Anemia and erythropoietin in cardiovascular disease

Kleijn, Lennaert

4

Chapter

Impact of postoperative anemia on cardiovascular outcome after Coronary artery bypass graft surgery; insights from the IMAGINE trial

B. Daan Westenbrink
Lennaert Kleijn
Rudolf A. de Boer
Wayne J. Warnica
Richard Baillot
R. Mark Iwanochko
Jean L. Rouleau
Wiek H. van Gilst

Abstract

Objective

To investigate the association between sustained postoperative anaemia and outcome after coronary artery bypass graft (CABG) surgery.

Design

Retrospective analysis of the IMAGINE trial, which tested the effect of the ACE inhibitor quinapril on cardiovascular events after CABG.

Setting

Thoracic surgery clinic/outpatient department. Patients 2553 stable patients with left ventricular ejection fraction >40% 2-7 days after scheduled CABG.

Interventions

Randomisation to quinapril or placebo. Main outcome measures Cox regression analysis for the association between postoperative anaemia and cardiovascular events and the effect of quinapril on the incidence of anaemia.

Results

Postoperative anaemia was sustained for >50 days in 44% of patients. Sustained postoperative anaemia was associated with an increased incidence of cardiovascular events during the first 3 months (adjusted HR (adjHR) 1.77, 95% CI 1.10 to 2.85, p=0.012) and during the maximum follow-up of 43 months (adjHR 1.37, 95% CI 1.14 to 1.65, p=0.008). When haemoglobin (Hb) was considered as a continuous variable, every 1 mg/dl decrease in Hb was associated with a 13% increase in cardiovascular events (adjHR 0.87, 95% CI 0.81 to 0.95, p=0.003) and a 22% increase in all-cause mortality (adjHR 0.78, 95% CI 0.60 to 0.99, P=0.034). Quinapril was associated with a slower postoperative recovery of Hb levels and a higher incidence of cardiovascular events in patients with anaemia (adjHR 1.60, 95% CI 1.1 to 2.4, p=0.024).

Conclusions

Postoperative anaemia is common, frequently persists for months after CABG surgery and is associated with an impaired outcome. In patients with anaemia, ACE inhibitors slowed recovery from postoperative anaemia and increased the incidence of cardiovascular events after CABG.

Introduction

Anaemia is a well-established predictor of impaired cardiovascular outcome in patients with coronary artery disease,[1] acute coronary syndromes,[2] chronic heart failure[3] as well as in the general population.[4] In addition, the presence of anaemia before cardiac and non-cardiac surgery and during extracorporeal bypass predicts postoperative cardiovascular events.[5-7] The consistent association between anaemia and cardiovascular events suggests that the severity and duration of postoperative anaemia should be limited in patients undergoing coronary artery bypass graft (CABG) surgery. There are, however, several reasons to suspect a high incidence of anaemia after CABG that may often persist for months after discharge. First, blood loss during CABG surgery is common owing to the nature and extent of the surgery and also because of required heparinisation and additional acquired defects in haemostasis during on-pump procedures. Second, during on-pump procedures anaemia is often induced in patients by mild euvolaemic haemodilution. Third, blood transfusions are deliberately avoided because they have been linked to impaired survival after CABG.[8-10] If a substantial proportion of patients remain anaemic for an extended period after CABG, this would suggest that patients are subjected to an established cardiovascular risk factor by an intervention that is intended to reduce that risk. Although the impact of preoperative anaemia and perioperative transfusions have been addressed extensively, the incidence of sustained postoperative anaemia and its impact on the outcome after CABG is unclear. We hypothesised that sustained postoperative anaemia after CABG surgery is common and associated with an increased incidence of cardiovascular events. In order to test our hypothesis we used the contemporary IMAGINE (Ischaemia Management with Acupril post bypass Graft via Inhibition of thecoNverting Enzyme) trial database of 2553 patients with preserved left ventricular function undergoing CABG.[11,12] Because ACE inhibitors have the capacity to reduce erythropoiesis activity and might increase the incidence and duration of sustained postoperative anaemia,[13,14] we also evaluated the effects of quinapril on postoperative anaemia.

Methods

Design

The design of the IMAGINE trial has been described in detail previously,[11] as well as the results of the main study.[12] In brief, the IMAGINE study was a double-blind placebo-controlled parallel-group randomised multicentre international trial conducted in

patients who underwent CABG surgery between November 1999 and September 2004. The main goal of the study was to test whether early initiation of ACE inhibitor therapy (initiated within the hospital phase) after CABG would reduce the rate of cardiovascular events in patients at relative low risk. The research protocol was approved by the ethics committees of all participating institutions and all patients provided written informed consent.

Patients

Patients were screened for eligibility within 4 weeks of surgery or following surgery and randomised within 7 days after CABG, except for patients included in France (N=235, 9.1%) where randomisation occurred within 10 days after CABG. Treatment consisted of the ACE inhibitor quinapril, with forced uptitration to 40 mg daily within 4 months if tolerated, or matching placebo. The final sample size of the IMAGINE study was 2553 patients.

