

# Twist and Shout: One Decade of Meta-Analyses of Erythropoiesis-Stimulating Agents in Cancer Patients

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## Key Words

Cancer-related anemia • Epoetin • Erythropoiesis-stimulating agents • Hemoglobin • Red blood cell transfusion • Thromboembolic events

## Abstract

Anemia associated with cancer and cancer therapy is a common and important issue in the treatment of patients with malignant disease. Conventionally, blood transfusions are used to treat severe cancer-related anemia. Short- and long-acting preparations of recombinant human erythropoiesis-stimulating agents (ESAs) offer an alternative treatment option. Multiple studies and subsequent meta-analyses have demonstrated that ESA treatment increases hemoglobin levels and reduces the likelihood of transfusion for a proportion of treated patients. However, studies that attempted to evaluate whether ESAs improve tumor response and survival have generated conflicting evidence. Results of smaller trials reporting improved survival outcomes were contradicted by large randomized controlled trials that reported more deaths in patients receiving ESAs. In addition, there is strong evidence that cancer patients receiving ESAs have an increased risk of thromboembolic and cardiovascular events. We herein review the main meta-analyses published in the field, their strengths and weaknesses, their contribution to patient management and future perspectives for systematic reviews.

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## Introduction

Anemia, defined as a deficiency in the concentration of hemoglobin (Hb)-containing red blood cells (RBCs), is a widely prevalent complication among cancer patients. About 32% of patients present with anemia at diagnosis and about 54% of initially non-anemic cancer patients develop anemia during treatment [1, 2]. Anemia is caused by either the cancer itself or by cytotoxic treatment [3]. For affected patients, anemia can be a debilitating problem; it negatively influences their quality of life (QoL) [4] and is associated with shorter overall survival [5]. Homologous blood transfusion is the fastest method to alleviate symptoms caused by anemia; however, short- and long-term risks such as transmission of infectious diseases, transfusion reactions and alloimmunization have to be faced [6]. Short- and long-acting preparations of recombinant human erythropoiesis-stimulating agents (ESAs) offer an alternative treatment option, reducing the risk for infections and adverse events associated with RBC transfusions.

Mainly three different recombinant erythropoietins are available to date: epoetin  $\alpha$  (Procrit<sup>®</sup>, Johnson & Johnson; Epogen<sup>®</sup>, Amgen), epoetin  $\beta$  (NeoRecormon<sup>®</sup>, Roche) and darbepoetin  $\alpha$  (Aranesp<sup>®</sup>, Amgen). Epoetins  $\alpha$  and  $\beta$  consist of 165 amino acids, but they differ in their carbohydrate content. Darbepoetin has a longer half-life

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compared to epoetin  $\alpha$  and  $\beta$ . The three erythropoietins have similar clinical efficacy [7, 8] and are considered as members of the same pharmacologic class [9]. Other novel molecules, i.e. the continuous erythropoietin receptor activator [10, 11] and biosimilars, including epoetin  $\alpha$ , epoetin  $\zeta$  and epoetin  $\delta$ , have been developed. Currently, epoetin  $\zeta$  is approved for the treatment of chemotherapy-induced anemia in patients with solid tumors, malignant lymphoma and multiple myeloma [12, 13].

Since ESAs were licensed for the treatment of anemia in cancer patients in 1993, more than 80 randomized controlled trials (RCTs) on the effects of ESAs versus control were conducted in cancer patients. In order to systematically organize these studies, several systematic reviews and meta-analyses were done. The first meta-analysis was published in 1997 [14]. Ever since, more than 20 meta-analyses and systematic reviews on the effects of ESAs in cancer patients have been published. We here discuss the main meta-analyses published in the field, their strengths and weaknesses, their contribution to patient management and future perspectives for systematic reviews in this field. These issues will be structured by selected clinical outcomes, i.e. RBC transfusions (RBCTs), thromboembolic events and survival. Systematic reviews and meta-analyses restricted to specific patient populations, i.e. patients with myelodysplastic syndrome [16, 17], head-and-neck cancer [18] or specific outcomes, i.e. hematological response [15] or QoL [19, 20], will not be reviewed here.

### Red Blood Cell Transfusions

ESAs efficiently increase Hb levels in cancer patients and reduce need for RBCTs. Up to now, more than 60 RCTs evaluated the risk for transfusion in patients receiving ESAs compared to controls. The benefit of ESAs in terms of reduced risk for RBCTs was shown in the majority of randomized trials, and most of these trials were sufficiently powered to detect statistically significant differences between experimental and control arms. Besides, RBCT risk was evaluated in eleven meta-analyses [14, 21–30]. One of the first meta-analyses was commissioned by the Agency for Health Research and Quality and published by Seidenfeld et al. [21] in 2001. This analysis was updated in a collaborative effort with the Cochrane Hematological Malignancies Group in 2002 [22]. In 2004/2005, these analyses were updated together with investigators from the University of Birmingham [23] and the Agency for Health Research and Quality [25]. Apart from

