Prognostic significance of anaemia in patients with heart failure with preserved and reduced ejection fraction: results from the MAGGIC individual patient data meta-analysis

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Summary

Background: Anaemia is common among patients with heart failure (HF) and is an important prognostic marker.

Aim: We sought to determine the prognostic importance of anaemia in a large multinational pooled dataset of prospectively enrolled HF patients, with the specific aim to determine the prognostic role of anaemia in HF with preserved and reduced ejection fraction (HF-PEF and HF-REF, respectively).

Design: Individual person data meta-analysis.

Methods: Patients with haemoglobin (Hb) data from the MAGGIC dataset were used. Anaemia was defined as Hb < 120 g/l in women and < 130 g/l in men. HF-PEF was defined as EF ≥ 50%; HF-REF was EF < 50%. Cox proportional hazard modelling, with adjustment for clinically relevant variables, was undertaken to investigate factors associated with 3-year all-cause mortality.
**Introduction**

Anaemia is common and important in heart failure (HF). Anaemia in HF is of multifactorial aetiology and is associated with worse symptoms and higher mortality.\(^1\) Several uncertainties remain about the clinical significance of anaemia. For example, the Norwegian HF registry found that severe anaemia at baseline did not predict all-cause mortality in community-dwelling patients with advanced HF, although anaemia that is sustained after optimization of HF treatment may be an independent adverse prognostic factor.\(^7\) The relationship between anaemia and quality of life is also uncertain.\(^8\) A recent literature-based meta-analysis has shown that anaemia predicts all-cause mortality in patients with HF with both preserved and reduced ejection fraction (HF-PEF and HF-REF).\(^9\) However, this meta-analysis was based on heterogeneous inclusion criteria, with inconsistent definitions of anaemia, and as the analysis did not include patient-level data, multivariable analyses were not performed. We aimed to study the characteristics and prognostic significance of anaemia in patients with HF-PEF and with HF-REF using pooled patient-level data.

**Methods**

The methods for study selection and data extraction for the MAGGIC individual patient data meta-analysis have been described previously.\(^9\) In brief, we pooled individual patient data from 31 studies that prospectively collected all-cause mortality in patients with HF with both preserved and reduced ejection fraction (HF-PEF and HF-REF).\(^4\) However, this meta-analysis was based on heterogeneous inclusion criteria, with inconsistent definitions of anaemia, and as the analysis did not include patient-level data, multivariable analyses were not performed. We aimed to study the characteristics and prognostic significance of anaemia in patients with HF-PEF and with HF-REF using pooled patient-level data.

Cox proportional hazard models were used to investigate the association between anaemia and 3-year all-cause mortality. Models were adjusted for age, gender, ischaemic aetiology, AF, diabetes, hypertension and estimated glomerular filtration rate (eGFR) and were stratified by study. An interaction between gender and anaemia was assessed. Imputation of missing data was not performed. Cox models were further used to model the relationship between Hb level (per 10 g/l) and 3-year mortality per EF group. As Hb is a continuous measure, containing more detail than the binary indicator of anaemia, there is potential for an interaction with Hb that may not be observed for anaemia. Consequently, an interaction between Hb and gender was assessed and a statistically significant interaction between Hb and gender within the HF-PEF group (P = 0.01) led to these models being stratified by gender. These models were adjusted for age only and used a referent concentration of 120–130 g/l for women and 130–140 g/l for men. SAS v9.2 was used for all analyses.

**Results**

Hb data were available for 13 295 patients from 19 studies. For the whole group, mean age was 68 years (SD 12 years), 36% were women, 46% had a history of hypertension, 56% ischaemic aetiology of HF, 23% AF, the majority (73%) had New York Heart Association (NYHA) Class II or III symptoms of HF and mean Hb was 126 g/l (SD 25 g/l). Nine thousand eight hundred and eighty-seven patients had HF-PEF of whom 4238 (43%) had anaemia, and 3408 patients had HF-PEF of whom 1419 (42%) had anaemia. Irrespective of EF group (HF-REF or HF-PEF), patients with anaemia were older, more likely to have had a myocardial infarction, to have diabetes, ischaemic aetiology of HF, NYHA class IV symptoms, lower eGFR and were more frequently prescribed a diuretic and less likely prescribed a beta-blocker, than those without anaemia (P-values < 0.05, Table 1).

Anaemia was associated with higher all-cause mortality among patients with HF-REF and patients with HF-PEF (Table 1, Figure 1). Among patients with HF-REF, 1325 (31.3%) patients with anaemia died compared with 889 (15.7%) patients without anaemia; for patients with HF-PEF, 283 (19.9%) patients with anaemia died compared with 229 (11.5%) patients without anaemia. In multivariable analysis, the presence of anaemia was independently associated with higher risk of death from any cause (adjusted hazard ratio [aHR] 1.38, 95% confidence interval [CI] 1.25–1.51), as were HF-REF, age, male gender, AF, ischaemic aetiology, diabetes and worsening renal function (Table 2). There was no interaction between anaemia and gender for either EF group (HF-REF P = 0.13, HF-PEF P = 0.08); therefore, these models were not stratified by gender.

The risk of death increased as Hb decreased through the anaemic range for all patients. However the risk of death among...
women with HF-PEF also increased as Hb increased through the non-anaemic range (Figure 2). Only 139 women with HF-PEF had Hb ≥ 150 g/l, and although the increase in mortality is close to reaching statistical significance (aHR = 1.67, 95% CI 0.99–2.79), this is based on only 23 deaths in that subgroup. Patient characteristics over the range of Hb values were consistent with the trends seen when classified by anaemia status (Supplementary Tables S1–S4).

