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Research article

The Impact of Antithrombotic Therapy in Patients with Decompensated Heart Failure and Iron

Ion Alexandru Cristian[1,2], Liviu Ionut Serbanoiu[1,2], Stefan Sebastian Busnatu[1,2], Valentin Chioncel[1,2], Catalina Liliana Andrei[1,2]

[1] Carol Davila University of Medicine and Pharmacy Bucharest
[2] Bagdasar Arseni Emergency Hospital, Cardiology Department

* Correspondence: liviu-ionut.serbanoiu@drd.umfcd.ro

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Abstract: The iron deficient anaemia is a common medical condition in patients with heart failure receiving antithrombotic therapy. Especially during the COVID19 pandemic period the rate of bleeding complications associated with the antithrombotic therapy tend to be higher, as the patient's referral to medical services is lower and the interaction doctor-patient is limited. In our retrospective observational study we included 300 consecutive patients with decompensated heat failure associating iron deficient anaemia. For defining the medical conditions we used the ESC guidelines terminology and diagnostic criteria. We assessed the association between the iron deficient anaemia and different antithrombotic therapies, recommended in concordance to ESC Guidelines. We found that aspirin 75mg/day was statistical significant associated with iron deficient anaemia (p 0.012) and anaemia severity (p 0.002), this association being assessed by Chi square and Pearson tests. Also, neither clopidogrel, ticagrelor, VKA or non-VKA were associated to the presence of anaemia. By assessing the mortality rate associated to anaemia severity, the severe anaemia was associated to higher mortality rate, meanwhile no antithrombotic therapy was associated with higher readmission or mortality rate (p<0.001). In conclusion, aspirin was the only antithrombotic therapy associated with the presence of anaemia and anaemia severity, while only severe anaemia was associated with statistic significant increase of patient's mortality, with nonstatistical result regarding the readmission rate. This finding is concordant to the necessity of a permanent evaluation of the antithrombotic therapy in heart failure patients.

Keywords: *antithrombotic therapy, decompensated heart failure, iron deficient anaemia, COVID 19 pandemic, mortality rate*

1. Introduction

Iron deficiency (ID) and anaemia are two comorbidities that are very frequently associated with heart failure (HF). These comorbidities are associated with higher readmission and mortality rates (1,2). In the study by Iorio et al. five non-cardiovascular comorbidities (anaemia, chronic kidney disease (CKD) , chronic obstructive pulmonary disease (COPD) , diabetes mellitus (DM) , and peripheral artery disease(PAD)) revealed an important impact on all cause mortality (hazard ratio (HR) 1.25; 95% confidence interval (CI) 1.10-1.26; P < 0.001), all-cause hospitalization (HR 1.17; 95% CI 1.12-1.23; P < 0.001), HF hospitalization (HR 1.28; 95% CI 1.19-1.38; P < 0.001) (2).

Anaemia is defined by World Health Organisation (WHO) by a haemoglobin (Hb) concentration < 12 g/dl in women and < 13 g/dl in men. Meanwhile, ID is defined by a serum ferritin (SF) concentration <100 ng/mL or 100–299 ng/mL with transferrin saturation (TSAT) <20% (3,4). According to Cappellini and al. (4) the role of SF and TSAT is essential in assessing the intravenous iron therapy in patients with HF and anaemia.

In a study by Okonko et al. (5) the disordered iron homeostasis, defined by low SF concentration and low TSAT, was present in both anaemic and non-anaemic patients with chronic HF. Also, disordered iron homeostasis was related to worsening of the disease severity and strongly predicted lower Hb levels independently of age, sex, erythrocyte sedimentation rate, New York Heart Association (NYHA) functional class, and creatinine (5). The etiologies of anemia varied with disease severity, with an ID etiology present in 16%, 72%, and 100% of anemic NYHA functional class I or II, III, and IV patients, respectively. As a result of these findings, the investigation of iron homeostasis is an essential step in all patients with HF.

Another problem that has to be taken into account is the correlation of anaemia with antithrombotic therapy in patients with HF. The antithrombotic therapy has an important role in patients with HF, taking into account the vast HF aetiology. The dual antiplatelet therapy (DAPT) is recommended in HF patients with acute coronary syndrome (ACS) for at least 6 month period (6). Also, for HF patients with atrial fibrillation (AF) the anticoagulant therapy is indicated, based on CHADS2Vasc score (6). Therefore, the evaluation of the effect of antithrombotic therapy on bleeding risk is essential to establish the benefit/risk ratio.