Anaemia

Anaemia was defined according to the WHO criteria (haemoglobin (Hb) <13.0 g/dl in men and Hb <12.0 g/dl in women). We explored the temporal characteristics of anaemia in the entire IMAGINE population. For outcome analysis, patients were classified into two groups: those with sustained anaemia at 50 days after randomisation (anaemic group) and those in whom Hb levels had recovered to normal values during that period (non-anaemic group). Because the definition of anaemia represents a relatively arbitrary Hb cut-off, we also evaluated the effects of Hb as a continuous variable at 50 days after randomisation. Because our analysis was focused on sustained postoperative anaemia, we excluded patients with normal Hb levels at randomisation and patients without documented Hb levels at 50 days (leaving 2400 subjects).

Endpoints

We used the same primary and secondary endpoints as in the IMAGINE trial, including an additional composite endpoint of major adverse cardiac events (MACE), and we also considered all individual endpoints separately. The primary endpoint was a composite of cardiovascular death or resuscitated cardiac arrest, non-fatal myocardial infarction, coronary revascularisation, unstable angina requiring hospitalisation, documented angina not requiring hospitalisation, stroke and congestive heart failure (CHF) requiring hospitalisation. The pre-specified secondary endpoint was a composite of the primary endpoint with the addition of transient ischaemic attack and any other cardiovascular

event requiring hospitalisation. MACE was defined as cardiovascular death or resuscitated cardiac arrest, acute coronary syndromes, coronary revascularisation and CHF requiring hospitalisation. Because we expected that postoperative anaemia would predominantly affect the early postoperative phase, we also separately evaluated the effect of sustained postoperative anaemia on the primary IMAGINE endpoint during and after the first 3 months of the study.

Statistical analysis

Data are shown as mean ± SD when normally distributed, as median (IQR) in cases of skewed distribution and as frequencies and percentages for categorical variables. Differences in variables between groups were compared with the Student t test, the ManneWhitney U test, χ^2 test or Fisher exact test, where appropriate. Time to the first event was calculated from 50 days onward, except for the analysis of the first 3 months where time to first event was calculated from randomisation. Temporal changes in Hb levels and the incidence of anaemia were compared using ANCOVA for repeated measurements. Differences between the anaemic and non-anaemic groups, use of Hb as a continuous variable and the effect of quinapril treatment were estimated as a HR with associated adjusted two-sided 95% CI from a Cox proportional hazards regression model that included the effects of age, gender, treatment assignment, country, transfusions, number of days after CABG surgery, cardiac medications, baseline Hb levels, left ventricular ejection fraction (LVEF), smoking status, systolic and diastolic blood pressure and creatinine values at baseline or at 50 days after randomisation, history of hypertension/diabetes/percutaneous coronary interventions/myocardial infarction/previous CABG surgery/peripheral vascular disease and stroke, vessel disease, number of distal anastomoses, completeness of revascularization (defined as complete when all vessels >1 mm with a stenosis >70% were bypassed) and beating heart (off pump) surgery.

Cumulative event rates were calculated by the Kaplan-Meier method and displayed graphically. Differences in the incidence of the component endpoints within or after the first 3 months were assessed by univariate logistic regression analysis. All statistical analyses were performed using SPSS Version 17.0.

Results
Incidence of anaemia

Patients were randomised an average of 462 days after CABG surgery. During randomisation, 2400 patients (94%) were anaemic according to the WHO criteria for anaemia

and 444 (19%) had Hb values <9 mg/dl. However, only 11 (3%) of the patients with Hb levels <9 mg/dl received a blood transfusion during the first 10 days after randomisation. Hb levels increased steadily during the first year (figure 1), at which point 163 (8%) of the patients were still anaemic (figure 1). Hb levels and the proportion of anaemic subjects remained constant after 1 year (figure 1). Throughout the study period anaemia was reported as an adverse event in 140 patients (6%). In 30 patients (1.2%), diagnostic or therapeutic measures were taken in response to anaemia. Blood transfusions were given to 21 patients (0.8%) during the entire study period. Of the 13 patients who received a blood transfusion within the first 50 days after randomisation, nine had recovered from anaemia at 50 days.

Demographic characteristics of the study population

The characteristics of the study group are given in table 1. At the visit 50 days after randomisation, 967 (44%) of the 2180 patients with anaemia at baseline and available Hb levels at 50 days were still anaemic. Patients with sustained postoperative anaemia were significantly older, had a higher incidence of previous CABG surgery and were more often current smokers. Anaemic patients had a higher incidence of anaemia at randomisation, lower red blood cell, white blood cell and platelet counts and significantly higher creatinine values. Preoperative LVEF was comparable between anaemic and non-anaemic patients with CHF, but systolic and diastolic blood pressures were
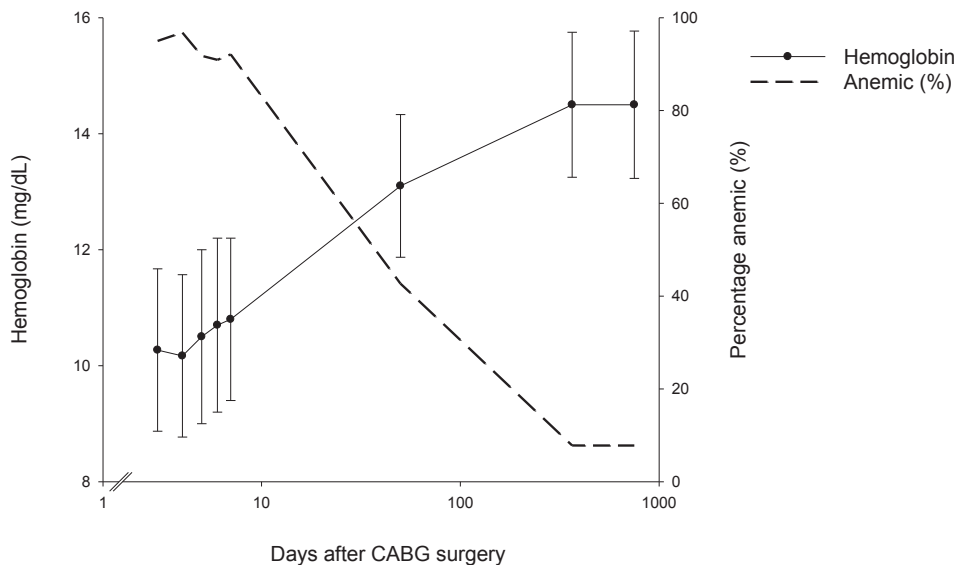

