Individual patient data meta-analysis on erythropoiesis-stimulating agents and mortality in patients with cancer

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Medical Background

- Erythropoietin (EPO) is a glycoprotein hormone controlling red blood cell production
- Erythropoiesis-stimulating agent (ESA) produced by recombinant DNA technology are utilised as treatment in anaemic patients (and as blood doping agent in cycling, ...)
- Main medical indication of ESAs:
  - Anaemia due to chronic kidney disease
  - Anaemia in cancer patients
- ESAs reduce the number of patients needing red blood cell transfusions, however increase the risk of thromboembolic events and may stimulate tumour growth
- Main pharmaceutical companies:
  Amgen, Johnson & Johnson, Hoffmann-La Roche

Cochrane review on ESAs for cancer patients

- Project leadership: Cochrane Haematological Malignancy Group (CHMG), Cologne, Germany (Prof. A. Engert, Dr. J. Bohlius)
- Bohlius et al. (2005), JNCI:
  - Overall survival: HR=0.84 [0.69; 1.02], 19 trials, n=2805
- Bohlius et al. (2006), JNCI:
  - Overall survival: HR=1.08 [0.99; 1.18], 42 trials, n=8167
- Newer trials
  - tend to enrol patients with higher baseline haemoglobin levels
  - tend to enrol patients who used higher ESA doses
  - target haemoglobin levels higher than 13g/dL to maintain high haemoglobin levels in non-anaemic cancer patients
- Meta-analyses based on aggregated/study-level data
  → Subgroup analyses only possible on study level

EPO IPD Project

- Project leadership: Cochrane Haematological Malignancy Group (CHMG), Cologne, Germany (Prof. A. Engert, Dr. J. Bohlius)
- Project funded by German Ministry of Education and Research and OncoSuisse, Switzerland
- Individual patient data (IPD) contributed by pharmaceutical companies (Amgen, Johnson & Johnson, Hoffmann-La Roche) and independent trialists

EPO IPD Project

- Objectives:
  - Examine ESA effects on survival of cancer patients
  - Identify factors that might modify ESA effects
- Endpoints:
  - On-study mortality
    → patient on trial treatment plus short follow-up period
    (four weeks or 28 days)
  - Overall survival
    → longest follow-up available
- Inclusion criteria:
  - Cancer patients
  - Anaemic or non-anaemic
  - Receiving chemotherapy, radiotherapy, radio-chemotherapy or no anti-cancer therapy
  - ESA plus transfusions if needed versus transfusions if needed
  - Randomised controlled trials

Legal setting

- Contract between University of Cologne (CHMG) and pharmaceutical companies setting regulatory framework
- Subcontracts between Universities of Cologne and Freiburg and Bern
- Steering Committee consisting of clinicians and methodologists from haematology, oncology, radiotherapy, clinical epidemiology, biostatistics and a consumer representative
- Advisory Board consisting of members of pharmaceutical companies and individual trialists providing IPD
- Advisory Board could give advise to the Steering Committee but had no decision-making authority

Methods

- Analyses predefined in peer-reviewed protocol approved by the Steering Committee and published in The Cochrane Library
- Statistical analyses described in detail in statistical analysis plan based on outline given in Cochrane protocol
- Data management, preprocessing and cleaning done in Cologne, Germany
- Main statistical analyses done independently:
  - Institute of Social and Preventive Medicine (ISPM), Bern, Switzerland (using Stata 10)
  - Institute of Medical Biometry and Medical Informatics (IMBI), Freiburg, Germany (using R 2.7.1)
- Standardised Operating Procedures for data security and confidentiality (Cologne, Freiburg, Bern)

Data management

- All data exchange encrypted using TrueCrypt
- Data entered in dedicated SAS database
- Data checked for accuracy, consistency, and completeness of follow-up
- Lists of data identified as missing, implausible or inconsistent sent to companies or independent investigators
- Discrepancies between published data and IPD (number of deaths, number of patients, hazard ratio) discussed with companies or independent investigators
- Main outcomes overall survival and on-study mortality were re-coded in duplicate in Cologne and Bern