Concerning the anticoagulant therapy in patients with HF, the indication refers to atrial fibrillation (AF) or atrial flutter (AFl) with high cardioembolic risk (assessed by CHADS2Vasc score). Regarding the bleeding risk, the HAS-BLED score is used, and a balance between the cardioembolic and bleeding risk has to be taken into account before deciding the anticoagulation therapy. Patients with HF are older and have associated comorbidities, therefore deciding the type of oral anticoagulant may be challenging. In patients with non-valvular AF or AFl the choice between non-vitamin K antagonists (non-VKA) and vitamin K antagonists (VKA) has to be made. The current data strongly supports the use of non-VKA, even in elderly patients, taking into account the lower bleeding risk associated with the modulated non-VKA dose. Meanwhile, the time in therapeutic range (TTR) for patients receiving VKA was identified to be 68% in a large follow-up cohort analysis including 3387 patients (7), which leaves a high number of patients taking VKA at risk for cardioembolic events.

A very important issue is related to the antithrombotic treatment in pts. associating AF and ACS (with or without revascularisation). The association between non-VKA and DAPT for a short period (1 month), followed by SAPT and non-VKA is probably the most common regimen. This treatment pattern proved to be more effective than VKA and DAPT therapy (8), without an increase of the stent thrombosis (ST) risk or mortality rate, but with a decrease of bleeding complications (8,9).

Another important aspect reveals the particular pattern of HF patients during pandemic period. HF patients tend to present later in the emergency rooms, due to the limited interaction imposed by the current situation. Also, the bleeding complications, associated with the antithrombotic treatment, tend to be more frequent, as the interaction clinician-patient is reduced in this period. Therefore, the assessment of HF patients associating iron deficient anaemia is very important, especially in the pandemic period.

To conclude, the present data reveal the importance of antithrombotic therapy in patients with heart failure, taking into account the frequency of the ischemic aetiology and association with AF or atrial flutter (AFl) . As the main risk associated with the antithrombotic therapy is represented by the bleeding complications, the aim of the current study being to investigate the association between iron deficient anaemia and the antithrombotic agents.

1. Methodology

This study is an observational retrospective one, including non-COVID admitted patients in our clinic in the period June 2020 – June 2021. We included 300 consecutive non-COVID patients with decompensated HF associated with ID anaemia. Anaemia was defined by the WHO criteria by serum haemoglobin concentration < 12g/dl in women and < 13g/dl in men. The mean follow-up period for the included patients was 6.3 months. For defining HF we used the ESC guidelines criteria, using clinical features and echocardiographic findings – in patients with HFrEF -, and adding the natriuretic peptides – in patients with HFpEF-.

The antithrombotic therapy was chosen taking into account the ESC Guidelines indications. Patients with AF or AFl with high CHADS2-Vasc score received non-VKA (most of them) or VKA (for valvular AF).

Post PCI patients with ACS received DAPT (aspirin plus ticagrelor or clopidogrel) for 12 months (in patients with high ischemic risk) or 3 months (in patients with high bleeding risk).

PCI patients with CCS received DAPT for 3 months (aspirin plus ticagrelor).

Patients associating AF or AFl and ACS received triple antithrombotic therapy (non-VKA, aspirin and clopidogrel) for 1 month post PCI, then non-VKA plus clopidogrel for up to 12 months.

Patients with CCS not receiving PCI were referred to single antiplatelet therapy (SAPT) (aspirin), while non-PCI patients with ACS were received DAPT for 12 months (when bleeding risk assessed by PRECISE-DAPT score was low) or 3 months (for patients with high bleeding risk).

On admission, patients were assessed regarding the etiology of decompensated HF and receiving specific interventional therapy (PCI revascularisation) if needed. Also, a full biochemical profile for all patients was performed.

Patients were assessed by the frequency and severity of the anaemic syndrome. The etiology of the HF was assessed, taking into account the indication of the antithrombotic therapy.

The association between the different antithrombotic therapy and the iron deficient anaemia and the anaemia severity was assessed using Chi squared test.

In the context of COVID 19 pandemic the assessment of bleeding complications may be affected by the limited interaction clinician-patient, which may lead to an increase in the bleeding rates. Patients presented in the emergency room later and in a more severe HF stage. The bleeding complications associated with the antithrombotic therapy were also more frequent than in non-pandemic period, due to the limited patient referral to medical services.

