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Effects of erythropoiesis-stimulating agents on fatigue- and anaemia-related symptoms in cancer patients: systematic review and meta-analyses of published and unpublished data

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Background: Erythropoiesis-stimulating agents (ESAs) reduce the need for red blood cell transfusions; however, they increase the risk of thromboembolic events and mortality. The impact of ESAs on quality of life (QoL) is controversial and led to different recommendations of medical societies and authorities in the USA and Europe. We aimed to critically evaluate and quantify the effects of ESAs on QoL in cancer patients.

Methods: We included data from randomised controlled trials (RCTs) on the effects of ESAs on QoL in cancer patients. Randomised controlled trials were identified by searching electronic data bases and other sources up to January 2011. To reduce publication and outcome reporting biases, we included unreported results from clinical study reports. We conducted meta-analyses on fatigue- and anaemia-related symptoms measured with the Functional Assessment of Cancer Therapy-Fatigue (FACT-F) and FACT-Anaemia (FACT-An) subscales (primary outcomes) or other validated instruments.

Results: We identified 58 eligible RCTs. Clinical study reports were available for 27% (4 out of 15) of the investigator-initiated trials and 95% (41 out of 43) of the industry-initiated trials. We excluded 21 RTCs as we could not use their QoL data for meta-analyses, either because of incomplete reporting (17 RCTs) or because of premature closure of the trial (4 RCTs). We included 37 RCTs with 10 581 patients; 21 RCTs were placebo controlled. Chemotherapy was given in 27 of the 37 RCTs. The median baseline haemoglobin (Hb) level was 10.1 g dl^{-1}; in 8 studies ESAs were stopped at Hb levels below 13 g dl^{-1} and in 27 above 13 g dl^{-1}. For FACT-F, the mean difference (MD) was 2.41 (95% confidence interval (95% CI) 1.39–3.43; $P<0.0001$; 23 studies, $n=6108$) in all cancer patients and 2.81 (95% CI 1.73–3.90; $P<0.0001$; 19 RCTs, $n=4697$) in patients receiving chemotherapy, which was below the threshold ($\geqslant 3$) for a clinically important difference (CID). Erythropoiesis-stimulating agents had a positive effect on anaemia-related symptoms (MD 4.09; 95% CI 2.37–5.80; $P=0.001$; 14 studies, $n=2765$) in all cancer patients and 4.50 (95% CI 2.55–6.45; $P<0.0001$; 11 RCTs, $n=2436$) in patients receiving chemotherapy, which was above the threshold ($\geqslant 4$) for a CID. Of note, this effect persisted when we restricted the analysis to placebo-controlled RCTs in patients receiving chemotherapy. There was some evidence that the MDs for FACT-F were above the threshold for a CID in RCTs including cancer patients receiving chemotherapy with Hb levels below 12 g dl^{-1} at baseline and in RCTs stopping ESAs at Hb levels above 13 g dl^{-1}. However, these findings for FACT-F were not confirmed when we restricted the analysis to placebo-controlled RCTs in patients receiving chemotherapy.

Conclusions: In cancer patients, particularly those receiving chemotherapy, we found that ESAs provide a small but clinically important improvement in anaemia-related symptoms (FACT-An). For fatigue-related symptoms (FACT-F), the overall effect did not reach the threshold for a CID.

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Erythropoiesis-stimulating agents (ESAs) reduce the need for red blood cell transfusions (Bohlius *et al*, 2006b; Ludwig *et al*, 2009; Tonelli *et al*, 2009) and may improve quality of life (QoL); however, they increase the risk of thromboembolic events and death. A large meta-analysis based on individual patient data (IPD) from 53 randomised controlled trials (RCTs) demonstrated a statistically significant, 17% higher risk of mortality during the active study phase in cancer patients who received ESAs compared with controls (Bohlius *et al*, 2009a, b). An increased risk of mortality was also reported in each of the more recent systematic reviews and meta-analyses, which were not funded by the pharmaceutical industry (Bennett *et al*, 2008; Tonelli *et al*, 2009; Tonia *et al*, 2012; Grant *et al*, 2013) but in none of the systematic reviews and meta-analyses sponsored by the pharmaceutical industry (Aapro *et al*, 2008b; Glaspy *et al*, 2010). Several meta-analyses have shown that ESAs increase the risk of thromboembolic events in cancer patients (Bohlius *et al*, 2006a, b; Seidenfeld *et al*, 2006; Aapro *et al*, 2008b, 2009; Bennett *et al*, 2008; Ludwig *et al*, 2009; Tonelli *et al*, 2009); the effects of ESAs on tumour progression remain uncertain (Aapro *et al*, 2012).

The impact of ESAs on QoL is controversial. Positive findings from observational studies (Glaspy *et al*, 1997; Demetri *et al*, 1998; Gabrilove *et al*, 2001; Quirt *et al*, 2001; Cella *et al*, 2003) and clinical trials (Littlewood *et al*, 2001; Fallowfield *et al*, 2002; Chang *et al*, 2005; Wilkinson *et al*, 2006) have not been confirmed in more recent RCTs (Smith *et al*, 2008; Hoskin *et al*, 2009; Engert *et al*, 2010; Fujisaka *et al*, 2011; Nitz *et al*, 2011). Previous meta-analyses have demonstrated that ESAs effectively reduce fatigue-related symptoms in cancer patients (Minton *et al*, 2008, 2010; Tonelli *et al*, 2009). However, these meta-analyses were restricted to the published literature and may be compromised by publication and outcome reporting biases (Egger and Smith, 1998; Dwan *et al*, 2011; Redmond *et al*, 2013). Publication bias refers to the fact that studies with positive results are more likely to be published compared with studies with negative results (Egger and Smith, 1998). Outcome reporting bias refers to the selective reporting of outcomes in a published study, where mainly the most statistically significant results or the ones meeting the authors' assumptions are reported (Dwan *et al*, 2011; Redmond *et al*, 2013). Meta-analyses including only published results may be prone to bias and overestimate treatment effects.

We aimed to critically evaluate and quantify the effects of ESAs on QoL in cancer. We systematically reviewed and meta-analysed RCTs that compared ESAs with controls in cancer patients. Our objectives were to examine the effects of ESAs on patient-rated fatigue- and anaemia-related symptoms and to identify groups of patients who may benefit most from treatment with ESAs. To reduce potential publication and outcome reporting biases, we included unpublished and unreported data.

MATERIALS AND METHODS

Study selection and data extraction. We included RCTs that compared epoetin or darbepoetin with placebo or best standard of care and assessed fatigue- and anaemia-related symptoms in cancer patients receiving or not receiving anticancer treatment. We excluded trials with high-dose myeloablative chemotherapy regimens followed by stem cell transplantation, trials in patients with myelodysplastic syndromes and acute leukaemia, and trials using ESAs for short-term pre-operative treatment. We included studies that prospectively evaluated QoL using a validated or generally accepted instrument and a planned sample size of >50 participants per study arm or 100 participants in total. Trials using different types of iron supplementation were included and evaluated in stratified analyses.