Milestones

- Kickoff meeting in Cologne: September 21, 2007
- Final protocol (Version 14): January 28, 2008
- Contract signed between CHMG and companies: January 31, 2008
- Final statistical analysis plan (Version 1.01): June 25, 2008
- Final analysis data set: August 7, 2008
- Advisory Board (AB) meeting in Bern: September 18, 2008
- Final report (AB & Steering Committee): November 13, 2008

Studies and Data (Lancet 2009)

> 5000 references screened

↓

> 400 papers assessed in full text

↓

63 eligible RCTs

↓

53 RCTs with individual patient data (14206 patients)

↓

273 patients excluded

↓

53 RCTs with 13933 patients analysed

Missing data

- Several variables not available/provided for entire studies
  - History of thromboembolic event, hypertension, diabetes mellitus or cardiovascular events
  - Previous or current chemotherapy or radiotherapy
- Information on treatment status (untreated, in complete response, partial response, stable disease) unknown in ≈70%
- No structured information on disease stage in ≈80%
  → Generated based on free text entries per patient and available study documents
- Missing or not reported data not balanced across studies

Outcomes / Populations / Objectives

Outcomes:

- (1) On-study mortality / (2) Overall survival (both of primary interest)

Populations (defined on study level):

- (1) All cancer / (2) Chemotherapy (both of primary interest)
- (3) Radiotherapy / (4) None / (5) Mixed (secondary interest)

Objective 1:

- Examine the effect of ESAs
  - Unadjusted models to assess overall treatment effect
  - Models adjusted for baseline imbalances to assess overall treatment effect

Objective 2:

- Identification of factors modifying the effect of ESAs
  - Evaluation of interaction between treatment and additional factor in regression models

Objective 1 – Unadjusted models

Model	Comment
Two-stage log-rank fixed effect model	Primary analysis
Two-stage log-rank random effects model	
Two-stage Cox fixed effect model	
Two-stage Cox random effects model	
Cox model stratified by study	One-stage, fixed effect

Two-stage methods – First step

- For each study i, calculate log-hazard ratio θ_i and its standard error
- Based on log-rank expected (E_i) and observed number of events (O_i):

$$\theta_i = \frac{O_i - E_i}{V_i}, \quad \text{SE}(\theta_i) = \sqrt{1/V_i}$$

with $1/V_i$ denoting the Mantel-Haenszel variance of the log-hazard ratio

- Based on separate Cox regression model for study i:

$$\lambda_{ij}(t) = \lambda_{0i}(t) \exp(\beta_i^{ESA} \cdot x_{ij}^{ESA})$$

with $\theta_i = \beta_i^{ESA}$ and treatment covariate x_{ij}^{ESA} for patient j

Two-stage methods – Second step

- Fixed effect and random effects (DerSimonian-Laird) meta-analysis:

$$\theta = \frac{\sum w_i \theta_i}{\sum w_i} \quad \text{with} \quad w_i = \frac{1}{[\mathrm{SE}(\theta_i)]^2} \text{ or } \frac{1}{[\mathrm{SE}(\theta_i)]^2 + \tau^2}$$

  with between-study variance τ^2

- Forest and funnel plot to display results
- Linear regression test for funnel plot asymmetry
- Assessing statistical heterogeneity:
  χ^2-Test, I^2 statistic
- Meta-analytic approach familiar to Cochrane reviewers

One-stage method

- Cox model stratified by study:

$$\lambda_{ij}(t) = \lambda_{0i}(t) \exp(\beta^{ESA} \cdot x_{ij}^{ESA}) \quad (1)$$

- Cox model allowing for heterogeneity in log-hazard ratio across studies:

$$\lambda_{ij}(t) = \lambda_{0i}(t) \exp(\beta_i^{ESA} \cdot x_{ij}^{ESA}) \quad (2)$$