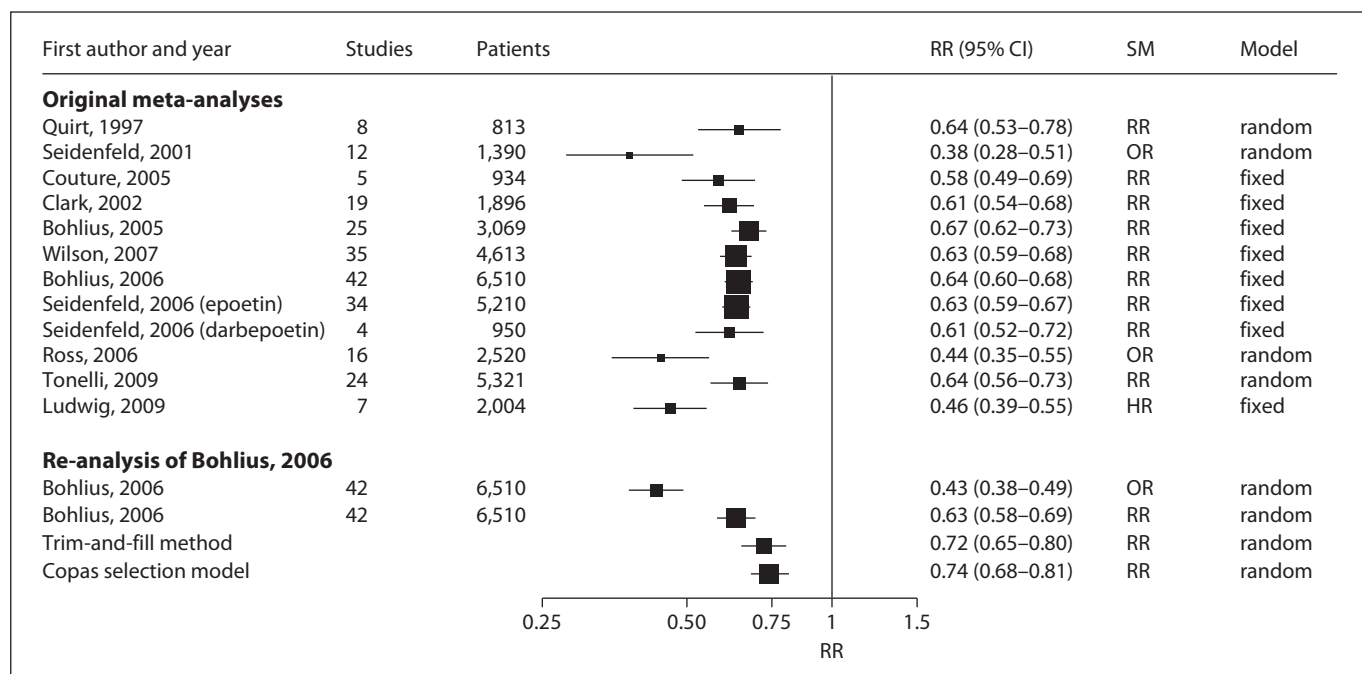
this collaboration, several other meta-analyses reported results for RBCTs [14, 26–30].

All meta-analyses demonstrated that ESAs reduce the risk for transfusions in a statistically and clinically meaningful way. Results of these meta-analyses are shown in the upper part of figure 1. At first glance, the results reported by Seidenfeld et al. [21] and by Ross et al. [27] are strikingly different from the other results. However, in these meta-analyses the odds ratio (OR) was used as effect measure whereas the risk ratio (RR) was used in the others. It is well known that OR and RR values can be very different if events are common [31]. RBCT is a very common event in cancer patients. Accordingly, results for meta-analyses using OR as summary measure show very different results. A re-analysis of Bohlius et al. [32] in 2006 using OR is shown in the lower part of figure 1. Their OR (0.43) is very similar to those reported by Seidenfeld et al. [21] (OR 0.38) and Ross et al. [27] (OR 0.44). All nine meta-analyses using RR as effect measure report very similar results (RR range 0.58–0.67).

However, most meta-analyses on RBCTs show some or even substantial heterogeneity. This indicates variation between trials that cannot be explained by chance. To explore this heterogeneity, several working groups conducted meta-regression analysis. For example in a multivariate stepwise meta-regression analysis, Bohlius et al. [24, 32] revealed that ESA effect size was influenced by the type of underlying malignancy and source of data. Unpublished data show more conservative results than data taken from full-text or abstract publications. Furthermore, in patients with hematological malignancies and myelodysplastic syndrome, the effect was similar, whereas the treatment effect was markedly different in patients with solid tumors. In summary, meta-regression analysis within a meta-analysis may help to identify factors that modify effect sizes and that may help to explain different effect sizes observed between different trials.

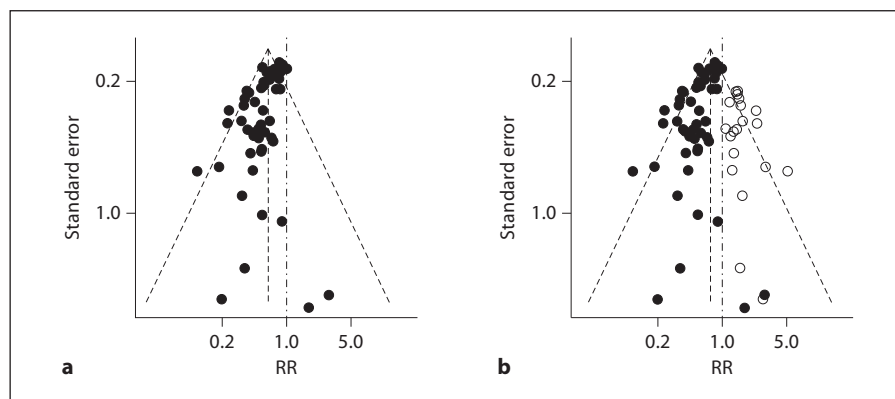
To avoid the perils of publication bias, additional unpublished or unreported data were requested from the clinical trial investigators and included in the meta-analysis published by Bohlius et al. [22]. Including these additional unreported data in the analysis generated a more conservative estimate. Thus, meta-analysis including unreported data may help to achieve more realistic estimates of the effectiveness of drugs.