Figure 1. Temporal changes of hemoglobin levels and the percentage of patients with anemia after coronary artery bypass graft surgery.

Table 1. Demographics of the study population at 50 days after randomization according to the presence of sustained postoperative anemia

Variable	Non-anemic (n=1327)	Anemic (n=988)	P
Age	59 ± 10	63 ± 9	>0.0001
Female, n (% of patients)	164 (12)	117 (12)	0.748
White, n (% of patients)	1278 (96)	949 (96)	0.741
Acupril group, n (% of patients)	637 (48)	505 (51)	0.110
Anemia at baseline, n (% of patients)	1213 (92)	967 (98)	>0.0001
Days after CABG surgery, Mean ± SD	24 (2)	24 (2)	0.661
Medical History, n (% of patients)			
Previous MI	529 (40)	382 (39)	0.576
Previous Stroke	17 (1)	33 (3)	0.001
Previous CABG	22 (2)	35(4)	0.004
Previous PCI	233 (18)	177 (18)	0.869
Diabetes	118 (9)	105 (11)	0.176
History of hypertension	598 (45)	476 (48)	0.152
Current smoker	288 (22)	176 (18)	0.021
Laboratory values, Mean ± SD			
Hemoglobin (mg/dL)	14 ± 0.8	12 ± 0.8	-
RBC (x10^{12}/L)	4.7 ± 035	4.1 ± 0.36	>0.0001
White blood count (x10^9/L)	7.2 ± 2	7.0 ± 2	0.064
Platelets (x10^9/ L)	292 ± 83	270 ± 68	>0.0001
Total cholesterol (mmol/L)	4.9 ± 1	4.8 ± 1	0.372
LDL cholesterol (mmol/L)	2.9 ± 1	23 ± 52	0.263
HDL cholesterol (mmol/L)	1.1 ± 0.3	1.1 ± 0.4	0.811
Creatinine (μmol/L)	88 ± 17	90 ± 19	>0.0001
Hemodynamic measurements, Mean ± SD			
LVEF (%)	60 ± 96	60 ± 96	0.341
Systolic blood pressure (mmHg)	128 ± 18	125 ± 18	>0.0001
Diastolic blood pressure (mmHg)	78 ± 10	74 ± 10	>0.0001
Operative characteristics			
Beating heart surgery, n (% of patients)	264 (20)	171 (17)	0.119
Number of distal anastomosis, Mean±SD	3.2 ± 1.2	3.3 ± 1.1	0.023
Vessel disease, Mean ± SD	2.5 ± 0.7	2.6 ± 0.6	0.003
Complete revascularization, n (% of patients)	723 (55)	523 (53)	0.448
Baseline medications, n (% of patients)	1044 (79)	778 (79)	1.000
Beta blocker	486 (37)	353 (36)	0.622
Calcium channel inhibitor	37 (2.8)	31 (3.1)	0.621
Angiotensin receptor blocker	969 (73)	751 (76)	0.113
Platelet inhibitor	854 (64)	633 (64)	0.895
Statin	125 (94)	84 (85)	0.464
Diuretic			

SD, standard deviation; MI, myocardial infarction; CABG, coronary artery bypass graft surgery; PCI, percutaneous coronary intervention; RBC, red blood cell count; LDL, low density lipoprotein; HDL, High density lipoprotein; LVEF, left ventricular ejection fraction.

significantly lower in the patients with anaemia. Anaemic patients more often had multivessel disease. There was no difference in the number of distal anastomoses or incomplete revascularisations between the groups. Finally, baseline medication was comparable between anaemic and non-anaemic patients.

Events

The median follow-up time was 1082 days (IQR 160e1323). Univariate differences in events according to the presence of sustained postoperative anaemia are shown in table 2. Anaemia resulted in a 77% increase in the primary endpoint within the first 3 months after randomisation (adjusted HR (adjHR) 1.77, 95% CI 1.10 to 2.85, p=0.012, table 2, figure 2). After 3 months the incidence of the different endpoints was comparable between groups (data not shown). Anaemia did not affect the incidence of the primary endpoint after 50 days. However, the incidence of the secondary IMAGINE endpoint and MACE were both increased by 40% in patients with anaemia (table 3, figure 3). When analysed as a continuous variable, lower Hb levels were also associated with an impaired outcome after CABG (table 3). In fact, every decrease in Hb of 1 mg/dl was associated with a 13% increase in the incidence of the secondary endpoint and MACE and a 22% increase in all cause death or resuscitated cardiac arrest (table 3). The primary endpoint was not associated with continuous Hb levels.