We updated literature searches from our previous meta-analyses on ESAs (Bohlius *et al*, 2006a, b, 2009a, b) in Medline, Embase, Cochrane Central Register of Controlled Trials and databases of conference proceedings for the years 2008 to January 2011 (for details, see Supplementary Webappendix Table 1). We screened the reference lists of relevant meta-analyses and clinical trials registries (http://clinicaltrials.gov/; http://www.isrctn.org/). Four reviewers (AM, JB, NR and TT) worked in pairs and independently determined study eligibility. Data on study characteristics, study quality and outcomes were extracted by one reviewer (TT) and checked for accuracy by another (JB). Our primary sources of data extraction were the published study documents. We complemented these data with information from study protocols and reports, which we had obtained from ESA manufacturers (Amgen, Thousand Oaks, CA, USA; Johnson & Johnson, New Brunswick, NJ, USA; Hoffmann-La Roche, Basel, Switzerland) and clinical study groups for a previous IPD meta-analysis (Bohlius *et al*, 2009a, b). For that meta-analysis, we had identified published and unpublished trials through electronic searches of published abstracts and articles, screening of clinical trials registries and Oncologic Drugs Advisory Committee hearing documents, and contacting ESA manufacturers and experts in the field. We had obtained clinical study reports as requested for 98% (48 out of 49) of the trials initiated by the ESAs manufacturers and 36% (5 out of 14) of the trials run by clinical study groups, for details see Bohlius *et al* (2009a, b). In addition, we searched for QoL results in clinical trials registries (http://clinicaltrials.gov/; http://www.isrctn.org/).

Outcomes. Our primary outcomes were fatigue- and anaemia-related symptoms measured with the Functional Assessment of Cancer Therapy-Fatigue (FACT-F) subscale and the FACT-Anaemia (FACT-An) subscale. The FACT-F includes 13 fatigue-related questions (range of scale 0–52). The FACT-An (range of scale 0–80) includes the 13 fatigue-related items plus 7 anaemia-related questions, for example, dizziness, headaches, pain in chest and trouble walking. These instruments are widely used in ESA trials, are highly responsive to change, and have good convergent and discriminant validity (Cella, 1997, 2007; Yellen *et al*, 1997; Cella *et al*, 2002b). Secondary outcomes included changes in the cancer-specific FACT-G total score (range 0–108) and the subscales on physical, functional and social/family well-being (range 0–28) and emotional well-being (range 0–24). For sensitivity analyses, we included the fatigue- and anaemia-related subscales from studies that used instruments other than FACT-F and FACT-An, that is, EORTC QLQ-C30 (Aaronson *et al*, 1993), SF-36 (Ware and Sherbourne, 1992), FACT-An subscale non-fatigue items (Cella, 1997), FACT-An full scale (Cella, 1997) and visual analogue scales (VAS) assessing energy, daily activities and overall health or QoL. For each instrument, we predefined the specific domain that best corresponded to fatigue- and anaemia-related symptoms, physical, functional, social/family, emotional well-being and overall QoL as measured by FACT-F, FACT-An, FACT-G and its subscales. We defined a clinically important difference (CID) as a mean difference (MD) of $\geqslant 3$ for FACT-F (Cella *et al*, 2002b) and $\geqslant 4$ for FACT-An (D Cella, personal communication, March 2010). For standardised effect sizes, an effect size of 0.20–0.50 s.d. units was considered small but clinically important, whereas effect sizes of 0.50–0.80 and >0.80 were considered to be moderate and large differences, respectively (Sloan and Dueck, 2004; Sloan *et al*, 2006).

Statistical methods. Results from individual studies were expressed either as differences in mean changes from baseline to study end or as effect sizes. Effect sizes were calculated as the differences in mean values at the end of treatment divided by the pooled s.d. (Cohen's *d*) (Cohen, 1988). If the required data were not reported, we used approximations (Reichenbach *et al*, 2007) to calculate differences or s.d. Data were analysed according to the intention-to-treat

approach, using the last observation carried forward if data were missing. In sensitivity analyses, we analysed the data measured closest to week 12, a time point frequently considered in ESA trials. We used random-effects meta-analyses to combine trials and quantified heterogeneity with the I^2 statistic (Higgins *et al*, 2003).

In stratified analyses, we aimed to identify patient characteristics, treatment strategies and aspects of study design associated with the effect of ESAs on QoL, see Supplementary Webappendix Table 2. Tests of interactions and trends were obtained from univariate random-effects meta-regression models (Thompson and Sharp, 1999). Analyses were conducted in the entire data set, including all RCTs, only in chemotherapy trials and only in placebo-controlled RCTs in patients receiving chemotherapy. We investigated the association between trial size and treatment effects in funnel plots and regression tests (Sterne and Egger, 2001). To adjust for potential publication bias, we used the trim and fill method (sensitivity analysis) (Duval 2005). Results are presented as MDs or standardised MDs (SMDs) with 95% confidence intervals (95% CIs). We estimated treatment response as the proportion of patients achieving a CID (threshold 3 for FACT-F and 4 for FACT-An subscales). To estimate this treatment response, we used hypothetical control group risks and the SMD and the corresponding 95% CI (Furukawa and Leucht, 2011). We derived numbers needed to treat (NNT) to cause one additional treatment response on FACT-F or FACT-An in patients receiving ESA compared with control from the inverse of the absolute difference between experimental and hypothetical control group risks. Study end points, eligibility criteria, search methods and main analyses were defined in a protocol. All analyses were performed using Stata 10.0 (StataCorp, College Station, TX, USA).

RESULTS

Number of eligible, included and excluded studies. We identified 58 eligible RCTs. Clinical study reports were available for 27% (4 out of 15) of the trials run by clinical study groups and 95% (41 out of 43) of the trials initiated by the ESAs manufacturers. Of the 58 eligible RCTs, we excluded 21 RTCs for the following reasons: QoL data were not reported because of premature closure of the trials (Machtay *et al*, 2007; Thomas *et al*, 2008; AGO-OVAR 2.7; CR002305); or data reporting was too incomplete to allow any analysis (Rose *et al*, 1994; Dammacco *et al*, 2001; Quirt *et al*, 2001; Thomas *et al*, 2002; INT-1; INT-3; Leyland-Jones *et al*, 2005; Goss *et al*, 2005; Aapro *et al*, 2008a; Suzuki *et al*, 2008; EPO-GER-20; Gupta *et al*, 2009; Ray-Coquard *et al*, 2009; Yoshizaki *et al*, 2010; Untch *et al*, 2011; CDR0000069148; Moebus *et al*, 2013) (Figure 1). Finally, we included 37 studies with 10 581 patients randomised (Abels, 1993; Case *et al*, 1993; Henry and Abels, 1994; Thatcher *et al*, 1999; Littlewood *et al*, 2001; Huddart *et al*, 2002; Kotasek *et al*, 2002, 2003; Osterborg *et al*, 2002; Vansteenkiste *et al*, 2002; Boogaerts *et al*, 2003; Hedenus *et al*, 2003; Iconomou *et al*, 2003; Milroy *et al*, 2003; P-174; Chang *et al*, 2005; Debus *et al*, 2005; Mystakidou *et al*, 2005; O'Shaughnessy *et al*, 2005; Savonije *et al*, 2005; Witzig *et al*, 2005; Wilkinson *et al*, 2006; Charu *et al*, 2007;

