PREGLEDNI RAD REVIEW ARTICLE

ANEMIA AND HEART FAILURE

Zorica Cvetković[1,2], Gligorije Marinković[1], Ilija Bukurecki[3], Olivera Marković[2,3]

[1] Kliničko-bolnički centar „Zemun", Klinika za internu medicinu, Služba hematologije, Beograd, Srbija

[2] Univerzitet u Beogradu, Medicinski fakultet, Beograd, Srbija

[3] Kliničko-bolnički centar „Bežanijska kosa", Klinika za internu medicinu, Odeljenje hematologije Beograd, Srbija

[1] *University Hospital Medical Center Zemun, Clinic for Internal Medicine, Department of Hematology, Belgrade, Serbia*

[2] *University of Belgrade, Faculty of Medicine, Belgrade, Serbia*

[3] *University Hospital Medical Center Bežanijska kosa, Clinic for Internal Medicine. Department of Hematology, Belgrade, Serbia*

SAŽETAK

Prisustvo anemije kod bolesnika sa srčanom slabošću predstavlja nezavisni loš prognostički faktor. Etiologija anemije je multifaktorijalna, a u njoj učestvuju kako priroda same hronične srčane slabosti, tako i starije životno doba ovih bolesnika i učestali komorbiditeti. Apsolutni ili funkcionalni deficit gvožđa, čak i u odsustvu anemije, kod bolesnika sa srčanom slabošću značajno utiče na opadanje kvaliteta života, te na povećanje učestalosti hospitalizacije i mortaliteta. Kompleksna etiologija i patofiziologija anemije otežavaju pravilno tumačenje laboratorijskih parametara metabolizma gvožđa, a takođe iziskuju i specifičan terapijski pristup.

Ključne reči: anemija, srčana slabost, etiologija, lečenje

ABSTRACT

The presence of anemia in patients with heart failure is a significant independent adverse prognostic factor. The etiology of anemia is multifactorial and the nature of heart failure itself, advanced age, and frequent comorbidities contribute to its development. Notably, absolute or functional iron deficiency, even in the absence of anemia, significantly diminishes the quality of life, increases hospitalization frequency, and raises mortality rates in patients with heart failure. The intricate etiology and pathophysiology of anemia present a challenge for the accurate interpretation of laboratory parameters of iron metabolism and necessitate a tailored therapeutic approach.

Keywords: anemia, heart failure, etiology, treatment

Autor za korespondenciju:
Zorica Cvetković
Služba hematologije, Klinika za internu medicinu,
Kliničko-bolnički centar „Zemun"
Vukova 9, 11080 Beograd, Srbija
Elektronska adresa: zcvetkovic06@gmail.com

Corresponding author:
Zorica Cvetković
Department of Hematology, Clinic for Internal Medicine,
University Hospital Medical Center Zemun
9 Vukova Street, 11080 Belgrade, Serbia
E-mail: zcvetkovic06@gmail.com

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UVOD

Anemija i dalje predstavlja veliki globalni zdravstveni problem, iako je poslednjih godina primećen značajan opadajući trend, nastao zahvaljujući preventivnim merama. Na osnovu analize sprovedene 2019. godine u 204 zemlje širom sveta, procenjeno je da 1,8 milijardi ljudi ima anemiju, sa starosno prilagođenom prevalencijom od 23% [1]. Najnoviji epidemiološki podaci pokazuju da oko 64 miliona ljudi u svetu boluje od srčane slabosti. Dok se incidencija srčane slabosti u razvijenim zemljama stabilizuje ili blago opada, njena prevalencija raste zbog uspešnijeg lečenja ishemijske bolesti srca, koja je glavni uzrok srčane slabosti, kao i zbog novih terapijskih pristupa u lečenju same srčane slabosti, te ukupnog starenja svetske populacije [2].

Prema važećim kriterijumima Svetske zdravstvene organizacije (SZO), anemija se kod odraslih osoba definiše kao pad nivoa hemoglobina (Hb) ispod 120 g/l kod žena, odnosno ispod 130 g/l kod muškaraca. U zavisnosti od stepena pada nivoa hemoglobina u krvi, anemija se klasifikuje na sledeći način: blaga (Hb ≥ 110 g/l), srednje teška (80 g/l – 109 g/l) i teška (Hb < 80 g/l) [3]. Srčana slabost (engl. *heart failure – HF*) je sindrom nastao kao rezultat strukturnih i/ili funkcionalnih oštećenja srca koji dovode do povećanja intrakardijalnog pritiska i/ili smanjenja minutnog volumena srca u mirovanju ili tokom fizičkog napora. Srčana slabost se može klasifikovati u sledeće tri grupe: 1) *HFrEF* – srčana slabost sa smanjenom ejekcionom frakcijom leve komore (engl. *HF with reduced left ventricular ejection fraction*), (*LVEF* ≤ 40%); 2) *HFmrEF* – srčana slabost sa umereno smanjenom *LVEF* (engl. *HF with moderately reduced LVEF*), (*LVEF* = 41% – 49%); i 3) *HFpEF* – srčana slabost sa očuvanom *LVEF* (engl. *HF with preserved LVEF*), (*LVEF* ≥ 50%) [4,5]. Najnoviji epidemiološki podaci pokazuju da oko 64 miliona ljudi širom sveta boluje od srčane slabosti.

Epidemiološka istraživanja su otkrila da je prevalencija anemije kod obolelih od srčane slabosti oko 30% kod ambulantnih pacijenata, a čak 50% kod hospitalizovanih pacijenata, što je mnogo više nego u opštoj populaciji [6]. Utvrđeno je da se incidencija anemije povećava sa stadijumom, odnosno funkcionalnom klasom srčane slabosti, u rasponu od 9%, kod *New York Heart Association* klase I (engl. *NYHA Class I*), do 79%, kod *NYHA* klase IV [7]. Štaviše, incidencija anemije progresivno raste sa trajanjem srčane slabosti. Rezultati studije *Studies of Left Ventricular Disfunction* (*SOLVD*) pokazali su da je 9% pacijenata sa normalnim nivoom hemoglobina u vreme dijagnoze srčane slabosti razvilo anemiju u prvoj godini praćenja [8], dok je u studiji *Carvedilol and Metoprolol European Trial* (*COMET*) prevalencija anemije bila iznad 25%, nakon petogodišnjeg praćenja [9].

INTRODUCTION

Anemia remains a major global health problem, although a significant downward trend has been observed in recent years, thanks to preventive measures. Based on the analysis conducted in 2019, in 204 countries worldwide, it has been estimated that 1.8 billion people have anemia, with an age-adjusted prevalence of 23% [1]. The latest epidemiological data show that around 64 million people in the world suffer from heart failure (HF). While the incidence of HF in developed countries is stabilizing or slightly declining, its prevalence is increasing due to the improved treatment of ischemic heart disease, which is the main cause of HF, as well as due to new therapeutic approaches to HF treatment and the overall aging of the global population [2].

According to the current World Health Organization (WHO) criteria, anemia in adults is defined as a drop in hemoglobin (Hb) levels below 120 g/l in women, i.e., below 130 g/l in men, and, depending on the degree of Hb reduction, it is graded in the following manner: mild (Hb ≥ 110 g/l), moderate (80 g/l – 109 g/l), and severe (Hb < 80 g/l) [3]. Heart failure (HF) is a syndrome resulting from structural and/or functional heart impairments leading to an increase in intracardiac pressures and/or a decrease in cardiac output at rest or during exertion. HF can be classified into the following three groups: 1) HF with reduced left ventricular ejection fraction (HFrEF), (LVEF ≤ 40%); 2) HF with moderately reduced LVEF (HFmrEF), (LVEF = 41% – 49%); and 3) HF with preserved LVEF (HFpEF), (LVEF ≥ 50%) [4,5]. The latest epidemiological data show that approximately 64 million people worldwide suffer from HF.

Epidemiological studies have revealed that the prevalence of anemia in patients with HF is around 30% in outpatients and as high as 50% in hospitalized patients, which is much higher than in the general population [6]. It has been found that the incidence of anemia increases with the HF stage, i.e., HF functional class, ranging from 9%, in New York Heart Association (NYHA) Class I, to 79%, in NYHA Class IV [7]. Furthermore, the incidence of anemia progressively increases with the duration of HF. The results of the Studies of Left Ventricular Dysfunction (SOLVD) showed that 9% of patients with normal Hb levels at the time of HF diagnosis developed anemia within the first year of follow-up [8], while in the Carvedilol and Metoprolol European Trial (COMET), the prevalence of anemia was above 25%, after five-year follow-up [9].

