The Impact of Anemia on Long-Term Clinical Outcome in Patients Undergoing Revascularization With the Unrestricted Use of Drug-Eluting Stents

Thomas Pilgrim, MD; Florian Vetterli, MSc; Bindu Kalesan, MPH; Giulio G. Stefanini, MD; Lorenz Räber, MD; Stefan Stortecky, MD; Steffen Gloekler, MD; Ronald K. Binder, MD; Peter Wenauswer, MD; Aris Moschovitis, MD; Ahmed A. Khattab, MD; Lutz Buuellesfeld, MD; Marcel Zwahlen, PhD; Bernhard Meier, MD; Peter Jüni, MD; Stephan Windecker, MD

Background—Anemia is frequent among patients with cardiovascular disease and adversely affects prognosis. The objective of this analysis was to assess the impact of anemia on long-term clinical outcomes among patients undergoing percutaneous coronary intervention (PCI) with the unrestricted use of drug-eluting stents (DES).

Methods and Results—Between April 2002 to March 2009, 6528 consecutive patients underwent PCI with the unrestricted use of DES. Among patients with anemia according to the criteria by the World Health Organization (WHO) (hemoglobin <130 g/L for men and <120 g/L for women, respectively) patients below the 25th percentile separately for men and women were defined to have severe anemia. We compared clinical outcomes among patients with severe anemia and no/mild anemia during long-term follow-up through 4 years. Whereas 21.6% of patients were found to have anemia according to the WHO definition, 347 patients (5.5%) had severe anemia (mean hemoglobin, 98±11 g/L). Severe anemia was more prevalent among the elderly (P<0.001), diabetics (P<0.001), and patients with chronic kidney disease (P<0.001). In adjusted analyses, severe anemia was associated with an increased risk of death (hazard ratio, 1.86; 95% confidence interval, 1.37–2.52; P<0.0001), cardiac death (hazard ratio, 2.32; 95% confidence interval, 1.57–3.43; P<0.0001), and myocardial infarction (hazard ratio, 2.02; 95% confidence interval, 1.36–3.01; P=0.00054) as compared with no/mild anemia without significant interaction across sexes (P=0.86) and acute coronary syndromes (P=0.61) and a trend toward a particularly high risk of mortality among anemic patients <65 years of age (P=0.07). Severe anemia resulted in a greater risk of overall definite stent thrombosis (hazard ratio, 2.59; 95% confidence interval, 1.48–4.54; P=0.00089).

Conclusions—Severe anemia is common among patients undergoing PCI with the unrestricted use of DES and adversely affects long-term prognosis, including survival. (Circ Cardiovasc Interv. 2012;5:202-210.)

Key Words: anemia ■ coronary artery disease ■ stent thrombosis ■ cardiac catheterization ■ drug-eluting stent

Anemia is frequently encountered among patients with cardiovascular disease and importantly affects the outcome of patients with heart failure,1 congenital heart disease,2 and coronary artery disease (CAD) undergoing revascularization by means of percutaneous coronary intervention (PCI)3–7 or coronary artery bypass graft surgery.8,9 Using the World Health Organization (WHO) definition, anemia has been diagnosed in as many as every fourth patient undergoing PCI3–4 comparable to the prevalence of diabetes in recent all-comers trials.10,11 Among patients undergoing PCI,3–7 anemia has been associated with adverse prognosis, particularly among those presenting with acute coronary syndromes (ACS).12–14 The guidelines for the diagnosis and treatment of non–ST-segment elevation–ACS of the European Society of Cardiology (ESC) therefore recommend to take baseline hemoglobin levels into consideration during the initial risk stratification.15