Statistical method:

Categorical variables were presented as frequency and percentage, and they were compared by chi-square test. Numerical variables were summarized as means ± SD. Differences between baseline variables were assessed using ANOVA test. A $p< 0.05$ was used to define statistical significance. All analyses were performed using SPSS version 26 software.

2. Results

3.1. Patient characteristics

300 patients aged from 40 years to 100 years with a diagnosis of heart failure and iron deficiency anaemia syndrome were included, comprising 157 (52.3%) male and 143 (47.7%) female patients. The mean age was 73.56±11.06, the majority of patients (178 = 59.3%) were in the age group of 61-80. Most of the patients (198 = 66%) belong to the Urban population. Table 1 shows the demographic data of the patients.

In the majority of the population mitral regurgitation was present (243 means 81%), chronic coronary syndrome in 155 (51.7%) and Type II Diabetes mellites in 144 (48%). Table 2 shows the associated risk factors.

3.2. Classification of patients

According to WHO classification for anaemia, patients were classified into 3 groups on the basis of haemoglobin level. Mild anemia (10-11 g/dl), moderate anemia (8-10 g/dl), and severe anemia (<8 g/dl). The mild anemia was present in 68 patients, moderate anemia in 95 patients and severe anemia was present in 31 patients, 106 patients had normal haemoglobin level (Figure 1).

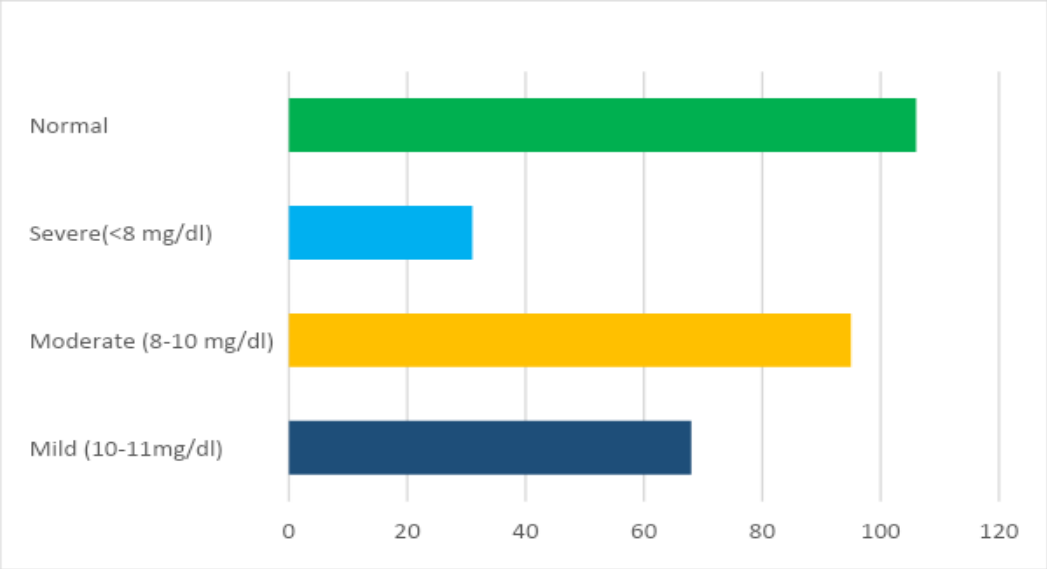

Figure 1: anemia classification

3.3. Antithrombotic therapy

Aspirin was used by 91 patients (30.3%), clopidogrel was taken by 70 patients (23.3%) and ticagrelor was used by 13 patients (4.3%). In addition, 25 patients (8.3%) used VKA, 110 (36.7%) used non-VKA, and 170 patients (56.7%) used injectable iron. Table 3 shows medication details.

3.4. Association of antithrombotic and anemia

The Chi-square test was applied to evaluate the comparison of the demographic and clinical characteristics with the level of anaemia. Patients receiving aspirin regularly develop significant anaemia (p=0.012); 20 patients had mild anaemia, 26 had moderate anaemia and 3 developed severe anaemia. Patients on ticagrelor showed non-significant anaemia development (p=0.66), 5 patients developed mild anaemia and only one patient developed severe anaemia. A non-significant association with anaemia was found in patients regularly receiving non-VKA; 29 patients developed mild anaemia, 33 developed severe anaemia and 7 developed severe anaemia.