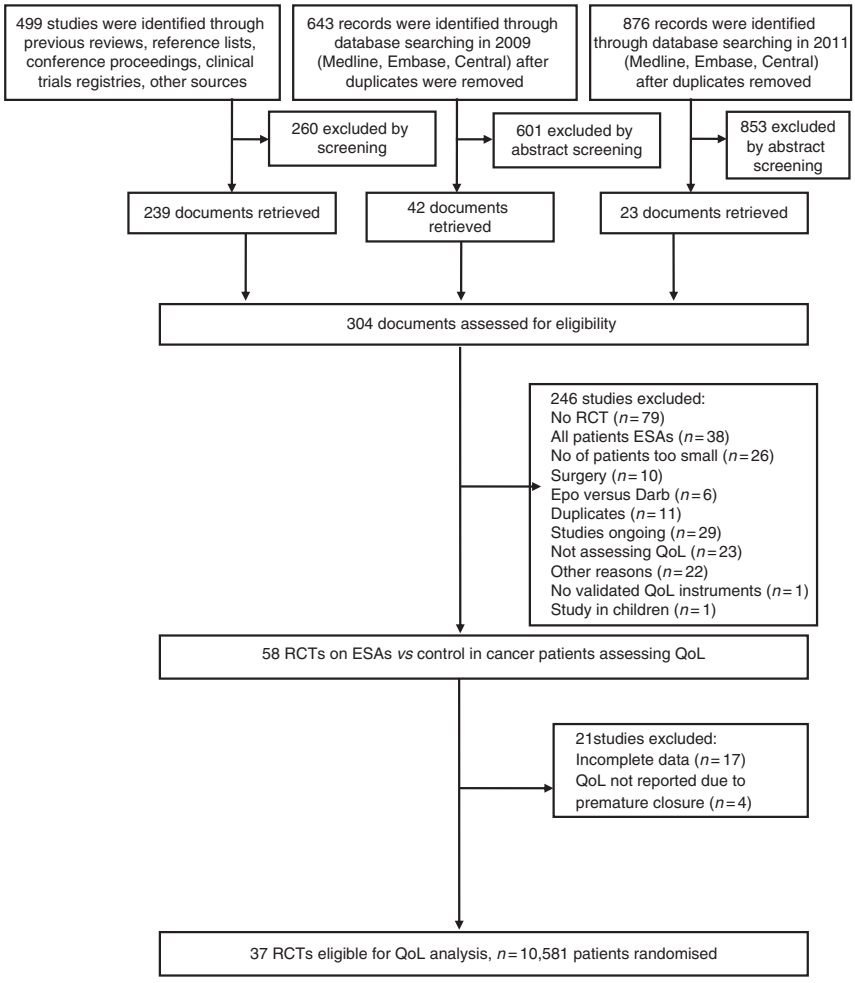

Figure 1. PRISMA flow diagram showing the identification of eligible trials (Moher *et al*, 2009).

Wright *et al*, 2007; Gordon *et al*, 2008; Krzakowski, 2008; Pirker *et al*, 2008; Smith *et al*, 2008; Strauss *et al*, 2008; Christodoulou *et al*, 2009; Hernandez *et al*, 2009; Hoskin *et al*, 2009; OBE/EPO-INT-03; Tsuboi *et al*, 2009; Winquist *et al*, 2009; Engert *et al*, 2010; Pronzato *et al*, 2010).

Characteristics of included studies. Characteristics of included studies are shown in Table 1 and Supplementary Webappendix Tables 3–5. Quality of life was the primary end point in 11 (30%) studies, a secondary end point in 25 trials, and was not mentioned as a study end point in one study. Most studies ($n=23$) used the FACT-F subscale and/or ($n=14$) the FACT-An subscale. Among the studies not reporting FACT-F or FACT-An, three studies reported the total score of the full FACT-An scale (47 items), one study used EORTC QLQ-C30, one SF-36 and five studies used VAS. Twenty-one (57%) studies were placebo controlled, 11 (30%) reported sample size calculations for a QoL end point, 9 (24%) defined a QoL hypothesis, 4 (11%) reported definitions for a clinically important change and 4 (11%) reported percentages of patients completing QoL questionnaires (submission rates). Chemotherapy was given in 27 of the 37 studies included (73%). Radiotherapy or radiochemotherapy was given in two studies and no anticancer treatment was given in six (16%). In one study, $<70\%$ of the included patients received chemotherapy (P-174) for another study, the underlying anticancer therapy was unclear (Winquist *et al*, 2009). These two studies were categorised as 'other/unclear'. Short-acting ESAs (epoetin α, β or δ) were given in 28 (76%) studies and darbepoetin in 9 studies. About half (20 studies, 54%) of the studies included patients with solid tumours; five included patients with haematological malignancies. Of the 37 studies included, 14 studies had a mean/median haemoglobin (Hb) at baseline below 10 g dl^{-1}; the lowest average Hb at baseline was 8.8 g dl^{-1} (P-174). Seventeen studies included patients with Hb baseline levels between 10 and 12 g dl^{-1} and six studies included patients with Hb baseline levels above 12 g dl^{-1}. The highest average Hb at baseline was 13.6 g dl^{-1} (Thatcher *et al*, 1999; Hoskin *et al*, 2009). The median baseline Hb level across all trials was 10.1 g dl^{-1}. Most studies gave ESAs for 9–16 weeks (18 studies, 49%) or until the end of chemotherapy (13 studies, 35%). None of the included studies recommended stopping treatment at a Hb level of 12 g dl^{-1} or below. Eight studies (22%) stopped ESAs at Hb levels $\leqslant$13 g dl^{-1} and 27 (73%) at Hb levels $>$13 g dl^{-1}. Two studies did not report the Hb target. Iron supplementations were given according to a patient's transferrin saturation or ferritin levels (29 studies) or according to a fixed schedule (7 studies). All but three studies were funded by the pharmaceutical industry.

Main results for the effects of ESAs on QoL. The analysis of FACT-F included results from 23 studies; 17 stemming from the published literature and 6 from clinical study reports. Of the 7624 patients initially randomised, 6108 (80%) were included in the analysis. Fatigue-related symptoms improved in patients receiving ESAs compared with controls, with a MD in FACT-F of 2.41 (95% CI 1.39–3.43, $P<0.001$; Figure 2), which is below the threshold ($\geqslant$3) of a CID. The SMD was 0.22 (95% CI 0.13–0.32, $P<0.001$). There was moderate heterogeneity among trials ($I^2=65\%$) and some evidence for funnel plot asymmetry (Egger's test $P=0.07$; Figure 3A). The CID for FACT-F ($>$3) was not reached in any of the analysis subsets, that is, all trials (see above), chemotherapy trials only (MD 2.81, 95% CI 1.73–3.90, 19 studies, $n=4697$) and placebo-controlled chemotherapy trials (MD 1.78, 95% CI 0.82–2.73, 10 studies, $n=2714$). The analysis of FACT-An included results from 14 studies; 7 were stemming from the published literature and 7 from clinical study reports. Of 3519 patients randomised, 2765 (79%) were included in the analysis. Anaemia-related symptoms improved with a MD in FACT-An of 4.09 (95% CI 2.37–5.80, $P=0.001$; Figure 2), which is above the threshold ($\geqslant$4) of a CID. The SMD was 0.30 (95% CI 0.17–0.42, $P=0.003$). There was moderate heterogeneity among trials ($I^2=63\%$) and no evidence for funnel plot asymmetry (Egger's test $P=0.38$; Figure 3B). Of note, the CID for FACT-An ($>$4) was reached throughout all analysis subsets, that is, all trials (see above), chemotherapy trials only (MD 4.50, 95% CI 2.55–6.45, 11 studies, $n=2436$) and placebo-controlled chemotherapy trials (MD 4.55, 95% CI 1.29–7.80, 3 studies, $n=721$). Results for FACT-F and FACT-An were similar when based on the data observed closest to week 12 (see Supplementary Webappendix Table 6). When using trim and fill methods, the overall result for FACT-F was reduced from MD 2.41 (95% CI 1.39 to 3.43) to MD 0.96 (95% CI -0.23 to 2.14); while the overall result for FACT-An remained unchanged (MD 4.09; 95% CI 2.37–5.80). There was little evidence for clinically important improvements in overall QoL, physical, functional, social or emotional well-being measured with FACT-G and its subscales, with MDs ranging from 0.25 (95% CI -0.09 to 0.59) for emotional well-being to 1.45 (95% CI 0.02 to 2.88) for FACT-G overall (Supplementary Webappendix Figure 1). Sensitivity analyses that included studies using other instruments produced similar results for fatigue- or anaemia-related symptoms, overall QoL and subscales (Supplementary Webappendix Table 6).

