

REVIEW

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Anemia and iron deficiency in patients with atrial fibrillation

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Abstract

Atrial fibrillation (AF) is the most common cardiac tachyarrhythmia and has a rising global prevalence. Given the increasing burden of AF-related symptoms and complications, new approaches to management are required. Anemia and iron deficiency are common conditions in patients with AF. Furthermore, emerging evidence suggests that the presence of anemia may be associated with worse outcome in these patients. The role of anemia and iron deficiency has been extensively explored in other cardiovascular states, such as heart failure and ischemic heart disease. In particular, the role of iron repletion amongst patients with heart failure is now an established treatment modality. However, despite the strong bidirectional inter-relationship between AF and heart failure, the implications of anemia and iron-deficiency in AF have been scarcely studied. This area is of mechanistic and clinical relevance given the potential that treatment of these conditions may improve symptoms and prognosis in the increasing number of individuals with AF. In this review, we summarise the current published literature on anemia and iron deficiency in patients with AF. We discuss AF complications such as stroke, bleeding, and heart failure, in addition to AF-related symptoms such as exercise intolerance, and the potential impact of anemia and iron deficiency on these. Finally, we summarize current research gaps on anemia, iron deficiency, and AF, and underscore potential research directions.

Keywords: Atrial fibrillation, Anemia, Iron-deficiency

Background

Atrial fibrillation (AF) is the most prevalent cardiac tachyarrhythmia encountered in clinical practice [1, 2]. In 2010, it was estimated that there were already 33 million people with AF worldwide, and projections suggest this may exceed 70 million in Asia alone by 2050 [2, 3]. Complications of AF include an elevated risk of stroke, heart failure, dementia, and premature death [4]. Additionally, associated symptoms include chest pain, palpitations, fatigue, dizziness, syncope, dyspnea, and a decrease in exercise capacity [5]. Furthermore, recent data suggest that there is an increasing burden of AF-related

symptoms and complications on healthcare systems. For example, hospitalizations for AF in Australia have demonstrated a 295% increase in recent years and now represent the most common cause for cardiovascular hospitalisation [6, 7]. These trends are concerning and suggest that there is a need to evaluate current management approaches and investigate new treatments.

Anemia is common in patients with AF [8]. As with AF, the prevalence of anemia increases with rising age [9]. An increasing number of studies have demonstrated that the presence of anemia is associated with increased risks of bleeding, cardiac events, and overall mortality in patients with AF [8–11]. However, the reasons for these associations remain unclear and have not been adequately explored. Recent cohort studies have also shown that lower hemoglobin levels and anemia may be associated with the development of new-onset AF [12,

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13]. Furthermore, patients with anemia may also be more likely to experience clinical recurrence of AF [14]. Anemia is also prevalent in other cardiac conditions where it has been more comprehensively characterised, and is frequently caused by iron deficiency. For example, in chronic heart failure, the prevalence of iron deficiency has been shown to be approximately 20–30% [15, 16]. Additionally, heart failure patients with iron deficiency have deleterious symptoms and cardiac outcomes, independent of anemia status [17]. However, despite the increasing prevalence of both AF and anemia with ageing populations, information on the prevalence and impact of anemia and iron deficiency in patients with AF remains limited.

In this review, we thus sought to summarise the current published literature on anemia and iron deficiency in patients with AF. We discuss AF complications such as stroke, bleeding, and heart failure, in addition to associated symptoms such as exercise intolerance, and the potential impact of anemia and iron deficiency on these. Finally, we summarize current research gaps on anemia, iron deficiency, and AF, and underscore potential research directions. Currently, anemia and iron deficiency are not routinely screened for or treated in patients with AF, compared to a more established role in heart failure management. Current international guidelines for heart failure management advise routine screening and treatment for iron deficiency and anemia to improve functional capacity, reduce hospitalisations, and treat related symptoms [18]. This review suggests further study in this area of research may potentially clarify whether routine screening and treatment for anemia and iron deficiency in patients with AF may improve symptoms and reduce the risk of complications.

Outcomes associated with AF

The presence of AF can lead to numerous complications with significant clinical impact. An increased risk of stroke, heart failure, renal disease, dementia, and premature mortality are amongst the most notable clinical concerns associated with AF [19]. Concerningly, the occurrence of stroke can be the first presenting symptom of AF in 15–20% of patients and contribute to future disability and cognitive decline [5]. Reassuringly, the risk of stroke can be reduced by approximately 70% with appropriate anticoagulation therapy [20]. Although outweighed by the benefits of stroke risk reduction, potential side effects of anticoagulants include an increased risk of both intracranial and extracranial bleeding [21]. Gastrointestinal bleeding may be one likely mechanism by which patients with AF are more susceptible to the development of iron deficiency and anemia.