- Test for heterogeneity in log-hazard ratio across studies: Likelihood ratio test comparing models (1) and (2)

Results: On-study mortality, all cancer patients (n =13933)

Model	ESA vs Control HR [95% CI]	p-value[1]	p-value[2]
Two-stage methods			
Log-rank fixed effect model	1.17 [1.06-1.30]	0.0025	0.87
Log-rank random effects model	1.17 [1.06-1.30]	0.0025	0.87
Cox fixed effect model	1.16 [1.05-1.29]	0.0042	0.93
Cox random effects model	1.16 [1.05-1.29]	0.0042	0.93
Cox model stratified by study	1.17 [1.06-1.30]	0.0025	0.63

[1] Test for overall treatment effect

[2] Test for heterogeneity

Results: On-study mortality, chemotherapy trials (n =10441)

Model	ESA vs Control HR [95% CI]	p-value[1]	p-value[2]
Two-stage methods			
Log-rank fixed effect model	1.10 [0.98-1.24]	0.12	0.72
Log-rank random effects model	1.10 [0.98-1.24]	0.12	0.72
Cox fixed effect model	1.09 [0.97-1.23]	0.16	0.88
Cox random effects model	1.09 [0.97-1.23]	0.16	0.88
Cox model stratified by study	1.10 [0.98-1.24]	0.12	0.46

[1] Test for overall treatment effect

[2] Test for heterogeneity

Objective 1 – Adjusted models

- Models adjusted for baseline imbalances to assess overall treatment effect
- Considered both pre-specified and exploratory variables
- “Pre-specified variables”:
  Variables defined for subset analyses in first Cochrane Protocol in 2002 (i.e. documented before the first trials with detrimental effects on survival were published)
- “Exploratory variables”:
  Variables proposed for subset analyses after detrimental study results became available

Objective 1 – Adjusted models

- List of “pre-specified variables”:
  - Haemoglobin at baseline
    (continuous, categorical: ≤8, 8–10, 10-12, 12–14, >14g/dL)
  - Tumour type (solid tumours vs haematological malignancies)
  - Cancer treatment modality
    (chemotherapy induced anaemia vs anaemia of cancer)
  - Tumour treatment
    (chemotherapy vs radiotherapy vs mixed vs other vs none)
  - Quality items: randomisation, concealment, placebo-controlled, blinding, less than 10% exclusions
  - Iron supplementation policy
    (fixed, as needed by protocol, discretion of physician, none)
  - Planned duration of ESA treatment
    (continuous, categorical: ≤8, 8–16, >16 weeks)
- List of “exploratory variables”:
  - Haematocrit, serum EPO level at baseline, sex, age, BMI, ECOG performance status, ...

Objective 1 – Adjusted models

- Stratified Cox regression model (1) plus an additional covariate
- All additional covariates with *p*-value below 0.1 (likelihood-ratio test comparing Cox models with and without additional covariate) suitable for multivariate model
- No formal stepwise model selection done due to large number of missing values
- Informal selection of additional covariates for multivariate model based on *p*-value of likelihood-ratio test and percentage of missing information resulting in multivariate models