Stratified analyses for FACT-F and FACT-An. We conducted stratified analyses to identify groups of patients and treatment strategies in which ESAs had more effect on fatigue- and anaemia-related symptoms. Concerning fatigue-related symptoms, patients receiving chemotherapy showed more pronounced effects than patients receiving radiotherapy or no therapy (test for interaction $P=0.079$); however, in patients receiving chemotherapy the threshold for a CID was not met, see Table 2. Within the group of chemotherapy studies, trials including patients with Hb baseline below 12 g dl^{-1} achieved differences above the CID threshold in contrast to studies with Hb baseline above 12 g dl^{-1}, however, the difference between these groups of trials was not statistically significant (P for interaction 0.11). Chemotherapy trials stopping ESAs at Hb levels $>$13 g dl^{-1} achieved differences above the CID threshold in contrast to studies stopping ESAs at Hb levels $\leqslant$13 g dl^{-1}; however, differences between these groups of studies were of borderline statistical significance (P for interaction 0.053). When we restricted the analysis to placebo-controlled chemotherapy trials, the MDs for FACT-F in trials including patients with Hb $<$12 g dl^{-1} at baseline and trials stopping ESAs at Hb levels $>$13 g dl^{-1} were below the CID threshold. The beneficial effect of ESAs on fatigue increased with the number of injections per week (test for trend $P=0.032$ in all trials and $P=0.044$ in chemotherapy trials). When we further restricted this analysis to placebo-controlled trials, the test for trend was not statistically significant (test for trend $P=0.134$). We observed that open-label studies showed MDs for FACT-F, which were above the CID and larger than the results stemming from placebo-controlled trials (test for interaction $P=0.054$ in all trials and $P=0.083$ in chemotherapy trials). There was some evidence that trials with QoL as primary end point achieved better results than trials with QoL as secondary end point (test for interaction $P=0.027$ in all trials and $P=0.091$ in chemotherapy trials), however, this was not confirmed when we further restricted the analysis to placebo-controlled trials. Of note, the CID was not met in trials in which a majority of patients had advanced disease ($>70\%$ of patients with metastatic/advanced disease). Results stemming from full publications and clinical study reports were similar. Studies with and without industry funding reported similar effect estimates. The corresponding results for anaemia-related symptoms (FACT-An) were similar to the FACT-F results, but were based on fewer trials; and tests for interaction failed to reach conventional levels of statistical significance, see Table 3. Additional stratified analyses for FACT-F and FACT-An are shown in Supplementary Webappendix Tables 7 and 8.

Table 1. Characteristics of included randomised controlled trials

Characteristic	*N* of studies (%)
Total number of studies	37 (100)
Number of patients randomised (median (range))	259 (45–1379)
Year of publication (median (range))	2005 (1993–2010)
Baseline Hb	
$\leqslant 10\,g\,dl^{-1}$	14 (37.84)
$10–12\,g\,dl^{-1}$	17 (45.95)
$>12\,g\,dl^{-1}$	6 (16.22)
Tumour type	
Solid	20 (54.05)
Haematological	5 (13.51)
Solid and haematological	12 (32.43)
Drug	
Epoetin α	23 (62.16)
Epoetin β	4 (10.81)
Epoetin δ	1 (2.70)
Darbepoetin	9 (24.32)
Anticancer treatment	
Chemotherapy	27 (72.97)
Radiotherapy	2 (5.41)
No anticancer therapy	6 (16.22)
Other/unclear	2 (5.41)
Duration of ESA treatment	
<9 Weeks	2 (5.41)
9–16 Weeks	18 (48.65)
⩾17 Weeks	4 (10.81)
Until end of chemotherapy	13 (35.14)
Planned weekly ESA dose	
<40 000 U epo α/δ or 30,000 U epo β or 100 μg darbepo	9 (24.32)
=40 000 U epo α/δ or 30,000 U epo β or 100 μg darbepo	9 (24.32)
>40 000 U epo α/δ or 30,000 U epo β or 100 μg darbepo	13 (35.14)
Other (e.g., weight based or Hb based)	6 (16.22)
Frequency of ESA administration	
TIW	19 (51.35)
QW	11 (29.73)
⩽ Q2W	6 (16.22)
Other	1 (2.70)
Target Hb	
$\leqslant 13\,g\,dl^{-1}$	8 (21.62)
$>13–15\,g\,dl^{-1}$	27 (72.97)
Not reported	2 (5.41)
Placebo controlled	
Yes	21 (56.76)
No	16 (43.24)
Study completed?	
Terminated/halted	7 (18.92)
Completed	30 (81.08)
Year last patient randomised	
<1995	5 (13.51)
1995–1999	4 (10.81)
2000–2004	18 (48.65)
2005–2009	7 (18.92)
Not reported	3 (8.11)
Disease stage	
>70% Advanced disease	16 (43.24)
>70% Early disease	3 (8.11)
Other	7 (18.92)
Not reported	11 (29.73)
QoL primary end point	
Yes	11 (29.73)
No	26 (70.27)
Study industry funded	
Yes	34 (91.89)
No	3 (8.11)

Abbreviations: ESA = erythropoiesis-stimulating agents; Hb = haemoglobin; QoL = quality of life; QW = once per week; ⩽Q2W = every second week or less frequent; TIW = three times per week.

Percentage of patients achieving a CID and NNT. We estimated the percentage of patients achieving a CID and corresponding NNTs based on hypothetical control groups. With a hypothetical response rate of 20% in the control group, the response rate in patients receiving ESAs is 27% (95% CI 24%–30%) for FACT-F and 29% (95% CI 25%–34%) for FACT-An with corresponding NNTs of 14 (95% CI 10–26) and 10 (95% CI 7–19). With a hypothetical response rate of 40% in the control group, the response rate in patients receiving ESAs is 49% (95% CI 45–52) for FACT-F and 52% (95% CI 47%–57%) for FACT-An with corresponding NNTs of 11 (95% CI 8–19) and 8 (95% CI 5–14).

DISCUSSION

We found that ESAs provide a small but clinically important improvement in anaemia-related symptoms (FACT-An), which was confirmed when the analysis was restricted to placebo-controlled RCTs in patients receiving chemotherapy. For fatigue-related symptoms (FACT-F), the overall effect did not reach the threshold for a CID. For FACT-F, there was some evidence that treatment effects were above the threshold for a CID in RCTs in patients receiving chemotherapy with Hb levels below $12\,g\,dl^{-1}$ at baseline and in RCTs stopping ESAs at Hb levels above $13\,g\,dl^{-1}$. However, these findings for FACT-F were not confirmed when we restricted the analysis to placebo-controlled RCTs in patients receiving chemotherapy.