Despite efforts to include unreported data in RBCT meta-analyses, some indication for publication bias still exists as tests for funnel plot asymmetry are significant in some meta-analyses. For example, a re-analysis of the



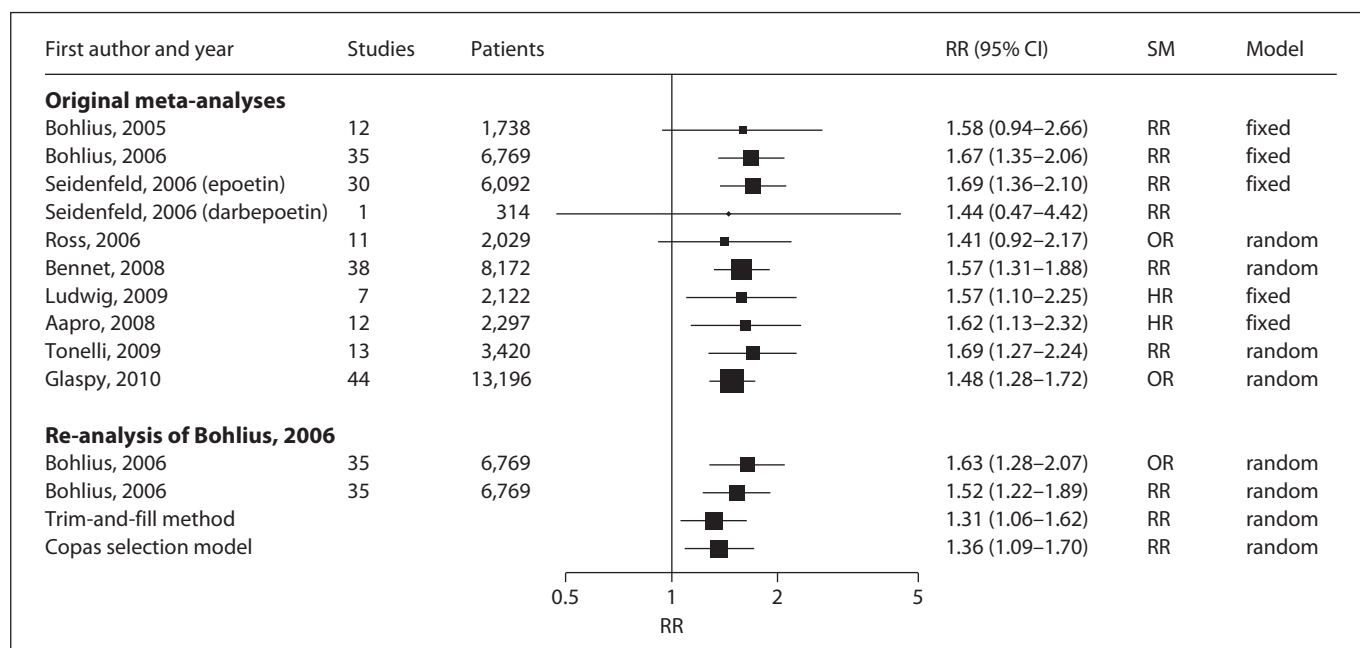
**Fig. 1.** Forest plot of meta-analyses on the effects of ESAs on the risk of RBCTs. Columns report on the total numbers of studies in meta-analysis (Studies) and participants (Patients); on effect measure (RR) and its 95% CIs; summary measures used in meta-analysis (SM), and the meta-analysis model (Model: fixed and random effect models).

**Fig. 2.** Funnel plot of studies on RBCTs included in the Cochrane review by Bohlius et al. [32]. **a** Original analysis. **b** Result of the trim-and-fill method applied to adjust for publication bias.



data of Bohlius et al. [32] using the test proposed by Harbord et al. [33] revealed a significant difference ( $p = 0.039$ ). The funnel plot of these data is shown in figure 2a. Statistical methods to adjust for potential publication bias have been developed during the last decade. In this paper, we apply two prominent adjustment methods, the trim-and-fill method [34] and the Copas selection model [35], to the data from Bohlius et al. [32] as a kind of sensitivity

analysis. The results for these two adjustment methods are given in the lower part of figure 1; the result for the trim-and-fill method is also shown in figure 2a. Both methods suggest that the effect estimate – adjusted for potential publication bias – is slightly smaller, i.e. closer to the null effect, but still highly statistically significant: OR 0.72 (trim-and-fill method) and OR 0.74 (Copas selection model).



**Fig. 3.** Forest plot of meta-analyses on the effects of ESAs on the risk of thromboembolic events. Columns report on the total numbers of studies in meta-analysis (Studies) and participants (Patients); on effect measure (RR) and its 95% CIs; summary measures used in meta-analysis (SM), and the meta-analysis model (Model: fixed and random effect models).

In conclusion, various meta-analyses have fairly consistently shown that the use of ESAs effectively reduces the RBCT risk. Inclusion of unreported data helped to generate a more conservative estimate. However, under constrained resources, efforts to obtain unreported data will most often only be an exception rather than a rule. Resource constraints apply to both investigators conducting the meta-analyses as well as clinical trial investigators who are requested to provide unreported data. Statistical adjustment methods can be useful to evaluate the sensitivity of results to potential publication bias.

