It is the paper published as:

Author: S.-w. He and L. Wang

Title: The impact of anemia on the prognosis of chronic heart failure: a meta-analysis and systemic review.

Journal: Congestive Heart FailureISSN: 1527-5299

Year: 2009 **Volume:** 15 **Issue:** 3 **Pages**: 123-130

Abstract: Objective: The aim of this study was to assess the impact of anemia on the clinical outcomes of chronic heart failure (CHF) by a meta-analysis and systemic review of published literatures. Methods: Twenty published English language articles were selected from Medline, PubMed and ISI Database. Clinical data were extracted, pooled and analyzed with a fixed or random effects model. Results: A total of 97,699 patients with CHF were identified from the published studies. Meta-analysis of these studies indicated that anemia is associated with a higher risk for death (relative risk or RR, 1.66, P<0.0001). In addition, anemic patients had more advanced NYHA class (NYHA III-IV, RR, 1.35, P<0.0001) and lower left ventricular ejection fraction (weight mean difference or WMD, -0.53, P<0.0001) than in non-anemic patients. Systemic review also revealed that the severity of anemia is closely related to the rate of mortality and hospitalization for heart failure. Conclusions: Anemia is associated with an increased risk of mortality and rate of hospitalization for heart failure. Anemia is an independent risk factor for adverse outcomes in patients with CHF.

URL: http://dx.doi.org/10.1111/j.1751-7133.2008.00030.x,
http://www.blackwellpublishing.com/aims.asp?ref=1527-5299&site=1,
http://researchoutput.csu.edu.au/R/-?func=dbin-jump-full&object_id=3867&local_base=GEN01-CSU01,

Author Address:
lwang@csu.edu.au

CRO Number: 3867

The impact of anemia on the prognosis of chronic heart failure: a meta-analysis and systemic review

Sheng-Wen He, MD,[1,2] Le-Xin Wang, MD, PhD[1]

[1] School of Biomedical Sciences, Charles Sturt University, Wagga Wagga, New South Wales, Australia

[2] Faculty of Preventive Medicine, Weifang Medical University, Shandong Province, PR China

Running title: Anemia in patients with heart failure

Corresponding author:

Professor Lexin Wang, School of Biomedical Sciences, Charles Sturt University, Wagga Wagga, NSW 2678, Australia

Tel: +61 2 69332905 Fax: +61 2 69332587 Email: lwang@csu.edu.au

Word count: 2,077 excluding tables and references.

Abstract

Objective: The aim of this study was to assess the impact of anemia on the clinical outcomes of chronic heart failure (CHF) by a meta-analysis and systemic review of published literatures.

Methods: Twenty published English language articles were selected from Medline, PubMed and ISI Database. Clinical data were extracted, pooled and analyzed with a fixed or random effects model.

Results: A total of 97,699 patients with CHF were identified from the published studies. Meta-analysis of these studies indicated that anemia is associated with a higher risk for death (relative risk or RR, 1.66, $P<0.0001$). In addition, anemic patients had more advanced NYHA class (NYHA III-IV, RR, 1.35, $P<0.0001$) and lower left ventricular ejection fraction (weight mean difference or WMD, -0.53, $P<0.0001$) than in non-anemic patients. Systemic review also revealed that the severity of anemia is closely related to the rate of mortality and hospitalization for heart failure.

Conclusions: Anemia is associated with an increased risk of mortality and rate of hospitalization for heart failure. Anemia is an independent risk factor for adverse outcomes in patients with CHF.

Keywords: anemia; chronic heart failure; prognosis; meta-analysis; mortality.

Introduction

Anemia frequently occurs in patients with chronic heart failure (CHF). Several studies suggest that anemia may be associated with poorer health status and increased adverse outcomes from CHF.[1-8] However, some other studies did not find anemia had significant impact on the prognosis of CHF, and reduced hemoglobin (Hb) levels are not independently associated with shorter survival.[9-13] Moreover, whether changes in Hb over time are also related to the risk of morbid events or mortality is not clear.[14-16] Given the inconsistencies in the published studies, we performed a meta-analysis and systemic review on the results from the recent publications. The goal of this analysis was to determine the predictive value of anemia on the clinical outcomes of CHF. The relationship between the severity of anemia and the left ventricular function or hospitalization rates was also explored.

Methods

Search Strategy

We conducted systematic searches of Medline (1966–2007), PubMed and ISI Database for English language articles. Search terms included "anemia", "heart failure", "chronic heart failure", and combined terms "anemia and heart failure", "anemia and chronic heart failure". Manual search of the reference lists of all selected publications in the three databases was also conducted.

Inclusion criteria and assessment of study quality

Published studies must meet all the following criteria: 1) prospective clinical observation;

2) no specific therapeutic intervention for anemia; 3) the endpoints of the study were all-cause or cardiovascular mortality, or hospitalization for heart failure. Case reports, abstracts and review articles, and articles written in language other than English were excluded from this data collection.

Of the 1,292 titles and abstracts identified, 20 articles met the above criteria and were selected for meta-analysis. The quality of eligible articles was assessed by Jadad's scale. [17] Two investigators independently evaluated studies for inclusion in the systematic review, and any disagreements were resolved by discussion between these two investigators.

The WHO criteria for diagnosing anemia were applied: Hb <13 g/dL in men and <12g/dL in women.