Multivariate models: On-study mortality, all cancer patients

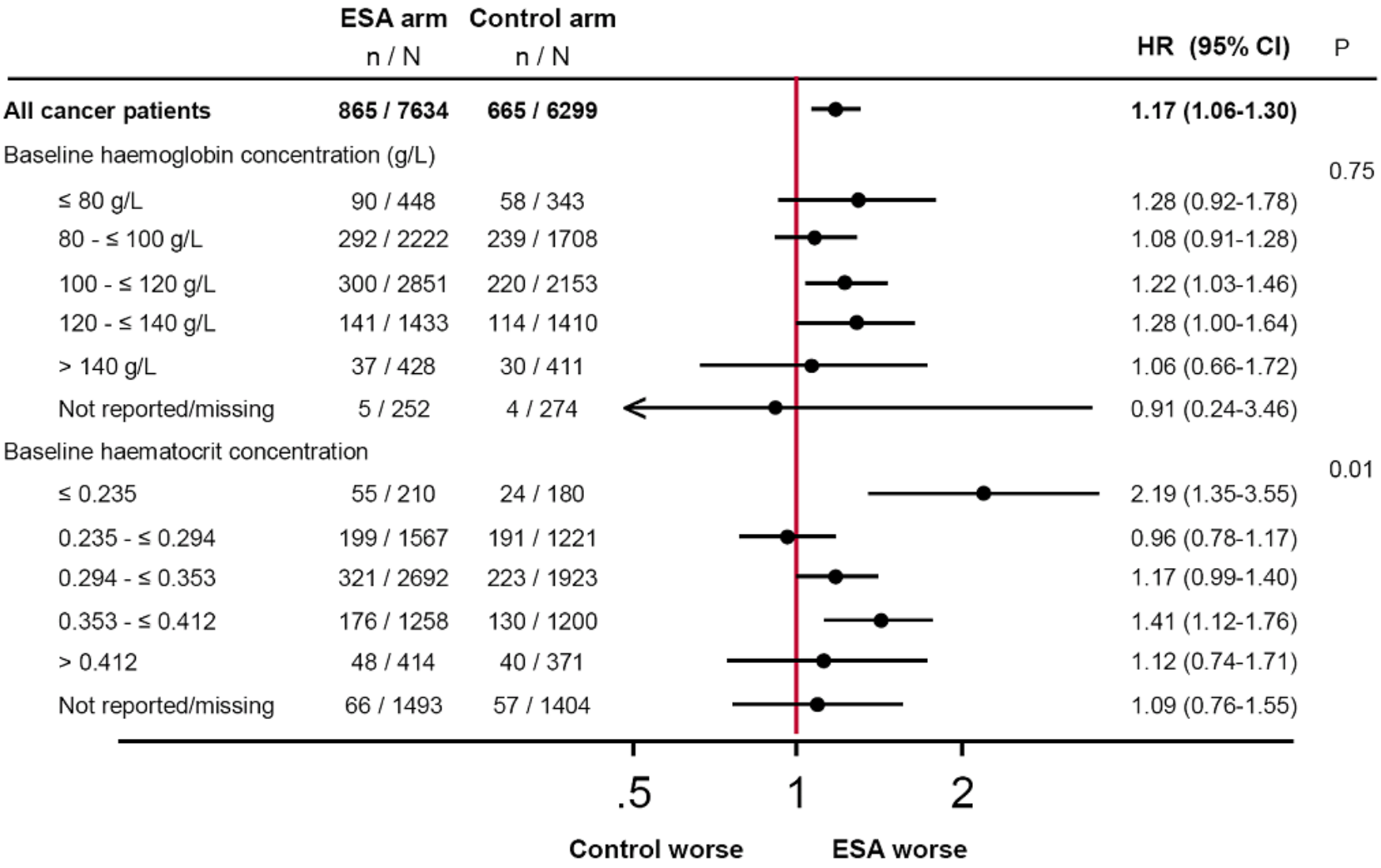
Model	*n*	ESA vs Control HR [95% CI]
Model 1 (unadjusted)	13353	1.17 [1.06-1.30]
Model 1 (adjusted)	13353	1.17 [1.06-1.30]
Model 2 (unadjusted)	11636	1.22 [1.09-1.36]
Model 2 (adjusted)	11636	1.21 [1.08-1.35]
Model 3 (unadjusted)	10599	1.16 [1.03-1.30]
Model 3 (adjusted)	10599	1.16 [1.03-1.30]

Model 1: ESA + Hb at baseline + Age + Sex + Tumour category
Model 2: Model 1 + Tumour stage
Model 3: Model 1 + Region + BMI