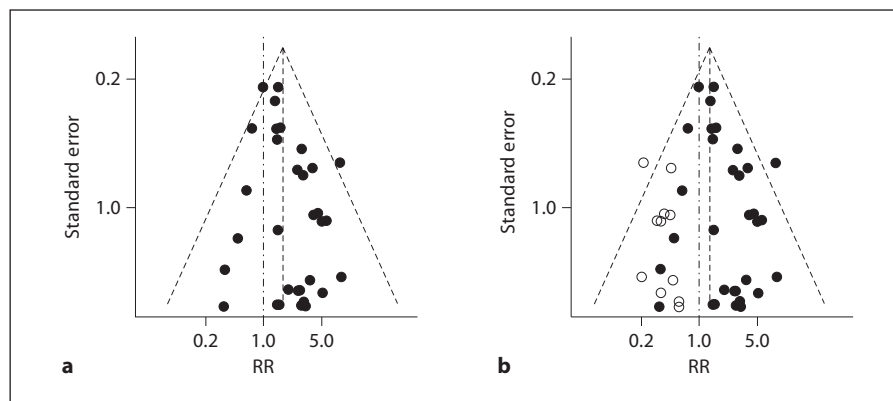
### Thrombovascular Events

ESAs have the potential to increase thrombogenic activity either by augmented Hb levels or other mechanisms. Healthy volunteers receiving recombinant ESAs demonstrate increased platelet reactivity and endothelial activation [36]. In general, cancer patients are at increased risk to develop thrombovascular events (TVEs); nevertheless it is a rare event. Therefore, a large sample size is needed to achieve sufficient power to detect differences between ESA and control groups if they exist. None of the

individual RCTs conducted to date was designed or powered to detect an increased risk for TVEs. In most studies, TVEs were evaluated as part of the general safety and adverse event assessment only. Today, data for thromboembolic events are available from about 50 RCTs comparing ESA with no ESA treatment in cancer patients. Although the majority of these studies showed an increased risk for thromboembolic events in ESA patients compared to controls, most studies failed to achieve conventional levels of statistical significance. In this situation, a meta-analysis may increase the statistical power and thus prevent undue delays in the detection of beneficial or harmful effects of medical treatments [37].

TVEs were evaluated in nine meta-analyses [22, 24–27, 30, 38–40] (fig. 3). The first meta-analysis that evaluated TVEs was based on 12 studies including 1,738 patients [22]. The overall estimate for RR to develop TVEs was increased by a factor of 1.58 (95% CI 0.94–2.66) for ESA-treated patients compared to controls [22]. However, the observed effect did not reach conventional levels of statistical significance. When this meta-analysis was updated in 2006, data from a total of 35 studies and 6,679 patients were analyzed [24]. In this updated analysis, the previously observed effect size was confirmed and statistical signifi-

**Fig. 4.** Funnel plot of studies on thromboembolic events included in the Cochrane review by Bohlius et al. [32]. **a** Original analysis. **b** Result of the trim-and-fill method applied to adjust for publication bias.



cance was reached (RR 1.67, 95% CI 1.35–2.06) [24]. All but one [27] subsequent meta-analyses confirmed the observed highly statistically significant effect. This example emphasizes the advantage of meta-analysis to increase statistical power by pooling across several (small) studies. In addition, it illustrates that meta-analyses may help to inform patients, physicians and decision-makers in a more timely manner; an increased risk for thromboembolic events was demonstrated in cancer patients receiving ESAs and published in a medical journal in 2006 based on a meta-analysis [24]. In contrast, the first RCTs showing statistically significant differences between ESA and control treatment were published in medical journals in 2008 [41, 42].

Main limitations of these literature-based meta-analyses are potential biases, e.g. outcome reporting and publication bias. Authors may highlight an increased risk of TVEs in ESA patients compared to controls but may be reluctant to report this if the opposite effect is observed, i.e. TVEs observed less frequently in the ESA group compared to controls [43]. The published literature may therefore represent a biased sample. A funnel plot for the data from Bohlius et al. [32] given in figure 4a suggests that negative results (in this case no thrombotic event) have been underreported [32]. Accordingly, the Harbord test for funnel plot asymmetry [33] is significant with  $p = 0.021$ . A sensitivity analysis to evaluate the impact of biases using the trim-and-fill method [34] and the Copas selection model [35] results in smaller but still statistically significant effect estimates (lower part of fig. 3, fig. 4b).

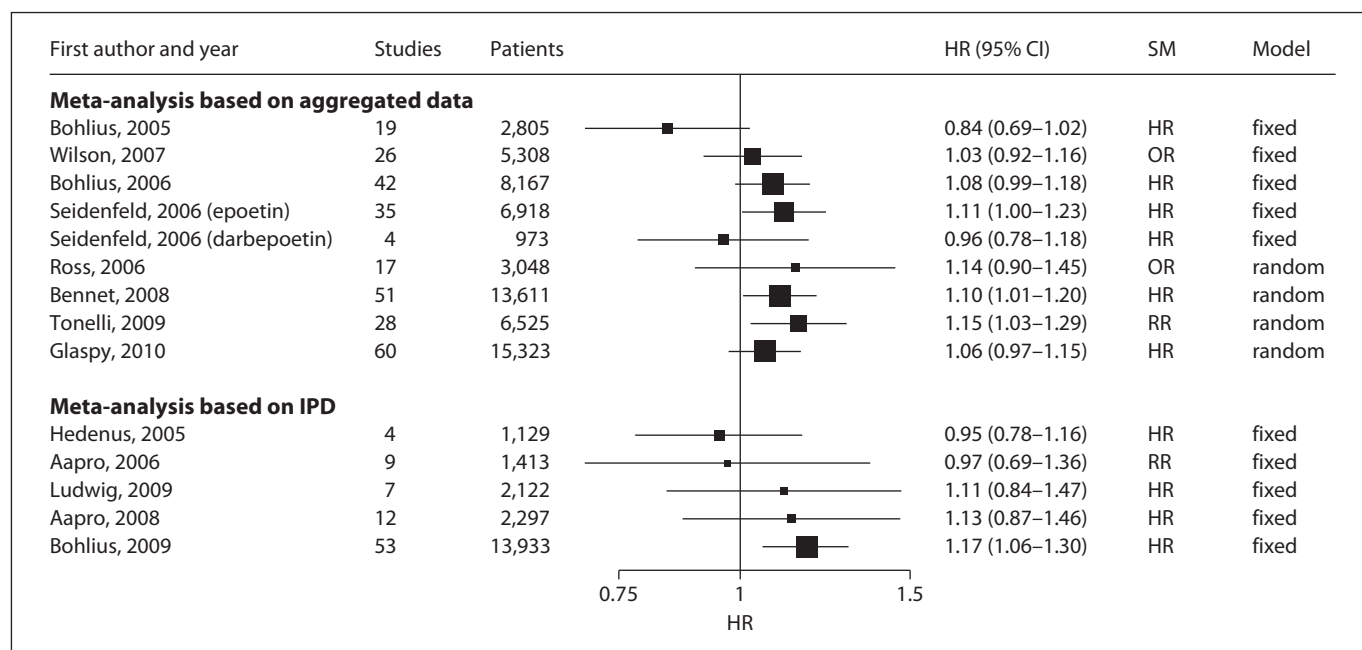
The concern of reporting biases may be less of an issue in meta-analyses of individual-patient data (IPD). Data for this type of meta-analyses are taken directly from published and unpublished RCTs and not from publications or reports, thus, publication or reporting biases are