Data extraction and statistical analysis

Two researchers abstracted data independently using a standardized form. In addition to the endpoints, the following information was extracted from all studies: author, year of publication, study location, number of patients, study or follow up period, prevalence of anaemia, New York Heart Association (NYHA) function class, and left ventricular ejection fraction. We also extracted data on demographics, causes of heart failure, body mass index, blood pressure, serum creatinine, glomerular filtration rate, serum sodium concentration, blood hemoglobin levels and all major cardiovascular drugs reported in these studies.

The numerical data were analyzed by weight mean difference (WMD) whereas the category data were assessed by relative risk (RR) and 95% confidence interval (95% CI), using a fixed or random effects model. Sources of heterogeneity were examined during

meta-analysis. The two-sided significance for heterogeneity was conventionally set at $P < 0.05$. We used sensitivity analysis to check stabilizations of results. Publication bias was assessed by funnel plot. All statistical analyses were performed using Cochrane Review Manager Software (version 4.2.7).

Results

General findings

Eighteen articles were regarded as high-quality because of the clear and detailed description of research methods such as randomization, follow up procedures and the end points. In the other two articles the description of follow up procedures was not very clear.[9,18] The funnel plot did not show significant publication bias in the 20 articles (Fig 1). A fixed or random effects model was used to determine if the findings from the original reports are consistent after incorporating different trials in the same analysis. This was done by varying the inclusion criteria and deleting small samples, and repeating the analysis with the new data set. The results indicated that the effect findings in this meta-analysis were sensitive and consistent.

Baseline characteristics of the original reports

Baseline characteristics of the patients included in the original publications are summarized in Table 1. Twenty-one studies from the 20 articles (one article included two studies) reported the relationship between anemia and the prognosis of CHF. These studies enrolled a total of 97,699 patients.

General characteristics of patients with anemia

The data were pooled from the 21 studies and the results are summarized in Table 2. In comparison with patients without anemia, anemic patients were older (WMD, 3.08, 2.06 to 4.10, $P<0.001$) with smaller body mass index (WMD -1.41, -1.72 to -1.10, $P<0.001$). There were fewer males in the anemia group (RR, 0.90, 95% CI 0.81 to 0.99, $P<0.001$). Anemia group also had a lower systolic (WMD, -2.14, -3.16 to -1.12, $P<0.001$) or diastolic blood pressure (WMD, -4.25,-4.83 to -3.66, $P<0.001$), and a lower heart rate (WMD,-1.03, -1.74 to -0.32, $P<0.01$) than in the non-anemia group.

The pooled data also showed that anemic patients had a higher frequency of ischemic heart disease (RR, 1.17, 1.05 to 1.29, $P<0.01$) and diabetes (RR, 1.27, 1.15 to 1.40, $P<0.001$) than the non-anemia group. In the anemia group, the serum creatinine (WMD, 20.46, 12.00 to 28.92, $P<0.001$) was higher while glomerular filtration rate (WMD, -8.15, -9.22 to -7.08, $P<0.001$) and plasma sodium levels (WMD, -1.05, -1.32 to -0.79, $P<0.001$) were lower than in the non-anemia group.

Anemia and mortality

We extracted 16 dichotomous and 9 continuous variables from 16 studies to perform meta-analysis. As shown in Tables 2, six studies reported baseline numbers of patients with or without anemia, and the number of deaths during the follow up. Meta-analysis of the six studies showed that anemia had a significant impact on the mortality of CHF (RR=1.66, 95% CI: 1.40-1.96, $P<0.001$) (Fig 2).

Fig 3 shows the combined results of nine studies where NYHA function class was reported. There was more NYHA class III-IV in patients with anemia than in patients without anemia (RR=1.35, 95% CI: 1.21-1.51, $P<0.001$). Patients with NYHA I-II were less likely than those with NYHA III-IV to have anemia (RR, 0.80 95% CI: 0.72-0.91, $P<0.001$).

Anemia and left ventricular function

Left ventricular ejection fraction was reported in five studies. Meta-analysis of the five studies showed that anemic patients had a lower left ventricular ejection fraction than non-anemic patients (Fig 4). The presence of anemia had a significant effect on the values of left ventricular ejection fraction (WMD =-0.53, 95% CI: -0.86, -0.21, $P=0.001$).

Use of medications

The pooled data from the 21 trials showed similar use of ACE-inhibitors, digitalis, diuretics, beta-blockers, aspirin and statins between anemia and non-anemia groups ($P>0.05$, Table 2).

Multivariable analysis for relationship between anemia and mortality or hospitalization

Systemic review found that Cox regression analysis was performed in 16 of the 21 studies, and logistic regression was performed in two. The results of these 18 multivariate regression analyses are summarized in Table 3. Four studies (No. 6, 7, 8, 20, Table 3) showed that the risk for mortality was directly related to the severity of anemia. Study No. 6 also demonstrated that the risk for hospitalization was closely associated with the severity of

anemia.

Discussion

Among the 21 studies reported in the 20 articles, the prevalence of anemia among the CHF patients varied from 10% to 58%.[8,12] Left ventricular ejection fraction was reported in five trials and NYHA function class in nine. The follow up periods ranged from two months to 10 years. Majority of these studies suggested that all-cause mortality or hospitalization rates in anemia patients were higher than in non-anemia patients, and anemia was an independent predictor of both mortality and hospitalization.[1-8,10-12] Some studies even suggested that baseline Hb concentrations as an independent risk factor for mortality, and low Hb was a marker of adverse outcome in CHF.[14-20] Every 1 g/dL increase or decrease in Hb value was associated with a significantly lower or higher risk of mortality or hospitalization for CHF.[3,4,7,14,19,20]

However, controversies exist in terms of the impact of anemia on the outcomes of CHF. A recent study found that anemia was strongly associated with mortality only in male patients.[16] Other studies reported that Hb was not independently associated with survival, and there was no significant correlation between Hb levels and all cause mortality.[9,13] In addition, older patients were reported more likely to have lower Hb levels than younger patients.[21] Lower Hb predicted worse survival in patients younger than 75 years, but Hb level was not related to mortality in patients 75 or older.[21]

The present meta-analysis and systemic review on the recent clinical studies has clearly demonstrated that anemia is associated with a higher all-cause mortality or hospitalization rate,

and anemia is an independent risk factor for worse survival in patients with CHF.