Iron deficiency caused by chronic bleeding is the most common cause of anemia, followed by conditions such as chronic infection, malignancy, autoimmune disease, and chronic kidney disease.16 Anemia of chronic disease is multifactorial and encountered with increasing frequency in the elderly population.17 Anemia caused by chronic bleeding frequently remains unrecognized and may be unmasked by intense and prolonged antiplatelet and antithrombotic therapies as applied among patients with CAD undergoing PCI. In
our center, drug-eluting stents (DES) are considered by default in nearly all patient subsets, as suggested by the ESC guidelines on myocardial revascularization,18 with the exception of patients with a recent history of active bleeding or planned surgery for noncardiovascular conditions within 6 months. This unrestricted use of DES among patients with severe anemia may be problematic for 2 reasons: first, there may be a procoagulant state in patients with anemia caused by chronic disease, which in turn could increase the risk of stent thrombosis (ST); second, anemia caused by occult bleeding may be exacerbated by the prolonged duration of DAPT required because of DES implantation. Moreover, premature discontinuation of DAPT may increase the risk of ST in patients treated with DES. Previous reports have mainly dealt with patients treated with bare metal stents, using shorter duration of DAPT and reported predominantly in-hospital or short-term outcomes.5–7 The purpose of the present analysis was to investigate the prevalence and impact of preprocedural anemia on clinical outcomes in a cohort of 6312 consecutive patients treated with the unrestricted use of DES during a follow-up period of up to 4 years.

WHAT IS KNOWN

- Anemia is frequently encountered among patients with cardiovascular disease.
- Anemia importantly affects outcome of patients with coronary artery disease undergoing revascularization.

WHAT THE STUDY ADDS

- Anemia does not appear to influence the type of antithrombotic therapy at the time of hospital discharge.
- Severe anemia is associated with impaired long-term survival and an increased risk of overall definite and definite or probable stent thrombosis.

Methods

Patient Population
All patients undergoing implantation of DES at Bern University Hospital, Switzerland, were entered into the Bern Drug-Eluting Stent registry. Between April 2002 and March 2009, a total of 6528 consecutive patients underwent PCI with the unrestricted use of early and new-generation DES. All patients with at least 1 blood sample during the hospital course and a follow-up contact were included into this study. In line with the registry character of the study, there were no formal exclusion criteria. Demographic and clinical characteristics, information on PCI, and hospital outcome data were systematically collected. Laboratory values during hospitalization were retrieved from the local central hematology laboratory, including hemoglobin and hematocrit values on admission. The registry was approved by the institutional ethics committee at Bern University Hospital, Switzerland, and complied with the Declaration of Helsinki. Written informed consent for prospective follow-up was obtained from all patients.

Procedures
PCI was performed in accordance with practice guidelines.18 Unfractionated heparin in a dose of 5000 IU or 70 to 100 IU/kg was administered during the procedure to maintain an activated clotting time >250 seconds. Dual antiplatelet therapy with at least 100 mg of acetylsalicylic acid and 300 to 600 mg of clopidogrel was installed before or at the time of the procedure; at discharge, acetylsalicylic acid was continued indefinitely, whereas clopidogrel was prescribed for a duration of at least 12 months. The periprocedural use of glycoprotein IIb/IIIa inhibitors was left to the discretion of the operator. A 12-lead ECG was routinely obtained before and after the procedure, and cardiac enzymes were assessed within 24 hours of the procedure. Creatinine kinase (CK), CK-MB, and troponin T were repeated every 6 to 8 hours until identification of the peak levels in patients with signs of ischemia.

Data Collection
Patients were actively followed-up for the ascertainment of major adverse cardiac events. Survival data for all patients were obtained from hospital records and municipal civil registries. A health questionnaire was sent to all living patients with questions on rehospitalization and major adverse cardiac events. In the case of missing response, patients were contacted by telephone. General practitioners, referring cardiologists, and patients were contacted as necessary for additional information. For patients who underwent treatment for major adverse cardiac events at other medical institutions, external medical records, discharge letters, and coronary angiography documentation were systematically collected and reviewed.