less likely to occur. For ESAs, TVEs were evaluated in two IPD meta-analyses [30, 39]. Both meta-analyses were restricted to selected ESA products. Epoetin  $\beta$  was evaluated in seven trials including 2,112 patients in one meta-analysis [39] and darbepoetin in 12 trials including 2,297 patients in the other meta-analysis [30]. RR for TVEs was increased (RR 1.57, 95% CI 1.10–2.26 [30], and RR 1.62, 95% CI 1.13–2.31 [39]). Thus, these IPD meta-analyses confirm the findings from previous literature-based meta-analyses.

Nevertheless, another source of bias, i.e. detection bias, cannot be excluded. None of the RCTs evaluating ESA therapy in cancer patients investigated systematically TVEs including a prospective definition for TVEs and standardized screening and diagnostic procedures. Physicians treating cancer patients with ESAs might be more observant towards TVEs in patients receiving ESAs compared to controls. Therefore, a risk for detection bias is inherent in each individual RCT included in the various meta-analyses. Since the quality of a meta-analysis is limited by the quality of the original studies, the quality of the primarily conducted RCTs remains the Achilles' heel of any meta-analysis.

### Survival and Mortality

Researchers have also hypothesized that strategies to diminish cancer-related anemia might alleviate not only anemia-related symptoms and improve QoL but also improve tumor response and possibly extend overall survival. This line of argument was mainly based on evidence from in vitro and animal model studies indicating that anemia, with the consequence of increased tumor hypoxia, might result in a poorer response to radiother-



**Fig. 5.** Forest plot of meta-analyses on the effects of ESAs on the mortality risk. Columns report on the total numbers of studies in meta-analysis (Studies) and participants (Patients); on effect measure (HR) and its 95% CIs; summary measures used in meta-analysis (SM), and the meta-analysis model (Model: fixed and random effect models).

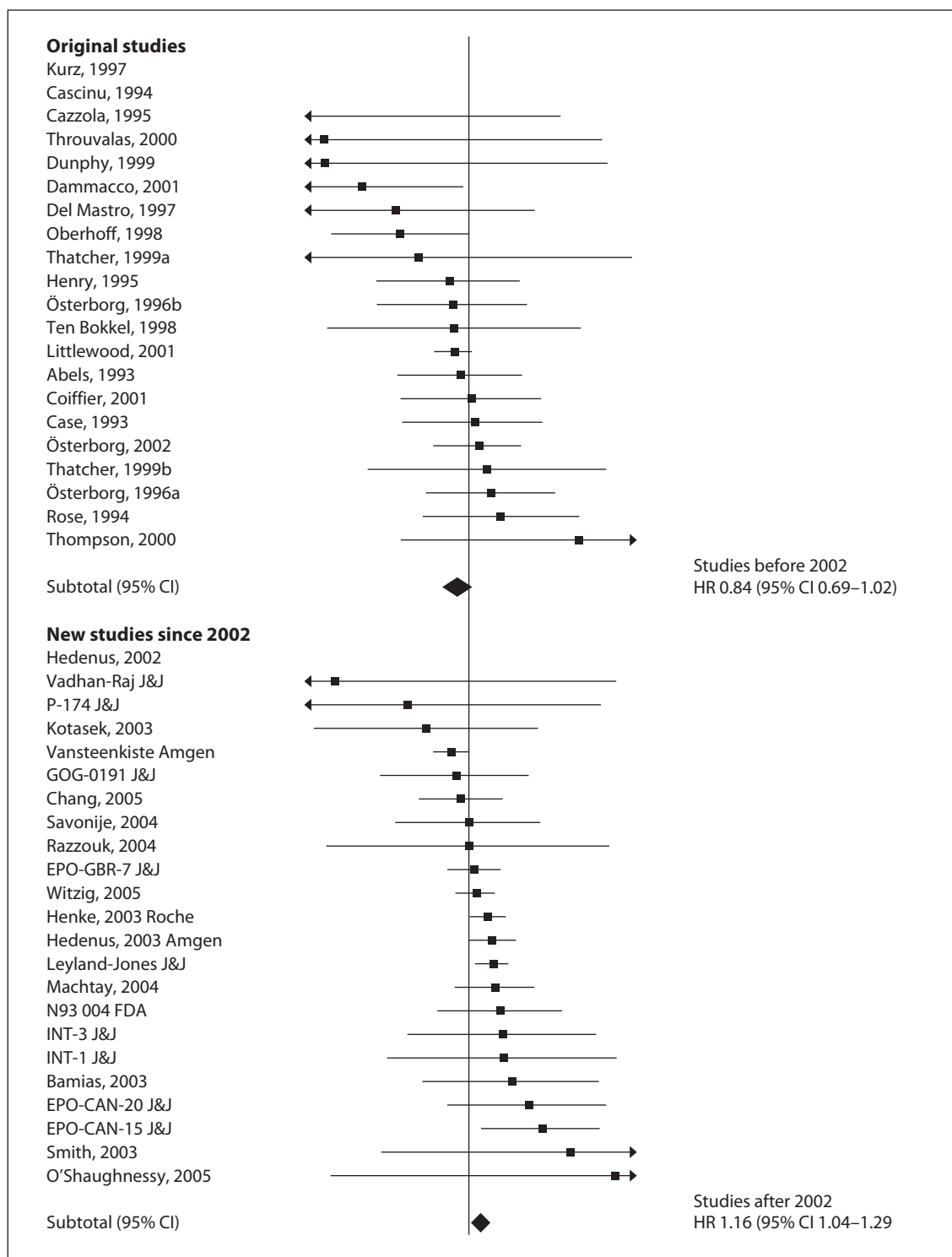
apy or oxygen-dependent chemotherapy [44, 45]. Strategies to improve tumor oxygenation could thus potentially improve tumor control and survival [46–50]. However, RCTs that have attempted to evaluate whether ESAs improve tumor response and survival have generated conflicting evidence. An early study, not primarily designed to evaluate survival and tumor progression, showed improved survival outcomes [51]. This study was in contrast to large RCTs that reported more deaths in ESA patients compared to controls in various clinical settings, i.e. patients with head-and-neck cancers undergoing radiotherapy [52, 53], patients with metastatic breast cancer undergoing chemotherapy [54, 55] and patients with advanced-stage cancers not receiving chemotherapy [56]. These conflicting data prompted three Oncologic Drug Advisory Committee hearings of the Federal Drug Administration in 2004, 2007 and 2008 where the safety of ESAs was discussed [9, 57, 58]. Several restrictions to ESAs were implemented following these hearings.