To reduce publication and outcome reporting biases, we included unpublished and unreported results from clinical study reports. This allowed us to include more studies and patients than previous meta-analyses (Tonelli *et al*, 2009; Minton *et al*, 2010; Tonia *et al*, 2012; Grant *et al*, 2013), and to explore the effects of ESAs in different populations. Clinical study reports are not peer reviewed and the quality of these reports and the validity of the reported study data is uncertain. However, when we restricted our analyses to data from full publications our overall conclusions did not change. Similarly, our conclusions did not change when we conducted trim and fill analyses to adjust for potential publication bias. Our study does not confirm a CID for FACT-F, which had been reported in two previous literature-based meta-analyses (Minton *et al*, 2008, 2010; Tonelli *et al*, 2009). Our findings for FACT-An are more conservative compared with a recent meta-analysis based on the published literature (Tonia *et al*, 2012). To account for the current licensed indication and to reduce the

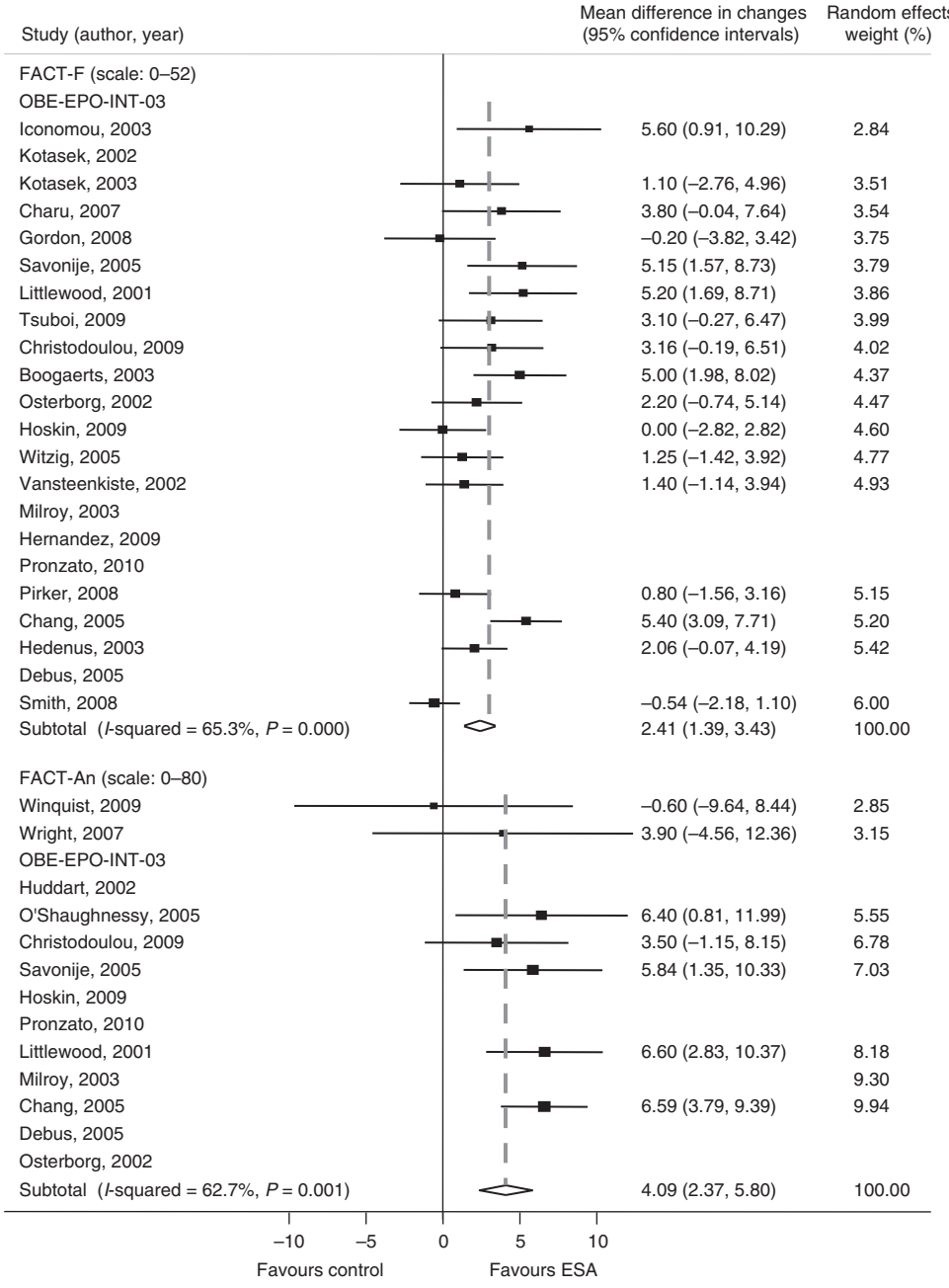

Figure 2. Forest plots of the effect of ESAs on QoL end points assessed by scales and subscales of the FACT questionnaire. Each solid square represents the SMD between groups for individual trials, and the size of the square represents the weight of the individual study in the meta-analysis. Horizontal lines indicate 95% CIs. The dashed vertical lines indicate the thresholds for clinical important differences for FACT-F (⩾3) and FACT-An (⩾4). The width of the diamond shows the 95% CI for the pooled SMD. Trials are sorted by weight. Confidential data are masked.

influence of placebo effects (a potential bias in self-reported measures such as fatigue- and anaemia-related symptoms), we conducted additional analyses restricted to (1) chemotherapy RCTs regardless of blinding and (2) only placebo-controlled chemotherapy RCTs. However, there were only few placebo-controlled RCTs reporting QoL outcomes for patients receiving chemotherapy, which limited our ability to conduct stratified analyses in this setting. For example, both in the overall analyses and in those restricted to chemotherapy studies, FACT-F results were more favourable in studies that chose QoL as primary end point, compared with those that chose QoL as secondary end point. Only one study evaluating FACT-F as primary end point in patients receiving chemotherapy was placebo controlled, and so we cannot gauge the extent to which the effect observed for primary *vs* secondary end point was confounded by lack of blinding. The design of the included studies did not permit us to estimate the relative benefit of ESAs in Hb responders *vs* non-responders. This would have required RCTs that identified responders in a run in period and then randomised these responders to either stop or continue ESAs. Finally, decreased QoL in cancer patients is affected by factors other than anaemia. Correction of a single factor, as did the studies included in our meta-analyses, may not have adequately reflected the complex pathophysiological and psychological dimensions of patient-reported QoL.

Several limitations of our study underscore the need for open access to all clinical trials results including study protocols, amendments, reports and IPD as currently discussed at the European Medicines Agency (Eichler *et al*, 2012). First, the quality

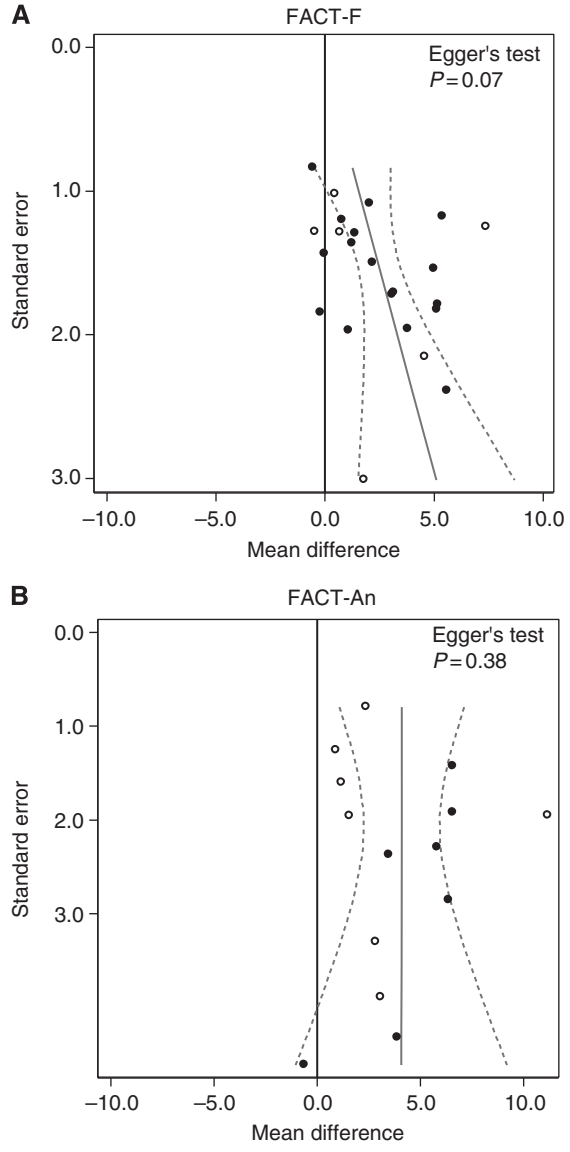

Figure 3. Funnel plots for FACT-F (**A**) and FACT-An (**B**). Closed circles = results from published literature, open circles = results from clinical study reports.