In the recommendations of the European Society of Cardiology (ESC) for the treatment of HF, iron deficiency (ID), irrespective of the presence of anemia, is particularly recognized as an adverse risk factor in

U preporukama Evropskog kardiološkog društva (engl. *European Society of Cardiology – ESC*) za lečenje srčane slabosti, deficit gvožđa (engl. *iron deficiency – ID*) je, bez obzira na to da li je prisutna i anemija, posebno prepoznat kao nepovoljan faktor rizika kod *HFmrEF* i *HFrEF*, koji značajno otežava tok bolesti. Zbog toga je neophodno proveriti prisustvo anemije i deficita gvožđa kod svih bolesnika sa srčanom slabošću [4,5]. Studija sprovedena u 48 medicinskih centara u Francuskoj (studijska grupa *CARENFER*), koja je obuhvatila 1.475 pacijenata sa dekompenzovanom srčanom slabošću i hroničnom srčanom slabošću, a čija je prosečna starost bila 78 godina, pokazala je ukupnu prevalenciju deficita gvožđa od 49,5%. Međutim, kada su bolesnici stratifikovani prema težini srčane slabosti – dekompenzovana srčana slabost (60,1% ispitanika) i hronična srčana slabost, i zatim podeljeni u tri kategorije prema preporukama *ESC*-a, prevalencija deficita gvožđa kod pacijenata sa dekompenzovanom srčanom slabošću je iznosila 58,1%, u poređenju sa prevalencijom od 39% kod onih sa hroničnom srčanom slabošću. Među pacijentima sa hroničnom srčanom slabošću, prevalencija deficita gvožđa je bila najveća u *HFpEF* grupi (*HFpEF* 57,3%; *HFmrEF* 47,4%; *HFrEF* 44,3%) [10]. Novija istraživanja ukazuju na to da anemija značajno doprinosi smanjenju tolerancijie fizičkog napora kod osoba sa *HFpEF* [11], ali i da sam deficit gvožđa značajno povećava rizik od mortaliteta kod pacijenata sa *HFpEF* [12].

ETIOLOGIJA I PATOFIZIOLOGIJA ANEMIJE KOD SRČANE SLABOSTI

Anemija kod srčane slabosti ima složenu i multifaktorsku etiologiju, u kojoj sama srčana slabost i prateća stanja igraju značajnu ulogu. Preko 85% pacijenata sa srčanom slabošću pati od dve ili više hroničnih bolesti, a prosečan broj kardiovaskularnih i nekardiovaskularnih komorbiditeta po hospitalizovanom pacijentu sa srčanom slabošću iznosi oko četiri. Pored anemije, uobičajeni nekardiovaskularni komorbiditeti srčane slabosti uključuju i gojaznost, dijabetes, bubrežnu insuficijenciju, neravnotežu elektrolita, poremećaj funkcije štitaste žlezde, hroničnu opstruktivnu bolest pluća, apneju u snu, i maligne bolesti [13,14]. Pacijenti sa srčanom slabošću su po pravilu starije osobe koje često ispoljavaju karakteristike anemije povezane sa starošću, što može biti u vezi sa nepravilnom ishranom (siromaštvo, neuhranjenost) i hroničnim zapaljenjem [15]. Anemija kod srčane slabosti je obično blaga do srednje teška, a njen primarni uzrok je često deficit gvožđa, bilo da je apsolutni ili funkcionalni. Čak i bez anemije, deficit gvožđa može značajno da smanji funkcionalnost i kvalitet života [1]. Procenjuje se da 47% – 68% pacijenata sa hroničnom srčanom slabošću ima apsolutni ili funkcionalni deficit gvožđa [16].

HFmrEF and HFrEF that significantly complicates the course of the disease. This is why it is necessary to carry out screening for the presence of anemia and ID in all patients with HF [4,5]. A study conducted in 48 medical centers in France (CARENFER study group), which included 1,475 patients with decompensated HF and chronic HF, whose average age was 78 years, showed a total prevalence of ID of 49.5%. However, when the patients were stratified according to the severity of HF – decompensated HF (60.1% of respondents) and chronic HF, and then divided into three categories according to ESC recommendations, the prevalence of ID among patients with decompensated HF was 58.1%, as compared to a prevalence of 39% in those with chronic HF. Among the latter, the prevalence of ID was the highest in the HFpEF group (HFpEF 57.3%; HFmrEF 47.4%; HFrEF 44.3%) [10]. New research indicates that anemia significantly contributes to reduced exercise tolerance in people with HFpEF [11], but also that ID itself markedly increases the risk of mortality in patients with HFpEF [12].

ETIOLOGY AND PATHOPHYSIOLOGY OF ANEMIA IN HEART FAILURE

The etiology of anemia in heart failure is complex and multifactorial, wherein HF itself and associated conditions play a significant role. Over 85% of patients with HF suffer from two or more chronic diseases, and the average number of cardiovascular and non-cardiovascular comorbidities per hospitalized patient with HF is approximately four. In addition to anemia, common non-cardiovascular comorbidities include obesity, diabetes, renal failure, electrolyte imbalance, thyroid gland dysfunction, chronic obstructive pulmonary disease, sleep apnea, and malignant diseases [13,14]. Patients with HF are typically older and often exhibit characteristics of anemia related to old age, which can be linked to improper nutrition (poverty, malnutrition) and chronic inflammation [15]. Anemia in HF is usually mild to moderate, and its primary cause is often iron deficiency, whether absolute or functional. Even without anemia, ID can significantly reduce functionality and quality of life [1]. It is estimated that 47% – 68% of patients with chronic HF have absolute or functional ID [16].

Iron is an integral component of the metalloprotein hemoglobin, essential for transporting oxygen to all cells in the body. Due to its chemical properties, which allow it to accept and release electrons easily, changing from a divalent (ferrous) to a trivalent (ferric) form, iron is also an integral part of enzymes and enzyme activators involved in crucial body processes. Iron controls the expression of aconitase, a key enzyme in the Krebs

Gvožđe je sastavni deo metaloproteina hemoglobina, koji je neophodan za transport kiseonika do svih ćelija u telu. Zbog svojih hemijskih osobina, koje mu omogućavaju da lako prima i otpušta elektrone, prelazeći iz dvovalentnog (fero) u trovalentni (feri) oblik, gvožđe je takođe sastavni deo enzima i aktivatora enzima uključenih u ključne procese u telu. Gvožđe kontroliše ekspresiju akonitaze, ključnog enzima u Krebsovom ciklusu (ciklus limunske kiseline), koji olakšava prenos elektrona u redoks reakcijama. Pošto srčani mišić obiluje mitohondrijama, neophodne su odgovarajuće koncentracije gvožđa za pravilan tok redoks reakcija i za sprečavanje stvaranja slobodnih radikala koji utiču na remodelovanje i apoptozu kod srčane slabosti [17].

Uzroci apsolutnog deficita gvožđa (engl. *iron deficiency – ID*) i sideropenijske anemije (engl. *iron deficiency anemia – IDA*) su raznovrsni, od nepravilne ishrane (npr. vegetarijanska ishrana; veganska ishrana; ishrana zasnovana uglavnom na mleku i mlečnim proizvodima; ishrana zasnovana na hrani bogatoj fitatima – žitarice, soja, mahunarke; prekomerno konzumiranje pića koja sadrže tanine – kafa, čaj, crno vino), preko malapsorpcije u dvanaestopalačnom crevu (npr. autoimuni atrofični gastritis, celijakija, necelijačna glutenska enteropatija i drugi sindromi malapsorpcije, barijatrijska hirurgija, zapaljenske bolesti creva); povećane potrebe za gvožđem (npr. tokom postoperativnog oporavka; tokom primene eritropoetina – EPO), urođenog nedostatka transportera gvožđa (npr. hem oksigenaza, dvovalentni metalni transporter 1 – DMT1), do povećanog gubitka krvi (npr. krvarenje iz urogenitalnog i digestivnog trakta), što je najčešći uzrok anemije u razvijenim zemljama [18,19].

Funkcionalni deficit gvožđa je nedostatak gvožđa u cirkulaciji koje ostaje zarobljeno u makrofagima, što se javlja u stanjima hronične upale. Prevalencija funkcionalnog deficita gvožđa kod pacijenata sa srčanom slabošću, koja je takođe hronično proinflamatorno stanje, iznosi oko 18% [20]. Povećana proizvodnja proinflamatornih citokina, kao što su interleukin-6 (IL-6), IL-1β, IL-2, IL-8, IL-33, interferon-g (IFN-g), galektin-3, faktor nekroze tumora-1 (engl. *tumor necrosis factor-1 – TNF-1*), pentraksin-3, te smanjena proizvodnja zaštitnih citokina, kao što je IL-10, dokazane su kod srčane slabosti, dovodeći do sledećih pojava: a) hipoferemije izazvane povećanom proizvodnjom hepcidina, što izaziva degradaciju feroportina, izvoznika intracelularnog gvožđa, zbog čega gvožđe ostaje zarobljeno u makrofagima, enterocitima i hepatocitima i nije dostupno prekursorima eritropoeze u koštanoj srži; b) direktnog suzbijanja eritropoeze; c) umerenog skraćivanja životnog veka eritrocita usled njihove pojačane razgradnje; g) smanjene proizvodnje EPO-a [21–24]. Hronična bubrežna insuficijencija takođe doprinosi smanjenoj proizvodnji EPO-a,

cycle (citric acid cycle) that facilitates electron transfer in redox reactions. Since the heart muscle is abundant with mitochondria, appropriate iron concentrations are necessary for the proper course of redox reactions and for preventing the formation of free radicals that affect remodeling and apoptosis in HF [17].