By doing correlation between the level of anaemia vs Aspirin it was noted that the Pearson correlation was 0.18 which was significant with p value of 0.002, so the severity of anaemia increases with the use of aspirin. Similarly, in the case of VKA vs anaemia it was 0.038 with p value of 0.510. However in the case of anaemia vs non-VKA it was -0.427 with p value <0.001. (Table 4)

Several studies have reported overt gastrointestinal bleeding as the cause of anaemia; however, occult faecal bleeding is another possible reason (10). Gaskell et al. in a narrative review found no clear correlation of low-dose aspirin and anaemia, the patients aged > 70 years developed a small but significant fall in haemoglobin levels (11). Meade et al. reported no fall in haemoglobin level during two-year treatment period with low intensity antithrombotic (12). Hurlen et al. found no anaemia or iron deficiency associated with long-term treatment with aspirin, warfarin, or both. The occult bleeding in urine and faeces was a temporary phenomenon in most of the patients, limiting the value of occult bleeding in comparison to macroscopic bleeding (13). However, our result showed significant effects of aspirin in the development of anaemia.

Table 1: demographic characteristics of the patients.

Variable	Frequency	Percentage
Gender		
Male	157	52.3%
Female	143	47.7%
Age group		
40- 60 years	32	10.7%
61-80 years	178	59.3%
81-100 years	90	30%
Origin		
Urban	198	66%
Rural	102	34%
Readmission	31	10.3%
Demise	46	15.3%

Table 2: Risk factor of patients in our study group.

Risk factors	Frequency	Percentage
Type 2 DM	144	48%
Acute coronary syndrome	77	25.7%
Chronic coronary syndrome	155	51.7%
Aortic stenosis	87	29%
Aortic regurgitation	112	37.33%
Mitral stenosis	12	4%
Mitral regurgitation	243	81%
Pulmonary hypertension	127	42.3%
Atrial fibrillation	132	44%
Atrial flutter	10	3.3%
Bundle branch block	91	30.33%
Endocarditis	1	0.3%

Table 3: medication used by our patients.

Medications	Frequency	Percentage
Aspirin	91	30.3%
Clopidogrel	70	23.3%
Ticagrelor	13	4.3%
Anti-Vitamin K	25	8.3%
NOAC	110	36.7%
Injectable Iron	170	56.7%

Table 4: Correlations

Correlations					
		Hemoglobin	Aspirin	Antivitamin K	NOAC
Hemoglobin	Pearson Correlation	1	.181**	.038	.102
	Sig. (2-tailed)		.002	.510	.076
	N	300	300	300	300
Aspirin	Pearson Correlation	.181**	1	-.094	-.427**
	Sig. (2-tailed)	.002		.104	.000
	N	300	300	300	300
Antivitamin K	Pearson Correlation	.038	-.094	1	-.229**
	Sig. (2-tailed)	.510	.104		.000
	N	300	300	300	300
NOAC	Pearson Correlation	.102	-.427**	-.229**	1
	Sig. (2-tailed)	.076	.000	.000	
	N	300	300	300	300
**. Correlation is significant at the 0.01 level (2-tailed).					

Table 5: cross tabulation of the demographic and clinical characteristic with the anemia.

Variable	Anemia			P value
	Mild (n=68)	Moderate (n=95)	Severe (n=31)	
Gender				
Male	35	42	18	0.20
Female	33	53	13	
Origin				
Urban	49	65	19	0.44
Rural	19	30	12	
Aortic stenosis	21	26	11	0.66
Mitral regurgitation	57	80	25	0.70
Ticagrelor	5	0	1	0.66
Aspirin	20	26	03	**0.012**
NOAC	29	33	07	0.25
Acute coronary syndrome	14	22	11	0.36
Chronic coronary syndrome	38	43	17	0.50
Dead	0	15	31	**<0.001**
Readmission	7	16	4	0.23

Table 6: Patients with aspirin treatment (total 91 patients)

Variable	Frequency	Percentage	Frequency of death	Percentage of death	Frequency of readmission	Percentage of readmission
Male	48	58.78%	5	5.49%	5	5.49%
Female	43	47.25%	8	8.79%	5	5.49%
Urban	52	57.15%	12	13.18%	4	4.39%
Rural	39	42.85%	1	1.09%	6	6.59%