Several systematic reviews and meta-analyses had attempted to evaluate survival and mortality. The majority of these meta-analyses were based on aggregated data published in the literature. The first literature-based sur-

vival analysis, supplemented with unpublished data, was published in 2005 by Bohlius et al. [22]. Another seven literature-based meta-analyses were published during the following years [23–27, 38, 40].

Intriguingly, the results of these meta-analyses changed over time (fig. 5, upper part). The first meta-analysis addressing survival [22] showed an overall survival benefit for ESA patients: unadjusted hazard risks (HRs) of 0.84 (95% CI 0.69–1.02) and 0.81 (95% CI 0.67–0.99) when including adjusted results for single studies. These results were contradicted by later meta-analyses showing effect estimates of 1.08 (95% CI 0.99–1.18) [24], 1.11 (95% CI 1.00–1.22) [25], 1.10 (95% CI 1.01–1.20) [38] and 1.15 (95% CI 1.03–1.29) [26] in favor of patients not receiving ESA. Figure 6 illustrates the shift of effect size in the cohort of studies published before 2002 (cutoff date for study inclusion for the first review) [22] and 2002–2005 (cutoff date for study inclusion for the second, updated review) [24].

Potential reasons for these observed changes can be found both at the level of the individual trials and at the level of the meta-analysis. Several characteristics of the clinical trials had changed between early and more recent studies, including study design, patient characteristics and ESA treatment schedules. For example, Hb



**Fig. 6.** Subgroup analysis of studies reporting mortality data published before and after the year 2002, data taken from Bohlius et al. [22] published in 2005 and Bohlius et al. [24] published in 2006.

levels when ESAs had to be started and stopped were raised, and ESA dose as well as treatment duration was augmented. Moreover, studies included more patients with solid tumors and less often patients with hematological malignancies. At the same time, later studies reported more often an increased risk for death in ESA patients compared to controls. However, based on single RCTs and literature-based meta-analyses it was unclear whether detrimental effects observed were due to chance, bias, confounding or whether ESA patients are truly at a higher risk to die. In literature-based meta-analyses methods to disentangle the effects of patient and study level covariates are limited and will be outlined below.

Meta-regression can be used to explore the effect of study level characteristics on the result of a meta-analysis [59]. Study level characteristics refer to variables that apply to the entire population of a given study. For example whether or not the study was placebo controlled or designed to assess a specific outcome. Meta-regression can investigate the impact of study level variables; however, the analysis of co-variables at patient level is problematic [59]. These refer to characteristics of individual patients in a given trial, such as age, sex, tumor stage and tumor type or Hb level at randomization. These data are usually aggregated per study arm when reported in the literature. However, aggregated mean or median values do not represent the individual patient. For example, to examine the association between Hb levels at randomization, ESA treatment and risk for death, the Hb value and the survival outcome must be known for each patient. Published literature usually provides only the mean Hb level of the whole study group as well as aggregated survival estimates. Regression analyses based on aggregated patient characteristics represented as average values or percentages are prone to the ecological fallacy [60, 61]. Thus, to explore the effect of risk factors at patient level, the use of IPD is strictly recommended [59].

Besides, timing of survival assessment may vary across studies with some studies reporting mortality during ESA treatment only and others only during long-term follow-up. This poses a problem if the death hazard changes over time. If ESA treatment increases mortality during administration but not thereafter the ability to analyze survival at different lengths of follow-up becomes crucial. In literature-based meta-analyses, authors have to rely on reported results, with absent or inconsistent reporting of survival. Survival may not have been reported at all, only during the study or for the last

follow-up available. Particular strategies, e.g. conducting a separate analysis or combination of these different time points, may lead to bias such as potential over- or underestimation of the effects of ESAs on mortality.