Definitions
Anemia was defined as a hemoglobin concentration of <120 g/L for women and <130 g/L for men, according to the definition of the WHO.19 Patients with hemoglobin levels below the 25th percentile of anemic patients separately assessed for men and women were defined to have severe anemia. Initial analyses explored the differences between the groups with severe anemia versus no anemia, severe anemia versus mild anemia, and mild anemia versus no anemia. Because of the lack of apparent differences between the groups with mild anemia versus no anemia, we decided to merge the lowest risk group, no anemia, with that of mild anemia. In further analyses, we focused our analysis to explore the differences between patients with severe anemia as compared with those with mild/no anemia. Cardiac death was defined as any death due to an immediate cardiac cause, procedure-related mortality, and death of unknown cause. Q-wave and non–Q-wave myocardial infarction were differentiated. Q-wave myocardial infarction involved symptoms or signs of ischemia in the presence of new pathological Q-waves in ≥2 contiguous leads on ECG. Non-Q-wave myocardial infarction required an elevation in CK to ≥2× upper limit of normal and a rise in CK-MB or troponin to ≥3× upper limit of normal in the presence of ischemic symptoms or ischemic ECG changes. Target vessel revascularization (TVR) involved any repeat revascularization within the major coronary vessel of the target-lesion. Target lesion revascularization (TLR) was determined as revascularization for a stenosis within the stent or the 5-mm borders adjacent to the stent. The diagnosis of ST was based on the Academic Research Consortium definitions.20 We prespecified the use of only the first event in each event category. Subsequent events in the same category have not been considered for the purpose of this analysis.

Statistical Analysis
The prespecified primary outcome was death overall. We used Cox proportional hazards models for comparisons between groups, after initial adjustment for type of stent only (early or newer generation), and full adjustment for type of stent, sex, diabetes, renal impairment, age, body mass index, hypertension, dyslipidemia, smoking, left ventricular ejection fraction, and acute coronary syndrome. Because the number of outcome events was low for definite ST and the composite of definite or probable ST, we were unable to use conventional multivariable analysis using all baseline characteristics as covariates. Therefore, we derived propensity scores for severe anemia using a probit model with the remaining 10 baseline characteristics as covariates.
characteristics as covariates. The propensity score represents the probability of a patient to have severe anemia at baseline, given the patient’s remaining baseline characteristics. Observations with the same propensity score for severe anemia have the same distribution of the remaining baseline characteristics. Fully adjusted analyses were then performed by including the propensity score as a continuous variable and stent type in the model. We then performed stratified analyses of the primary outcome of death overall according to the following characteristics: age (≥65 versus <65 years), sex, diabetes status, renal failure, and presence of ACS at baseline. Clinical outcome data are presented as number of events and cumulative incidence rates. Categorical characteristics at baseline were compared using a χ² test and continuous variables using univariable regression analysis. All analyses were performed using STATA 11.0. Probability values and 95% confidence intervals (CI) are 2-sided.

**Results**

Between April 2002 and March 2009, 6528 consecutive patients underwent PCI with the unrestricted use of early and newer generation DES. Patients with missing hemoglobin values (n=216) were excluded, resulting in 6312 patients for the purpose of this study. For the overall cohort and those alive throughout the study period, the mean duration of follow-up and standard deviation (SD) was 3.1 years (0.8); the median and interquartile range was 3.1 (interquartile range, 2.5–4 years). The follow-up duration was comparable among the two categories of anemia with median (interquartile range) for no/mild anemia being 3.0 years (2.0–3.9) and severe anemia being 3.0 years (2.3–4.0). In total, 127 patients did not have adequate follow-up as defined as a duration of follow-up of 900 days.

**Baseline Characteristics**

Anemia as defined by the WHO definition was observed among 1366 (21.6%) patients without differences in the prevalence of anemia among patients with ACS and stable CAD (22.1% versus 21.1%; P=0.31). Anemia was severe in 347 patients (5.5%). Anemia was more prevalent among the elderly (P<0.001), diabetics (P<0.001), and patients with chronic kidney disease (P<0.001) (Table 1). There were no differences between patients with severe anemia or mild/no anemia in the prescription of antiplatelet agents at the time of hospital discharge (Table 2).