The causes of absolute iron deficiency (ID) and iron deficiency anemia (IDA) are diverse, ranging from improper nutrition (e.g., vegetarian diet; vegan diet; diet based mainly on milk and dairy products; diet based on foods rich in phytates – cereals, soy, legumes; excessive intake of beverages with tannins – coffee, tea, red wine), malabsorption in the duodenum (e.g., autoimmune atrophic gastritis, celiac disease, non-celiac gluten enteropathy and other malabsorption syndromes, bariatric surgery, inflammatory bowel diseases – IBD), increased iron needs (e.g., during postoperative recovery; during the administration of erythropoietin – EPO), congenital deficiency of iron transporters (e.g., heme oxygenase, divalent metal transporter 1 – DMT1), to increased blood loss (e.g., bleeding from the urogenital and digestive tract), which is the most common cause of anemia in developed countries [18,19].

Functional ID is a deficiency of circulating iron that remains trapped in macrophages, which occurs in states of chronic inflammation. The prevalence of functional ID in patients with HF, which is also a chronic proinflammatory condition, is about 18% [20]. Increased production of proinflammatory cytokines, such as interleukin-6 (IL-6), IL-1β, IL-2, IL-8, IL-33, interferon-γ (IFN-γ), galectin-3, tumor necrosis factor-1 (TNF-1), pentraxin-3, and reduced production of protective cytokines, such as IL-10, have been proven in HF, leading to the following: a) hypoferremia caused by the increased secretion of hepcidin, which causes the degradation of ferroportin, the exporter of intracellular iron, which is why iron remains captured in macrophages, enterocytes, and hepatocytes and is not available to the precursors of erythropoiesis in the bone marrow; b) direct suppression of erythropoiesis; c) moderate shortening of the lifespan of erythrocytes due to their increased destruction; d) reduced production of EPO [21–24]. Chronic kidney failure also contributes to reduced EPO production, and almost 45% of patients with terminal renal failure develop HF, i.e., cardiorenal syndrome type 4 [25,26].

It's important to note that various medications can often cause ID/IDA. Certain drugs like antihistamines (H2 blockers), antacids, proton pump inhibitors (PPIs), some antibiotics (penicillin, ciprofloxacin, tetracyclines), cholestyramine, and anticonvulsants reduce iron absorption. On the other hand, nonsteroidal antirheumatic drugs, antiplatelet drugs, and anticoag-

a kod skoro 45% pacijenata sa terminalnom bubrežnom insuficijencijom dolazi do razvoja srčane slabosti, odnosno kardiorenalnog sindroma tipa 4 [25,26].

Važno je naglasiti da različiti lekovi često mogu izazvati deficit gvožđa/sideropenijsku anemiju. Određeni lekovi, kao što su antihistaminici (H2 blokatori), antacidi, inhibitori protonske pumpe (engl. *proton pump inhibitors – PPIs*), neki antibiotici (penicilin, ciprofloksacin, tetraciklini), holestiramin i antikonvulzanti, smanjuju apsorpciju gvožđa. S druge strane, nesteroidni antireumatski lekovi, antiagregacioni lekovi i antikoagulansi dovode do krvarenja [18]. Štaviše, *ACE* inhibitori (engl. *angiotensin-converting enzyme inhibitors – ACE inhibitors*) i AT1-antagonisti (blokatori angiotenzina) deluju preko renin-angiotenzin-aldosteron sistema (RAAS), umanjujući na taj način efekte remodelovanja i simpatičke efekte, a svojim uticajem na angiotenzin II suzbijaju sintezu EPO-a i proliferaciju eritroidnih progenitora u koštanoj srži [20,27]. Uz to, *ACE* inhibitori dovode do povećane proizvodnje N-acetil-seril-aspartil-lizil-prolina, što utiče na smanjenje sekrecije EPO-a, a ovo dovodi do smanjenja eritrocitopoeze i pada koncentracije hemoglobina za 5 g/l [27,28].

Maligna oboljenja su, uz kardiovaskularne bolesti, glavni uzrok morbiditeta i mortaliteta, kao i vodeći uzrok prerane smrti u razvijenim zemljama. Antineoplastična terapija (konvencionalni citostatici, imunoterapija i ciljana terapija, terapija zračenjem) može dovesti do ranih i kasnih kardiovaskularnih komplikacija, najčešće do srčane slabosti [29,30], ali i do pojave ili pogoršanja anemije [31]. Sa druge strane, primećeno je da upotreba *SGLT2* inhibitora (engl. *sodium-glucose cotransporter 2 inhibitors*), koja značajno smanjuje mortalitet kod pacijenata sa kardiorenalnim sindromom, ima povoljan efekat i na anemiju. Iako tačan mehanizam nije poznat, veruje se da *SGLT* inhibitori deluju na homeostazu gvožđa, smanjuju lučenje proinflamatornih citokina i indukuju lučenje EPO-a [27,32,33].

Pored gore opisanih uzroka, pad nivoa hemoglobina kod pacijenata sa kongestivnom srčanom slabošću može se pripisati hipervolemiji, koja dovodi do hemodilucije, a koju karakteriše povećanje zapremine plazme uz normalnu masu eritrocita. Do 46% pacijenata sa srčanom slabošću ima hemodiluciju [34].

UTICAJ ANEMIJE NA KVALITET ŽIVOTA I MORTALITET PACIJENATA SA SRČANOM INSUFICIJENCIJOM

Čak i kad nema srčane slabosti, teška anemija (pad nivoa hemoglobina na 40 g/l – 50 g/l) dovodi do zadržavanja natrijuma i vode, smanjene bubrežne perfuzije, smanjene glomerularne filtracije, kao i neurohormonske aktivacije. Ovaj kardiorenalni odgovor proizilazi iz

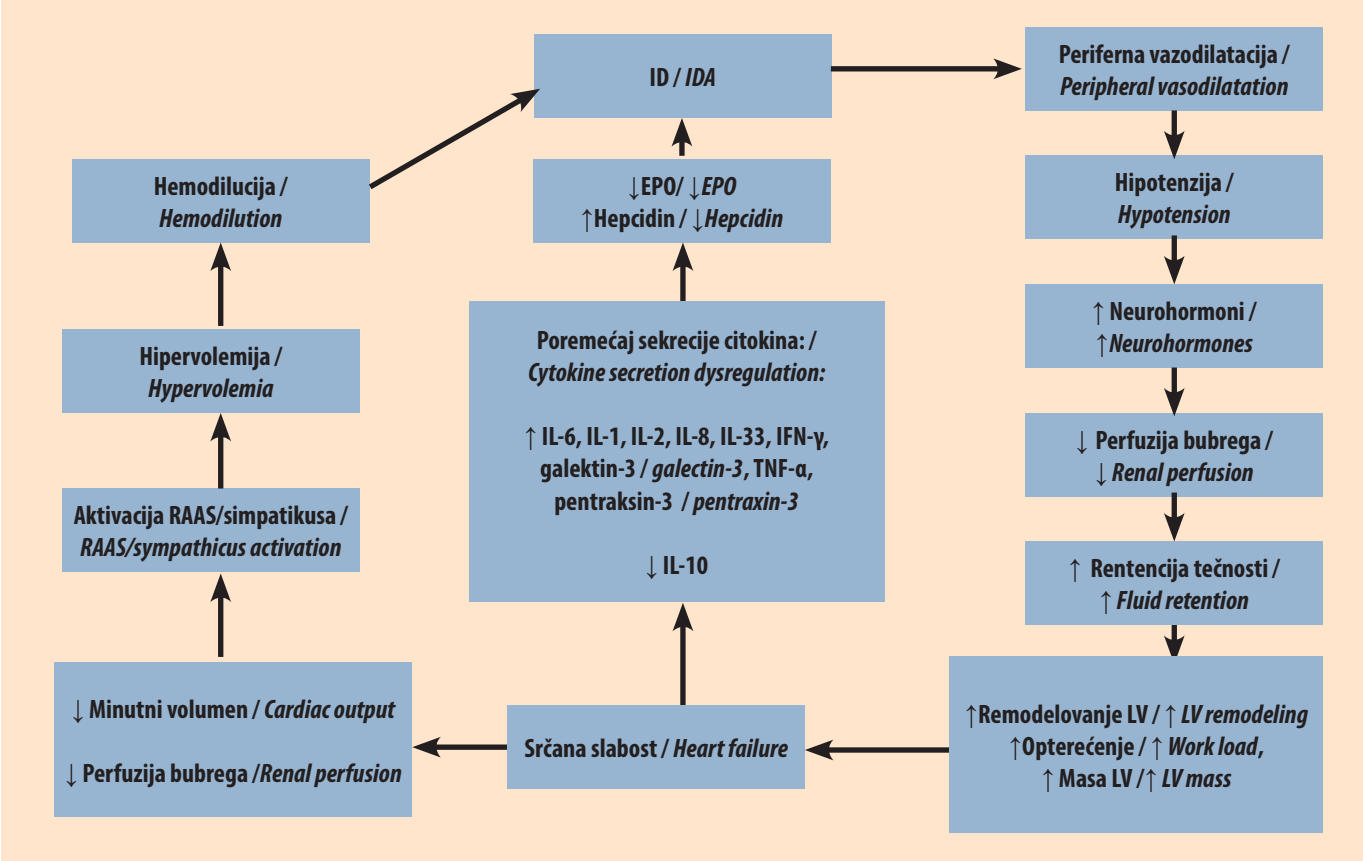
ulants lead to bleeding [18]. Furthermore, angiotensin-converting enzyme inhibitors (ACE inhibitors) and AT1-antagonists (angiotensin blockers) act via the renin-angiotensin-aldosterone system (RAAS), thereby curtailing remodeling and sympathetic effects, and, by affecting angiotensin II, they suppress the synthesis of EPO and the proliferation of erythroid progenitors in the bone marrow [20,27]. Additionally, ACE inhibitors lead to an increase in N-acetyl-seryl-aspartyl-lysyl-proline production, which affects the reduction of EPO secretion, leading to decreased erythrocytopoiesis and a drop in Hb concentration by 5 g/l [27,28].