Finally, bias at the meta-analysis level may have contributed to the optimistic early meta-analysis results, too. There is evidence that positive results are published earlier than results showing neutral or detrimental effects [62]. Thus, desirable results for survival when receiving ESAs may have been published earlier while neutral or even unfavorable results of ESA studies were potentially not reported or reported later. Of note, in a recently conducted IPD meta-analysis including both published and unpublished survival data, there was no evidence for a survival advantage in patients recruited early, i.e. before 2000 (HR 0.95, 95% CI 0.60–1.30 for patients randomized between 1990 and 1994, and HR 0.96, 95% CI 0.60–1.32, for patients randomized between 1995 and 1999) [63]. This underlines the observation that more beneficial survival data might have been published earlier than less beneficial results, which in turn may have led to a bias regarding the effect of ESAs on survival in the first literature-based meta-analysis [22]. Thus, literature-based meta-analyses are more prone to publication bias and delay of publication than IPD meta-analyses. Ideally, these limitations should be overcome by timely publication of all study results independent from the effect sizes achieved. In the meantime, meta-analyses of early studies should be judged with caution, and regular updates of literature-based meta-analyses are needed.

In contrast to literature-based meta-analysis, IPD enable researchers to access both published and unpublished data, harmonize outcome definitions and apply standardized analysis techniques across studies. In addition, time-to-event analyses based on IPD allow investigating subgroups of interest and to explore potential confounders and effect modifiers both at patient and study level [64]. Finally, IPD meta-analyses have larger power to find treatment interactions with co-variables at patient level [59].

To date, five meta-analyses on the effects of ESAs on survival were based on IPD [30, 39, 63, 65, 66] (fig. 5, lower part). Four of the studies were conducted or funded by pharmaceutical companies manufacturing ESAs [30, 39, 65, 66] and one was conducted by an independent working group [63]. Two of the manufacturers' meta-analyses were restricted to specific erythropoiesis-stimulating drugs such as epoetin  $\beta$  [39, 66] or darbepoetin [30, 65], which led to the omission of detrimental

studies [52, 55] and reduced the statistical power of the meta-analyses. The meta-analysis on epoetin  $\beta$  [39, 66] was recently updated, including new analyses but no additional study data [67].

The independent IPD meta-analysis included 53 studies with 13,933 patients [63]. Access to IPD allowed differentiating study mortality, defined as treatment period plus 30-day follow-up, from overall survival, defined as last follow-up available. The risk for death during the study period was increased in ESA patients compared to controls: HR 1.17 (95% CI 1.06–1.30). For overall survival, the detrimental effects of ESAs were smaller: HR 1.06 (95% CI 1.00–1.12). Similar results were generated in the other IPD meta-analyses conducted [30, 39]. These meta-analyses did not reach conventional levels of statistical significance which in part might be due to a lack of power because only selected drugs, i.e. epoetin  $\beta$  or darbepoetin, were considered.

Another potential advantage of IPD meta-analyses is the ability to identify effect modifiers indicating whether certain subgroups of patients are either at increased or decreased risk to die when receiving ESAs compared to controls. The independent IPD meta-analysis conducted by Bohlius et al. [63] generated some evidence for such subgroups. ESA-treated patients with low hematocrit at baseline (<23.5%) had an increased risk of death compared with other subgroups. A low hematocrit might be a marker for advanced cancer and increased susceptibility to the detrimental effects of ESAs. Patients with previous thromboembolic events being treated with ESAs were less likely to die when receiving ESAs. Hypothetically, prophylactic anticoagulation during cancer treatment in patients with previous thromboembolic events might have protected them against the thrombogenic effects of ESAs. Lastly, patients with increased frequency of ESA treatments had a reduced likelihood of death compared with others, and the association was confounded by other study characteristics. For other covariates such as Hb concentration at baseline, target Hb or planned ESA doses, there was no evidence for an interaction. Overall, it was not possible to identify with certainty a group of patients that is either at increased or decreased risk to die when receiving ESAs compared to other patients. Although these are disappointing findings, they illustrate that IPD meta-analyses can help to generate new hypotheses which then need to be tested in clinical trials.

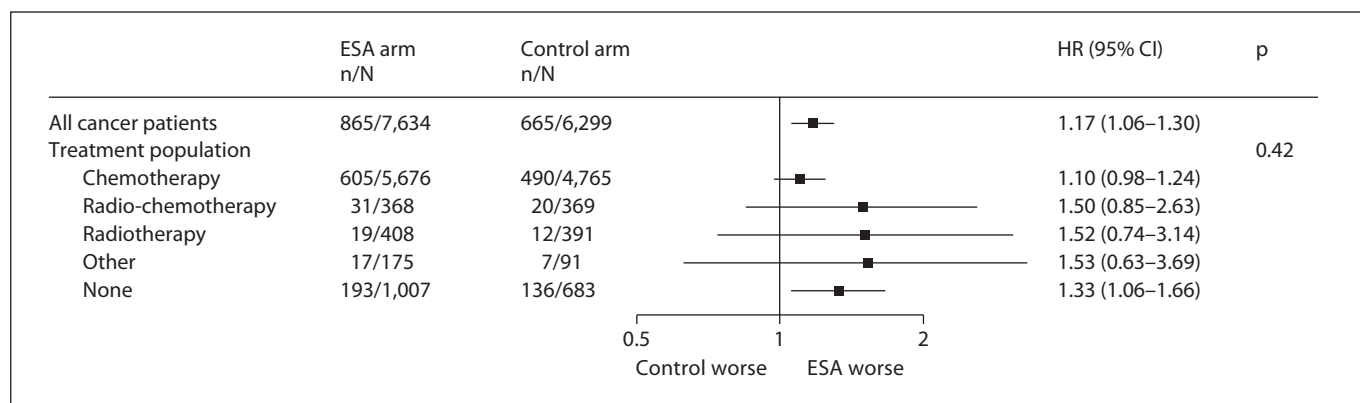
There is an ongoing debate whether ESAs increase mortality in patients undergoing chemotherapy. From a clinical point of view, patients receiving concurrent che-