Effect of quinapril on postoperative anaemia

Hb levels were identical at baseline in patients randomized to quinapril and placebo (10.43 ± 61.45 vs 10.41 ± 61.45 mg/dl, p=0.783). Similarly, the proportion of anaemic patients was similar at baseline in the quinapril and placebo groups (1198 (94%) vs 1202 (95%), p=0.796). The proportion of patients with diabetes was comparable between the quinapril and placebo groups and background medications were also comparable (data not shown). After randomisation, recovery of Hb levels was slower in patients randomised to quinapril than in those receiving placebo and remained lower in the quinapril group throughout the follow-up period (figure 4A). Similarly, a higher proportion of patients remained anaemic in the quinapril group than in the placebo group throughout the follow-up period (figure 4A).

Effect of quinapril on outcome in anaemic patients

In the subgroup of patients who were anaemic at randomisation, 99 patients (4.1%) experienced a primary endpoint during the first 3 months, 61 (5.1%) in the quinapril group and 38 (3.2%) in the placebo group (HR 1.62, 95% CI 1.1 to 2.4, figure 4B). A sec-

Table 2. Univariate and multivariate hazard ratios for primary and secondary endpoints

	Persistent anemia		Hemoglobin continuous	
Endpoints	Unadjusted HR (95% CI)	Adjusted †‡ HR (95% CI)	Unadjusted HR (95% CI)	Adjusted † HR (95% CI)
Primary composite	1.19 (0.95-1.50)	1.16 (0.91-1.49)	0.89 (0.81- 0.97)*	0.89 (0.81-0.98)[#]
- First 3 months	1.94 (1.04- 3.02)*	1.78 (1.10 - 2.87)*	0.78 (0.66- 0.92)*	0.83 (0.68- 0.99)*
- After 3 months	1.00 (0.77- 1.32)	1.00 (0.75 -1.35)	0.92 (0.82-1.02)	0.92 (0.81-1.04)[#]
Secondary composite	1.30 (1.08 - 1.57)*	1.32 (1.08-1.61)[#]	0.87 (0.81- 0.94)[§]	0.88 (0.81 -0.95)

HR, hazard ratio; CI, confidence intervals; †; Adjusted for, age, gender, treatment assignment, country, days after CABG-surgery, transfusions, left ventricular ejection fraction, systolic and diastolic blood pressure, creatinine, history of hypertension / diabetes / percutaneous coronary interventions / myocardial infarction / previous CABG surgery / peripheral vascular disease / stroke, number of distal anastomosis, completeness of revascularization and beating heart (off pump) surgery, ‡; also adjusted for baseline hemoglobin levels. *, P<0.05; #, P<0.005; §, P<0.0005

ondary event was experienced in 102 (43%) patients, 62 (5.2%) in the quinapril group and 40 (3.3%) in the placebo group (HR 1.57, 95% CI 1.1 to 2.3, p=0.026). Quinapril significantly increased the incidence of the primary and secondary endpoints during the first 3 months. It did not affect the incidence of the primary and secondary endpoints after 3 months, nor did it affect the outcome when the entire study period was considered (data not shown).

Discussion

In this study we show for the first time that sustained postoperative anaemia after CABG surgery is associated with an impaired outcome. Although some degree of mild to moderate anaemia might be expected in the immediate postoperative period, we show that postoperative anaemia is the rule rather than the exception, is frequently severe and often persists for months in a substantial proportion of patients. Moreover, anaemia generally seems to be regarded as a benign condition, as it was sparsely reported as an adverse event and only very few patients were diagnosed or treated in our contemporary population. In this study we show that sustained postoperative anaemia may not be benign, but is rather associated with an impaired outcome even in low-risk patients. In addition, we show that the initiation of an ACE inhibitor in the early postoperative phase after CABG slows postoperative recovery of Hb levels and is associated with an increase in early cardiovascular events. We therefore propose that more aggressive measures to prevent or limit postoperative anaemia and perioperative discontinuation of ACE inhibitors could improve the outcome after CABG.
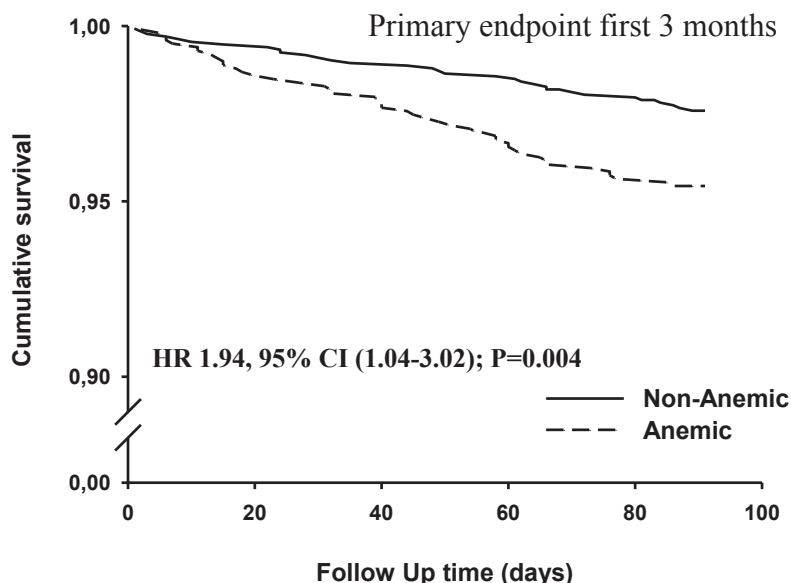
Figure 2. Kaplan-Meier analysis of event free survival of the primary endpoint during the first 3 months according to the presence or absence of sustained postoperative anemia. Primary composite endpoint of the IMAGINE trial comprising time to first occurrence of cardiovascular death or resuscitated cardiac arrest, nonfatal myocardial infarction, coronary revascularization, unstable angina that required hospitalization, documented angina that did not require hospitalization, stroke and congestive heart failure that required hospitalization. HR, Hazard Ratio; 95% CI, 95 percent confidence interval.