Previous studies showed that anemia patients were more likely to be older, with smaller body mass index , raised serum creatinine or reduced glomerular filtration rate.[1-3,5-6,8,10-12,16] Anemic patients also had more severe functional impairment of the heart and were more likely to have lower systolic blood pressure.[1,3] Lower mean baseline Hb concentrations correlated significantly with greater CHF severity as assessed by NYHA classification.[1-3,7-8,10-11,14,16] In multivariate analysis, anemia remained a significant, independent predictor of death or hospitalization for heart failure, with both outcomes being significantly higher in all NYHA classes.[4,13,16] Anemia was an independent predictor of in-hospital mortality in symptomatic patients with heart failure, regardless of whether the patients had preserved or reduced left ventricular ejection fraction.[12,14]

In consistent with the previous individual studies, this meta-analysis has shown that in comparison with non-anemia patients, anemia group had a higher prevalence of diabetes and ischemic heart disease as the aetiology of heart failure. Patients with anemia were also older, with smaller body mass index, lower mean systolic and diastolic blood pressure, lower levels of serum sodium, and greater renal function impairment. The meta-analysis on the 18 studies, in which left ventricular ejection fraction or NYHA class were reported, indicate that anemia is closely associated with lower left ventricular ejection fraction and more NYHA class III-IV versus I-II.

Previous studies suggested that beta-blockers, ACE inhibitors, diuretic and aspirin were slightly less likely to be received in anemia than in non anemia patients on admission.[3,6-7,9-12,14,16,19,20] The present study did not find significant differences between

the anemia and non-anemia patients in the use of the beta-blockers, ACE inhibitors, diuretics, digoxin, statins or aspirin.

The factors contributing to the pathogenesis of anemia in patient with CHF are not entirely clear. Blunted erythropoietin production, defective iron supply for erythropoiesis are believed to be the major causes of anemia in patients with CHF.[22-27] Our systemic review of the 21 studies have found that four of the studies applied multivariable analysis in an effort to ascertain the factors causing anemia in patients with CHF. [3,5,7,14] It appears that a history of diabetes mellitus, lower body mass index, more severe left ventricular dysfunction or renal failure collectively contributed to the development of anemia.[3,5,7,14] Non-white patients, patients with higher diastolic blood pressure and serum albumin, and patients who received aspirin were also found to be more likely to develop anemia.[3,5,7,14]

In conclusion, the present meta-analysis and systemic review has demonstrated that anemia is associated with an increased risk of all-cause mortality and hospital admission in patients with CHF. The levels of Hb, or the severity of anemia, are closely related to mortality and the rate of hospitalization for heart failure. The presence of anemia is often accompanied by advanced NYHA functional class and the lower levels of left ventricular ejection fraction. Anemia is also more common in older patients, in patients with renal insufficiency, smaller body mass index, lower systolic blood pressure and lower plasma levels of sodium. The results of this study may help to screen or manage anemia in CHF patients.

References

1. Komajda M, Anker SD, Charlesworth A, Okonko D, Metra M, Di Lenarda A, Remme W, Moullet C, Swedberg K, Cleland JG, Poole-Wilson PA. The impact of new onset anemia on morbidity and mortality in chronic heart failure: results from COMET. *Eur Heart J* 2006; 27:1440-1446.
2. Sharma R, Francis DP, Pitt B, Poole-Wilson PA, Coats AJ, Anker SD. Haemoglobin predicts survival in patients with chronic heart failure: a substudy of the ELITE II trial. *Eur Heart J* 2004; 25:1021–1028.
3. Anand IS, Kuskowski MA, Rector TS, Florea VG, Glazer RD, Hester A, Chiang YT, Aknay N, Maggioni AP, Opasich C, Latini R, Cohn JN. Anemia and change in hemoglobin over time related to mortality and morbidity in patients with chronic heart failure: results from Val-HeFT. *Circulation* 2005; 112:1121–1127.
4. Anand I, McMurray JV, Whitmore J, Warren M, Pham A, McCamish MA, Burton PB. Anemia and its relationship to clinical outcome in heart failure. *Circulation* 2004; 110:149–154.
5. Ezekowitz JA, McAlister FA, Armstrong PW. Anemia is common in heart failure and is associated with poor outcomes: insights from a cohort of 12 065 patients with new-onset heart failure. *Circulation* 2003; 107:223–225.
6. Go AS, Yang J, Ackerson LM, Lepper K, Robbins S, Massie BM, Shlipak MG. Hemoglobin level, chronic kidney disease, and the risks of death and hospitalization in adults with chronic heart failure: the Anemia in Chronic Heart Failure: Outcomes and Resource Utilization (ANCHOR) Study. *Circulation* 2006; 113:2713-2723.
7. Valeur N, Nielsen OW, McMurray JJ, Torp-Pedersen C, Kober L. Anemia is an independent predictor of mortality in patients with left ventricular systolic dysfunction following acute myocardial infarction. *Eur J Heart Fail* 2006; 8:577-584.
8. Szachniewicz J, Petruk-Kowalczyk J, Majda J, Kaczmarek A, Reczuch K, Kalra PR, Piepoli MF, Anker SD, Banasiak W, Ponikowski P. Anemia is an independent predictor of poor outcome in patients with chronic heart failure. *Int J Cardiol* 2003; 90:303-308.
9. Kalra PR, Collier T, Cowie MR, Fox KF, Wood DA, Poole-Wilson PA, Coats AJ, Sutton GC. Haemoglobin concentration and prognosis in new cases of heart failure. *Lancet* 2003;

362:211-212.