motherapy may reach lower Hb levels under ESA treatment compared to patients not receiving chemotherapy. This may translate into a lower risk for lethal TVEs and impaired tumor control. When comparing the two most recent meta-analyses of IPD addressing this issue, both meta-analyses [30, 63] found an increased risk for on-study mortality in cancer patients undergoing both chemotherapy and ESA treatment compared to controls (HR 1.11, 95% CI 0.84–1.47,  $n = 2,112$  [30], and HR 1.10, 95% CI 0.98–1.24,  $n = 10,441$  [63]). In both meta-analyses the observed effect for on-study mortality was not statistically significant. Assuming a mortality rate of 10% during an average trial duration of 16 weeks in cancer patients receiving chemotherapy, the HR for on study mortality of 1.10 is equivalent to an absolute risk difference of 1%. In order to detect this difference in a clinical study with an  $\alpha$  level set at 5% and  $\beta$  of 20%, about 30,000 patients would be needed to reach sufficient statistical power to detect this difference. Thus, even current meta-analyses of IPD on 2,122 [30] and 10,441 [63] patients do not provide sufficient power to detect this small difference.

However, it is questionable whether restriction to a specific subgroup of interest is the most adequate approach to explore the effects of ESAs in cancer patients receiving chemotherapy. An alternative approach utilizing all available data is to compare different subgroups of patients, i.e. patients undergoing radiotherapy, radiochemotherapy, chemotherapy or no anticancer treatment when receiving ESAs, using an interaction test. Figure 7 shows the results of different treatment subgroups and the test for interaction [63]. Importantly, the test for interaction between subgroups was not statistically significant ( $p = 0.42$ ). Thus, from a statistical point of view, the HR to die when receiving ESAs compared to controls did not differ between subgroups. Currently, an increased risk to die cannot be excluded in ESA patients undergoing chemotherapy compared to other subgroups receiving other anticancer interventions.

## Discussion

From a methodological and clinical point of view, systematic reviews and meta-analyses have several advantages over single studies or narrative reviews [37] and can help to improve patient management. In the case of ESAs, literature-based meta-analyses convincingly helped to inform patients and caregivers about the beneficial effects of ESAs by reducing the RBCT risk.



**Fig. 7.** Subgroup analysis of different treatment groups in the meta-analysis by Bohlius et al. [63]. The p value for interaction is based on Cox regression stratified by study. n = Number of deaths; N = number of patients.

Inclusion of unreported data helped to obtain a more conservative and realistic estimate of the expected treatment effect. Based on the large number of studies and patients included in the ESA meta-analyses, smaller risks associated with ESAs could be detected, which were not observed in single studies. For example, an increased risk for thromboembolic events could be identified based on the analysis of >6,600 patients from 35 trials [24].

Drawbacks of literature-based meta-analyses include inconsistent and incomplete reporting of outcomes across trials. Therefore, literature-based meta-analyses were not particularly suited to quantify the mortality risks associated with ESAs. In this situation, IPD meta-analyses helped to standardize and harmonize outcomes and analyses across trials. Nevertheless, even with a large-scale IPD meta-analysis it was not possible to identify with certainty patient groups that were at either increased or decreased risk to die when receiving ESAs [63].

Meta-analyses of IPD have some capacity to explore causal pathways of treatment actions. However, these are in principle of observational nature only and help to generate hypotheses on the causal pathways which then need to be tested in subsequent clinical trials. The main limitation of these meta-analyses are barriers to the access of clinical trial data and resource constraints both at the side of the meta-analysis team and the original investigator. In the case of ESAs, a large collaboration between manufacturers, clinical trialists and a meta-analysis team was established, which enabled to conduct an IPD meta-analysis on the effects of ESAs in cancer patients [63].

Given that IPD accumulated in meta-analyses offer a rich source for further analyses, in certain situations these efforts are worthwhile and should be encouraged. Sufficient independent funding and formal agreements on data sharing with the principal investigators of the respective studies constitute key factors for any IPD meta-analysis.

### Considerations for Patient Treatment

The findings of several meta-analyses on ESAs in cancer patients demonstrate that ESAs reduce the risk for RBCT and increase the risk for TVEs and mortality. There is an ongoing debate whether or not ESAs increase mortality in cancer patients receiving chemotherapy as well. However, the currently available data are insufficient to exclude an increased risk for death in cancer patients undergoing chemotherapy and receiving ESAs. In clinical practice, the increased risks of death and TVEs should be balanced against the benefits of treatment with ESAs, taking into account each patient's clinical circumstances and preferences.

### Considerations for Further Systematic Reviews and Meta-Analyses

Further literature-based systematic reviews and meta-analyses should focus on adjacent topics such as iron supplementation with ESAs and different ESA management schedules. Given that ESAs are widely used in cancer pa-

tients and considering the possible detrimental effects on important clinical outcomes, such as risk for thromboembolic events and death, a better understanding of the potential benefits of ESAs in cancer patients is urgently needed. Currently, there is no consensus whether ESAs improve QoL in cancer patients. An IPD meta-analysis on the effects of ESAs on QoL in cancer patients would provide a

unique opportunity to gather appropriate data from a large number of RCTs to define the potential impact of ESAs on QoL in cancer patients and to better define the risk-benefit ratio of ESAs in cancer patients. Definite results concerning the risks and benefits would help patients, physicians, guideline committees and health authorities to make informed decisions about the use of ESAs.

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