**Anemia and Outcome**

Clinical outcomes during long-term follow-up are summarized in Table 3. Severe anemia was associated with an increased risk of all-cause mortality (hazard ratio [HR], 1.86; 95% CI, 1.37–2.52; P<0.0001), cardiac death (HR, 2.32; 95% CI 1.57–3.43; P<0.0001), and myocardial infarction (HR, 2.02; 95% CI, 1.36–3.01; P=0.0054) compared with no or mild anemia in adjusted analyses during long-term follow-up to 4 years. The increased risk of death emerged early and continued to accrue during long-term follow-up (Figure 1). Whereas a landmark analysis with a cutoff set at 30 days after the procedure showed no difference with regard to mortality during the periprocedural period (severe versus mild/no anemia: HR, 1.51; 95% CI, 0.68–3.33; P=0.31), an increased risk of death was observed for patients with severe anemia as compared with patients with mild/no anemia during late follow-up (HR, 1.97; 95% CI, 1.41–2.73; P<0.0001) (Figure 2). In stratified analyses across various subgroups, the increased risk of mortality related to severe anemia was consistent without significant interaction among female patients (Pinteraction=0.857), diabetic patients (Pinteraction=0.119), those with chronic renal failure (Pinteraction=0.975), and patients presenting with ACS (Pinteraction=0.613); we observed a trend toward a particularly high risk of mortality among anemic patients <65 years of age (Pinteraction=0.066) (Figure 3). The risk of overall definite ST was higher among patients with severe anemia as compared with patients with mild/no anemia after initial (HR, 2.33; 95% CI, 1.34–4.06; P=0.00287) and full adjustment (HR, 2.59, 95% CI, 1.48–4.54; P=0.00089) (Table 3 and Figure 4). The risk difference reached statistical significance in the early follow-up period but was also apparent during the late follow-up period (Figure 5). In a stratified analysis according to dual antiplatelet status (off versus on) at the end of follow-up, we observed no significant interaction in the relative risk for all major ischemic end points between patients with severe anemia and those without.

**Discussion**

The present study investigating the impact of anemia on outcomes among patients undergoing revascularization with the unrestricted use of DES has the following findings:
The prevalence of anemia in an unselected patient cohort undergoing PCI was high and associated with advanced age, diabetes, and chronic kidney disease.

Anemia did not appear to influence the type of anti-thrombotic therapy at the time of hospital discharge.

Severe anemia was associated with impaired long-term survival. Differences emerged early and continued to accrue during long-term follow-up.

Severe anemia was associated with an increased risk of overall definite and definite or probable ST.

Consistent with previous reports of patients undergoing PCI, the prevalence of anemia amounted to 21.6% in the present study and was comparable to the incidence of diabetes in all-comers trials. The observed association of severe anemia with advanced age, diabetes, and renal insuf-
efficiency has been reported in previous registries of patients undergoing PCI and reflects well-known clinical relationships. Accordingly, the relatively high prevalence of anemia in patients with CAD undergoing PCI as compared with patients in a primary care setting may be explained by common risk factors such as advanced age, diabetes, and chronic kidney disease. In addition, anemia may precipitate myocardial ischemia and unmask significant coronary steno-