Incidence, aetiology and impact of sustained postoperative anaemia

The few studies that have addressed the impact of postoperative anaemia on outcome in patients undergoing CABG surgery were restricted to the immediate postoperative ICU period.[10,15,16] One of the most surprising findings of our study is that it frequently takes months to recover from anaemia after CABG, even in a lowrisk population with few co-morbidities. Similar to other cardiac populations, the aetiology of anaemia after CABG surgery is likely to be multifactorial including perioperative blood loss, haemodilution, bone marrow depression and persisting preoperative causes for anaemia such as hae-matinic deficiencies or renal dysfunction.[17-19] Despite its high incidence, anaemia was documented as an adverse event in only 6%, and diagnosed and treated in only 1% of anaemic patients. These findings strongly suggest that anaemia is not considered as an important comorbidity after CABG. However, we clearly show that sustained anaemia is associated with a marked increase in cardiovascular events. In our opinion, postoperative anaemia should therefore not be regarded as a benign condition and increased awareness of the importance of anaemia after cardiac surgery is thus warranted. Effect

Table 3. Incidence of the primary and secondary endpoints and their components during the first 3 months after randomization

Variable	Non-anemic (n=1327)	Anemic (n=988)	P
Primary composite endpoint	33 (2.5)	47 (4.8)	0.004
Cardiovascular death or resuscitated cardiac arrest	1 (0.1)	1 (0.1)	1.000
Non-fatal myocardial infarction	3 (0.2)	3 (0.3)	0.705
Unstable angina requiring hospitalization	7 (0.5)	11 (1.1)	0.150
Documented angina not requiring hospitalization	20 (1.5)	15 (1.5)	1.000
Coronary revascularisation	0 (0)	1 (0.1)	0.427
Stroke or TIA	0 (0)	2 (0.2)	0.182
CHF requiring hospitalization	2 (0.2)	11 (1.1)	0.003
Any other cardiovascular event	0 (0)	3 (0.3)	0.078
Cardiac ischemia composite endpoint*	31 (2.3)	31 (3.4)	0.244
Cardiac composite endpoint [#]	33 (2.5)	42 (4.5)	0.024

*Composite of cardiovascular death or resuscitated cardiac arrest, nonfatal myocardial infarction, coronary revascularization, unstable angina that required hospitalization, documented angina that did not require hospitalization. # composite of the above with the addition of congestive heart failure requiring hospitalization; TIA, transient ischemic cerebrovascular attack; CHF, congestive heart failure