10. Grigorian Shamagian L, Varela Roman A, Garcia-Acuna JM, Mazon Ramos P, Virgos Lamela A, Gonzalez-Juanatey JR. Anaemia is associated with higher mortality among patients with heart failure with preserved systolic function. *Heart* 2006; 92:780-784.
11. Felker GM, Stough WG, Shaw LK, O'Connor CM. Anemia and coronary artery disease severity in patients with heart failure. *Eur J Heart Fail* 2006; 8:54-57.
12. Latado AL, Passos LC, Darzé ES, Lopes AA. Comparison of the effect of anemia on in-hospital mortality in patients with versus without preserved left ventricular ejection fraction. *Am J Cardiol* 2006; 98:1631-1634.
13. Tanner H, Moschovitis G, Kuster GM, Hullin R, Pfiiffner D, Hess OM, Mohacsi P. The prevalence of anemia in chronic heart failure. *Int J Cardiol* 2002; 86:115–121.
14. Maggioni AP, Opasich C, Anand I, Barlera S, Carbonieri E, Gonzini L, Tavazzi L, Latini R, Cohn J. Anemia in patients with heart failure: Prevalence and prognostic role in a controlled trial and in clinical practice. *J Cardiac Fail* 2005; 11:91-98.
15. Newton JD, Squire IB. Glucose and haemoglobin in the assessment of prognosis after first hospitalization for heart failure. *Heart* 2006; 92:1441-1446.
16. Hebert K, Horswell R, Arcement L, Hare J. Stevenson L. The effect of anemia on mortality in indigent patients with mild-to-moderate chronic heart failure. *Congest Heart Fail* 2006; 12:75-79.
17. Jadad A, Moore A, Carrol D, Jenkinson C, Reynolds DJ, Gavaghan DJ, McQuay HJ. Assessing the quality of reports of randomized trials: is blinding necessary? Control Clin Trial 1996; 17:1-12.
18. van der Meer P, Voors AA, Lipsic E, Smilde TD. van Gilst WH. van Veldhuisen DJ. Prognostic value of plasma erythropoietin on mortality in patients with chronic heart failure. *J Am Coll Cardiol* 2004; 44:63-67.
19. Horwich TB, Fonarow GC, Hamilton MA, MacLellan WR, Borenstein J. Anemia is associated with worse symptoms, greater impairment in functional capacity and a significant increase in mortality in patients with advanced heart failure. *J Am Coll Cardiol* 2002; 39:1780–1786.
20. Felker GM, Gattis WA, Leimberger JD, Adams KF, Cuffe MS, Gheorghiade M, O'Connor

CM. Usefulness of anemia as a predictor of death and re-hospitalization in patients with decompensate heart failure. *Am J Cardiol* 2003; 92:625–628.

21. Kerzner R, Gage BF, Rich MW. Anemia does not predict mortality in elderly patients with heart failure. *Am J Geriatr Cardiol* 2007; 16:92-96.
22. Philipp S, Ollmann H, Schink T, Dietz R, Luft FC, Willenbrock R. The impact of anemia and kidney function in congestive heart failure and preserved systolic function. *Nephrol Dial Transpl* 2005; 20:915-919.
23. Mozaffarian D, Nye R, Levy WC. Anemia predicts mortality in severe heart failure. The prospective randomized amlodipine survival evaluation (PRAISE). *J Am Coll Cardiol* 2003; 41:1933–1939.
24. Komajda M. Prevalence of anemia in patients with chronic heart failure and their clinical characteristics. *J Card Fail* 2004; 10:S1–S4.
25. Al-Ahmad A, Rand WM, Manjunath G, Konstam MA, Salem DN, Levey AS, Sarnak MJ. Reduced kidney function and anemia as risk factors for mortality in patients with left ventricular dysfunction. *J Am Coll Cardiol* 2001; 38:955–962.
26. Opasich C, Cazzola M, Scelsi L, De Feo S, Bosimini E, Lagioia R, Febo O, Ferrari R, Fucili A, Moratti R, Tramarin R, Tavazzi L. Blunted erythropoietin production and defective iron supply for erythropoiesis as major causes of anemia in patients with chronic heart failure. *Eur Heart J* 2005; 26: 2232–2237.
27. Silverberg DS, Wexler D, Blum M, Keren G, Sheps D, Leibovitch E, Brosh D, Laniado S, Schwartz D, Yachnin T, Shapira I, Gavish D, Baruch R, Koifman B, Kaplan C, Steinbruch S, Iaina A. The use of subcutaneous erythropoietin and intravenous iron for the treatment of the anemia of severe, resistant congestive heart failure improves cardiac and renal function and functional cardiac class, and markedly reduces hospitalizations. *J Am Coll Cardiol* 2000; 35:1737–1744.