<table>
<thead>
<tr>
<th>Clinical Outcomes</th>
<th>Severe Anemia (n=347)</th>
<th>Mild/No Anemia (n=5965)</th>
<th>Initial Adjusted HR (95% CI)</th>
<th>Initial Adjusted P Value</th>
<th>Full Adjusted HR (95% CI)</th>
<th>Full Adjusted P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality (%)</td>
<td>55 (17.9)</td>
<td>490 (10.0)</td>
<td>2.02 (1.53–2.67)</td>
<td>&lt;0.0001</td>
<td>1.86 (1.37–2.52)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cardiac death (%)</td>
<td>33 (10.7)</td>
<td>241 (4.7)</td>
<td>2.44 (1.69–3.51)</td>
<td>&lt;0.0001</td>
<td>2.32 (1.57–3.43)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MI (%)</td>
<td>30 (10.4)</td>
<td>280 (5.5)</td>
<td>1.97 (1.35–2.87)</td>
<td>0.0043</td>
<td>2.02 (1.36–3.01)</td>
<td>0.0054</td>
</tr>
<tr>
<td>Q-wave MI (%)</td>
<td>10 (4.2)</td>
<td>93 (1.9)</td>
<td>2.02 (1.05–3.89)</td>
<td>0.0416</td>
<td>2.04 (1.03–4.07)</td>
<td>0.04217</td>
</tr>
<tr>
<td>Non-Q-wave MI (%)</td>
<td>20 (6.3)</td>
<td>180 (3.5)</td>
<td>2.00 (1.26–3.17)</td>
<td>0.0337</td>
<td>2.10 (1.29–3.42)</td>
<td>0.00929</td>
</tr>
<tr>
<td>TLR (%)</td>
<td>37 (12.8)</td>
<td>478 (9.1)</td>
<td>1.43 (1.02–2.00)</td>
<td>0.03655</td>
<td>1.35 (0.94–1.95)</td>
<td>0.10388</td>
</tr>
<tr>
<td>TVR (%)</td>
<td>51 (17.8)</td>
<td>754 (14.4)</td>
<td>1.26 (0.95–1.67)</td>
<td>0.11371</td>
<td>1.25 (0.92–1.70)</td>
<td>0.14977</td>
</tr>
<tr>
<td>Death/MI (%)</td>
<td>77 (25.1)</td>
<td>735 (14.6)</td>
<td>1.92 (1.52–2.43)</td>
<td>&lt;0.0001</td>
<td>1.81 (1.40–2.34)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cardiac death/Mi (%)</td>
<td>55 (18.2)</td>
<td>501 (9.7)</td>
<td>2.00 (1.52–2.65)</td>
<td>&lt;0.0001</td>
<td>1.96 (1.45–2.63)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cardiac death/Mi/TLR (%)</td>
<td>79 (25.3)</td>
<td>849 (16.1)</td>
<td>1.72 (1.37–2.17)</td>
<td>&lt;0.0001</td>
<td>1.63 (1.27–2.10)</td>
<td>0.00014</td>
</tr>
<tr>
<td>Cardiac death/Mi/TVR (%)</td>
<td>92 (29.7)</td>
<td>1094 (20.6)</td>
<td>1.57 (1.27–1.95)</td>
<td>&lt;0.0001</td>
<td>1.53 (1.21–1.93)</td>
<td>0.0003</td>
</tr>
</tbody>
</table>

Definite ST

Early, 0 to 30 d (%) | 8 (2.3) | 43 (0.7) | 3.25 (1.53–6.91) | 0.00224 | 3.75 (1.74–8.10) | 0.00077 |
Late, 31 to 360 d (%) | 1 (0.3) | 15 (0.3) | 1.33 (0.18–10.10) | 0.78298 | 1.42 (0.19–10.91) | 0.73476 |
Very late, 361 to 1440 d (%) | 5 (2.5) | 54 (1.3) | 1.76 (0.71–4.41) | 0.22453 | 1.92 (0.76–4.81) | 0.16624 |
Overall, 0 to 1440 d (%) | 14 (5.1) | 111 (2.3) | 2.33 (1.34–4.06) | 0.00287 | 2.59 (1.48–4.54) | 0.00089 |