Malignant diseases, along with cardiovascular diseases, are the main cause of morbidity and mortality, as well as the leading cause of premature death in developed countries. Antineoplastic therapy (conventional cytostatics; immunotherapy and targeted therapy; radiation therapy) can lead to early and late cardiovascular complications, most often HF [29,30], as well as the onset or worsening of anemia [31]. On the other hand, the use of sodium-glucose cotransporter (2SGLT2) inhibitors, which has significantly reduced mortality in patients with cardiorenal syndrome, has also been observed to have a beneficial effect on anemia. Although the exact mechanism is not known, it is believed that SGLT inhibitors act on iron homeostasis, reduce the secretion of pro-inflammatory cytokines, and induce the secretion of EPO [27,32,33].

In addition to the causes described above, a decline in Hb levels in patients with congestive HF can be attributed to hypervolemia, leading to hemodilution, which is characterized by an increase in plasma volume with a normal erythrocyte mass. Up to 46% of patients with HF have hemodilution [34].

THE IMPACT OF ANEMIA ON THE QUALITY OF LIFE AND MORTALITY OF PATIENTS WITH HEART FAILURE

Even in the absence of HF, severe anemia (a drop in Hb to 40 g/l – 50 g/l) leads to sodium and water retention, decreased renal perfusion, decreased glomerular filtration, and neurohormonal activation. This cardiorenal response stems from the effect of anemia on blood viscosity, oxygen pressure in the microvasculature, and nitric oxide availability. Mild anemia also contributes to neurohormonal activation (catecholamines; natriuretic peptides) and exacerbation of HF [35]. Anemia is an independent factor of poor prognosis in HF with left ventricular dysfunction, and its incidence increases with the severity of HF. According to the study: Randomized Etanercept North American Strategy to Study Antagonism of Cytokines (RENAISSANCE), the annual mortality risk in anemic HF patients is 28%, compared to 16%



Legenda: *ID* – deficit gvožđa (engl. *iron deficiency*); *IDA* – sideropenijska anemija (engl. *iron deficiency anemia*); RAAS – renin-angiotenzin-aldosteron sistem; IL – interleukin; IFN – interferon; TNF – tumor nekrotišući faktor; *LV* – leva komora (engl. *left ventricle*)

Legend: ID – iron deficiency; IDA – iron deficiency anemia; RAAS – renin-angiotensin-aldosterone system; IL – interleukin; TNF – tumor necrosis factor; LV – left ventricle

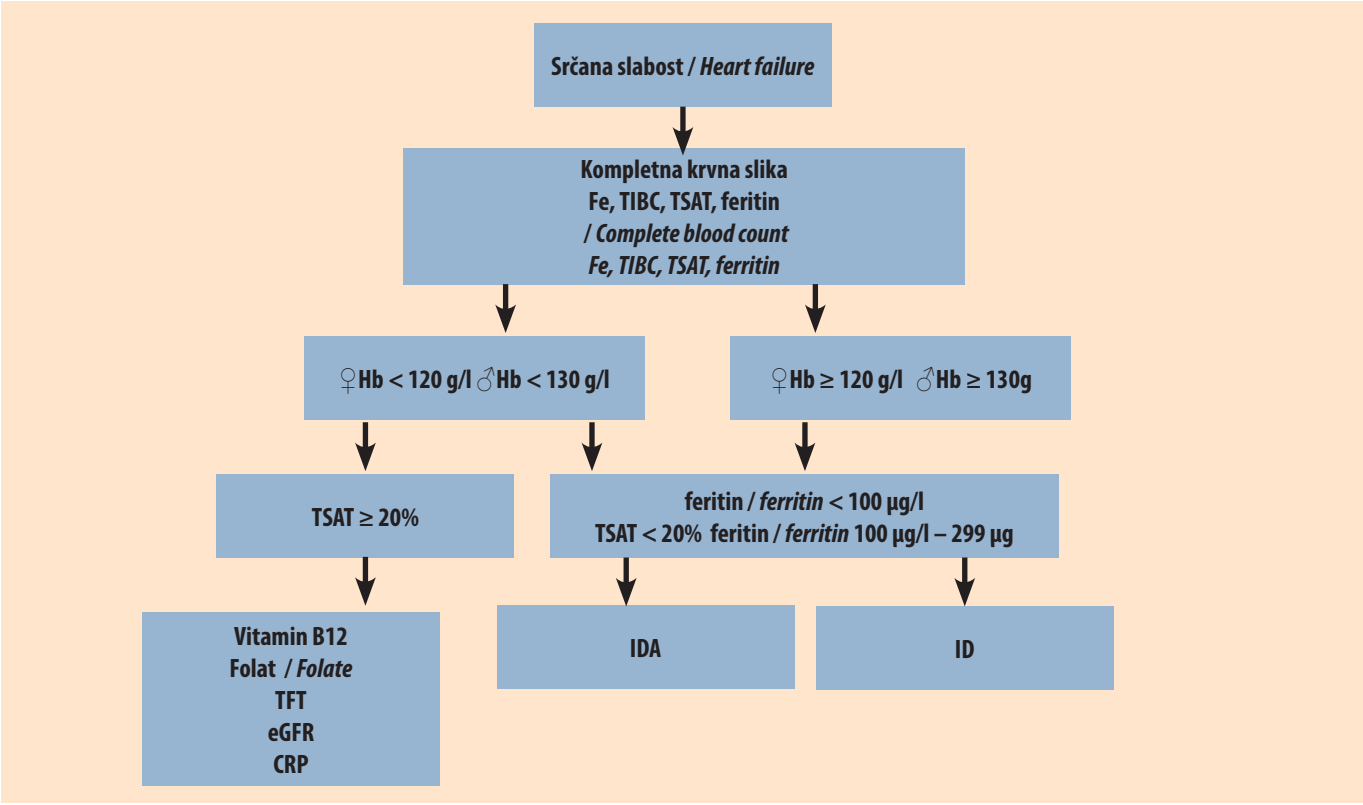
Slika 1. Patofiziološki mehanizmi međusobnog uticaja anemije i srčane slabosti

Figure 1. Pathophysiological mechanisms of the mutual effects of anemia and heart failure

uticaja anemije na viskozitet krvi, pritisak kiseonika u mikrovaskulaturi i dostupnost azot-oksida. Blaga anemija takođe doprinosi neurohormonskoj aktivaciji (kateholamini; natriuretski peptidi) i pogoršanju srčane slabosti [35]. Anemija je nezavisan faktor loše prognoze kod srčane slabosti sa disfunkcijom leve komore, a njena incidencija raste sa težinom srčane slabosti. Prema studiji: *Randomized Etanercept North American Strategy to Study Antagonism of Cytokines* (*RENAISSANCE*), godišnji rizik od smrtnosti kod anemičnih pacijenata sa srčanom slabošću je 28%, u poređenju sa 16% kod pacijenata sa srčanom slabošću bez anemije. Porast nivoa hemoglobina za 10 g/l smanjuje rizik od mortaliteta za 15,8%, a rizik od hospitalizacije za 14,2% [7]. Nasuprot tome, svako smanjenje hematokrita za 1% nosi povećanje rizika od smrtnosti od 11%, kao što je pokazano u studiji: *Prospective Randomized Amlodipine Survival Evaluation* (*PRAISE*) [36]. Rizik od ponovne hospitalizacije je takođe veći, a povećava se za 3,3% pri svakom padu nivoa hemoglobina od 10 g/l, nakon otpusta iz bolnice [20]. Studija: *Carvedilol Prospective Randomized Cumulative Survival* (*COPERNICUS*) je pokazala da je korekcija anemije i povećanje nivoa hemoglobina za

in HF patients without anemia. An increase in Hb by 10 g/l reduces the risk of mortality by 15.8% and the risk of hospitalization by 14.2% [7]. Conversely, every decrease in hematocrit by 1% carries an 11% increase in mortality risk, as shown in the study: Prospective Randomized Amlodipine Survival Evaluation (PRAISE) [36]. The risk of rehospitalization is also higher, increasing by 3.3% for every drop in the Hb level by 10 g/l, upon discharge from hospital [20]. The study: Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) showed that correction of anemia and an increase in Hb by 10 g/l was associated with a reduction in left ventricular mass by 4.1 g/m^2, over a period of 24 weeks [37]. Anemic patients with HF have a reduced exercise tolerance and poorer quality of life, and the costs of treating these patients are up to 25% higher [38].

In the absence of anemia, ID alone is also an independent factor of poor prognosis in HF. Doppler echocardiographic monitoring has shown that iron substitution in HF patients with ID significantly improves cardiac function [38]. Additionally, the six-year survival rate is significantly lower in non-anemic patients with HFpEF who have ID [12].