of reporting QoL data was low. Both in the published articles and the clinical study reports key information such as percentage of patients completing QoL questionnaires was missing or not clearly reported for the majority of studies. Critical review of clinical study documents by the academic community may help to improve the quality of reporting in these reports, which will only be possible with open access to these documents. Second, we identified another 16 trials (Kotasek *et al*, 2002, 2003; Thomas *et al*, 2002; Vansteenkiste *et al*, 2002; Boogaerts *et al*, 2003; Hedenus *et al*, 2003; Goss *et al*, 2005; Mystakidou *et al*, 2005; Witzig *et al*, 2005; Wilkinson *et al*, 2006; Aapro *et al*, 2008a; Gordon *et al*, 2008; Krzakowski, 2008; Pirker *et al*, 2008; Strauss *et al*, 2008; EPO-GER-20, 2009a) measuring FACT-An that did not or only incompletely report their FACT-An results and could therefore not be included in our analyses. Access to IPD may have permitted to include these studies in our analysis and it is possible that including these studies would change the results of our analyses. We unsuccessfully tried to retrieve the IPD and hence evaluated unpublished aggregated QoL data found in clinical study reports. However, for results, which were not reported in these documents, we made no additional attempts to obtain these results from the investigators. We also assessed whether QoL results had been published in clinical trials registries, which was not the case. Finally, our analyses are based on aggregated data and therefore analyses of variables at patient level, such as Hb at baseline and stage of disease, are prone to ecological bias (Berlin *et al*, 2002). This limitation could be overcome with a meta-analysis based on IPD, but this was not available for the current analyses.

When judging the efficacy of ESAs on fatigue- and anaemia-related symptoms, it is important to differentiate clinical from statistical significance. The concept of CIDs has been developed to address this problem (Cella *et al*, 2002a). However, defining CIDs is not straightforward. Depending on the clinical context and the methods selected, the threshold for CID could be set at different levels. For our primary analyses, we used the definition of Cella *et al* (2002b), which was developed to combine anchor- and distribution-based methods in populations similar to those we studied. Notably, the CIDs defined for FACT-F and FACT-An refer to changes from baseline to end of treatment. In our analyses, we used this yardstick to measure the differences in mean changes between groups from baseline to treatment, according to current practice in QoL studies (Tonelli *et al*, 2009; Minton *et al*, 2010).

Harmful effects of ESAs should be balanced against potential benefits. Previous meta-analyses have consistently shown that ESAs increase the risk of thromboembolic events in cancer patients by approximately factor 1.6 (Bohlius *et al*, 2006a, b; Seidenfeld *et al*, 2006; Aapro *et al*, 2008b, 2009; Bennett *et al*, 2008; Ludwig *et al*, 2009; Tonelli *et al*, 2009). Literature-based and IPD meta-analyses showed increased mortality (Bohlius *et al*, 2009a, b) or shortened overall survival in patients receiving ESAs (Bennett *et al*, 2008; Tonelli *et al*, 2009). Whether ESAs are safe for patients undergoing chemotherapy is a matter of debate. Our meta-analyses, and those of others based on IPD, have shown that ESAs increased short-term mortality in patients receiving chemotherapy by approximately 10% (Bohlius *et al*, 2009a, b; Ludwig *et al*, 2009), not reaching conventional levels of statistical significance. Statistically, the estimated mortality increase in chemotherapy trials can be explained by the same underlying effect as that in non-chemotherapy trials (Bohlius *et al*, 2009a, b). Clinically, the increase in mortality associated with ESAs may be less pronounced, or even absent, in patients receiving chemotherapy than in those undergoing other anticancer treatments. Two recent studies in cancer patients receiving chemotherapy did not find evidence for survival differences in patients receiving ESAs compared with controls (Engert *et al*, 2010; Moebus *et al*, 2013). In these studies, cancer patients were receiving chemotherapy with a curative intent and ESAs were stopped at Hb levels of 12 g dl^{-1} (Engert *et al*, 2010) and 14 g dl^{-1} (Moebus *et al*, 2013). Nevertheless, current evidence does not allow to conclude that ESAs are safe in patients receiving chemotherapy. Basic science studies have evaluated the presence of erythropoietin (EPO) receptors and its functionality in tumour cells (Arcasoy *et al*, 2005; Szenajch *et al*, 2010; Kumar *et al*, 2012). Interestingly, researchers without funding from ESA manufacturers were more likely to identify EPO receptors on cancer cells, EPO-induced signalling events or EPO-induced harmful changes of cellular function; or to conclude that ESAs had potentially harmful effects on cancer cells as compared with investigators receiving funding or being employed by ESA manufacturers (Bennett *et al*, 2010). Similarly, of the seven meta-analyses on the effects of ESAs in cancer patients conducted since 2008 none of the meta-analyses with funding from ESA manufacturers identified an increased mortality risk (Aapro *et al*, 2008b; Glaspy *et al,* 2010). In contrast, each of the meta-analyses conducted by researchers not receiving funding from ESA manufacturers found an increased risk either for on study mortality or overall survival

Table 2. Stratified analyses for FACT-F in (i) all included RCTs, (ii) RCTs in patients receiving chemotherapy and (iii) placebo-controlled RCTs in patients receiving chemotherapy