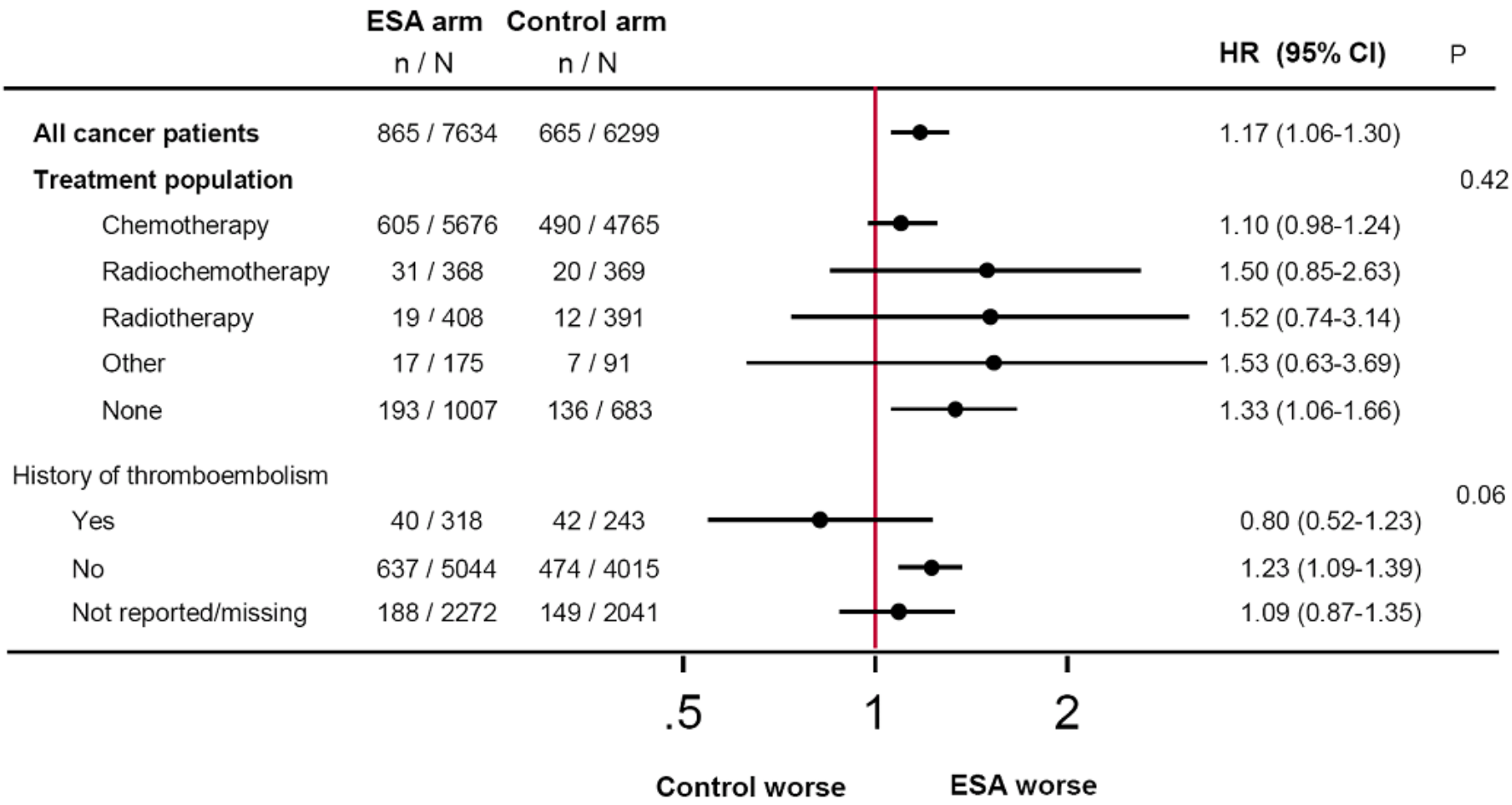
Objective 2 – Evaluation of interactions