Table 1. Overview of baseline characteristics

Study number	Author	Publication year	No. patients	Mean age (y)	NYHA class	LVEF	Criteria for anemia Hb (g/dL)	Prevalence of anemia (%)	Mean Hb	No. anemia patients	Study period /Follow –up	Outcome	
												Mortality	hospitalization
1	M Komajda	2006	2996		II-IV	<35%	WHO men <13 women <12 severe men <11.5 women <10.5 moderate men 11.5-13.0 women 10.5-12.0	15.9 men 16.0 women15.2 severe3.3 men3.6 women2.0 moderate12.6 men12.4 women13.2	14.2 +/- 1.5	475	58months (median)	1096	
2	R Sharma	2004	3044	71.5 +/- 6.8	2.5 +/- 0.6	31+/- 7%	<12.5		14.0 +/- 1.6	513	551 days (median)	515	
3	I Anand	2005	5002				men <13 women <12	23 men23 women24	13.1 +/- 1.0	1145	12 months		
4	I Anand	2004	912				<12	12	13.8 +/- 1.6	108	12 .7months	159	327
5	J Ezekowitz	2003	12065	78				17		2083	573 days (median)		
6	AS. Go	2006	59772	71.8+/-12.2			men <13 women <12	42.6	12.9 +/- 1.9	25452	2.07years	23901	
7	N Valeur	2006	1731			≤35%	men <13 women <12 severe men <11 women <10 moderate men 11-12 women 10-11 mild men 12-13 women 11-12	25	13.7 +/- 1.6	314	26months 10years	1268	
8	J Szachniewicz	2003	176	63	I/II/III/IV: 15/81/51/29	42%	<12	10	14 +/- 1.5	18	18months	32	
9	P Kalra	2003	552	76	III-IV				13.3	262	3years	343	

Table 1. continued

Study number	Author	Publication year	No. patients	Mean age (y)	NYHA class	LVEF	Criteria for anemia Hb (g/dL)	Prevalence of anemia (%)	Mean Hb	No. anemia patients	Study period /Follow –up	Outcome Mortality	hospitalization
10	L Shamagian	2006	210	73		≥50%	men <13 women <12	46	12.7 +/- 2.1	97	1.5years	46	
11	G Felker	2006	4951		≥II		men <13 women <12	39	12.8	1946			
12	A Latado	2006	303	69 +/- 13			men <13 women <12	58		144		52	
13	H Tanner	2002	193	54 +/- 11			<12	15		28	1.4-3.3years	32	
14	A Maggioni	2005	2411 5010				men <12 women <11	IN-CHF Registry 15.5 Val-HeFT 9.9		375 453	12 months 22.4 months	 979	
15	J Newton	2006	528	70			men <13 women <12	men 39 women43			1257 days	240	
16	K Hebert	2006	410			≤40%	men <13 women <12	28	13.5 +/- 1.9	113	436 days	59	
17	P Meer	2004	74	61 +/- 2		0.31+/-0.01	men <13 women <12	24	13.9 +/- 0.2	18	3years	22	
18	T Horwich	2002	1061		III-IV	<40%	men <13 women <12	30	13.6 +/- 1.9	318	5years 1years	360 212	
19	G Felker	2003	949			<23%	men <13 women <12	49	12.6 +/- 1.8	465	60 days		
20	R Kerzner	2007	359	69.4+/-15.2					11.7 +/- 1.9		25months		

Table 2. Summary of meta-analyses

Comparison	Studies Included	Participants	Statistical method in fixed effect model	Statistical method in random effect model	Effect size (95%CI)	Test for overall effect (P)	Test for heterogeneity (P)
Age(year)	9	83978		WMD	3.08(2.06, 4.10)	<0.00001	<0.00001
Male	6	24461		RR	0.90(0.81, 0.99)	0.04	<0.00001
Female	8	78948		RR	1.09(0.87, 1.37)	0.43	<0.00001
White	3	69725		RR	0.89(0.85, 0.93)	<0.00001	<0.00001
Smoking	4	6532	RR		0.93(0.88, 0.98)	0.004	0.17
NYHAI-II	4	9552		RR	0.80(0.72, 0.91)	0.0003	0.001
NYHAIII-IV	9	22361		RR	1.35(1.21, 1.51)	<0.00001	<0.00001
BMI(kg/m^2)	3	6216	WMD		-1.41(-1.72, -1.10)	<0.00001	0.45
Systolic BP (mmHg)	2	7998	WMD		-2.14(-3.16, -1.12)	<0.0001	0.64
Diastolic BP (mmHg)	2	7998	WMD		-4.25(-4.83, -3.66)	<0.00001	0.23
Heart rate (bpm)	2	7998	WMD		-1.03(-1.74, -0.32)	0.004	0.90
Mortality	6	12475		RR	1.66(1.40, 1.96)	<0.00001	0.008
Ischemic heart disease	9	33124		RR	1.17(1.05, 1.29)	0.003	<0.00001
Hypertension	6	76541		RR	1.04(0.94, 1.16)	0.46	<0.00001
Diabetes	9	86670		RR	1.27(1.15, 1.40)	<0.00001	<0.00001
LVEF(%)	5	11628	WMD		-0.53 (-0.86, -0.21)	0.001	0.07
Serum creatinine （μmol/L）	7	66911		WMD	20.46 (12.00, 28.92)	<0.00001	<0.00001
GFR($ml/min/1.73m^2$)	3	5622	WMD		-8.15(-9.22, -7.08)	<0.00001	0.32
Serum sodium(mmol/L)	4	6519	WMD		-1.05(-1.32, -0.79)	<0.00001	0.44

Diuretics	5	68156		RR	1.04(0.93, 1.17)	0.47	<0.00001
ACE-inhibitors	9	77182		RR	0.95(0.90, 1.00)	0.06	<0.00001
Digitalis	3	8208		RR	1.00(0.90, 1.12)	0.96	0.04
Aspirin	3	9193		RR	1.03(0.93, 1.15)	0.57	0.03
Beta-blocker	7	72991	RR		1.00(0.97, 1.03)	0.99	0.28
Statins	3	67770	RR		1.04(0.99, 1.08)	0.12	0.27

NYHA, New York Heart Association function class; BMI, body mass index; LVEF, left ventricular ejection fraction; GFR, glomerular filtration rate.