Definite or probable ST

Early, 0 to 30 d (%) | 25 (7.3) | 226 (3.8) | 1.92 (1.27–2.91) | 0.00196 | 2.09 (1.34–3.27) | 0.00117 |
Late, 31 to 360 d (%) | 4 (1.2) | 28 (0.5) | 2.71 (0.95–7.73) | 0.06291 | 2.81 (0.97–8.12) | 0.05628 |
Very late, 361 to 1440 d (%) | 7 (3.3) | 104 (2.5) | 1.28 (0.59–2.74) | 0.53546 | 1.23 (0.55–2.81) | 0.62667 |
Overall, 0 to 1440 d (%) | 36 (11.7) | 358 (6.8) | 1.82 (1.29–2.56) | 0.00063 | 1.93 (1.33–2.78) | 0.00046 |

Initial model adjusted for type of stent generation.
Full model adjusted for type of stent generation, age, sex, body mass index, hypertension, dyslipidemia, diabetes, smoking, renal failure, left ventricular ejection fraction, and acute coronary syndrome, except for all ST.
Full model for definite ST and definite or probable ST adjusted for type of stent generation and propensity score.
HR indicates hazard ratio; CI, confidence interval; MI, myocardial infarction; TLR, target lesion revascularization; TVR, target vessel revascularization; ST, stent thrombosis.

Figure 1. All-cause mortality through 4 years of follow-up. Kaplan-Meier cumulative estimates for all-cause mortality up to 4 years of follow-up stratified by anemia status. Continuous line indicates severe anemia; dashed line indicates mild/no anemia. PCI indicates percutaneous coronary intervention; HR, hazard ratio; and CI, confidence interval.
ses eventually leading to revascularization. Furthermore, antiplatelet therapy initiated before PCI may have led to undetected chronic bleeding exacerbating anemia.

Conversely, severe anemia as assessed during hospital admission did not influence the choice of periprocedural antithrombotic treatment nor the antiplatelet regimen at the time of hospital discharge, despite the known correlation of anemia and the subsequent risk of bleeding in ACS patients.\(^{25}\) This observation contrasts with a previous report, in which patients with anemia did not receive optimal antiplatelet treatment due to concerns of bleeding complications.\(^{13}\) The importance of dual antiplatelet therapy has repeatedly been stressed in the DES era and might explain the strict adherence to antiplatelet agents after stent implantation in the present study. Moreover, because anemia was manifest before the intervention with no active source of bleeding, the use of dual antiplatelet therapy was not formally contraindicated. Patients with anemia caused by manifest bleeding typically will not undergo elective PCI or be treated with bare metal stents and therefore are not reflected in the present study. Finally, compliance with dual antiplatelet therapy after hospital discharge was not regularly monitored and might have shown differences between patients with and without anemia during longer-term follow-up.

Severe anemia was associated with impaired survival. Differences in survival emerged early and continued to accrue during long-term follow-up to 4 years. Our findings corroborate the results from a pooled analysis from the EPIC, EPILOG, and EPISTENT trials in the balloon angioplasty and bare-metal stent era for patients with severe anemia, as shown in Figure 2. The Kaplan-Meier cumulative estimates for all-cause mortality up to 4 years of follow-up stratified by anemia status with a landmark set at 30 days. The continuous line indicates severe anemia; the dashed line indicates mild/no anemia. PCI indicates percutaneous coronary intervention; HR, hazard ratio; and CI, confidence interval.

![Cumulative Mortality](image)

**Figure 2.** All-cause mortality with landmark analysis at 30 days. Kaplan-Meier cumulative estimates for all-cause mortality up to 4 years of follow-up stratified by anemia status with a landmark set at 30 days. The continuous line indicates severe anemia; the dashed line indicates mild/no anemia. PCI indicates percutaneous coronary intervention; HR, hazard ratio; and CI, confidence interval.