Symptoms associated with AF

Although there is often a focus on associated complications, patients with AF can experience a diverse range of symptoms that significantly impacts on quality of life [5]. Typical symptoms associated with AF include chest pain, palpitations, dyspnea, fatigue, exercise-intolerance, dizziness, and syncope. A majority of individuals will experience one or more of these symptoms attributable to AF at some point in time [5]. However, as many as 25–30% of patients may ostensibly not experience, or more likely not recognize, AF-related symptoms that may limit earlier diagnosis and treatment [22]. There is also a high proportion of co-existing cardiac diseases amongst patients with AF, such as heart failure and valvular disease. These conditions may also present with similar symptoms and can thus delay the diagnosis of paroxysmal AF or confound the assessment of AF-related symptoms [5]. There is also established evidence that exercise intolerance is highly prevalent in patients with AF [5]. More than half of all AF patients experience a reduced exercise capacity in the order of 15–20%, and this can lead to symptoms of dyspnea, fatigue, and a poorer quality of life [5].

Despite being a major contributor to impaired quality of life and healthcare presentation, the mechanisms underlying AF symptoms are largely under-researched. Although many individuals experience palpitations, the pathways leading to this sensation remain unclear [23]. Chest pain often occurs in patients with AF, and this is generally attributed to a reduction in coronary perfusion due to rapid and irregular ventricular rates [24]. Exercise limitation, dyspnea and fatigue may be caused by multiple mechanisms. AF can disrupt normal hemodynamics by impairing diastolic filling, causing a loss of atrioventricular synchrony, and predisposing to cardiomyopathy [25–28]. In non-AF patients, anemia is associated with increased cardiac output and workload and left ventricular hypertrophy [29]. Both anemia and AF are independently associated with alterations in cardiac function and output, yet interactions with the co-existence of both conditions have yet to be studied. Although exercise performance depends on both cardiac output and oxygen transport, there has been little investigation into the impact and mechanisms of anemia and iron deficiency on AF-related symptoms, discussed further below.

Symptomatic treatment for AF

Physical tests for exercise capacity have been utilized as a measure of assessing improvement in AF symptoms, cardiac events, and overall quality of life. For example, it has been shown that increases in exercise performance associated with maintenance of sinus rhythm correlate with physical activity, functional capacity, and overall vitality [30]. Furthermore, exercise capacity was shown to

be a significant predictor of emotional as well as physical health [30].

Studies for exercise training have shown a substantial benefit in the management of heart failure. The HF-ACTION clinical trial, which involved 1620 heart failure patients, demonstrated that every incremental increase of 6% in peak oxygen consumption (VO₂) can result in a 5% improvement in all-cause mortality and rates of hospitalization [31]. Based on the above, investigators have subsequently evaluated the effect of introducing supplementary exercise programs on AF-related symptoms and quality of life. One study assessed a 3-month exercise training program in AF patients and controls. Despite a lower peak oxygen uptake in the AF group, training resulted in a similar increase in oxygen uptake in both groups [32]. A reduction in resting heart rate was also observed in the AF cohort, suggesting that improving exercise performance may improve AF rate control [32]. Another study using an 8-week training program showed a positive correlation between exercise performance and outcomes of physical functioning, bodily pain, vitality, and emotion at 8-weeks post baseline [33].

Finally, it has also been shown that rhythm control for AF can subsequently improve exercise capacity. For example, two studies that studied patients with persistent AF treated with catheter ablation reported a significant improvement in exercise performance when sinus rhythm was restored [34, 35]. Pharmacological strategies using anti-arrhythmic medication for restoration of sinus rhythm can additionally improve exercise capacity and overall vitality in persistent AF patients [36].

In contrast, despite the evidence suggesting their relevance outlined below, there is no data on the role of anemia and iron deficiency management for symptom improvement in patients with AF.

Anemia and iron deficiency

Anemia is a hematological condition that results from a deficiency of red blood cells and is most commonly defined as a reduced hemoglobin concentration [37]. Estimates of anemia prevalence vary between sex and age. The worldwide prevalence of anemia is estimated to be 30% in non-pregnant women, 12% of all men, and 24% of the elderly [38]. Anemia prevalence also increases exponentially with increasing age. In Australia and the United States, the prevalence of anemia is approximately 10% in young non-pregnant women, 11% in males aged ≥ 65 years, and 20% in those aged 85 years or older [39–41]. Amongst various causes, anemia due to iron deficiency is most common. Similarly, the prevalence of iron deficiency varies by ethnicity, sex, and age. In developing countries, the prevalence of iron deficiency can be as high as 41–63% in women and 13% in men, whilst iron

deficiency anemia may be present in 20–39% of women and 4% of men [42]. However, as comprehensive data is limited, it is possible that the true burden of iron deficiency, particularly non-anemic iron deficiency, may be underestimated by these figures.