of ACE inhibitors on postoperative anaemia ACE inhibitors reduce erythropoiesis in patients with heart failure through increased levels of N-acetyl-seryl-aspartyl-lysylproline, a haematopoiesis inhibitor exclusively depredated by ACE.[13] Moreover, a small Italian study showed that enalapril slowed postoperative recovery of Hb levels when given early after CABG.[20] In our analysis, the early initiation of quinapril after CABG slowed recovery of Hb levels and was also associated with early cardiovascular events. Due to the expanding indications for ACE inhibitors in patients with coronary artery disease, a large number of patients scheduled for CABG surgery will be treated with these drugs. Importantly, a recent retrospective study of 10 000 British patients undergoing CABG surgery showed that ACE inhibitors are often continued during surgery or re-initiated early after CABG. Furthermore, the authors showed that preoperative treatment with an ACE inhibitor was linked to increased mortality.[21] Our finding that quinapril increased early cardiovascular events when given to anaemic patients in the early postoperative phase suggests that the detrimental effects of perioperative ACE inhibitor therapy can in part be explained by the delayed recovery of Hb levels.
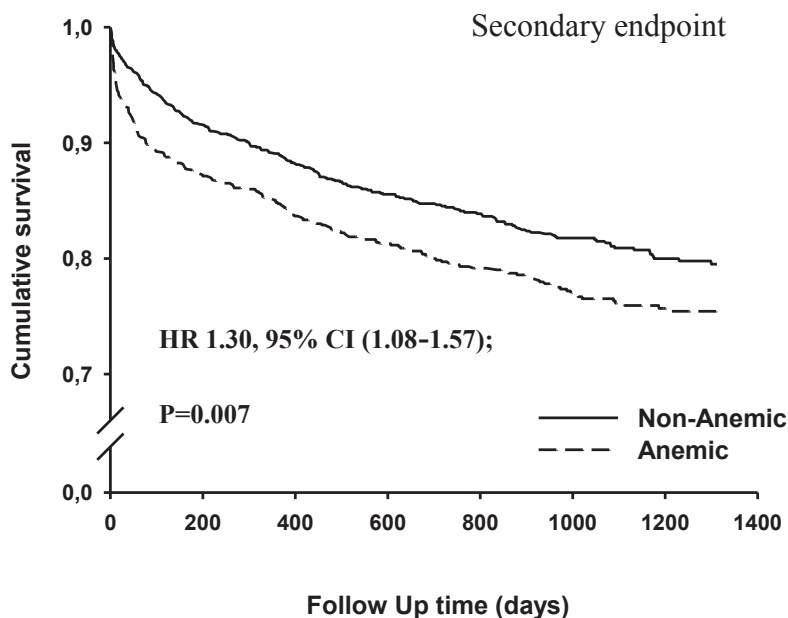
Figure 3. Kaplan-Meier analysis of event free survival of the secondary endpoint during the maximal follow up of 43 months according to the presence or absence of sustained postoperative anemia. Secondary composite endpoint of the IMAGINE trial comprising time to first occurrence of cardiovascular death or resuscitated cardiac arrest, nonfatal myocardial infarction, coronary revascularization, unstable angina that required hospitalization, documented angina that did not require hospitalization, stroke or TIA, congestive heart failure that required hospitalization and all other cardiovascular hospitalizations. HR, Hazard Ratio; 95% CI, 95 percent confidence interval.

Transfusions

Another important observation in our analysis was that blood transfusions were only sparsely administered, despite the high incidence of severe anaemia. While this approach is in accordance with current guidelines, it may in part explain the high incidence of sustained postoperative anaemia.[17] Koch et al recently showed that the use of older blood products is associated with mortality after CABG, suggesting that the risks of transfusions are more related to the quality of the blood than the transfusion itself.[22] Together these findings suggest that the balance between risk and benefit of transfusions after CABG should be reconsidered. Our study does not, however, address the safety and efficacy of blood transfusions after CABG surgery and we cannot recommend more lenient transfusions based on our retrospective study. A prospective evaluation is urgently awaited.[23]

Limitations

Ideally, we would have liked to have data on the exact duration of postoperative anae-

A

Days after randomisation
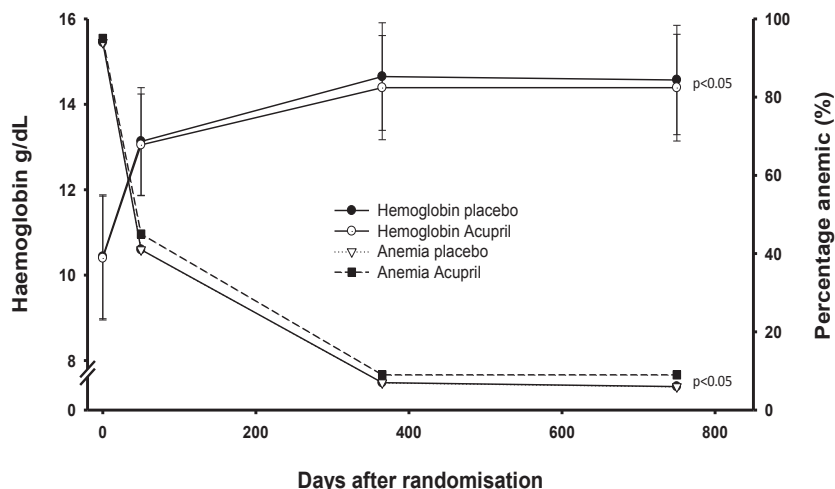
B   **Primary endpoint first 3 months in patients with anemia**

HR 1.62 95% CI (1.1-2.4), P=0.020
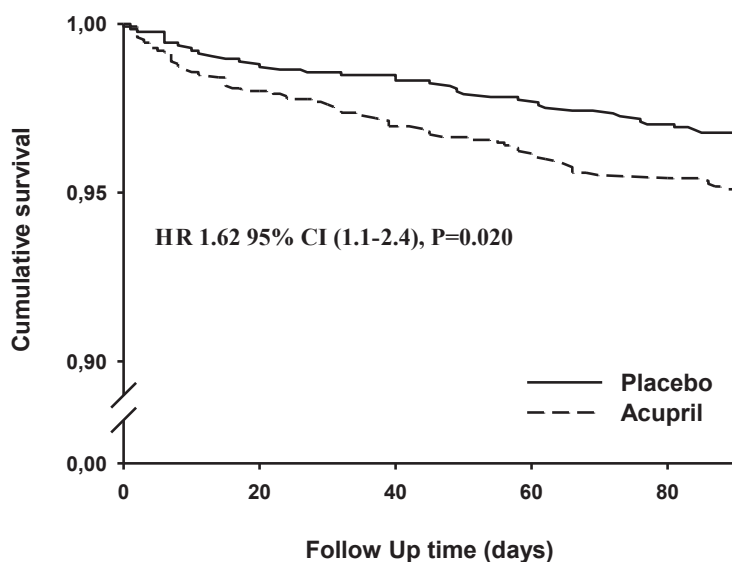
Follow Up time (days)