<table>
<thead>
<tr>
<th>Severe Anemia</th>
<th>No or mild Anemia</th>
<th>HR (95% CI)</th>
<th>(P)</th>
<th>(P_{\text{Interaction}})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Mortality</td>
<td>55 (17.9)</td>
<td>490 (10.0)</td>
<td>1.86 (1.37-2.52)</td>
<td>0.001</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 years</td>
<td>36 (12.7)</td>
<td>125 (4.7)</td>
<td>2.82 (1.63-4.83)</td>
<td>0.001</td>
</tr>
<tr>
<td>(\geq 65) years</td>
<td>39 (21.6)</td>
<td>365 (15.7)</td>
<td>1.58 (1.09-2.28)</td>
<td>0.117</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>35 (12.7)</td>
<td>190 (4.7)</td>
<td>1.64 (0.88-3.09)</td>
<td>0.117</td>
</tr>
<tr>
<td>Men</td>
<td>40 (21.6)</td>
<td>360 (15.7)</td>
<td>1.94 (1.36-2.77)</td>
<td>0.117</td>
</tr>
<tr>
<td>Diabetes mellitus (n [%])</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>30 (12.7)</td>
<td>361 (4.7)</td>
<td>1.51 (1.00-2.30)</td>
<td>0.051</td>
</tr>
<tr>
<td>Yes</td>
<td>25 (21.6)</td>
<td>129 (15.7)</td>
<td>2.69 (1.70-4.25)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Renal failure (n [%])</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>40 (12.7)</td>
<td>430 (4.7)</td>
<td>1.83 (1.31-2.50)</td>
<td>0.001</td>
</tr>
<tr>
<td>Yes</td>
<td>32 (21.6)</td>
<td>60 (15.7)</td>
<td>1.79 (0.84-3.84)</td>
<td>0.133</td>
</tr>
<tr>
<td>Acute coronary syndrome (n [%])</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>24 (12.7)</td>
<td>272 (4.7)</td>
<td>2.02 (1.31-3.12)</td>
<td>0.002</td>
</tr>
<tr>
<td>Yes</td>
<td>31 (21.6)</td>
<td>273 (15.7)</td>
<td>1.73 (1.13-2.66)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

*Adjusted for type of stent generation, age, gender, BMI, hypertension, dyslipidemia, diabetes, smoking, renal failure, LVEF, ACS

**Figure 3.** Stratified analysis of mortality across several subgroups. Stratified analyses across various patient subsets are summarized in this Forrest plot. Probability values for interaction between the effects of anemia and patient characteristics are shown for age (\(\geq 65\) years), female patients, diabetics, patients with chronic kidney disease, and acute coronary syndromes (ACS). CI indicates confidence interval; BMI, body mass index; and LVEF, left ventricular ejection fraction.
although we failed to document an adverse clinical outcome for patients with mild anemia.\textsuperscript{26}

The association of anemia with impaired periprocedural outcome\textsuperscript{3} or survival at 1 year\textsuperscript{4,5} among patients undergoing PCI is well established and appears not to be affected by the implementation of DES in clinical practice. Several mechanisms can be held responsible for the observed increase in all-cause mortality and cardiac death in particular. Reduced blood hemoglobin levels may compromise myocardial oxygen delivery and therefore result in ischemia when they fall below the functional capacity of myocardial reserve. As a physiological adaptative mechanism, cardiac output, does increase in response to anemia to maintain systemic oxygen delivery. This in turn results in tachycardia and ventricular

\textbf{Figure 4.} Definite stent thrombosis through 4 years of follow-up. Kaplan-Meier cumulative estimates of all-cause mortality up to 4 years of follow-up stratified by anemia status. \textbf{Continuous line} indicates severe anemia; \textbf{dashed line} indicates mild/no anemia. PCI indicates percutaneous coronary intervention; HR, hazard ratio; and CI, confidence interval.