3.5. Mortality and readmission

Regarding the association between anaemia and clinical prognostic markers, a non-significant readmission rate was observed (p=0.23), only 7 patients with mild anaemia were readmitted, 16 with moderate and 4 with severe anaemia were readmitted. Also significant results were observed in association mortality - anaemic patients (p<0.001), showing that mortality rate was more pronounced in patients with severe anaemia (n=31). Lower rates were noticed in moderate anaemia (n=15) and no death occured in mild anaemia group (n=0) (Table 5). In total there were 13 patients (5 male and 8 female) who used Aspirin and died, that means 12,48% (5.49% male and 8.79% female). Only 10 patients (5 male and 5 female) were readmitted with aspirin treatment (10,98%). (Table 6)

Michalak et al. found that anaemia and heart failure were significantly correlated with mortality, concluding that the anaemia can be more pronounced in older individuals > 60 year old, and aggravated by associated comorbidities (14). In a meta-analysis, Groenveld et al. found that the anaemia was associated with an increased risk of mortality in heart failure patients (15). He et al. reported that the severity of anaemia is associated with an increase rate of mortality and hospitalization for heart failure, thus anaemia is an independent factor contributing to the adverse effects (16).

3. Discussion

The first point needing to be discussed is reffered to the ID etiology. Regarding the cause of ID the etiology can be related to the etiology of HF (patients with aortic stenosis have a higher incidence of iron deficient anaemia), the inflammation status (inflammatory diseases are related to a higher incidence of anaemia) and the associated treatment (antithrombotic treatment) (17).

In the same time, as inflammatory status leads to an increased SF level, in patients with HF higher cut-off values may be needed to define iron deficiency (17). Serum high soluble transferrin receptors (HSTR) is another marker reflecting the ID, which can be used in patients with HF, as SF levels can be increased due to the pro-inflammatory status of these patients. In HF patients the pro-inflammatory status induces an increasement in the level of HSTR. The HSTR level is related to high mortality rates (18), but its role to identify the intravenous iron therapy is still to be established.

According to Rocha et al. (19), iron deficiency is present in 30-50% of pts. with HF, with an increasing rate in acute heart failure (AHF), reaching almost 80%. Even in non-anaemic patients the iron deficiency was associated with higher hospitalization rates and decreased functional capacity (20).

The effect of ID treatment has also to be assessed. The RED-HF trial, investigating the role of erythropoietin stimulating agents, failed to reveal a positive role on mortality and re-hospitalization rates in patients with HF with reduced ejection fraction (HFrEF) and moderate anaemia (21). The treatment was associated with higher thromboembolic complications (21).

A large meta-analyse of RCTs regarding the treatment with i.v. ferric carboxymaltose in patients with HFrEF and ID (12) showed an improvement of combined end-points. The all-cause death and cardiovascular hospitalization rate (odds ratio (OR) 0.44, 95% confidence interval (CI) 0.30-0.64, $P < 0.0001$), and the combined endpoint of cardiovascular death or hospitalization for worsening HF (OR 0.39, 95% CI 0.24-0.63, $P = 0.0001$) were statistic significant improved in patients receiving i.v. ferric carboxymaltose vs placebo (22).

In another study (AFFIRM-HF), hospitalized patients with HF with ejection fraction (EF) <50% and ID, the therapy with ferric carboxymaltose did not reduce the primary composite outcome of total HF hospitalizations and cardiovascular (CV) death at 52 weeks (rate ratio 0.79, 95% CI 0.62–1.01, $P = 0.059$). It reduced the composite endpoint of first HF hospitalization or CV death (HR 0.80, 95% CI 0.66–0.98, $P = 0.030$) and total HF hospitalizations (rate ratio 0.74, 95% CI 0.58–0.94, $P = 0.013$) (23). The i.v. iron therapy in patients with HF with preserved EF (HFpEF) is not fully established, as no clinical trial showed a benefit for intravenous ferric carboxymaltose treatment in these patients.

As antithrombotic therapy is associated with bleeding complications, the risk/benefit ratio for this therapy has to be taken into acount. In our study, we included 300 consecutive patients with diagnosed HF and ID anaemia, assessing the association between the antithrombotic treatment and the anaemia.

The antithrombotic treatment was administered in concordance to the present guidelines, taking into account the CHADS-Vasc and HAS-BLED scores for patients with AF or AFl, and the association between oral anticoagulant and antiaggregant therapy in patients with ACS (both revascularized by PCI or not) or CCS (both revascularized by PCI or not). In order to analyse the effect of antithrombotic treatment we first assessed some demographic patterns of the study population which can influence the effects of antithrombotic treatment. We also assessed the prevalence of the HF comorbidities in our study, compared to the results from previous ones.