Legenda: Fe – gvožđe; TIBC – ukupni kapacitet vezivanja gvožđa (engl. *total iron binding capacity*); *TSAT* – saturacija transferina (engl. transferrin saturation); Hb – hemoglobin; *TFT* – testovi funkcije tireoidne žlezde; *eGFR* – procenjena brzina glomerulske filtracije (engl. *estimated glomerular filtration rate*); CRP – C reaktivni protein; *IDA* – sideropenijska anemija (engl. iron deficiency anemia); *ID* – deficit gvožđa (engl. *iron deficiency*)

Slika 2. Pojednostavljeni algoritam dijagnostike deficita gvožđa kod bolesnika sa srčanom slabošću

Legend: Fe – iron; TIBC – total iron binding capacity; TSAT – transferrin saturation; Hb – hemoglobin; TFT – thyroid function tests; eGFR – estimated glomerular filtration rate; CRP – C reactive protein; IDA – iron deficiency anemia; ID – iron deficiency

Figure 2. Simplified algorithm of iron deficiency diagnostics in patients with heart failure

10 g/l povezana sa smanjenjem mase leve komore za 4,1 g/m^2, tokom perioda od 24 nedelje [37]. Anemični bolesnici sa srčanom slabošću imaju smanjenu toleranciju fizičkog napora i lošiji kvalitet života, a troškovi lečenja ovih bolesnika su i do 25% veći [38].

U odsustvu anemije, sam deficit gvožđa je takođe nezavisan faktor loše prognoze kod srčane slabosti. Praćenje Dopler ehokardiografijom je pokazalo da supstitucija gvožđa kod pacijenata sa srčanom slabošću koji imaju deficit gvožđa značajno poboljšava srčanu funkciju [38]. Pored toga, šestogodišnja stopa preživljavanja je značajno niža kod neanemičnih pacijenata sa *HFpEF* koji imaju deficit gvožđa [12].

LABORATORIJSKE KARAKTERISTIKE ANEMIJE KOD SRČANE SLABOSTI I DIJAGNOSTIČKI ALGORITAM

Standardni laboratorijski pokazatelji sideropenijske anemije –mikrocitni eritrociti (*MCV* < 80 fl); hipoferemija (↓Fe); povećan ukupni kapacitet vezivanja gvožđa (engl. *total iron binding capacity – TIBC*); smanjena saturacija transferina (engl. *transferrin saturation – TSAT*), (*TSAT* < 20%); kao i smanjen feritin (< 30 mg/l), obično

LABORATORY CHARACTERISTICS OF ANEMIA IN HEART FAILURE AND THE DIAGNOSTIC ALGORITHM

The standard laboratory indicators of IDA – microcytic erythrocytes (MCV < 80 fl), hypoferremia (↓Fe), increased total iron binding capacity (TIBC), decreased transferrin saturation (TSAT < 20%), and reduced ferritin (< 30 µg/l) are usually absent in patients with HF, due to the above-described pathophysiological mechanisms of anemia in HF. In HF and other chronic inflammatory conditions, due to the fact that ferritin is a reactant of the acute phase, its values of up to 100 µg/l speak in favor of absolute ID, if all other laboratory characteristics of ID/IDA are present. In patients with HF whose blood ferritin level is 100 ng/ml – 299 ng/ml, ID is considered to exist, if TSAT is < 20%. These cut-off values were taken from nephrology, as they are acceptable and specific for diagnosing and treating ID [39]. When all the obtained laboratory findings are inconclusive, additional tests, such as reticulocyte hemoglobin content (CHr), soluble transferrin receptor (sTfR), and the sTfR-transferrin index, can be performed

nisu prisutni kod pacijenata sa srčanom slabošću zbog gore opisanih patofizioloških mehanizama anemije kod srčane slabosti. Kod srčane slabosti i drugih hroničnih inflamatornih stanja, zbog činjenice da je feritin reaktant akutne faze, njegove vrednosti do 100 mg/l govore u prilog apsolutnog deficita gvožđa, ukoliko su prisutne sve druge laboratorijske karakteristike deficita gvožđa/sideropenijske anemije. Kod pacijenata sa srčanom slabošću čiji je nivo feritina u krvi 100 ng/ml – 299 ng/ml, smatra se da postoji deficit gvožđa ukoliko je *TSAT* < 20%. Ove granične vrednosti su uzete iz nefrologije, pošto su prihvatljive i specifične za dijagnostikovanje i lečenje deficita gvožđa [39]. Kada se na osnovu svih dobijenih laboratorijskih nalaza ne može doneti zaključak o vrsti anemije, u specijalizovanim laboratorijama se mogu uraditi ispitivanja dodatnih parametara, kao što su sadržaj retikulocitnog hemoglobina (engl. *reticulocyte hemoglobin content – CHr*), solubilni transferinski receptor (engl. *soluble transferrin receptor – sTfR*) i *sTfR*-transferinski indeks (engl. *sTfR-transferrin index*). Pored testova gvožđa, neophodno je testirati nivoe C-reaktivnog proteina (CRP), vitamina B12, folata, tiroidnih hormona i renalnih parametara [38], kao i ispitati znakove manifestnog odnosno okultnog krvarenja [40].

Kako normalan nivo hemoglobina ne isključuje postojanje deficita gvožđa, prema aktuelnim preporukama, kod svih bolesnika sa srčanom slabošću treba sprovesti laboratorijsko testiranje pokazatelja metabolizma gvožđa [4,5,14]. Pojednostavljeni algoritam laboratorijske dijagnostike za ispitivanje deficita gvožđa/sideropenijske anemije predstavljen je na Slici 2.

LEČENJE ANEMIJE KOD SRČANE SLABOSTI

Prema preporukama Svetske zdravstvene organizacije, nadoknadu gvožđa treba započeti pri nivoima feritina ispod 30 mg/l, pošto se simptomi kod zdravih osoba javljaju već u fazi pojave deficita gvožđa [3]. Zbog povoljne cene i lakoće primene, u lečenju deficita gvožđa/sideropenijske anemije, lekovi prvog izbora su standardni oralni preparati (dvovalentnog i trovalentnog) gvožđa [3,19]. Međutim oko 30% – 70% pacijenata ne podnosi dobro terapiju standardnim oralnim preparatima gvožđa. Unos hrane i istovremena upotreba drugih lekova, kao što su H2-blokatori i inhibitori protonske pumpe koji menjaju pH duodenuma, mogu umanjiti apsorpciju Fe3+ u digestivnom traktu, što dovodi do simptoma kao što su mučnina, povraćanje, poremećaj varenja i zatvor [41]. Štaviše, standardni oralni preparati gvožđa imaju ograničenu efikasnost kod srčane slabosti zbog edema crevne sluzokože i pojačanog lučenja hepcidina. Sveukupno gledano, stepen crevne apsorpcije standardnih oralnih preparata gvožđa smanjen je na svega 5% [42]. U studijama *IRON-HF* [43] in specialized laboratories. Along with iron tests, it is essential to test the levels of C-reactive protein (CRP), vitamin B12, folate, thyroid hormones, and renal parameters [38], as well as to test for signs of manifest or occult bleeding [40].

As a normal Hb level does not rule out iron deficiency, according to current recommendations, all patients with HF should undergo iron metabolism laboratory tests [4,5,14]. A simplified algorithm of ID/IDA laboratory diagnostics is presented in Figure 2.

TREATMENT OF ANEMIA IN HEART FAILURE

According to WHO recommendations, iron replacement should be started at ferritin levels below 30 µg/l, as symptoms in healthy persons already appear in the ID phase [3]. Due to their low cost and ease of administration, in the treatment of ID/IDA the drugs of first choice are standard (divalent and trivalent) oral iron supplements [3,19]. However, in about 30% – 70% of patients, standard orally administered iron supplements are not well tolerated. Food intake and concomitant use of other medications, such as H2-blockers and proton pump inhibitors that change duodenal pH, can decrease Fe3+ absorption in the digestive tract, leading to symptoms such as nausea, vomiting, indigestion, and constipation [41]. Furthermore, standard oral iron supplements have limited efficacy in HF due to edema of the intestinal mucosa and high hepcidin secretion. Overall, the degree of intestinal absorption of standard oral iron supplements is reduced to only 5% [42]. The ineffectiveness of standard oral iron supplements in HF was demonstrated in the IRON-HF [43] and IRONOUT-HF [44] studies.

A pilot study conducted on 50 patients with symptomatic HFrEF indicated that oral sucrosomial iron (SI) can overcome the hepcidin-ferroportin barrier and lead to a slight increase in ferritin, as well as to the improvement in exercise tolerance and quality of life, after six months of therapy [45]. SI is an oral supplement wherein ferric-pyrophosphate is coated with a matrix containing phospholipids and sucrester (tricalcium phosphate and starch), which is absorbed from the digestive tract in a hepcidin-independent way – paracellularly and transcellularly via enterocytes and M cells, throughout the entire small intestine [46]. The release of iron from SI during digestion is less than 5%, unlike all other oral preparations (75% – 85%), which significantly reduces the possibility of toxic effects of iron on the mucosa of the digestive tract, leading to improved intestinal tolerance and high bioavailability [47,48]. However, the increase in ferritin, although significantly higher during SI supplementation, as compared to standard oral iron supplementation, is markedly infe-

i *IRONOUT-HF* [44], pokazana je neefikasnost standardnih oralnih preparata gvožđa kod srčane slabosti.