Figure 4. Effect of Acupril on postoperative recovery of hemoglobin levels and the effect of Acupril on survival in patients with anemia. A. Temporal changes of hemoglobin levels and percentage of patients with anemia after coronary artery bypass graft surgery, in patients randomized to Acupril or placebo. B. Kaplan-Meier analysis of event free survival of the primary endpoint during the first 3 months according to treatment groups, namely Acupril or placebo. Primary composite endpoint of the IMAGINE trial comprised time to first occurrence of cardiovascular death or resuscitated cardiac arrest, nonfatal myocardial infarction, coronary revascularization, unstable angina that required hospitalization, documented angina that did not require hospitalization, stroke and congestive heart failure that required hospitalization. HR, Hazard Ratio; 95% CI, 95 percent confidence interval.

mia in all patients. Unfortunately, the frequency of Hb measurements in the IMAG-INE protocol was fairly sparse and the first post-discharge Hb value was measured 50 days after randomisation. Early events that occurred while a patient was anaemic but in whom Hb had recovered at the 50-day post-randomisation visit were therefore attributed to the non-anaemic group. Therefore, the number of early events associated with the presence of anaemia is potentially underestimated in our analysis. Similarly, we cannot exclude the possibility that events that occurred before 50 days affected the duration of postoperative anaemia. This limitation should be borne in mind when interpreting the analysis of the early events. In addition, defining groups at 50 days after randomization excludes patients who died before 50 days. The IMAGINE study involved a relatively healthy low-risk population, so the deleterious effects of anaemia might be different in the general CABG population. Finally, despite the use of extensive multivariable adjustments, we cannot be certain that the relation between anaemia and events is causal since we employed a retrospective analysis of prospectively-collected data. Alternatively, sustained postoperative anaemia might be a marker for a high-risk subgroup of patients. Future studies are needed to further define the impact of postoperative anaemia on outcome after CABG surgery.

Clinical implications

Our study shows that the duration of postoperative anaemia is an important determinant of outcome after CABG. We therefore propose more aggressive measures to limit the severity and duration of postoperative anaemia. This could, for instance, be achieved by increased utilisation of contemporary strategies to limit the duration and severity of postoperative anaemia, such as minimal invasive surgery, autologous blood transfusions, thrombostatic drugs and perhaps erythropoiesis-stimulating proteins.[17] It also seems logical to evaluate Hb levels early after discharge in order to identify and treat patients with sustained postoperative anaemia in an early phase. Furthermore, our data suggest that perioperative discontinuation of ACE inhibitors could prevent sustained postoperative anaemia. Prospective studies are required to determine whether these measures will reduce postoperative anaemia and improve the outcome after CABG surgery.

Conclusions

Postoperative anaemia is common, frequently persists for months after CABG surgery and is associated with an impaired cardiovascular outcome. ACE inhibitors slow postoperative recovery of Hb levels after CABG and increase cardiovascular events in pa-

tients with anaemia.

References

1. Reinecke H, Trey T, Wellmann J, Heidrich J, Fobker M, Wichter T, Walter M, Breithardt G, Schaefer RM. Haemoglobin-related mortality in patients undergoing percutaneous coronary interventions. Eur Heart J 2003;24:2142-2150.

2. Sabatine MS, Morrow DA, Giugliano RP, Burton PB, Murphy SA, McCabe CH, Gibson CM, Braunwald E. Association of hemoglobin levels with clinical outcomes in acute coronary syndromes. Circulation 2005;111:2042-2049.

3. van der Meer P, Groenveld HF, Januzzi JL, Jr, van Veldhuisen DJ. Erythropoietin treatment in patients with chronic heart failure: a meta-analysis. Heart 2009;95:1309-1314.

4. Sarnak MJ, Tighiouart H, Manjunath G, MacLeod B, Griffith J, Salem D, Levey AS. Anemia as a risk factor for cardiovascular disease in The Atherosclerosis Risk in Communities (ARIC) study. J Am Coll Cardiol 2002;40:27-33.

5. Wu WC, Schifftner TL, Henderson WG, Eaton CB, Poses RM, Uttley G, Sharma SC, Vezeridis M, Khuri SF, Friedmann PD. Preoperative hematocrit levels and postoperative outcomes in older patients undergoing noncardiac surgery. JAMA 2007;297:2481-2488.

6. van Straten AH, Hamad MA, van Zundert AJ, Martens EJ, Schonberger JP, de Wolf AM. Preoperative hemoglobin level as a predictor of survival after coronary artery bypass grafting: a comparison with the matched general population. Circulation 2009;120:118-125.

7. Ranucci M, Conti D, Castelvecchio S, Menicanti L, Frigiola A, Ballotta A, Pelissero G. Hematocrit on cardiopulmonary bypass and outcome after coronary surgery in nontransfused patients. Ann Thorac Surg 2010;89:11-17.

8. Koch CG, Li L, Duncan AI, Mihaljevic T, Loop FD, Starr NJ, Blackstone EH. Transfusion in coronary artery bypass grafting is associated with reduced long-term survival. Ann Thorac Surg 2006;81:1650-1657.