In our study, the mean age of the admitted patients was 73.56±11.06 years old. The majority of the patients 178(59.3%) were in the age group of 61-80 years. We underline the high percentage of patients over 80 years old (30%), this feature being explained by the vast etiology of the ID anaemia in older patients. In comparison, in a large study

including 23000 patients from 40 countries (Global Congestive Heart Failure Study), the mean age of the included patients was 65 years old (24). The main difference regarding the higher mean age in our study resulted from the inclusion criteria, as all our patients had anaemic syndrome, which is related to older age, and also from the fact that in the comparison study the study-population was more heterogeneous – including patients with a different pathophysiological pattern of HF.

Meanwhile, in our study the mean ejection fraction was 42,2%, this result being concordant to those in other studies assessing HF epidemiology (25). Also, 51% of the included patients had preserved EF, this result being discordant to those from other studies. In a study by Sacha Bhatia et al. (26) the percentage of patients with preserved EF was 31%, this difference was explained by the higher mean age in our study. Patients with heart failure with preserved EF tend to be older, therefore the higher percentage of preserved EF patients was correlated to the higher mean age. In another study by Bursi et al. (27) the percentage of preserved HF patients was 55%, which is concordant to the result from our study. Therefore, regarding the EF distribution pattern, in our study this was concordant to the results from other studies, as the study included older patients, and age is related to a higher percentage of HF with preserved EF.

Taking into account the associated pathologies, the association of diabetes mellitus (DM) in patients with HF is a common finding. In our study, the percentage of DM in the study group was 52%. This percentage may seem higher, but taking into consideration the fact that we included only admitted patients – with worsened HF – this may be explained by the fact that DM itself can be a factor for worsening HF. In a large HF cohort, including both HFrEF and HFpEF, the DM prevalence ranges from 10 to 47%. For example, in a study by From et al. (28) among a cohort of 665 subjects with HF (mean age 77±12 years, 46% male), 20% had prior DM. Subjects with DM were younger, had greater body mass index (BMI), and lower left ventricular EF than subjects without diabetes. In this study was noted an increasing prevalence of DM in time (3.8% per year). Regarding this survey, it included both patients with AHF and CHF, which may lead to a different result from our study which included only AHF patients.

Regarding the ACS, the percentage of included patients with AHF associating this pathology was 25.7%. In our study, we considered ACS rather a precipitating factor for worsening HF than an associated pathology. In large surveys, the percentage of ACS in AHF patients was lower, but some facts have to be taken into consideration. For example, in a large registry (European Society of Cardiology Heart Failure Long-Term (ESC-HF-LT) Registry) which included 6629 patients with 1 year follow up period, the percentage of ACS was 14.4% (29), but in this registry only patients with acute myocardial infarction were included, while we included in ACS pattern patients with unstable angina also.

Considering AF or AFl as an associated pathology for patients with AHF, we identified it in 47% of patients presenting with AHF included in our study. This data may seem discordant to a lower prevalence of 35% shown by other large studies (30), but taking into consideration the fact that the population from our study had a higher mean age and a significantly higher percentage of ACS, this difference is reasonable.

Finally, the considerations regarding the antithrombotic treatment association with ID anaemia and anaemia severity have to be taken into consideration. In our study the percentage for antithrombotic treatment revealed a low VKA usage (8.3%), explained by the non-VKA choice for patients without valvular AF. Meanwhile, referring to the antiplatelet therapy Clopidogrel was preferred to Ticagrelor in most patients (23.3 % vs 4.3 %), mainly due to the indication of triple antithrombotic therapy need (by the association of AF) and the high percentage of CCS (51.7%). These are the main features which have to be taken into account when assessing the effect of the antithrombotic treatment on ID anaemia and anaemia severity. Regarding the first issue, the choice between non-VKA and VKA, the results from a 2020 large meta-analysis show that the non-VKA choice is associated with 37% relative risk reduction (RRR) of major bleeding events when

assessing the triple antithrombotic therapy risk (TAT) in post PCI patients (31). The reduction of major bleeding risks is a class effect of non-VKA, as this meta-analysis included 10.969 patients from 4 major trials (PIONEER AF-PCI, RE-DUAL PCI, AUGUSTUS, and ENTRUST-AF PCI). Combination strategies of non-VKA vs. VKAs resulted in a comparable risk of major adverse cardiovascular events (MACE), myocardial infarction (MI), stroke, stent thrombosis (ST), or death (32). Therefore, the choice for non-VKA is explained by the lower bleeding risk, both in AF patients requiring TAT or DAT post-PCI and in patients requiring anticoagulation alone.