In addition, there are numerous definitions and guidelines for diagnosing iron deficiency [43]. An indication of iron stores can be obtained from serum iron, ferritin, and transferrin levels [44]. However, elevated levels of serum ferritin also occur in other chronic inflammatory conditions independently of iron status due to the nature of ferritin as an acute phase reactant. Production of serum ferritin increases 2.5-fold in chronic inflammatory states [45, 46]. To better evaluate for iron-deficiency in these cases, additional evidence of a low transferrin saturation under 20% and an assessment of inflammatory markers (such as erythrocyte sedimentation rate and C-reactive protein) are indicated [47, 48]. Notably, a ferritin level of less than 100 ug/L, or a combination of a ferritin level between 100 and 299 ug/L and transferrin saturation under 20%, are now guideline-recommended cut-offs for diagnosing iron deficiency in patients with heart failure, as discussed below [49].

Anemia and iron deficiency in systolic heart failure

Iron supplementation is a now an established treatment for heart failure patients with comorbid iron deficiency. Up to half of all heart failure with reduced ejection fraction patients have evidence of iron deficiency [50], and the prevalence may be even higher in patients with heart failure with preserved ejection fraction, reaching almost 60% [51]. Furthermore, this high prevalence of iron deficiency occurs even in the absence of anemia [16, 17, 48, 52]. Although treatment of anemia and iron deficiency with subcutaneous erythropoietin and oral iron supplementation has not been shown to be beneficial, trials of intravenous iron repletion have demonstrated consistent benefits [50]. The FAIR-HF trial that recruited heart failure patients with iron-deficiency showed a significant benefit of intravenous ferric carboxymaltose compared to placebo for improvements in patient global assessment, 6-min walk test, and quality of life [50]. Importantly, these benefits were similar regardless of whether patients were anemic. The CONFIRM-HF trial also demonstrated that ferric carboxymaltose compared to placebo resulted in improvements in 6-min walk test, New York Heart Association class, patient global assessment, and health-related quality of life [50]. Finally, the EFFECT-HF trial studied the effect of intravenous iron supplementation on peak oxygen consumption and found that the treatment group were able to maintain peak oxygen consumption, compared to a reduction in the control group, at 24 weeks follow up [53]. A meta-analysis pooling data