Pilot studija sprovedena na 50 pacijenata sa simptomatskom *HFrEF* je pokazala da sukrozomalno gvožđe (engl. *sucrosomial iron – SI*), koje se unosi oralnim putem, može da prevaziđe hepcidin-feroportin barijeru i da dovede do blagog povećanja feritina, kao i do poboljšanja tolerancije fizičkog napora i unapređenja kvaliteta života, nakon šest meseci terapije [45]. *SI* je oralni preparat u kojem je feri-pirofosfat obložen matriksom koji sadrži fosfolipide i estar sukroze (trikalcijum fosfat i skrob), a koji se apsorbuje iz digestivnog trakta na način koji je nezavisan od hepcidina – paracelularno i transcelularno putem enterocita i ćelija, u celom tankom crevu [46]. Oslobađanje gvožđa iz sukrozomalnog gvožđa tokom varenja je manje od 5%, za razliku od svih ostalih oralnih preparata (75% – 85%), čime se značajno smanjuje mogućnost toksičnog dejstva gvožđa na sluzokožu digestivnog trakta, što dovodi do poboljšanja crevne tolerancije i do visoke bioraspoloživosti [47,48]. Međutim, povećanje nivoa feritina, iako značajno veće pri suplementaciji sukrozomalnim gvožđem, u poređenju sa standardnim oralnim preparatima gvožđa, značajno je inferiornije u odnosu na intravenoznu (iv) primenu gvožđa, koja ima stopostotnu bioraspoloživost. Neophodne su studije na mnogo većem broju pacijenata, kao i duže praćenje pacijenata, kako bi se utvrdilo mesto sukrozomalnog gvožđa u lečenju deficita gvožđa/sideropenijske anemije kod pacijenata sa srčanom slabošću [49].

Prema evropskim i američkim preporukama, intarvensko davanje gvožđa je zamenska terapija prvog izbora u lečenju deficita gvožđa/sideropenijske anemije kod pacijenata sa srčanom slabošću [4,5,14]. Rezultati dve velike međunarodne studije: *FAIR-HF*, sprovedene na 459 pacijenata sa srčanom slabošću *NYHA* klase II i III [50], kao i *CONFIRM-HF*, sprovedene na 304 ambulantna pacijenta sa simptomatskom slabošću i EF ≤ 45% [51], pokazali su značajno smanjenje simptoma, bolju toleranciju fizičkog napora i poboljšanje kvaliteta života, kod pacijenata koji su primali gvožđe karboksimaltozu, tokom dvadesetčetvoronedeljnog odnosno jednogodišnjeg praćenja. Rezultati randomizovane studije *IRONMAN*, sprovedene na 1.137 pacijenata u 70 bolnica u Velikoj Britaniji, pokazali su da je lečenje gvožđe derizomaltozom značajno smanjilo broj hospitalizacija i mortalitet od kardiovaskularnih događaja [52]. Za razliku od pacijenata sa hroničnom srčanom slabošću, intravenozno davanje gvožđa pacijentima sa akutnom srčanom slabošću, nakon stabilizacije epizode srčane insuficijencije, ne utiče na preživljavanje pacijenata, što pokazuje studija *AFFIRM-AHF*, koja je obuhvatila 1.107 pacijenata sa akutnom srčanom slabošću [53]. Intravenozna terapija gvožđem ima veće

rior to intravenous (I.V.) iron administration, which has 100% bioavailability. Studies on a much larger number of patients and longer follow-ups are necessary to determine the place of SI in ID/IDA treatment in HF [49].

According to European and American guidelines, I.V. iron is the replacement therapy of choice for ID/IDA in HF [4,5,14]. The results of two large international studies: FAIR-HF, conducted on 459 patients with HF NYHA class II and III [50], as well as CONFIRM-HF, conducted on 304 outpatients with symptomatic HF and EF ≤ 45% [51], showed a significant reduction of symptoms, better exercise tolerance, and improvement in quality of life, in patients who received ferric carboxymaltose during 24-week or one-year follow-up. The results of the randomized IRONMAN study, conducted on 1,137 patients in 70 hospitals in Great Britain, showed that treatment with ferric-derisomaltose significantly reduced the number of hospitalizations and mortality from cardiovascular events [52]. Unlike patients with chronic HF, the administration of I.V. iron in patients with acute HF, after the stabilization of the heart failure episode, does not affect patient survival, as shown by the AFFIRM-AHF study, which included 1,107 patients with acute HF [53]. I.V. iron has higher direct costs (use of hospital resources) and indirect costs (absence from work) than oral therapy. However, a drop in the total number of hospitalizations due to the exacerbation of HF or complications in patients with HF who had received I.V. iron indicates its long-term economic cost-effectiveness [54]. More recent I.V. iron preparations have a significantly lower rate of reported side effects than earlier preparations, such as ferridextran. Based on the results of individual randomized clinical trials, as well as a meta-analysis of published results that showed a decrease in the risk of hospitalization [55,56], in the ESC guidelines, I.V. iron is recommended in patients with symptomatic HFmrEF as well as in patients with HFrEF and ID, to reduce HF symptoms and improve quality of life (recommendation class I, level of evidence A), while ferric carboxymaltose and ferric derisomaltose are listed as recommended I.V. replacement therapy for the treatment of ID in patients with symptomatic HFmrEF and HFrEF, to reduce the risk of hospitalization (recommendation class IIa, level of evidence A) [5]. The American guidelines do not single out specific I.V. forms [14].

In patients with coexisting HF and renal failure, the administration of EPO can be effective. It is important to note that correcting anemia until the Hb level reaches the normal level (130 g/l) does not reduce cardiovascular mortality. In fact, normalization of Hb significantly increases the risk of thromboembolic complications [57], which is why it is not recommend-

direktne troškove (korišćenje bolničkih resursa) i indirektne troškove (odsustvo sa posla) od oralne terapije. Međutim, smanjenje ukupnog broja hospitalizacija usled pogoršanja srčane slabosti ili komplikacija, kod pacijenata sa srčanom slabošću koji su primili gvožđe intravenozno, ukazuje na njegovu dugoročnu ekonomsku isplativost [54]. Noviji iv preparati gvožđa imaju značajno nižu stopu prijavljenih neželjenih efekata od ranijih preparata, kao što je feridekstran. Na osnovu rezultata pojedinačnih randomizovanih kliničkih studija, kao i meta-analize objavljenih rezultata koji su pokazali smanjenje rizika od hospitalizacije [55,56], u ESC smernicama, intravenozno gvožđe se preporučuje kod pacijenata sa simptomatskom *HFmrEF* i pacijenata sa *HfrEF* i deficitom gvožđa, u cilju ublažavanja simptoma srčane slabosti i unapređenja kvaliteta života (preporuka klase I, nivo dokaza A), dok se gvožđe karboksimaltoza i gvožđe derizomaltoza navode kao preporučena intravenozna supstituciona terapija za lečenje deficita gvožđa kod pacijenata sa simptomatskom *HFmrEF* i *HfrEF*, radi smanjenja rizika od hospitalizacije (preporuka klase IIa, nivo dokaza A) [5]. Američke smernice ne izdvajaju konkretne intravenozne oblike terapije [14].

Kod pacijenata sa istovremenom srčanom slabošću i bubrežnom insuficijencijom, primena EPO-a može biti delotvorna. Važno je napomenuti da korekcija anemije do postizanja normalnog nivoa hemoglobina (130 g/l) ne smanjuje kardiovaskularni mortalitet. Štaviše, normalizacija hemoglobina značajno povećava rizik od tromboembolijskih komplikacija [57], zbog čega se ne preporučuje [5,14]. Pošto je anemija kod srčane slabosti obično blaga, transfuzije eritrocita su retko indikovane. Meta-analiza objavljenih studija o preživljavanju pacijenata sa akutnim koronarnim sindromom i anemijom, pokazala je da je preživljavanje bilo značajno bolje kada su transfuzije davane pri nivoima hemoglobina ispod 100 g/l, u poređenju sa restriktivnom strategijom transfuzije, pri nivoima hemoglobina ispod 80 g/l [58]. Međutim, za anemične pacijente sa srčanom slabošću ne postoje definitivne preporuke niti randomizovane studije i meta-analize koje procenjuju njihovo preživljavanje i njihove ishode u odnosu na restriktivni odnosno liberalni pristup transfuzijskoj podršci. U nedostatku zvaničnih smernica, pojedini autori predlažu da se razmotri liberalan pristup transfuzijama eritrocita (Hb = 80 g/l – 90 g/l) za kritično bolesne pacijente sa srčanom slabošću [59].

ZAKLJUČAK

Visoka prevalencija deficita gvožđa/sideropenijske anemije kod srčane slabosti zahteva blagovremenu dijagnozu i lečenje kod svih pacijenata, kako bi se unapredio njihov kvalitet života i poboljšalo preživljavanje.