- Cox regression model stratified by study with treatment factor and an additional covariate plus interaction between treatment and additional variable
- All additional covariates with p-value below 0.1 for interaction terms (likelihood-ratio test comparing Cox models with and without interaction term) evaluated in more detail
- No formal stepwise model selection done due to large number of missing values
- Covariates with a significant interaction term were included as additional covariate plus interaction term in multivariate model derived for Objective 1

Effect modifiers for on-study mortality (Lancet 2009)



Effect modifiers for on-study mortality (Lancet 2009)



Discussion

- Most comprehensive meta-analysis on ESAs in cancer patients based on individual patient data
- Main results:
  - ESAs increased on-study mortality and worsened overall survival in cancer patients
    (less pronounced for patients undergoing chemotherapy)
  - No strong evidence for effect modifiers

  → Confirmation of results based on aggregated/study-level data
- Current indication for ESA treatment (FDA, August 2008):
  - Treatment of anaemia due to concomitant chemotherapy
  - Not indicated when anticipated outcome is cure
  - Use of lowest dose to avoid red blood cell transfusion

Discussion

- Remarkable cooperation between academia and pharmaceutical companies:
  - Academia: Cochrane protocol, SOPs, statistical analysis plan
  - Companies: Provided restricted access to IPD, study protocols, full study reports
- Access to unpublished data from pharmaceutical companies and independent investigators
- Independence of research of EPO IPD project:
  - Only public funding / no industry funding
  - Power of decision by Steering Committee
- Future research:
  - Analysis of progression-free survival and quality of life
  - Impact of post baseline Hb levels on mortality
    ($\rightarrow$ time-dependent covariate)

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Reviewer for study selection and data extraction: Julia Bohlius, Sabine Kluge, Olaf Weingart

Advisory Board: Jesse Berline for J&J PRD, Peter Bowers for J&J PRD, Ulrich Burger for F. Hoffmann-La Roche Ltd, Tom Lillie for Amgen, Volker Moebus for the AGO ETC trial, Isabelle Ray-Coquard for the ELYPSE-4 study, Armin Scherhag for F. Hoffmann-La Roche Ltd, Gillian Thomas for the GOG-191 study, Dianne Tomita for Amgen, Michael Untch for the AGO PREPARE study

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Cochrane review on ESAs for cancer patients

- Project leadership: Cochrane Haematological Malignancy Group (CHMG), Cologne, Germany (Prof. A. Engert, Dr. J. Bohlius)
- Meta-analyses based on aggregated/study-level data
- Bohlius et al. (2005), JNCI:
  - 27 trials (3287 patients, published 01/1985 – 12/2001)
  - Red blood cell transfusion: RR=0.67 [0.62; 0.73], 25 trials, n=3069
  - Thromboembolic events: RR=1.58 [0.95; 2.66], 12 trials, n=1738
  - Overall survival: HR=0.84 [0.69; 1.02], 19 trials, n=2805
  - Overall survival (adjusted): HR=0.81 [0.67; 0.99], 19 trials, n=2805
- Bohlius et al. (2006), JNCI:
  - 57 trials (9353 patients, published 01/1985 – 04/2005)
  - Red blood cell transfusion: RR=0.64 [0.60; 0.68], 42 trials, n=6510
  - Thromboembolic events: RR=1.67 [1.35; 2.06], 35 trials, n=6769
  - Overall survival: HR=1.08 [0.99; 1.18], 42 trials, n=8167

Sensitivity analyses: On-study mortality

	n	ESA vs Control HR [95% CI]
All cancer patients	13933	1.17 [1.06-1.30]
Excluding Leyland-Jones 2005	12994	1.13 [1.02-1.27]
Aapro et al. 2008, BJC[1]	2297	1.13 [0.87-1.46]
Chemotherapy trials	10441	1.10 [0.98-1.24]
Excluding Leyland-Jones 2005	9502	1.03 [0.90-1.18]
Ludwig et al. 2009, JCO[2]	2122	1.11 [0.84-1.47]

[1] Chemo- and/or radiotherapy or surgery, placebo or standard therapy

[2] Chemotherapy only, placebo controlled only