9. Murphy GJ, Reeves BC, Rogers CA, Rizvi SI, Culliford L, Angelini GD. Increased mortality, postoperative morbidity, and cost after red blood cell transfusion in patients having cardiac surgery. Circulation 2007;116:2544-2552.

10. Oliver E, Carrio ML, Rodriguez-Castro D, Javierre C, Farrero E, Torrado H, Castells E, Ventura JL. Relationships among haemoglobin level, packed red cell transfusion and clinical outcomes in patients after cardiac surgery. Intensive Care Med 2009;35:1548-1555.

11. Warnica JW, Gilst WV, Baillot R, Johnstone D, Block P, Myers MG, Chocron S, Ave SD, Martineau P, Rouleau JL. Ischemia Management with Accupril post bypass Graft via Inhibition of angiotensin coNverting enzyme (IMAGINE): a multicentre randomized trial - design and rationale. Can J Cardiol 2002;18:1191-1200.

12. Rouleau JL, Warnica WJ, Baillot R, Block PJ, Chocron S, Johnstone D, Myers MG, Calciu CD, Dalle-Ave S, Martineau P, Mormont C, van Gilst WH, IMAGINE (Ischemia Management with Accupril post-bypass Graft via Inhibition of the coNverting Enzyme) Investigators. Effects of angiotensin-converting enzyme inhibition in low-risk patients early after coronary artery bypass surgery. Circulation 2008;117:24-31.

13. van der Meer P, Lipsic E, Westenbrink BD, van de Wal RM, Schoemaker RG, Vellenga E, van Veldhuisen DJ, Voors AA, van Gilst WH. Levels of hematopoiesis inhibitor N-acetyl-seryl-aspartyl-lysyl-proline partially explain the occurrence of anemia in heart failure. Circulation 2005;112:1743-1747.

14. Ishani A, Weinhandl E, Zhao Z, Gilbertson DT, Collins AJ, Yusuf S, Herzog CA. Angiotensin-converting enzyme inhibitor as

a risk factor for the development of anemia, and the impact of incident anemia on mortality in patients with left ventricular dysfunction. J Am Coll Cardiol 2005;45:391-399.

15. Surgenor SD, DeFoe GR, Fillinger MP, Likosky DS, Groom RC, Clark C, Helm RE, Kramer RS, Leavitt BJ, Klemperer JD, Krumholz CF, Westbrook BM, Galatis DJ, Frumiento C, Ross CS, Olmstead EM, O'Connor GT. Intraoperative red blood cell transfusion during coronary artery bypass graft surgery increases the risk of postoperative low-output heart failure. Circulation 2006;114:I43-8.

16. Spiess BD, Ley C, Body SC, Siegel LC, Stover EP, Maddi R, D'Ambra M, Jain U, Liu F, Herskowitz A, Mangano DT, Levin J. Hematocrit value on intensive care unit entry influences the frequency of Q-wave myocardial infarction after coronary artery bypass grafting. The Institutions of the Multicenter Study of Perioperative Ischemia (McSPI) Research Group. J Thorac Cardiovasc Surg 1998;116:460-467.

17. Society of Thoracic Surgeons Blood Conservation Guideline Task Force, Ferraris VA, Ferraris SP, Saha SP, Hessel EA,2nd, Haan CK, Royston BD, Bridges CR, Higgins RS, Despotis G, Brown JR, Society of Cardiovascular Anesthesiologists Special Task Force on Blood Transfusion, Spiess BD, Shore-Lesserson L, Stafford-Smith M, Mazer CD, Bennett-Guerrero E, Hill SE, Body S. Perioperative blood transfusion and blood conservation in cardiac surgery: the Society of Thoracic Surgeons and The Society of Cardiovascular Anesthesiolo-

gists clinical practice guideline. Ann Thorac Surg 2007;83:S27-86.

18. Westenbrink BD, Visser FW, Voors AA, Smilde TD, Lipsic E, Navis G, Hillege HL, van Gilst WH, van Veldhuisen DJ. Anaemia in chronic heart failure is not only related to impaired renal perfusion and blunted erythropoietin production, but to fluid retention as well. Eur Heart J 2007;28:166-171.

19. Westenbrink BD, de Boer RA, Voors AA, van Gilst WH, van Veldhuisen DJ. Anemia in chronic heart failure: etiology and treatment options. Curr Opin Cardiol 2008;23:141-147.

20. Ripamonti V, Racca V, Calvo MG, Castiglioni P, Ferratini M. Angiotensin-converting enzyme inhibitors slow recovery from anemia following cardiac surgery. Chest 2006;130:79-84.

21. Miceli A, Capoun R, Fino C, Narayan P, Bryan AJ, Angelini GD, Caputo M. Effects of angiotensin-converting enzyme inhibitor therapy on clinical outcome in patients undergoing coronary artery bypass grafting. J Am Coll Cardiol 2009;54:1778-1784.

22. Koch CG, Li L, Sessler DI, Figueroa P, Hoeltge GA, Mihaljevic T, Blackstone EH. Duration of red-cell storage and complications after cardiac surgery. N Engl J Med 2008;358:1229-1239.

23. Murphy GJ. Does blood transfusion harm cardiac surgery patients? BMC Med 2009;7:38-7015-7-38.