Sukob interesa: Nije prijavljen.

ed [5,14]. Since anemia in HF is usually mild, RBC transfusions are seldom indicated. A meta-analysis of published studies on the survival of patients with acute coronary syndrome and anemia showed that survival was significantly better when transfusions were given at Hb levels below 100 g/l, as compared to a restrictive transfusion strategy, with Hb levels below 80 g/l [58]. However, for anemic HF patients, there are no definitive recommendations nor randomized studies and meta-analyses evaluating their survival and outcomes, in relation to the restrictive or liberal approach to transfusion support. In the absence of official guidelines, individual authors suggest considering a liberal approach regarding erythrocyte transfusions (Hb = 80 g/l – 90 g/l) for critically ill HF patients [59].

CONCLUSION

The high prevalence of ID/IDA in HF requires timely diagnosis and treatment for all patients, to improve their quality of life and survival.

Conflict of interest: None declared.

LITERATURA / *REFERENCES*

1. Safiri S, Kolahi AA, Noori M, Nejadghaderi SA, Karamzad N, Bragazzi NL, et al. Burden of anemia and its underlying causes in 204 countries and territories, 1990-2019: results from the Global Burden of Disease Study 2019. J Hematol Oncol. 2021 Nov 4;14(1):185. doi: 10.1186/s13045-021-01202-2.
2. Savarese G, Becher PM, Lund LH, Seferovic P, Rosano GMC, Coats AJS. Global burden of heart failure: a comprehensive and updated review of epidemiology. Cardiovasc Res. 2023 Jan 18;118(17):3272-87. doi: 10.1093/cvr/cvac013.
3. World Health Organization (WHO). Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity; WHO/NMH/NHD/MNM/11.1. [Internet]. [Pristupljeno: May 30, 2024]. Dostupno: https://apps.who.int/iris/bitstream/handle/10665/85839/WHO_NMH_ NHD_MNM_11.1_eng.pdf.
4. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al.; ESC Scientific Document Group. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. 2021 Sep 21;42(36):3599-726. doi: 10.1093/eurheartj/ehab368.
5. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al; ESC Scientific Document Group. 2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) With the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail. 2024 Jan;26(1):5-17. doi: 10.1002/ejhf.3024.
6. Chopra VK, Anker SD. Anaemia, iron deficiency and heart failure in 2020: facts and numbers. ESC Heart Fail. 2020 Oct;7(5):2007-11. doi: 10.1002/ehf2.12797.
7. Anand I, McMurray JJ, Whitmore J, Warren M, Pham A, McCamish MA, et al. Anemia and its relationship to clinical outcome in heart failure. Circulation. 2004 Jul 13;110(2):149-54. doi: 10.1161/01.CIR.0000134279.79571.73.
8. Al-Ahmad A, Rand WM, Manjunath G, Konstam MA, Salem DN, Levey AS, et al. Reduced kidney function and anemia as risk factors for mortality in patients with left ventricular dysfunction. J Am Coll Cardiol. 2001 Oct;38(4):955-62. doi: 10.1016/s0735-1097(01)01470-x.
9. Komajda M, Anker SD, Charlesworth A, Okonko D, Metra M, Di Lenarda A, et al. The impact of new onset anaemia on morbidity and mortality in chronic heart failure: results from COMET. Eur Heart J. 2006 Jun;27(12):1440-6. doi: 10.1093/eurheartj/ehl012.
10. Cohen-Solal A, Philip JL, Picard F, Delarche N, Taldir G, Gzara H, et al; CARENFER Study Group. Iron deficiency in heart failure patients: the French CARENFER prospective study. ESC Heart Fail. 2022 Apr;9(2):874-84. doi: 10.1002/ehf2.13850.
11. Naito A, Obokata M, Kagami K, Harada T, Sorimachi H, Yuasa N, et al. Contributions of anemia to exercise intolerance in heart failure with preserved ejection fraction-An exercise stress echocardiographic study. Int J Cardiol Heart Vasc. 2023 Aug 20;48:101255. doi: 10.1016/j.ijcha.2023.101255.
12. Köseoğlu FD, Özlek B. Anemia and Iron Deficiency Predict All-Cause Mortality in Patients with Heart Failure and Preserved Ejection Fraction: 6-Year Follow-Up Study. Diagnostics (Basel). 2024 Jan 18;14(2):209. doi: 10.3390/diagnostics14020209.
13. Siddiqui SW, Ashok T, Patni N, Fatima M, Lamis A, Anne KK. Anemia and heart failure: a narrative review. Cureus. 2022 Jul 23;14(7):e27167. doi: 10.7759/cureus.27167.
14. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, et al. 2022 AHA/ACC/HFSA Guideline for the management of heart failure: Executive Summary: A report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. J Am Coll Cardiol. 2022 May 3;79(17):1757-80. doi: 10.1016/j.jacc.2021.12.011.
15. Cvetković Z. Suvajdžić-Vuković N. Epidemiologija i etiologija »nemaligne«anemije kod starih. U: Marisavljević D, Milošević DP, Nikolić-Žugić J, Čokić V, Prostan M, priređivači. Poremećaji i bolesti krvi i krvotvornih organa kod starih osoba. Beograd: Zavod za udžbenike; 2017. p. 320-31.
16. Masini G, Graham FJ, Pellicori P, Cleland JGF, Cuthbert JJ, Kazmi S, et al. Criteria for iron deficiency in patients with heart failure. J Am Coll Cardiol. 2022 Feb 1;79(4):341-51. doi: 10.1016/j.jacc.2021.11.039.
17. Kaiafa G, Kanellos I, Savopoulos C, Kakaletsis N, Giannakoulas G, Hatzitolios AI. Is anemia a new cardiovascular risk factor? Int J Cardiol. 2015;186:117-24. doi: 10.1016/j.ijcard.2015.03.159.
18. Pasricha SR, Tye-Din J, Muckenthaler MU, Swinkels DW. Iron deficiency. Lancet. 2021 Jan 16;397(10270):233-48. doi: 10.1016/S0140-6736(20)32594-0.
19. Snook J, Bhala N, Beales ILP, Cannings D, Kightley C, Logan RP, et al. British Society of Gastroenterology guidelines for the management of iron deficiency anaemia in adults. Gut. 2021 Nov;70(11):2030-2051. doi: 10.1136/gutjnl-2021-325210.
20. Anand IS, Gupta P. Anemia and iron deficiency in heart failure: current concepts and emerging therapies. Circulation. 2018 Jul 3;138(1):80-98. doi: 10.1161/CIRCULATIONAHA.118.030099.
21. Mann DL. Innate immunity and the failing heart: the cytokine hypothesis revisited. Circ Res. 2015 Mar 27;116(7):1254-68. doi: 10.1161/CIRCRESAHA.116.302317.
22. Röhrig G. Anemia in the frail, elderly patient. Clin Interv Aging. 2016 Mar 17;11:319-26. doi: 10.2147/CIA.S90727.
23. Cappellini MD, Comin-Colet J, de Francisco A, Dignass A, Doehner W, Lam CS, et al.; IRON CORE Group. Iron deficiency across chronic inflammatory conditions: International expert opinion on definition, diagnosis, and management. 017 Oct;92(10):1068-78. doi: 10.1002/ajh.24820.
24. Rosenblum SL. Inflammation, dysregulated iron metabolism, and cardiovascular disease. Front Aging. 2023 Feb 3;4:1124178. doi: 10.3389/fragi.2023.1124178.
25. Rangaswami J**,** Bhalla V, Blair JEA, Chang TI, Costa S, Lentine KL, et al; American Heart Association Council on the Kidney in Cardiovascular Disease and Council on Clinical Cardiology. Cardiorenal Syndrome: Classification, pathophysiology, diagnosis, and treatment strategies: A scientific statement from the American Heart Association. Circulation. 019 Apr 16;139(16):e840-78. doi: 10.1161/CIR.0000000000000664.
26. Xanthopoulos A, Papamichail A, Briasoulis A, Loritis K, Bourazana A, Magouliotis DE, et al. Heart failure in patients with chronic kidney disease. J Clin Med. 2023 Sep 21;12(18):6105. doi: 10.3390/jcm12186105.
27. Hullon D, Taherifard E, Al-Saraireh TH. The effect of the four pharmacological pillars of heart failure on haemoglobin level. Ann Med Surg (Lond). 2024 Jan 29;86(3):1575-1583. doi: 10.1097/MS9.0000000000001773.
28. Chatterjee B, Nydegger UE, Mohacsi P. Serum erythropoietin in heart failure patients treated with ACE-inhibitors or AT(1) antagonists. Eur J Heart Fail. 2000 Dec;2(4):393-8. doi: 10.1016/s1388-9842(00)00110-0.
29. Cvetković Z, Suvajdžić-Vuković N. Kasne komplikacije hematoloških bolesti i njihovog lečenja. U: Marisavljević D, Mihaljević B, Elezović I, Popović S, Suvajdžić-Vuković N, Vujić D, Janić D, Milenković P, Mostarica M, Bogdanović G, priređivači. Klinička hematologija. Beograd: Zavod za udžbenike; 2012. p. 1182-94.
30. Cvetković Z, Marković O, Mitrović M. Cardiotoxicity of antineoplastic therapy: Underlying mechanisms, clinical manifestations, and basic principles of cardio-oncology. Serbian J Med Chamb. 2023; 4(3):256-71. doi: 10.5937/smclk4-45065.
31. Aapro M, Beguin Y, Bokemeyer C, Dicato M, Gascón P, Glaspy J, et al.; ESMO Guidelines Committee. Management of anaemia and iron deficiency in patients with cancer: ESMO Clinical Practice Guidelines. Ann Oncol. 2018 Oct 1;29(Suppl 4):iv96-110. doi: 10.1093/annonc/mdx758.

