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Review

Is anemia a new cardiovascular risk factor?

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ABSTRACT

Anemia is frequent in patients with cardiovascular disease and is often characterized as the fifth cardiovascular risk factor. It is considered to develop due to a complex interaction of iron deficiency, cytokine production and impaired renal function, although other factors, such as blood loss, may also contribute. Unfortunately, treatment of anemia in cardiovascular disease lacks clear targets and specific therapy is not defined. Treatment with erythropoietin-stimulating agents in combination with iron is the basic strategy but clear guidelines are not currently available. This review aims to clarify poorly investigated and defined issues concerning the relation of anemia and cardiovascular risk – in particular in patients with acute coronary syndromes and chronic heart failure – as well as the current therapeutic strategies in these clinical conditions.

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Cardiovascular disease is a significant health issue around the world and accounts for a majority of deaths each year in westernized countries. In the United States cardiovascular disease accounts for one of every two deaths [1]. This increased death rate, despite advances in medical treatment, points to the importance of identifying factors related to poor outcomes and developing new treatment and prevention modalities. Anemia is common in patients with cardiovascular disease and is a multifactorial problem especially in the elderly population [2]. The odds ratio of mortality, morbidity and hospitalization in patients with anemia is similar to those of four other common cardiovascular risk factors, such as smoking, diabetes mellitus (DM), arterial hypertension and hypercholesterolemia. Consequently, anemia has lately been characterized as "the fifth cardiovascular risk factor" [2]. The purpose of the present review is to investigate most of the related issues and treatment options in the management of cardiovascular risk in anemic patients. In specific, the relationship of anemia with acute coronary syndromes (ACS) and CHF is sought.

1. Definitions

According to WHO criteria, anemia is defined as a concentration of Hb <13 g/dl in men and <12 g/dl in women [3]. In general, risk factor is defined as any biological condition, substance, or behavior which has an association with, but has not been proven to cause an event or disease. Furthermore, cardiovascular risk is defined as the ten-year risk of cardiovascular disease occurrence and is divided into low, moderate, high and very high additional risk [3]. According to Framingham, the low cardiovascular risk is <15%, moderate is 15–20%, high is 20–30% and very high is >30%, while according to the European cardiovascular disease risk assessment model (SCORE) which concerns ten-year risk of fatal cardiovascular disease, the low is <1%, moderate is 1–5%, high is 5–10% and very high is >10% [4].

2. Anemia & acute coronary syndromes

Anemia is present in one third of patients with ACS; in particular, in 12.8% of patients with acute myocardial infarction (AMI), in 43% of the elderly patients with ST-elevation myocardial infarction (STEMI) and in 5–10% of non-ST elevation ACS patients [5]. Patients without coronary heart disease have a tremendous ability to compensate for diseases in coronary arterial oxygen content, while those with coronary artery disease have a limited ability to compensate for or to tolerate uncompensated decreases in myocardial oxygen delivery. At the coronary level, ischemia causes a critical imbalance in oxygen supply and demand to the myocardium. Protracting this condition induces necrosis since, when the heart surpasses certain limits, it is incapable of modulating

Abbreviations: ACS, acute coronary syndromes; AMI, acute myocardial infarction; CHF, chronic heart failure; CHOIR trial, Correction of Hb and Outcomes in Renal Insufficiency; CPG, Committee for Practice Guidelines; DM, diabetes mellitus; EAS, European Atherosclerosis Society; ESAs, erythropoiesis-stimulating agents; ESC, European Society of Cardiology; HMW, high molecular weight; LDL, low density lipoproteins; PCI, percutaneous coronary intervention; RDW, red cell distribution width; STEMI, ST-elevation myocardial infarction; sTfR, soluble transferrin receptor; TSAT, transferrin saturation.

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its metabolism in relation to the availability of energy substrates. The drop in circulating erythrocyte mass and the consequent decrease in hemoglobin and hematocrit represent obstacles to oxygen transport and delivery to tissues. Tachycardia secondary to anemia leads to a shorter diastolic phase and reduction in arterial pressure, phenomena which are particularly prominent in acute anemia. Such changes can result in serious repercussions for patients suffering from coronary disease, leading often to documentable myocardial damage [6].

The high risk for ACS in anemic patients is also probably associated with the low levels of high-molecular-weight adiponectin, which has anti-inflammatory and atherosclerotic effects [7]. Recent data also suggest that ACS patients with anemia demonstrate a reduced number of peripheral endothelial progenitor cells with impaired function, possibly representing a lower capacity for vascular healing. These phenomena may partly explain the poor prognosis observed in anemic patients with ACS [8].

Furthermore, anemia may predispose patients to recurrent ischemia, which can be an important underlying mediator of worse outcomes [9]. Recent studies suggest that patients with anemia have a greater burden of necrotic core and thin-cap fibroatheroma, which may contribute to future adverse events including recurrent AMI. In one study, virtual histology intravascular ultrasound analysis demonstrated that anemia at the time of clinical presentation was associated with more vulnerable plaque component in patients with ACS [10].