	All RCTs			Chemotherapy RCTs			Placebo-controlled chemotherapy RCTs		
FACT-F	Studies/ ESA/ control	MD (95% CI)	*P*-value[a]	Studies/ ESA/ control	MD (95% CI)	*P*-value[a]	Studies/ ESA/ control	MD (95% CI)	*P*-value[a]
Overall	23/3389/2719	2.41 (1.39 to 3.43)		19/2566/2131	2.81 (1.73 to 3.90)		10/1543/1171	1.78 (0.82 to 2.73)	
Anticancer treatment			0.218			NA			NA
Chemotherapy	19/2566/2131	2.81 (1.73 to 3.90)		19/2566/2131	2.81 (1.73 to 3.90)		10/1543/1171	1.78 (0.82 to 2.73)	
Radiotherapy	1/127/134	0.00 (−2.82 to 2.82)		—	—		—	—	
None	3/696/454	0.62 (−1.83 to 3.07)		—	—		—	—	
Anticancer treatment (condensed)			0.079			NA			NA
Chemotherapy	19/2566/2131	2.81 (1.73 to 3.90)		19/2566/2131	2.81 (1.73 to 3.90)		10/1543/1171	1.78 (0.82 to 2.73)	
Radiotherapy, none	4/823/588	0.28 (−1.34 to 1.90)		—	—		—	—	
Baseline Hb			0.424			0.362			0.153
$>12\,g\,dl^{-1}$	3/474/478	0.43 (−0.94 to 1.80)		2/347/344	0.56 (−1.01 to 2.13)		—	—	
$10–12\,g\,dl^{-1}$	12/1535/1172	3.07 (1.47 to 4.67)		10/1182/1080	3.31 (1.52 to 5.09)		4/596/573	0.97 (−0.34 to 2.28)	
$\leqslant 10\,g\,dl^{-1}$	8/1380/1069	2.32 (0.74 to 3.90)		7/1037/707	2.82 (1.57 to 4.08)		6/947/598	2.41 (1.19 to 3.62)	
Baseline Hb (condensed)			0.098			0.11			NA
$>12\,g\,dl^{-1}$	3/474/478	0.43 (−0.94 to 1.80)		2/347/344	0.56 (−1.01 to 2.13)				
$\leqslant 12\,g\,dl^{-1}$	20/2915/2241	2.78 (1.64 to 3.92)		17/2219/1787	3.15 (2.00 to 4.29)		10/1543/1171	1.78 (0.82 to 2.73)	
Disease stage			0.025[b]			0.005[b]			0.225[b]
>70% not metastatic/advanced	1/168/170	5.40 (3.09 to 7.71)		1/168/170	5.40 (3.09 to 7.71)		—	—	
>70% metastatic/advanced	11/1977/1650	1.15 (0.21 to 2.08)		10/1634/1288	1.41 (0.49 to 2.32)		7/1131/879	1.40 (0.37 to 2.42)	
Other	6/699/476	3.12 (0.31 to 5.93)		3/219/250	5.59 (2.93 to 8.25)		—	—	
Unknown[c]	5/545/423	3.21 (1.64 to 4.77)		5/545/423	3.21 (1.64 to 4.77)		3/412/292	2.95 (0.68 to 5.23)	
Frequency			0.032[b]			0.044[b]			0.134[b]
⩽Q2W	6/1170/685	0.85 (−0.79 to 2.49)		3/474/231	1.37 (−1.49 to 4.23)		3/474/231	1.37 (−1.49 to 4.23)	
QW	7/849/848	2.20 (0.81 to 3.59)		7/849/848	2.20 (0.81 to 3.59)		4/491/481	1.85 (0.56 to 3.14)	
TIW	9/1125/947	3.72 (1.91 to 5.54)		8/998/813	4.22 (2.47 to 5.97)		2/333/220	3.54 (0.62 to 6.46)	
Other[c]	1/245/239	0.80 (−1.56 to 3.16)		1/245/239	0.80 (−1.56 to 3.16)		1/245/239	0.80 (−1.56 to 3.16)	
Target Hb			0.008			0.053			0.105
$>13–15\,g\,dl^{-1}$	17/2486/1903	3.00 (1.91 to 4.09)		15/2156/1727	3.17 (2.02 to 4.31)		9/1380/1019	2.06 (1.11 to 3.01)	
$\leqslant 13\,g\,dl^{-1}$	5/846/761	−0.13 (−1.20 to 0.93)		3 /353/349	0.22 (−1.29 to 1.74)		1/163/152	−0.45 (−2.97 to 2.07)	
Not reported[c]	1/57/55	5.60 (0.91 to 10.29)		1/57/55	5.60 (0.91 to 10.29)		—	—	
Placebo control			0.054			0.083			NA
Yes	12/2036/1583	1.36 (0.39 to 2.34)		10/1543/1171	1.78 (0.82 to 2.73)		10/1543/1171	1.78 (0.82 to 2.73)	
No	11/1353/1136	3.46 (1.77 to 5.16)		9/1023/960	3.85 (1.96 to 5.74)		—	—	
QoL primary end point			0.027			0.091			0.724
Yes	8/850/878	3.87 (1.98 to 5.76)		8/850/878	3.87 (1.98 to 5.76)		1/151/148	1.25 (−1.42 to 3.92)	
No	15/2539/1841	1.53 (0.58 to 2.48)		11/1716/1253	1.93 (0.88 to 2.98)		9/1392/1023	1.87 (0.80 to 2.95)	
Source of data			0.907			0.537			0.446
Full publication	17/2628/2053	2.41 (1.35 to 3.47)		13/1805/1465	2.98 (1.97 to 4.00)		8/1258/990	1.92 (0.94 to 2.90)	
Clinical study report	6/761/666	2.36 (−0.37 to 5.10)		6/761/666	2.36 (−0.37 to 5.10)		2/285/181	1.78 (−3.14 to 6.69)	
Study industry funded			0.362			0.476			NA
Yes	21/3256/2588	2.29 (1.22 to 3.35)		17/2433/2000	2.70 (1.54 to 3.85)		10/1543/1171	1.78 (0.82 to 2.73)	
No	2/133/131	3.99 (1.26 to 6.71)		2/133/131	3.99 (1.26 to 6.71)		—	—	

Abbreviations: CI = confidence interval; ESA = erythropoiesis-stimulating agents; FACT-F = Functional Assessment of Cancer Therapy-Fatigue subscale; Hb = haemoglobin; MD = mean difference; NA = not applicable; QoL = quality of life; RCT = randomised controlled trial. Frequency: ⩽Q2W = every second week or less frequent, QW = once per week, TIW = three times per week, other = frequency changing during the study. Planned weekly ESA dose: high = >40 000 U epoetin α/δ or 30 000 U epoetin β or 100 μg darbepoetin, middle = 40 000 U epoetin α/δ or 30 000 U epoetin β or 100 μg darbepoetin, low = <40 000 U epoetin α/δ or 30 000 U epoetin β or 100 μg darbepoetin, other = weight based or Hb based.

[a] *P*-value: refers to test for interaction unless otherwise specified.

[b] Test for trend.

[c] Not used for interaction/trend test.

(Bennett *et al*, 2008; Bohlius *et al*, 2009a, b; Tonelli *et al*, 2009; Tonia *et al*, 2012; Grant *et al*, 2013). This observation highlights the importance of conflicts of interest both in the clinical and the basic sciences. In the case of ESAs and mortality in cancer patients, this led to misleading results and conclusions in meta-analyses funded by the pharmaceutical industry. Of note, in our analyses we found no evidence that results from industry-funded studies differed from those not funded by the industry. However, this may be due to a lack of power in a setting were >90% of studies were funded by the industry.

Table 3. Stratified analyses for FACT-An in (i) all included RCTs, (ii) RCTs in patients receiving chemotherapy and (iii) placebo-controlled RCTs in patients receiving chemotherapy