**Discussion**

Our analysis has revealed important findings in HF-REF and HF-PEF patients. The main findings of our study are first, HF patients with anaemia were more likely to be older, have ischaemic aetiology and have more severe signs and symptoms. Second, anaemic patients were less likely to be treated with a beta-blocker and more likely to be receiving a diuretic, regardless of whether they had HF-REF or HF-PEF. Third, anaemia was an independent predictor of adverse outcome for patients with HF-REF and those with HF-PEF.

As has been established in a number of prior studies, anaemia is of prognostic importance in patients with HF, particularly among those with HF-REF. The current analyses clearly now confirm the prognostic importance of anaemia among patients with HF-PEF. The worst prognosis was observed among those patients with anaemia and HF-REF, followed by patients with HF-PEF with anaemia, who had similar prognosis to those with HF-REF without anaemia. We have previously reported
from this meta-analysis that patients with HF-PEF have lower mortality than patients with HF-REF. These findings suggest that one simple marker, the Hb, is able to further stratify patients with HF-PEF (and HF-REF) into higher and lower risk subgroups. The influence of anaemia on mortality was independent of other common predictors of outcome regardless of the EF group.

The independent relationship between anaemia and quality of life is less clear. For example, in the HF-ACTION randomized controlled trial of exercise training in HF patients with REF, Hb concentration at baseline did not correlate with health-related quality of life (HRQoL) and was not associated with the beneficial effects of exercise on HRQoL. On the other hand, previous studies involving patients with HF with iron deficiency (with or without anaemia) have shown that treatment with iron supplements results in an improvement in quality of life and functional capacity. However, the recent Reduction of Events by Darbepoetin Alfa in Heart Failure (RED-HF) trial, which assessed the use of this erythropoietin analogue in patients with HF-REF and anaemia, showed that correction of anaemia did not improve survival. Although large-scale clinical outcome studies of the effects of erythropoietin analogues in patients with HF-PEF and anaemia are not available, a recent phase II study reported that treatment with epoetin alfa did not improve left ventricular volumes or mass, submaximal exercise capacity or quality of life. These results suggest that anaemia may be a marker of poor prognosis rather than a therapeutic target for patients with HF. Reflecting these results, the recent American College of Physicians guidelines on treatment of anaemia in patients with heart disease now recommend against the use of erythropoiesis-stimulating agents in patients with anaemia and heart failure. Small-scale studies of the effects of intravenous iron infusions in patients with HF and anaemia with low ferritin levels suggest beneficial effects on exercise tolerance and quality of life. However, longer-term effects on clinical events remain uncertain. Such treatment is not approved for use in USA at present, although it is discussed as a potential option for appropriate patients in the 2012 European Society of Cardiology HF guidelines.

The causes of anaemia in chronic HF may be multifactorial and include haemodilution, iron loss or impaired utilization, chronic renal failure, bone marrow suppression, inflammation and chronic disease. Across a range of clinical trials and cohort studies, including the RED-HF trial and The Study of Anemia in Heart Failure Trial (STAMINA-HeFT), community studies and those in the current analysis, HF patients with anaemia were older and had worse functional capacity than those who were not anaemic. Advanced HF is a pro-inflammatory condition which, together with the common comorbidities such as renal dysfunction, will contribute to increasing frailty. Thus anaemia is a common co-morbidity which is prognostically important.

The results from our analysis suggest the possibility of higher mortality among women with non-anaemic, higher Hb
levels. The prognostic significance of higher Hb levels among women with HF-PEF may be influenced by other gender-related differences in cardiovascular disease, such as proximal arterial stiffness. Women may be more susceptible to the deleterious effects of greater pulsatile and early arterial load on diastolic function and ventricular-arterial interaction, and higher Hb levels (and blood viscosity) may enhance vascular stiffness in women more than in men. However women with HF-PEF and Hb > 150 g/l were not older than other women with HF-PEF, and did not have a significantly higher prevalence of hypertension, so the reasons behind the suggested increase in mortality in this group are unclear. While a ‘U-shaped’ relationship between Hb and mortality in patients with HF has been reported in this group are unclear. While a ‘U-shaped’ relationship between Hb and mortality in patients with HF has been reported in previous studies, this finding needs further evaluation. Finally, beta-blocker use in patients with HF-REF was lower in this population than in most clinical trials, which we think reflects a lower adoption of beta-blocker therapy in populations of patients out with clinical trials.

Our study has some limitations. The definition of anaemia is based on a single determination of the blood count, and other potentially relevant information, such as treatment for anaemia, intercurrent bleeding, fluid overload, haematocrit, iron or variations in Hb levels over time were not available, or not available with sufficient data. A minority of the cohort were women with HF-PEF and Hb > 150 g/l thus limiting the conclusions in this sub-group. With regards to drug therapy, we lack information on contraindications or intolerance to evidence-based drugs. Finally, we were unable to adjust the analyses for the extent and nature of unmeasured comorbidity other than the clinical variables incorporated in the multivariable model. Variables were included on the basis of clinical relevance, and each were missing <10% of data in the MAGGIC meta-analysis. A greater number of variables were included in the MAGGIC HF risk score as multiple imputation was used to help account for missing data. Although different approaches were used, the associations between predictors and mortality in the current model are consistent with those found in the HF risk score.

In conclusion, this large individual patient data meta-analysis has demonstrated that the increased risk of death among patients with anaemia is observed among those with HF-PEF and HF-REF, and the risk is independent of other common prognostic variables. Although correcting anaemia for all patients does not appear to improve outcomes, anaemia is a marker of increased risk which should trigger greater vigilance in follow-up and management.

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Supplementary material
Supplementary material is available at QJMED online.

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