Baseline anemia with lower admission Hb levels is associated with longer duration of symptoms in men with STEMI and inversely related to their admission inflammatory surrogate (CRP) levels [11]. It is known that CRP induces plasminogen activator inhibitor-1 expression and activity in human aortic endothelial cells and thus could have implications in the development of atherothrombosis. Elevated inflammatory levels in anemic patients might be a contributor to adverse clinical events [12]. Anemia on admission provides independent prognostic information on top of the GRACE score for the prediction of mortality or recurrent AMI in ACS patients at 1-month follow-up with a decrease of Hb of more than 0.9 g/dl indicating high-risk ACS [5].

Moderate and severe in-hospital acquired new-onset anemia, in patients admitted with normal hemoglobin, is a common complication during AMI, frequently persists after discharge and is associated with poor outcomes, namely a higher mortality rate and incidence of complications in comparison with patients who maintain normal Hb values [13].

It could be explained by in-hospital antithrombotic therapy, obscure bleeding, repeating blood withdrawal, as well as hemodilution due to iv fluid administration as preparation prior to coronary angiography. The incidence of in-hospital acquired anemia varies significantly across hospitals and this variability may reflect that different processes of in-hospital care [14].

Anemia may be caused by bleeding episodes during invasive procedures and intensive anticoagulation in the setting of ACS, but it is also observed in AMI patients who are treated conservatively without bleeding complications [15], which suggests that mechanisms other than bleeding may play a role to the development of anemia. Tissue injury in AMI incites an acute inflammatory response that may persist for a long time [16]. The inflammation interacts with the hematopoietic system at various levels and results in reduced erythropoiesis, accelerated destruction of erythrocytes and erythropoietin resistance [17].

Preprocedural anemia is associated with increased adverse in-hospital events after primary percutaneous coronary intervention (PCI) [18]. Patients with anemia undergoing primary PCI are at a higher risk of an adverse outcome. Although anemia does not appear to be an independent predictor of all-cause mortality or major adverse cardiac events after primary PCI on multivariate analysis, there appears to be a threshold value of Hb among men, below which there is an associated increased risk [19]. Another analysis from the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) trial demonstrated that baseline anemia was an independent predictor of in-hospital and 1-year mortality. Patients with anemia had more bleeding complications and blood transfusions along with increased 30-day and 1-year rates of disabling stroke [20]. Furthermore, an association between low serum iron concentration before primary PCI and impaired recovery of LV systolic function 6 months later has been found. The circulating concentration of IL-6 was increased after STEMI and negatively correlated with serum iron concentration. Thus serum iron concentration is associated with a cardioprotective phenotype and is a potential biomarker for complications after STEMI [21].

Although, there is a clear correlation between anemia and mortality in patients with ACS (Table 1), there is little clinical evidence that permits prediction of the critical hemoglobin or hematocrit at which significant ischemia will develop in any given patient [22]. According to Sabatin et al. [23], Hb levels <10 g/dl are related to a significant risk of cardiovascular death in patients with ACS (Fig. 1). The higher Ht is associated with a lower risk of cardiovascular death and it seems that for each Ht increase of 1% there is a 4% reduction of cardiovascular risk [24]. However, it is also worth mentioning that Hb >17 g/dl brings about very serious risks [25].

3. Anemia & chronic heart failure

CHF is a complex clinical syndrome of symptoms and signs in which the efficiency of the heart as a pump is impaired. It is caused by cardiac dysfunction, generally resulting from any structural or functional impairment of ventricular ejection or filling of blood characterized by either LV dilation or hypertrophy or both. Whether the dysfunction is primarily systolic or diastolic or mixed, it leads to neurohormonal and circulatory abnormalities, usually resulting in characteristic symptoms such as dyspnea and fatigue, which may limit exercise tolerance, and fluid retention in the pulmonary and/or splanchnic circulation, and/or peripheral edema [26,27].

Table 1
The five main studies concerning occurrence of cardiovascular risk in anemic patients.

Studies	Results
ARIC study [76] (Atherosclerosis Risk in Communities)	14,410 people aged 45–64 years from the general population without cardiovascular disease. 1358 of them had low Hb. In 6.1 years cardiovascular–coronary events were observed at a rate of 3.8%. Anemia is an independent prognostic marker with regard to coronary disease risk.
CADILLAC study [20] (Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications)	2082 patients of any age with acute myocardial infarction. Anemia was present in 260 (12.8%) and is strongly associated with adverse outcomes and increased mortality.
Meneveau et al. [5] (Registre Franc Comtois des Syndromes Coronariens Aigus)	1410 consecutive patients with acute coronary syndromes. Anemia was detected in 381 patients (27%). Anemia was an independent predictive factor of mortality and had incremental predictive value to the GRACE score system for early clinical outcomes.
NHANES II survey [77] (National Health And Nutrition Examination Survey)	8896 persons from NHANES II survey. 1629 men and 1706 women were with Ht in the lower tertile. There is no specific correlation between anemia and cardiovascular risk.
SOLVD study [29,30] (Studies Of Left Ventricular Dysfunction)	6538 patients with depressed left ventricular function. After adjusting for possible confounders, including renal function, low Ht was associated with the risk of CV mortality, HF death, HF hospitalization and cardiac ischemic events.

Abbreviations as in the text.

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