\textbf{Figure 5.} Definite stent thrombosis through 4 years of follow-up with landmark analysis at 30 days. Kaplan-Meier cumulative estimates of all-cause mortality up to 4 years of follow-up stratified by anemia status with a landmark set at 30 days. \textbf{Continuous line} indicates severe anemia; \textbf{dashed line} indicates mild/no anemia. PCI indicates percutaneous coronary intervention; HR, hazard ratio; and CI, confidence interval.
hypertrophy associated with a further increase in myocardial oxygen demand and might provide a basis for the higher rate of myocardial infarction in patients with severe anemia. Alternatively, anemia might be the manifestation of some underlying chronic disease interfering with long-term survival. Even though survival analysis was adjusted for known confounding factors such as advanced age, diabetes, and chronic kidney disease, the prevalence of malignancies was not assessed and may become increasingly important with longer durations of follow-up. Finally, patients with severe anemia tend to receive more blood transfusions, which in turn have been shown to exert an adverse impact on survival independent of hemoglobin levels.

Our findings suggest that patients undergoing PCI with severe anemia at baseline are at risk for overall definite and definite or probable ST. The risk was apparent during the early study but also during the late follow-up period. Even though no difference in the prescription of dual antiplatelet therapy was noted at the time of hospital discharge, the increased risk of early ST may have been related to premature discontinuation of antiplatelet agents—a strong predictor of ST in the DES era. Alternatively, patients who had early ST also had anemia of chronic disease associated with malignancies or autoimmune diseases, which may in turn be associated with prothrombotic activity.

In conclusion, our results suggest alarmingly high rates of overall mortality and ST among patients with severe anemia treated with DES. Several reasons may explain this finding. First, the implantation of DES in patients with anemia due to chronic disease and a procoagulant state may increase the risk of ST. Second, prolonged DAPT in patients with DES may exacerbate anemia caused by occult bleeding. Third, anemia may be a more marker for adverse outcome: patients with anemia at baseline could be more likely to have adverse events because of conditions that caused anemia, irrespective of the selected type of stent. If the first 2 reasons apply, DES may be contraindicated. We therefore conclude that in patients with severe anemia, it is unclear whether the potential advantages of DES justify its use. Caution requires that unless data from randomized trials indicate otherwise, bare metal stents should be used instead. The high event rate found in our analysis suggests that a 2-arm trial with approximately 1200 patients would have enough power to detect superiority of DES over bare metal stents in terms of a clinically relevant 30% relative risk reduction in the composite of cardiac death, myocardial infarction, or TVR, and also noninferiority in terms of overall mortality at a margin of 1.3 on a relative risk scale.

Limitations
This study has several limitations. First, the presented data reflect the prospective experience of a tertiary care cardiology unit; patients with ACS referred from primary and secondary care facilities may have been pretreated (intravenous fluids, antiplatelet agents) before presentation to our institution, which might have influenced the laboratory evaluation at baseline (which was assessed immediately before PCI). Second, the observed association between anemia and clinical outcome in this observational study may be confounded by variables that were not recorded and hence could not be adjusted for (such as subclinical malignancies or inflammation). We deem it unlikely, however, that this could fully explain the associations as observed after initial and full adjustment. Bare metal stents may have been preferred in patients with severe anemia potentially caused by known chronic bleeding to circumvent the need for prolonged dual antiplatelet therapy.

Conclusions
Anemia is a common finding in patients undergoing revascularization by PCI, and severe anemia is associated with an increased risk of overall and cardiac mortality, myocardial infarction, and ST during long-term follow-up. Therefore, hemoglobin levels at presentation should be routinely considered as part of the risk stratification in patients undergoing PCI irrespective of clinical presentation with stable or unstable CAD.

Disclosures
None.

References


The Impact of Anemia on Long-Term Clinical Outcome in Patients Undergoing Revascularization With the Unrestricted Use of Drug-Eluting Stents


Circ Cardiovasc Interv. 2012;5:202-210; originally published online March 27, 2012; doi: 10.1161/CIRCINTERVENTIONS.111.965749

Circulation: Cardiovascular Interventions is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2012 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-7640. Online ISSN: 1941-7632

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circinterventions.ahajournals.org/content/5/2/202

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation: Cardiovascular Interventions can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation: Cardiovascular Interventions is online at:
http://circinterventions.ahajournals.org/subscriptions/