Table 3. Listing of results from published studies on the relationship between baseline anemia and all-cause mortality or hospitalization.

Study number	Cox regression	Logistic regression		Mortality	Hospitalization
				RR, HR or OR , 95%CI	RR, HR or OR , 95%CI
1	yes			RR 1.47(1.27–1.71)	RR 1.28(1.14–1.44)
3	yes			HR,1.21	HR,1.17
4	yes			HR,0.842	HR,0.858
5	yes			HR,1.34 (1.24 - 1.46)	
6	yes		Hb≥17	HR,1.42 (1.24 - 1.63)	HR,1.14 (1.03 - 1.27)
			<13		
			12.0-12.9	HR,1.16 (1.11 - 1.21)	HR,1.12 (1.09 - 1.16)
			11.0-11.9	HR,1.50(1.44 - 1.57)	HR,1.33 (1.28 - 1.38)
			10.0-10.9	HR,1.89(1.80 - 1.98)	HR,1.64 (1.58 - 1.71)
			9.0-9.9	HR,2.31(2.18 - 2.45)	HR,1.89 (1.80 - 1.99)
			<9.0	HR,3.48(3.25 - 3.73)	HR,1.99 (1.86 - 2.13)
7	yes		WHO anemia	HR,1.16(1.01-1.34)	
			mild anemia	HR,1.05(0.88-1.25)	
			moderate anemia	HR,1.20(0.93-1.56)	
			severe anemia	HR,1.65(1.21-2.25)	
8	yes			HR,2.61(1.05-6.47)	
10	yes			RR 2.647(1.308–5.357)	
11	yes			HR,1.12	
12		yes		OR,2.7(1.47-5.04)	
14	yes		IN-CHF registry	HR,0.903(0.839-0.973)	
			Val-HeFT	HR,0.922(0.881-0.966)	
15	yes			HR,1.415(1.087-1.841)	
16	yes			HR,1.64(0.95-2.85)	
			men	HR,2.54(1.31-4.93)	
			women	HR,0.49(0.16-1.54)	
17	yes			HR,0.408(0.219-0.759)	
18	yes		one year mortality		
			Hb <12.3	RR,1.861(1.215-2.852)	
			12.3-13.6	RR,1.369(0.871-2.145)	
			13.7-14.8	RR,1.298(0.826-2.039)	
			>14.8	RR,1.0	
19		yes		OR,0.89(0.82-0.97)	
20	yes		Age<75 year		
			Hb<11.5	HR,2.3(1.2-4.3)	
			11.5-13.4	HR,2.0(1.1-3.8)	

RR, relative risk; HR, hazard ratio; OR, odds ratio.

Figure legends

Figure 1. Funnel plot of published articles on anemia and heart failure.

Figure 2. Meta-analysis of the impact of anemia on the mortality of chronic heart failure. RR, relative risk in random effect model.

Figure 3. Meta-analysis on the combined effect of NYHA III-IV versus I-II. RR, relative risk in random effect model.

Figure 4. Meta-analysis on the combined effect of left ventricular ejection fraction. WMD, weighted mean difference in fixed effect model.

