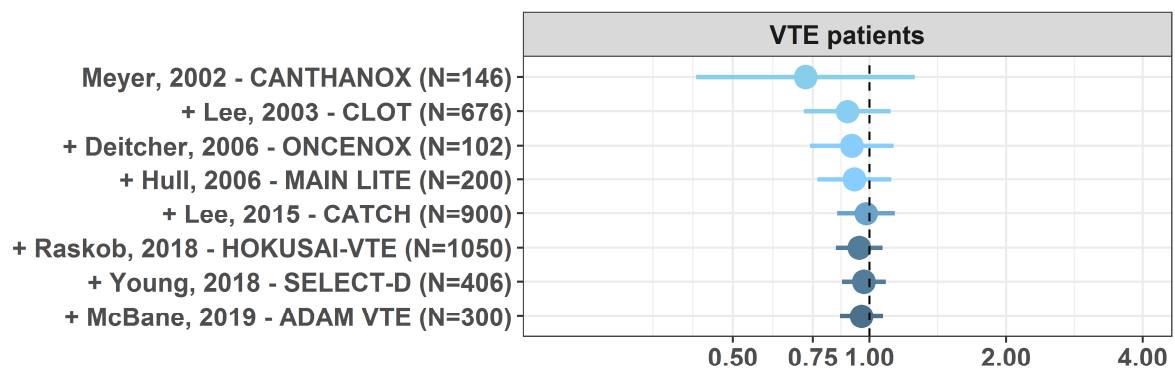
Appendix 4. Funnel plot assessing the publication bias



Appendix 5. Cumulative meta-analysis according to the type of cancer.



Appendix 6. Cumulative posthoc meta-analysis including LMWHs versus vitamin K antagonists trials and LMWHs versus direct oral anticoagulants in cancer patients with VTE*.



* data extracted from Mai et al. (Mai V, Tanguay VF, Guay CA, Bertoletti L, Magnan S, Turgeon AF, Lacasse Y, Lega JC, Provencher S. DOAC compared to LMWH in the treatment of cancer related-venous thromboembolism: a systematic review and meta-analysis. J Thromb Thrombolysis. 2020; doi: 10.1007/s11239-020-02055-1)