Anaemia predicts cardiovascular events in patients with stable coronary artery disease

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Background. Anaemia is an independent risk factor for cardiovascular (CV) events in patients with heart failure and patients with chronic kidney disease. The effect of anaemia on CV outcomes in patients with coronary artery disease (CAD) remains unclear. Therefore, we investigated the prognostic value of anaemia in this group of patients.

Methods. Patients with stable angina pectoris, referred for a first diagnostic coronary angiography, were eligible for this study. Only subjects with significant coronary artery disease (>50% luminal narrowing) were used for analysis (n=143). Cardiovascular events were defined as cardiovascular death, acute myocardial infarction and hospitalisation for unstable angina pectoris. Anaemia was defined according to WHO criteria as haemoglobin level ≤8 mmol/l in men and ≤7.5 mmol/l in women.

Results. The mean age of the population was 61.5±9.4 years. During follow-up (44±19 months), 19 CV events occurred. The diagnosis of anaemia predicted CV events, even when adjusted for other risk factors (hazard ratio 5.73, 95% confidence interval 1.49-22.13, p=0.01). In univariate analysis, serum erythropoietin levels predicted CV outcomes (p<0.05); however, this association was lost when adjusted for haemoglobin concentration.

Conclusion. Anaemia is associated with worse outcome in patients with established CAD and could be used as a prognostic indicator in this group of patients. (*Neth Heart J* 2005;13:254-8.)

Key words: anaemia, coronary artery disease, prognostic factors

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Anaemia is an established risk factor for cardiovascular (CV) disease outcomes in patients with chronic kidney disease and patients with heart failure.[1] A gradual decrease in haemoglobin (Hb) levels has been associated with a higher risk for CV events in dialysis patients.[2] Several studies have demonstrated the inverse relationship between Hb levels and mortality in patients with chronic heart failure.[3,4] In these patients even mild degrees of anaemia lead to poorer survival rates. Chronic anaemia has also been shown to be associated with a significantly higher rate of CV events in a low-risk population not preselected for having CV or kidney disease.[5]

Studies of anaemia treatment in patients with chronic heart failure and chronic kidney disease have shown significant improvement in cardiac function. In patients with end-stage renal disease, correction of anaemia to values above 6.2 mmol/l was associated with regression of left ventricular (LV) hypertrophy[6] and improved ischaemic tolerance.[7] Increasing the levels of Hb in dialysis patients improved the survival rate.[8] Anaemia treatment with erythropoietin (EPO) and iron in patients with chronic heart failure led to improved cardiac functional parameters and number of hospitalisations.[9]

However, the long-term prognostic value of anaemia in patients with coronary artery disease (CAD) remains ambiguous and the results of recent studies are largely inconclusive. Al Falluji et al.[10] conducted a retrospective cohort study to evaluate the effect of anaemia on one-year mortality in patients after acute MI.

Although anaemia was associated with higher unadjusted mortality, the effect was lost when corrected for other variables. Recently, Reinecke et al.[11] showed that anaemia is associated with reduced survival in patients with CAD after elective percutaneous coronary intervention. Therapy with blood transfusions in elderly patients with myocardial infarction and a haematocrit below 30% was associated with reduced 30-day mortality.[12]

In general, in response to hypoxia, kidneys produce erythropoietin (EPO), which in turn stimulates red blood cell production. Although the pathogenesis of anaemia in CV diseases is probably multifactorial, reduced response to EPO could play a significant role.[13] Consequently, EPO has been shown to be elevated in heart failure patients.[14] Elevated plasma EPO levels are also associated with impaired prognosis in patients with chronic heart failure.[15] There is little known about prognostic value of EPO serum levels in a setting of CAD.

In our study, we investigated the prognostic value of anaemia and serum EPO levels in patients with established CAD.

Methods

Study population and data collection

Patients between 18 and 80 years with angina pectoris referred for their first diagnostic coronary angiography from November 1996 to November 2000 and enrolled for the Intervention Cardiology Risk Stratification Study[16] were included in the study. Excluded were patients with unstable angina, recent (<3 months) myocardial infarction, valvular heart disease requiring surgical intervention, clinical evidence of heart failure, a history of previous coronary intervention (PTCA or CABG) or any serious disease that may interfere with the follow-up.

Baseline screening included history of traditional cardiovascular risk factors, physical examination, 12-lead electrocardiogram (ECG) and fasting whole blood collection for haematocrit, serum EPO, serum lipid profile, serum creatinine and blood glucose. A standard diagnostic catheterisation procedure was performed.