Fig 1

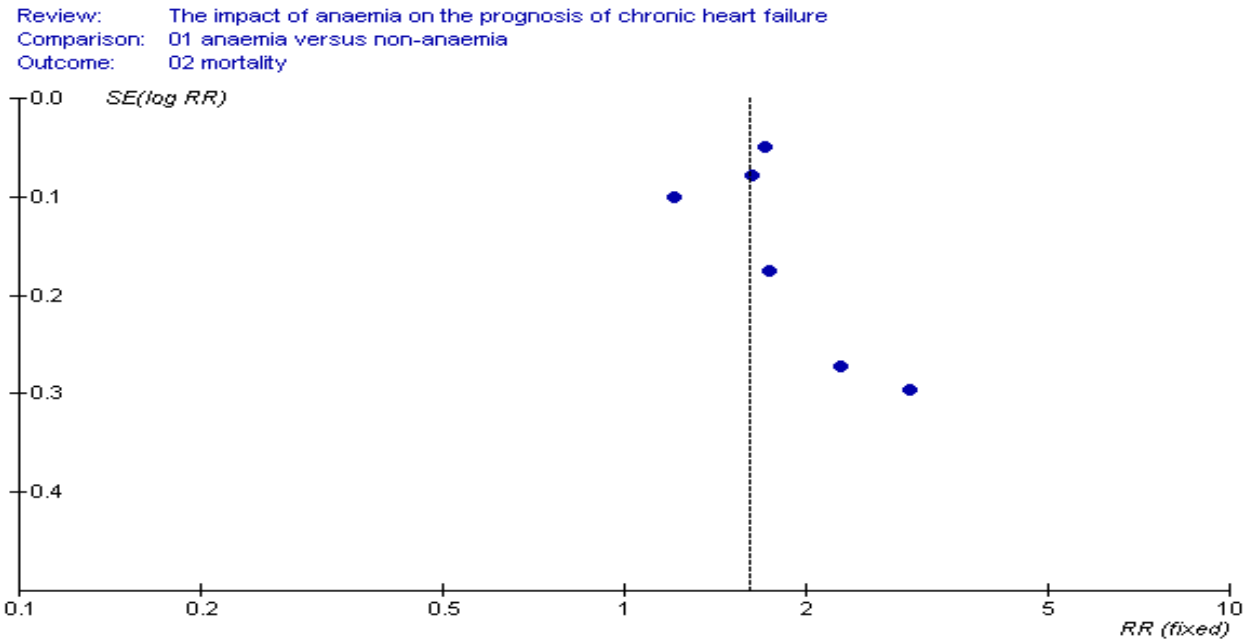

Review: The impact of anaemia on the prognosis of chronic heart failure
Comparison: 01 anaemia versus non-anaemia
Outcome: 02 mortality
SE(log RR)
0.0
0.1
0.2
0.3
0.4
0.1
0.2
0.5
1
2
5
10
RR (fixed)