The choice for Clopidogrel is explained by the fact that in TAT or DAT using non-VKA the only antiplatelet therapy recommended to be used by the ESC Guidelines is Clopidogrel. Also, in the included patients we identified a high percentage of CCS (51.7%), and the post-PCI antithrombotic therapy guideline recommends the use of Clopidogrel instead of Ticagrelor.

In a large meta-analysis which included eleven RCTs the relative risk (RR) of 'major' incident GI bleeding in subjects who had been randomised to low-dose aspirin was 1.55 (95% CI 1.33, 1.83), and the risk of a bleed attributable to aspirin being fatal was 0.45 (95% CI 0.25, 0.80). In all the subjects randomised to aspirin, compared with those randomised not to receive aspirin, there was no significant increase in the risk of a fatal bleedinh (RR 0.77; 95% CI 0.41, 1.43) (33).

Reffering to dual antiplatelet therapy after ACS, the European Guidelines recommend the association between aspirin and the new potent P2Y12 inhibitors (prasugrel, ticagrelor) (34). The DAPT duration is variable, taking into account the patient bleeding risk, the PRECISE-DAPT score being used to assess this problem. In PLATO study, the comparison of ticagrelor with clopidogrel for DAPT therapy in ACS patients revealed no significant difference in the rates of major bleeding between the ticagrelor and clopidogrel groups (11.6% and 11.2%, respectively; P=0.43). Also, ticagrelor was associated with a higher rate of major bleeding not related to coronary-artery bypass grafting (4.5% vs. 3.8%, P=0.03), including more instances of fatal intracranial bleeding and fewer of fatal bleeding of other types (35). This bleeding risk is associated with a benefit regarding the 1 year cardiovascular mortality rate and re-infarction rate which were lower in the ticagrelor arm (35). The DAPT duration is a very debatable issue, as prolonged therapy (>12 month) is associated to lower cardiovascular events than short DAPT therapy (6 month or 12 month). A large meta-analysis (36) which included patients with ACS and chronic coronary syndrome (CCS) revealed a lower myocardial infarction rate but with a possible higher bleeding risk in patients receiving longer DAPT period. Longer treatment periods reduced the incidence of myocardial infarction and stent thrombosis but with a cost of increased major bleeding and with a tendency to increase overall mortality because of an increase in non-cardiovascular death (36). However, the majority of patients included in these analyses had stable coronary artery disease and few patients with acute coronary syndrome were treated with ≤6 months of dual antiplatelet therapy. In a recent meta-analysis that included only patients with a history of acute coronary syndrome, prolonged dual antiplatelet therapy reduced the risk of cardiovascular death (RR 0.85; 95% CI: 0.74 to 0.98, p=0.03) without an increase in non-cardiovascular death (RR 1.03, 95% CI 0.86 to 1.23; p=0.76) or all-cause mortality (RR 0.92, 95% CI 0.83 to 1.03) (37).

The results from our study reveal that aspirin was associated statistic significant with the presence of the ID anaemia and the anaemia severity (using Chi square test, p value 0.012). The results from previous studies are discordant, as revealed by a large review taking into account the association between low dose aspirin (LDA) and ID anaemia (38). The main issue about this review is the inclusion of various studies (from 1980 to 2010), assessing both the use of LDA as preventive therapy and therapeutic role in post PCI patients. Especially in one study (M.Hurlen et al.) (38) it was studied the presence of occult bleeding in post myocardial infarction patients treated with 160 mg aspirin, warfarin (therapeutical INR), and aspirin-warfarin association. None of the three variants

was not statistic significant associated with occult bleeding or ID anaemia. The study included 267 patients, and the main issue regarding this study is the fact that it took into consideration only a drop in haemoglobin level, without assessing the presence of anaemia itself. Nevertheless, no data regarding the iron ID treatment is present in this study. The main reason for explaining the results from our study which may seem discordant to those from past studies is the fact that the study population was older (73.56 y.o) and there was a high percentage of DAT or TAT therapy including aspirin.