	All RCTs			Chemotherapy RCTs			Placebo-controlled chemotherapy RCTs		
FACT-An	**Studies/ ESA/ control**	**MD (95% CI)**	***P*-value[a]**	**Studies/ ESA/ control**	**MD (95% CI)**	***P*-value[a]**	**Studies/ ESA/ control**	**MD (95% CI)**	***P*-value[a]**
Overall	14/1466/1299	4.09 (2.37 to 5.80)		11/1310/1126	4.50 (2.55 to 6.45)		3/413/308	4.55 (1.29 to 7.80)	
Anticancer treatment			0.709			NA			NA
Chemotherapy	11/1310/1126	4.50 (2.55 to 6.45)		11/1310/1126	4.50 (2.55 to 6.45)		3/413/308	4.55 (1.29 to 7.80)	
Radiotherapy	1/126/133	1.60 (−2.24 to 5.44)		—	—		—	—	
None	1/14/20	3.90 (−4.56 to 12.36)		—	—		—	—	
Unclear[b]	1/16/20	−0.60 (−9.64 to 8.44)		—	—		—	—	
Anticancer treatment (condensed)			0.458			NA			NA
Chemotherapy	11/1310/1126	4.50 (2.55 to 6.45)		11/1310/1126	4.50 (2.55 to 6.45)		3/413/308	4.55 (1.29 to 7.80)	
Radiotherapy, none	2/140/153	1.99 (−1.50 to 5.49)		—	—		—	—	
Unclear[b]	1/16/20	−0.60 (−9.64 to 8.44)		—	—		—	—	
Baseline Hb			0.389			0.567			0.695
$>12\,g\,dl^{-1}$	4/511/514	1.64 (−0.09 to 3.36)		3/385/381	1.91 (−0.58 to 4.39)		1/40/42	6.40 (0.81 to 11.99)	
10–$12\,g\,dl^{-1}$	7/540/477	5.89 (3.31 to 8.48)		5/510/437	6.57 (3.83 to 9.31)		—	—	
$<10\,g\,dl^{-1}$	3/415/308	3.76 (0.87 to 6.64)		3/415/308	3.76 (0.87 to 6.64)		2/373/266	4.14 (0.08 to 8.19)	
Baseline Hb (condensed)			0.087			0.137			0.695
$>12\,g\,dl^{-1}$	4/511/514	1.64 (−0.09 to 3.36)		3/385/381	1.91 (−0.58 to 4.39)		1/40/42	6.40 (0.81 to 11.99)	
$\leqslant 12\,g\,dl^{-1}$	10/955/785	5.09 (2.89 to 7.29)		8/925/745	5.44 (3.04 to 7.83)		2/373/266	4.14 (0.08 to 8.19)	
Disease stage			0.06[c]			0.064[c]			0.277[c]
>70% not metastatic/advanced	2/208/212	6.55 (4.05 to 9.06)		2/208/212	6.55 (4.05 to 9.06)		1/40/42	6.40 (0.81 to 11.99)	
>70% metastatic/advanced	7/741/661	2.14 (1.01 to 3.28)		5/711/621	2.15 (0.98 to 3.32)		1/173/176	2.40 (0.84 to 3.96)	
Other	3/254/273	5.50 (−1.43 to 12.43)		2/128/140	7.85 (0.03 to 15.67)		—	—	
Unknown[b]	2/263/153	5.36 (2.39 to 8.34)		2/263/153	5.36 (2.39 to 8.34)		1/200/90	6.60 (2.83 to 10.37)	
Frequency			0.992[c]			0.801[c]			0.64[c]
QW	5/409/424	4.11 (0.96 to 7.25)		4/395/404	4.16 (0.55 to 7.76)		1/40/42	6.40 (0.81 to 11.99)	
TIW	9/1057/875	4.09 (1.84 to 6.34)		7/915/722	4.73 (2.10 to 7.36)		2/373/266	4.14 (0.08 to 8.19)	
Target Hb			0.25			0.201			NA
>13–$15\,g\,dl^{-1}$	12/1279/1107	4.52 (2.63 to 6.41)		9/1123/934	5.10 (2.92 to 7.29)		3/413/308	4.55 (1.29 to 7.80)	
$\leqslant 13\,g\,dl^{-1}$	2/187/192	1.13 (−1.22 to 3.47)		2/187/192	1.13 (−1.22 to 3.47)		—	—	
Placebo control			0.985			0.912			NA
Yes	5/443/348	3.91 (1.49 to 6.32)		3/413/308	4.55 (1.29 to 7.80)		3/413/308	4.55 (1.29 to 7.80)	
No	9/1023/951	4.12 (1.67 to 6.56)		8/897/818	4.46 (1.74 to 7.17)		—	—	
QoL primary end point			0.471			0.489			NA
Yes	7/568/591	4.69 (1.48 to 7.91)		5/538/551	5.29 (1.58 to 9.00)		—	—	
No	7/898/708	3.21 (1.53 to 4.90)		6/772/575	3.55 (1.60 to 5.50)		3/413/308	4.55 (1.29 to 7.80)	
Source of data			0.229			0.24			0.259
Full publication	7/652/469	5.71 (4.02 to 7.39)		5/622/429	6.02 (4.27 to 7.77)		2/240/132	6.54 (3.41 to 9.66)	
Clinical study report	7/814/830	3.18 (0.72 to 5.64)		6/688/697	3.48 (0.63 to 6.33)		1/173/176	2.40 (0.84 to 3.96)	
Study industry funded			0.864			0.777			NA
Yes	13/1403/1236	4.13 (2.30 to 5.97)		10/1247/1063	4.61 (2.50 to 6.72)		3/413/308	4.55 (1.29 to 7.80)	
No	1/63/63	3.50 (−1.15 to 8.15)		1/63/63	3.50 (−1.15 to 8.15)		—	—	

Abbreviations: CI = confidence interval; ESA = erythropoiesis-stimulating agents; FACT-An = Functional Assessment of Cancer Therapy-Anaemia subscale; Hb = haemoglobin; MD = mean difference; NA = not applicable; QoL = quality of life; RCT = randomised controlled trial. Frequency: ⩽Q2W = every second week or less frequent, QW = once per week, TIW = three times per week, other = frequency changing during the study. Planned weekly ESA dose: high ⩾40 000 U epoetin α/δ or 30 000 U epoetin β or 100 μg darbepoetin, middle = 40 000 U epoetin α/δ or 30 000 U epoetin β or 100 μg darbepoetin, low = <40 000 U epoetin α/δ or 30 000 U epoetin β or 100 μg darbepoetin, other = weight based or Hb based.

[a] *P*-value: refers to test for interaction unless otherwise specified.

[b] Not used for interaction/trend test.

[c] Test for trend.

These observations on the harmful effects of ESAs in cancer patients led to different recommendations of medical societies and authorities in the USA and Europe (Information for Health Professions, 2007; Aapro and Link, 2008; Rizzo *et al*, 2010; Schrijvers *et al*, 2010). The FDA and the American Societies of Clinical Oncology (ASCO) and Hematology (ASH) recommend the use of ESAs only in anaemic cancer patients receiving chemotherapy (Rizzo *et al*, 2010) with palliative treatment intent (Information for Health Professions, 2007) up to Hb level 12 g dl^{-1} (Information for Health Professions, 2007) with the goal of

avoiding red blood cell transfusions (Information for Health Professions, 2007; Rizzo *et al*, 2010). The FDA and ASCO/ASH explicitly do not recommend the use of ESAs to improve QoL because they consider the evidence inconclusive (Information for Health Professions, 2007; Rizzo *et al*, 2010). Similarly, in 2007, the FDA removed the claim for ESA-related QoL improvements in patients with chronic kidney disease from the product labels because of a lack of evidence from well-conducted trials. In contrast, the European Organization for Research and Treatment of Cancer (Aapro and Link, 2008) and the European Society of Medical Oncology (Schrijvers *et al*, 2010) recommend the use of ESAs to improve QoL in cancer patients.

Our overall analyses showed a small yet clinically important improvement for FACT-An, which was confirmed when the analysis was restricted to placebo-controlled RCTs in patients receiving chemotherapy. Of 100 patients treated, approximately 10 to 13 patients will have a clinically important improvement of anaemia-related symptoms, which can be attributed to ESA treatment. However, in patients treated with a curative approach it is unlikely that the observed benefits will outweigh the negative effects of ESAs on short-term mortality and thromboembolic events. Studies in cancer patients receiving chemotherapy with a palliative intent and receiving ESAs in accordance to current guideline recommendations (i.e., starting ESAs at Hb $<10\,g\,dl^{-1}$ and stopping at $12\,g\,dl^{-1}$) and reporting QoL outcomes were not available. In this setting, the impact of ESAs on QoL remains unclear.

CONCLUSION

We found that ESAs provide a small but clinically important improvement in anaemia-related symptoms (FACT-An). For fatigue-related symptoms (FACT-F), the overall effect did not reach the threshold for a CID.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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