Figure 2

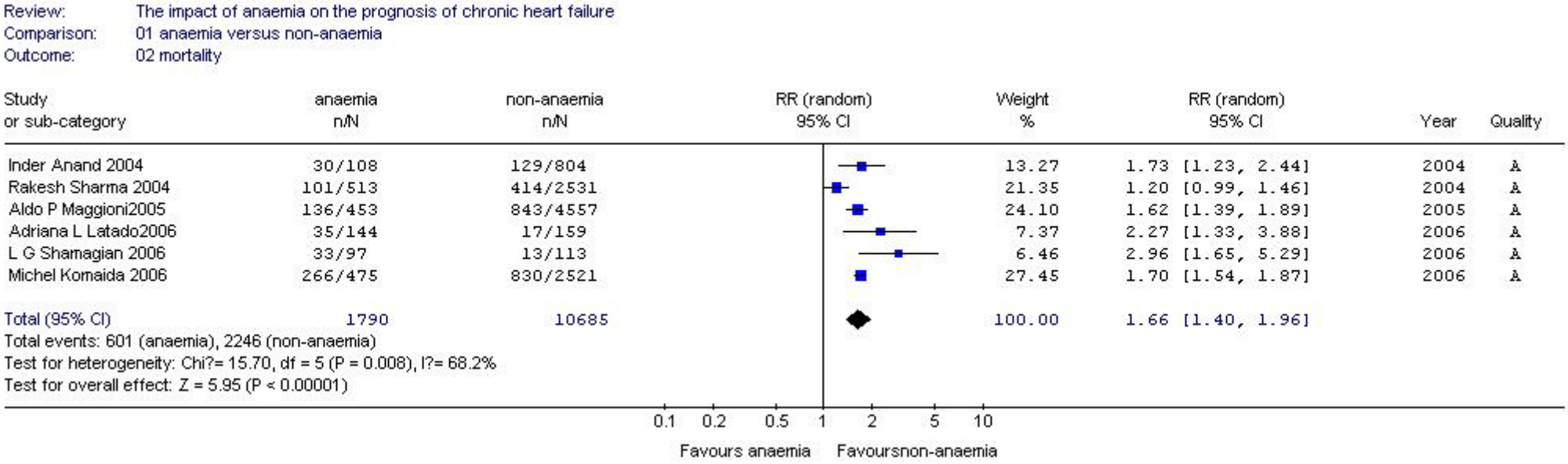


Figure 3

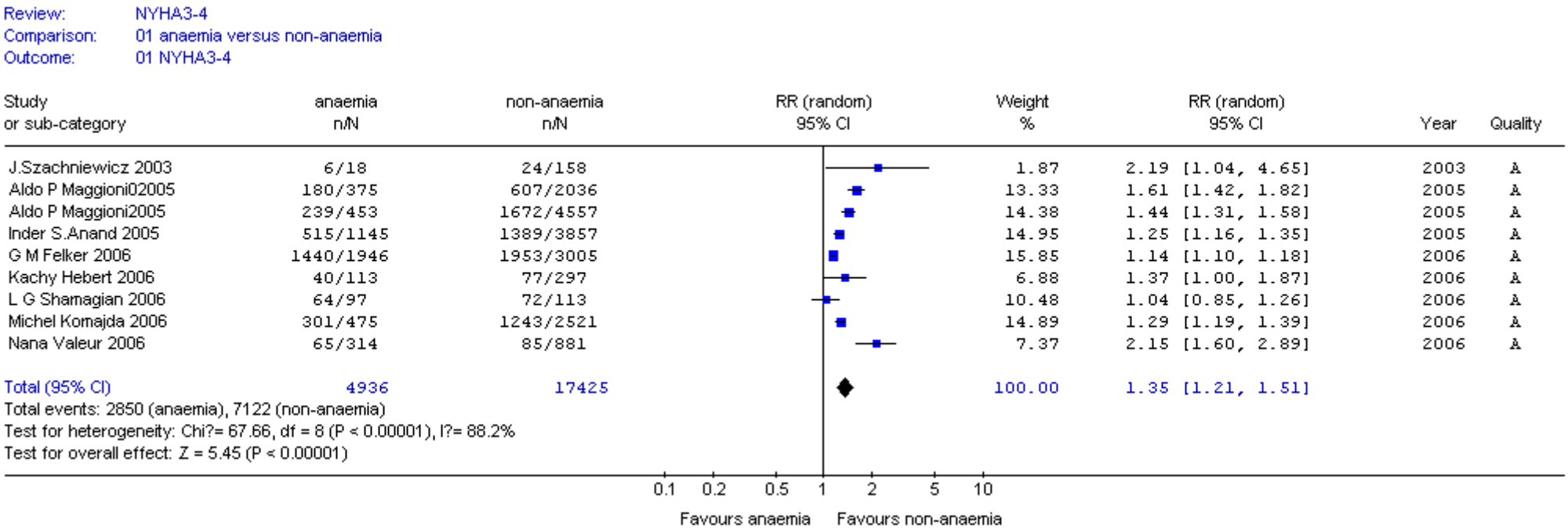
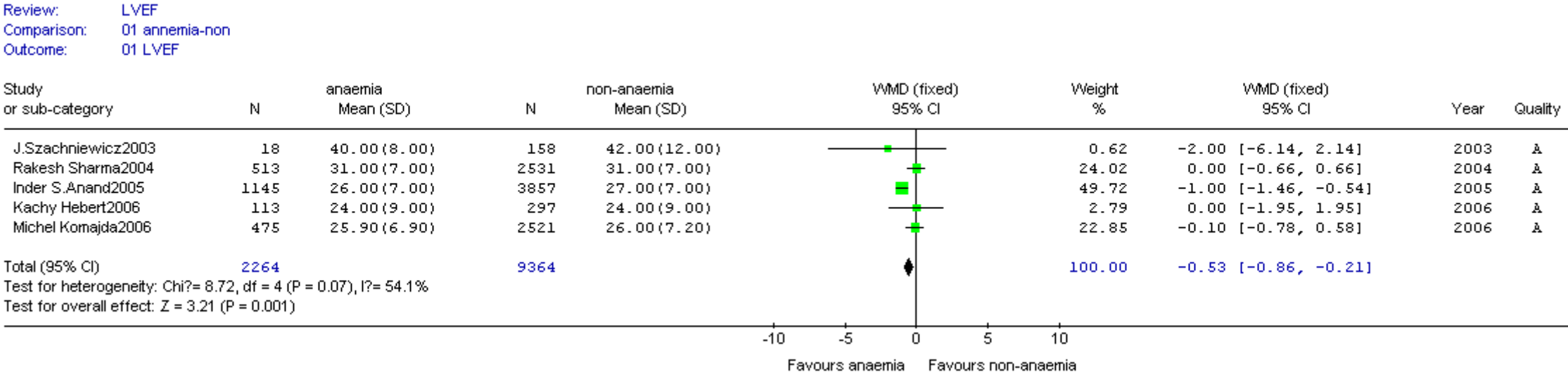

Review: NYHA3-4
Comparison: 01 anaemia versus non-anaemia
Outcome: 01 NYHA3-4
Study or sub-category
anaemia n/N
non-anaemia n/N
RR (random) 95% CI
Weight %
RR (random) 95% CI
Year
Quality
J.Szachniewicz 2003 6/18 24/158 1.87 2.19 [1.04, 4.65] 2003 A
Aldo P Maggioni02005 180/375 607/2036 13.33 1.61 [1.42, 1.82] 2005 A
Aldo P Maggioni2005 239/453 1672/4557 14.38 1.44 [1.31, 1.58] 2005 A
Inder S.Anand 2005 515/1145 1389/3857 14.95 1.25 [1.16, 1.35] 2005 A
G M Felker 2006 1440/1946 1953/3005 15.85 1.14 [1.10, 1.18] 2006 A
Kachy Hebert 2006 40/113 77/297 6.88 1.37 [1.00, 1.87] 2006 A
L G Shamagian 2006 64/97 72/113 10.48 1.04 [0.85, 1.26] 2006 A
Michel Komajda 2006 301/475 1243/2521 14.89 1.29 [1.19, 1.39] 2006 A
Nana Valeur 2006 65/314 85/881 7.37 2.15 [1.60, 2.89] 2006 A
Total (95% CI) 4936 17425 100.00 1.35 [1.21, 1.51]
Total events: 2850 (anaemia), 7122 (non-anaemia)
Test for heterogeneity: Chi?= 67.66, df = 8 (P < 0.00001), I?= 88.2%
Test for overall effect: Z = 5.45 (P < 0.00001)
0.1 0.2 0.5 1 2 5 10
Favours anaemia
Favours non-anaemia

Figure 4


Review: LVEF
Comparison: 01 annemia-non
Outcome: 01 LVEF
Study or sub-category
anaemia N
anaemia Mean (SD)
non-anaemia N
non-anaemia Mean (SD)
WMD (fixed) 95% CI
Weight %
WMD (fixed) 95% CI
Year
Quality
J.Szachniewicz2003 18 40.00(8.00) 158 42.00(12.00) 0.62 -2.00 [-6.14, 2.14] 2003 A
Rakesh Sharma2004 513 31.00(7.00) 2531 31.00(7.00) 24.02 0.00 [-0.66, 0.66] 2004 A
Inder S.Anand2005 1145 26.00(7.00) 3857 27.00(7.00) 49.72 -1.00 [-1.46, -0.54] 2005 A
Kachy Hebert2006 113 24.00(9.00) 297 24.00(9.00) 2.79 0.00 [-1.95, 1.95] 2006 A
Michel Komajda2006 475 25.90(6.90) 2521 26.00(7.20) 22.85 -0.10 [-0.78, 0.58] 2006 A
Total (95% CI) 2264 9364 100.00 -0.53 [-0.86, -0.21]
Test for heterogeneity: Chi?= 8.72, df = 4 (P = 0.07), I?= 54.1%
Test for overall effect: Z = 3.21 (P = 0.001)
-10 -5 0 5 10
Favours anaemia
Favours non-anaemia