Cardiovascular risk factors

The following traditional cardiovascular risk factors were predefined. The smoking status was divided into two categories: no cigarette smoking for >3 months or currently a cigarette smoker. Hypercholesterolaemia was defined as a fasting serum cholesterol value >6.5 mmol/l or a history of hypercholesterolaemia for >3 months that led to the initiation of lipid-lowering therapy by the primary physician. Hypertension was defined as a systolic blood pressure >160 mmHg or a diastolic blood pressure >90 mmHg (measured twice), or a history of high blood pressure that led to the initiation of antihypertensive therapy by the primary physician. Diabetes was defined as high blood glucose levels requiring glucose-lowering therapy. A family history of CAD was defined as evidence of the disease in a parent or sibling before 60 years of age at the time of diagnosis. Patients had a history of a myocardial infarction when pathological Q waves >0.04 s in duration were present in two adjacent leads on the 12-lead ECG or they had a history of hospitalisation with ST-segment elevation >0.1 mV measured 80 ms after the J point in two adjacent leads on the 12-lead ECG, eventually supported by biological markers of myocardial necrosis. A stenosis was defined as >50% luminal narrowing in a coronary artery. Anaemia was defined according to WHO criteria as a haemoglobin level ≤8 mmol/l (13 g/dl) in men and ≤7.5 mmol/l (12 g/dl) in women.[17]

Measurement of haemoglobin and EPO levels

Venous blood samples were taken in the morning before the PTCA procedure, to avoid circadian influences. Plasma was stored at –80 °C and EPO levels measured using IMMULITE EPO assay (DPC, Los Angeles, CA), which has been described before.[18]

Follow-up

The primary endpoint of the study was occurrence of a cardiovascular event. The events, including cardiovascular death, acute myocardial infarction and hospitalisation for unstable angina pectoris, were recorded for a mean period of 44 months. An independent event classification committee blinded to the grouping of patients assessed all documented events.

Statistics

Data are given as mean ± SD and as frequencies for categorical variables. We included the following risk factors in our analysis: gender, age, diabetes, smoking, hypertension, calculated glomerular filtration rate (GFR_C) and hypercholesterolaemia. Differences in basic clinical characteristics between the groups were tested by t-test for continuous variables and by χ^2 test for categorical variables.

Event rates were compared by Kaplan-Meier curves calculated for anaemic and nonanaemic patients. Stepwise Cox regression analysis was used to identify risk factors which are independently associated with cardiovascular events.

All reported probability values were two-tailed, and a p value <0.05 was considered statistically significant. For all statistical analysis SPSS version 11.0 was used.

Ethical considerations

Written informed consent was obtained from all patients before the study and the Institutional Review Board of the University Medical Centre of Groningen approved the study protocol. The study was consistent with the principles outlined in the Declaration of Helsinki.

Table 1. Baseline characteristics.

	No anaemia (n=129)	Anaemia (n=14)	Total	P
Sex (% male)	71.3	71.4	71.3	0.99
Age at inclusion CAG (years)	61.2±9.2	64.4±11.2	61.5±9.4	0.99
Smoking (%)	24.8	28.6	25.2	0.83
History of MI (%)	31.0	50.0	32.9	0.15
Family history of CAD (%)	45.7	35.7	44.8	0.47
Hypertension (%)	65.9	50.0	64.3	0.24
Hypercholesterolaemia (%)	73.6	50.0	71.3	0.06
Diabetes (%)	15.5	28.6	16.8	0.21
Epo levels (mU/ml)	6.57±4.35	21.20±26.68	7.94±9.86	0.07
Calculated GFR (ml/min)	79.61±19.10	78.59±18.47	79.51±18.98	0.85
Haemoglobin (mmol/l)	8.92±0.63	6.84±1.06	8.71±0.94	<0.001
Medication (%)				
- Aspirin	72.1	71.4	72.0	0.95
- β-blocker	72.9	64.3	72.0	0.5
- Calcium blocker	51.2	57.1	51.7	0.67
- ACE inhibitor	26.4	28.6	26.6	0.86
- Nitrate	32.6	42.9	33.6	0.44
- Lipid-lowering agent	45.0	21.4	42.7	0.09

Results

Patient population

The study population (>50% luminal narrowing assessed by coronary angiography) consisted of 143 patients, aged 61.5±9.4 years, of whom 71% were male. Other baseline characteristics are given in table 1. Mean follow-up period was 44±19 months. During this period, 19 cardiovascular events occurred: two cardiovascular deaths, five acute myocardial infarctions, and 12 hospitalisations for unstable angina.

Association of anaemia with CV outcomes

Anaemia was present in 9.8% (n=14) of the patients with significant CAD. In the group of patients with an endpoint, 21.1% had anaemia at baseline in comparison with 8.1% of the patients without a cardiovascular event. Patients with anaemia had a significantly worse prognosis (figure 1). In Cox regression analysis, anaemia remained an independent predictor of cardiovascular events, even after adjusting for gender, age, diabetes, smoking, hypertension, GFR_C and hypercholesterolaemia (hazard ratio 5.73, 95% confidence interval 1.49-22.13, p=0.01, table 2). In univariate analysis, serum erythropoietin levels predicted CV outcomes (p<0.05); however, this association was lost when adjusted for haemoglobin levels.