32. Savarese G, von Haehling S, Butler J, Cleland JGF, Ponikowski P, Anker SD. Iron deficiency and cardiovascular disease. Eur Heart J. 2023 May 7;44(18):1607. doi: 10.1093/eurheartj/ehad043.
33. Tziastoudi M, Pissas G, Golfinopoulos S, Filippidis G, Dousdampanis P, Eleftheriadis T, et al. Sodium-glucose transporter 2 (SGLT2) inhibitors and iron deficiency in heart failure and chronic kidney disease: a literature review. Life (Basel). 2023 Dec 13;13(12):2338. doi: 10.3390/life13122338.
34. Androne AS, Katz SD, Lund L, LaManca J, Hudaihed A, Hryniewicz K, et al. Hemodilution is common in patients with advanced heart failure. Circulation. 2003 Jan 21;107(2):226-9. doi: 10.1161/01.cir.0000052623.16194.80.
35. Tang YD, Katz SD. Anemia in chronic heart failure: prevalence, etiology, clinical correlates, and treatment options. Circulation. 2006 May 23;113(20):2454-61. doi: 10.1161/CIRCULATIONAHA.105.583666.
36. Mozaffarian D, Nye R, Levy WC. Anemia predicts mortality in severe heart failure: the prospective randomized amlodipine survival evaluation (PRAISE). J Am Coll Cardiol. 2003 Jun 4;41(11):1933-9. doi: 10.1016/s0735-1097(03)00425-x.
37. Packer M, Fowler MB, Roecker EB, Coats AJ, Katus HA, Krum H, et al; Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) Study Group. Effect of carvedilol on the morbidity of patients with severe chronic heart failure: results of the carvedilol prospective randomized cumulative survival (COPERNICUS) study. Circulation. 2002 Oct 22;106(17):2194-9. doi: 10.1161/01.cir.0000035653.72855.bf.
38. Tim Goodnough L, Comin-Colet J, Leal-Noval S, Ozawa S, Takere J, Henry D, et al. Management of anemia in patients with congestive heart failure. Am J Hematol. 2017 Jan;92(1):88-93. doi: 10.1002/ajh.24595.
39. Babitt JL, Eisenga MF, Haase VH, Kshirsagar AV, Levin A, Locatelli F, et al.; Conference Participants. Controversies in optimal anemia management: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Conference. Kidney Int. 2021 Jun;99(6):1280-1295. doi: 10.1016/j.kint.2021.03.020.
40. Anand I, Gupta P. How I treat anemia in heart failure. Blood. 2020 Aug 13;136(7):790-800. doi: 10.1182/blood.2019004004.
41. DeLoughery TG. Safety of Oral and Intravenous Iron. Acta Haematol. 2019;142(1):8-12. doi: 10.1159/000496966.
42. Sandek A, Bauditz J, Swidsinski A, Buhner S, Weber-Eibel J, von Haehling S, et al. Altered intestinal function in patients with chronic heart failure. J Am Coll Cardiol. 2007 Oct 16;50(16):1561-9. doi: 10.1016/j.jacc.2007.07.016.
43. Beck-da-Silva L, Piardi D, Soder S, Rohde LE, Pereira-Barretto AC, de Albuquerque D, et al. IRON-HF study: a randomized trial to assess the effects of iron in heart failure patients with anemia. Int J Cardiol. 2013 Oct 9;168(4):3439-42. doi: 10.1016/j.ijcard.2013.04.181.
44. Lewis GD, Malhotra R, Hernandez AF, McNulty SE, Smith A, Felker GM, et al.; NHLBI Heart Failure Clinical Research Network. Effect of oral iron repletion on exercise capacity in patients with heart failure with reduced ejection fraction and iron deficiency: The IRONOUT HF randomized clinical trial. JAMA. 2017 May 16;317(19):1958-66. doi: 10.1001/jama.2017.5427.
45. Karavidas A, Troganis E, Lazaros G, Balta D, Karavidas IN, Polyzogopoulou E, et al. Oral sucrosomial iron improves exercise capacity and quality of life in heart failure with reduced ejection fraction and iron deficiency: a non-randomized, open-label, proof-of-concept study. Eur J Heart Fail. 2021 Apr;23(4):593-7. doi: 10.1002/ejhf.2092.
46. Gómez-Ramírez S, Brilli E, Tarantino G, Girelli D, Muñoz M. Sucrosomial® Iron: An updated review of its clinical efficacy for the treatment of iron deficiency. Pharmaceuticals (Basel). 2023 Jun 6;16(6):847. doi: 10.3390/ph16060847.
47. Fabiano A, Brilli E, Fogli S, Beconcini D, Carpi S, Tarantino G, et al. Sucrosomial® iron absorption studied by in vitro and ex-vivo models. Eur J Pharm Sci. 2018 Jan 1;111:425-31. doi: 10.1016/j.ejps.2017.10.021.
48. Girelli D, Ugolini S, Busti F, Marchi G, Castagna A. Modern iron replacement therapy: clinical and pathophysiological insights. Int J Hematol. 2018 Jan;107(1):16-30. doi: 10.1007/s12185-017-2373-3.
49. Barakat MF, Amin-Youseff G, Okonko DO. Oral sucrosomial iron in heart failure with a reduced ejection fraction. Eur J Heart Fail 2021 Apr;23(4):598-600. doi: 10.1002/ejhf.2176.
50. Anker SD, Comin Colet J, Filippatos G, Willenheimer R, Dickstein K, Drexler H, et al.; FAIR-HF Trial Investigators. Ferric carboxymaltose in patients with heart failure and iron deficiency. N Engl J Med. 2009 Dec 17;361(25):2436-48. doi: 10.1056/NEJMoa0908355.
51. Ponikowski P, van Veldhuisen DJ, Comin-Colet J, Ertl G, Komajda M, Mareev V, et al.; CONFIRM-HF Investigators. Beneficial effects of long-term intravenous iron therapy with ferric carboxymaltose in patients with symptomatic heart failure and iron deficiency†. Eur Heart J. 015 Mar 14;36(11):657-68. doi: 10.1093/eurheartj/ehu385.
52. Kalra PR, Cleland JGF, Petrie MC, Thomson EA, Kalra PA, Squire IB, et al.; IRONMAN Study Group. Intravenous ferric derisomaltose in patients with heart failure and iron deficiency in the UK (IRONMAN): an investigator-initiated, prospective, randomised, open-label, blinded-endpoint trial. Lancet. 2022 Dec 17;400(10369):2199-209. doi: 10.1016/S0140-6736(22)02083-9.
53. Filippatos G, Ponikowski P, Farmakis D, Anker SD, Butler J, Fabien V, et al.; AFFIRM-AHF Investigators. Association between hemoglobin levels and efficacy of intravenous ferric subgroup analysis. Circulation. 2023 May 30;147(22):1640-53. doi: 10.1161/CIRCULATIONAHA.122.060757.
54. Jacob C, Altevers J, Barck I, Hardt T, Braun S, Greiner W. Retrospective analysis into differences in heart failure patients with and without iron deficiency or anaemia. ESC Heart Fail. 2019 Aug;6(4):840-55. doi: 10.1002/ehf2.12485.
55. Jankowska EA, Tkaczyszyn M, Suchocki T, Drozd M, von Haehling S, Doehner W, et al. Effects of intravenous iron therapy in iron-deficient patients with systolic heart failure: a meta-analysis of randomized controlled trials. Eur J Heart Fail. 2016 Jul;18(7):786-95. doi: 10.1002/ejhf.473.
56. Anker SD, Kirwan BA, van Veldhuisen DJ, Filippatos G, Comin-Colet J, Ruschitzka F, et al. Effects of ferric carboxymaltose on hospitalisations and mortality rates in iron-deficient heart failure patients: an individual patient data meta-analysis. Eur J Heart Fail. 2018 Jan;20(1):125-33. doi: 10.1002/ejhf.823.
57. Swedberg K, Young JB, Anand IS, Cheng S, Desai AS, Diaz R, et al.; RED-HF Committees; RED-HF Investigators. Treatment of anemia with darbepoetin alfa in systolic heart failure. N Engl J Med. 2013 Mar 28;368(13):1210-9. doi: 10.1056/NEJMoa1214865.
58. Mistry N, Hare GMT, Shehata N, Belley-Cote E, Papa F, Kramer RS, et al. Transfusion Thresholds for acute coronary syndromes-insights from the TRICS-III randomized controlled trial, systematic review, and meta-analysis. J Am Heart Assoc. 2023 Jan 3;12(1):e028497. doi: 10.1161/JAHA.122.028497.
59. Ding YY, Kader B, Christiansen CL, Berlowitz DR. Hemoglobin level and hospital mortality among icu patients with cardiac disease who received transfusions. J Am Coll Cardiol. 2015 Dec 8;66(22):2510-8. doi: 10.1016/j.jacc.2015.09.057.