Regarding the non-VKA, we found no statistically significant correlation between this therapy and the presence or severity of ID anaemia (Chi squared test p value 0.258). In our study, the most used non-VKA was apixaban, with dose adjustment related to age, chronic kidney disease and low weight. This result is concordant to the result from ARISTOTLE study which proved that apixaban was associated with lower major bleeding rates than warfarin in non-valvular AF patients (39). In the RE-LY study 150 mg bid dabigatran was associated with similar major bleeding rates with warfarin (40), but in our study the dabigatran dose was adapted to age and creatinine clearance. Taking into account the result from the ROCKET-AF study which showed no statistical significance between the major bleeding rates and stroke rates between rivaroxaban and warfarin we did not use rivaroxaban in the antithrombotic therapy of the included patients.

The result regarding the clopidogrel and ticagrelor association with the ID anaemia revealed no statistically significant association between these therapies and this medical condition (Chi squared test p value 0.06). Nevertheless, the usage of this therapy was mainly in the TAT regimen, therefore the association may be close to the statistical significance. In our study only 4.3% of patients received ticagrelor and 23% received clopidogrel, because of the large use of TAT regimen or DAT in patients with CCS. Regarding this issue, as a result of a large meta-analysis including 1.327 patients taking post PCI DAPT (54.03% were treated with clopidogrel-based DAPT, 38.13% with ticagrelor-based DAPT, and 7.84% with prasugrel-based DAPT), 29.5% had at least one gastrointestinal event (41). Patients taking clopidogrel-DAPT were older, with more comorbidities, and higher gastrointestinal risk compared to those taking other DAPT regimens. Adjusted hazard ratios (HRs) showed no between-group differences in the risk for major (clopidogrel vs. new antiplatelets: HR 0.996; 95% confidence interval 0.497–1.996) and minor (HR 0.920; 0.712–1.189) gastrointestinal events (41). Therefore, no difference between these two regimens was identified.

4. Conclusions

During the pandemic period the antiplatelet therapy has become a real challenge as rigorous screening for bleeding complications was hampered by the social conditions. Therefore, an analysis of the ID anaemia associated with antithrombotic therapy is very important. In our study, we proved that by choosing the right antithrombotic regimen (in compliance to the bleeding risk and the thrombotic risk) the bleeding risk can be lowered, even in these particular conditions. The only association between the antithrombotic therapy and ID anaemia was identified for aspirin, while no statistically significant association was identified for non-VKA, clopidogrel or ticagrelor. Further studies regarding antithrombotic therapy must be assessed in order to fully present/show the effects of these medications on bleeding risk in patients with heart failure.

Ethical statement

We have the ethical endorsement of the publication of the original research article: "" THE IMPACT OF ANTITHROMBOTIC THERAPY IN PATIENTS WITH DECOMPENSATED HEART FAILURE AND IRON DEFICIENT ANAEMIA DURING COVID 19 PANDEMIC". Ethics commitee approval No. 47976/15.12.2021. Our research is based on data. The data is completely anonymous with no personal or sensitive information being collected. Also, the data is not considered to be confidential in nature and the issues are not likely to provoke emotional harm to the participants. Moreover, our study included

adults and participation was completely voluntary. The subjects were not in any case constrained or pressured to participate. Also, the identity of the respondents is unknown to us and hence, there is no risk of disclosures. We mention that the study was retrospective without being an interventional study. We used the patient's medical data for which they agreed to use it for scientific purposes. The patient data confidentiality was guaranteed and all study data were de-identified and fully compliant with the Health Insurance Portability and Accountability Act (HIPAA). This study was carried out in accordance with the principles of the Declaration of Helsinki and have respected the GDPR of patients.

Author contributions:

Conceptualization, A.C.I., L.I.S., V.C., C.L.A., C.J.S.. Methodology, validation, investigation, A.C.I., L.I.S., S.S.B., V.C. Resources, A.C.I., L.I.S., V.C., S.S.B, C.L.A., C.J.S.. Data curation, software, formal analysis, V.C., S.S.B., C.J.S.. Writing—original draft preparation, review and editing, A.C.I., L.I.S., V.C., C.L.A., C.J.S. Visualization: A.C.I., L.I.S., S.S.B., C.L.A..Supervision, A.C.I., L.I.S., V.C., C.L.A., C.J.S. project administration, C.J.S.

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