Discussion

In our study, anaemia is associated with a worse outcome in patients with significant CAD verified by coronary angiography. We found a marked increase in the rate of cardiovascular events in patients with preprocedural levels of haemoglobin below 8 mmol/l in men and 7.5 mmol/l in women. This significant association between anaemia and CV outcomes was confirmed by a Cox regression model including potential covariates, such as age, gender, classical CV risk factors and GFR_C. In particular, reduced renal

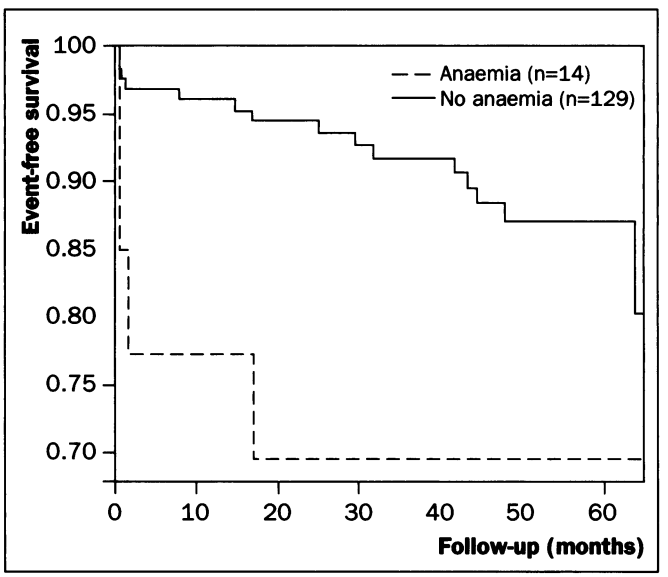

Figure 1. Kaplan-Meier survival curve for coronary artery disease patients with and without anaemia.

Table 2. Univariate and multivariate predictors of CV outcomes.

Variable	Univariate			Multivariate		
	HR	CI	P	HR	CI	P
Age (years)	1.019	0.974-1.067	0.41			
Sex (male)	1.831	0.585-5.737	0.30			
Anaemia	4.781	1.369-16.698	0.01	5.737	1.488-22.126	0.01
GFR_C (ml/min)	0.996	0.977-1.016	0.68			
EPO serum (mU/ml)	1.019	1.002-1.036	0.02			
Hypertension	2.151	0.770-6.004	0.14			
Hypercholesterolaemia	3.318	1.181-9.325	0.02	3.735	1.264-11.039	0.02
Diabetes	0.514	0.174-1.516	0.23			

function may have influenced the haemoglobin levels (anaemia diagnosis), as well as CV outcomes. However, the association of anaemia and CV events remained significant, also after adjustment for GFR_C.

Importantly, the mean haemoglobin values in the anaemic group were 6.8±1.1 mmol/l. Levels of haemoglobin above 6.2 mmol/l (10 g/dl) have not previously been related to higher CV risk even in patients with pre-existing CV disease.[5]

There are several potential mechanisms by which anaemia may worsen the prognosis of patients with CAD. Although the resting human heart can withstand acute severe isovolaemic anaemia as low as 3.0 mmol/l, CV disease significantly impairs the heart's ability to tolerate low levels of haemoglobin.[19]

Anaemia causes hypoxia-induced vasodilatation leading to increased cardiac output and sympathetic activity. In the long-term, these alterations lead to gradual development of cardiac enlargement and LV hypertrophy.[20] This can cause higher oxygen consumption and aggravate ischaemia. Moreover, patients with CAD already have a limited coronary reserve because of a high extraction rate of oxygen in the cardiac circulation.[21] In the clinical situation, anaemia exacerbates myocardial ischaemia and intensifies angina.

Conversely, elevated haemoglobin levels have also been associated with a worse CV prognosis. High blood viscosity[22] and increased thrombus formation[23] have been implicated as causative factors. Some studies have also suggested a protective role for iron depletion and thus iron deficiency anaemia against CAD.[24] Lower levels of redox-active iron may decrease the oxidative stress and thus attenuate endothelial dysfunction.[25] Studies in the general population[26] and recently also in patients with CAD[11] suggested a U-shaped relationship between levels of haemoglobin and CV diseases. The association of high haematocrit with CV disease may, however, reflect presence of chronic obstructive lung disease causing both polycythaemia and poorer CV survival.[27]

There are some limitations to our analysis. First, anaemia may be associated with other risk factors for CV disease that were not ascertained in this study, such as decreased nutritional status or increased inflammatory status.[5] Second, our analysis is based on only one haemoglobin measurement before the coronary angiography, without taking into account the duration or possible type of anaemia. Consequently, no conclusions can be drawn on possible mechanisms relating anaemia to CV outcomes. Also the relatively small number of women in our population prevents drawing conclusions as to the predictive value of anaemia in this subpopulation.

Nevertheless, our findings suggest that lower haemoglobin levels are associated with impaired prognosis in patients with established CAD. This is the first report to show the prognostic value of anaemia in this group of patients. In the future, strategies for anaemia management in patients with CAD should be evaluated. ■

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