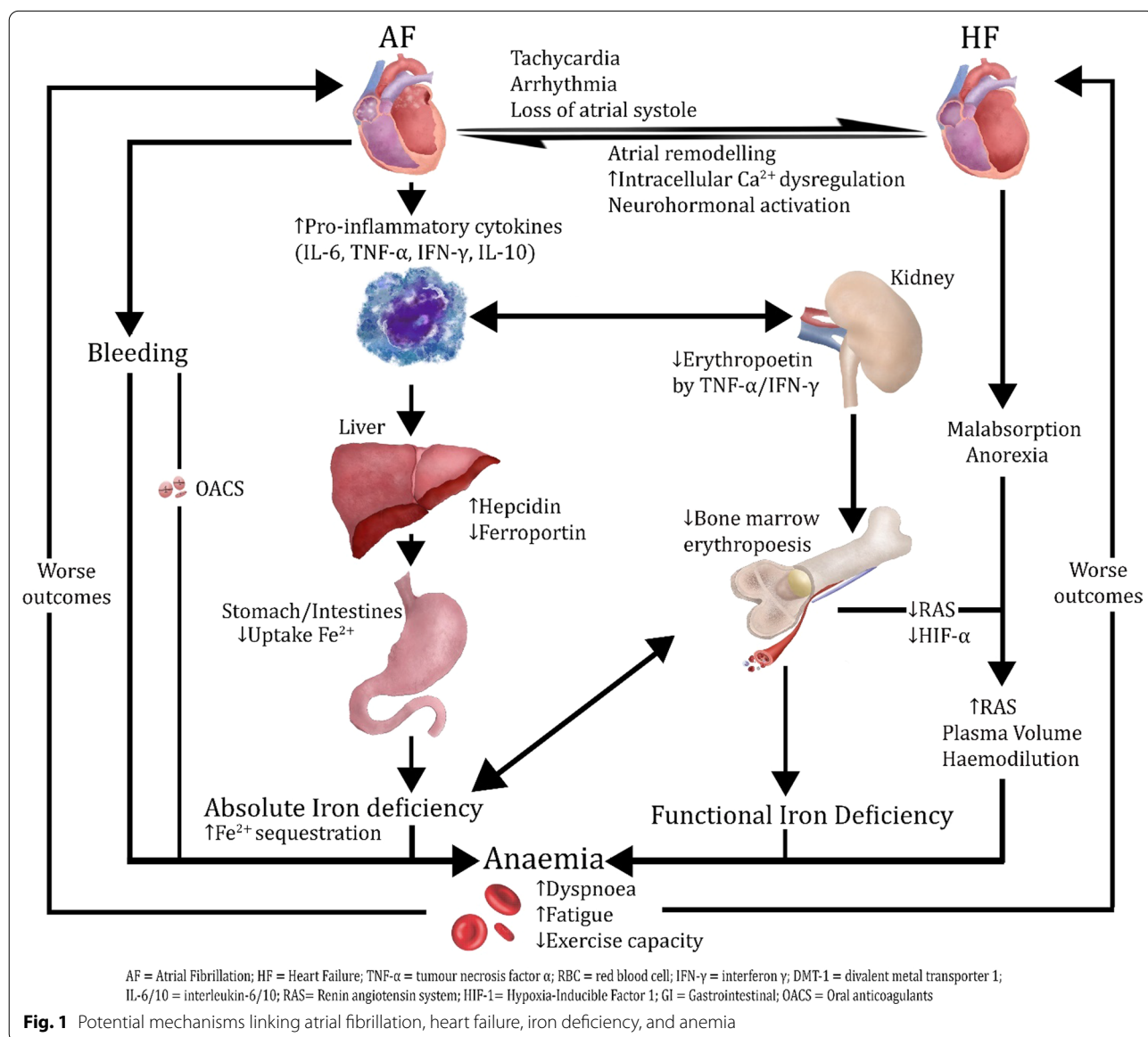
trials on intravenous iron therapy compared to placebo concluded that intravenous iron in chronic heart failure reduced cardiac related hospitalizations, cardiac-related mortality, and all-cause mortality [54]. More recently, the AFFIRM-AHF trial demonstrated that intravenous iron supplementation also reduced recurrent hospitalizations after recent discharge following acute heart failure [55].

Mechanisms of iron deficiency in other chronic inflammatory diseases

Iron supplementation is thought to be beneficial in part because heart failure, similar to chronic kidney disease, cancer, and other inflammatory disorders, is associated with an increase in systemic inflammation

and subsequent abnormal homeostasis of systemic iron (Fig. 1) [56, 57].

Our understanding of potential mechanisms for this phenomenon, termed functional iron deficiency, has been advanced by several observations in chronic inflammatory conditions. Proinflammatory cytokines such as interleukin-6 mediate the production and release of hepcidin [58]. Hepcidin is a peptide that regulates iron storage and release by mediating activity of ferroprotein, an iron transporter protein [50]. In chronic inflammatory states, there is an over-expression of hepcidin which predominantly contributes to iron deficiency by decreasing ferroprotein and results in a trapping of iron in duodenal enterocytes and macrophages [50, 56]. Furthermore,



interferon- γ , lipopolysaccharide and tumour necrosis factor- α upregulate the expression of divalent metal transporter 1, which increases the uptake of iron by macrophages [56]. Thus, an abnormally greater uptake and retention of iron occurs within the storage cells of the reticuloendothelial system, which limits iron availability for erythroid progenitor cells and erythropoiesis. Finally, inflammatory cytokines such as interleukin-1 and tumour necrosis factor- α inhibit erythropoietin expression and increase erythrophagocytosis, thus also contributing to eventual anemia [59].

Thus, chronic inflammatory conditions such as heart failure result in a multi-faceted pathophysiological process that precedes the development of anemia by reducing the amount available iron for erythropoiesis. This reduced availability of iron underpins the benefit of intravenous iron supplementation in heart failure patients [60]. Notably, oral supplementation of iron has not been shown to be beneficial in contrast to intravenous replacement. Oral dosing of iron typically has poor compliance, has limited gastrointestinal absorption through mucosal edema, and is thus insufficient to counteract the sequestration of stored iron out of enterocytes and macrophages [61].

Potential role for anemia and iron deficiency in atrial fibrillation

The role of anemia and iron-deficiency is well-established in patients with heart failure. However, there has been comparatively less research into the potential impact of these conditions in patients with AF. This is despite the fact that AF and heart failure commonly co-exist, share key risk factors, have similar pathophysiological mechanisms, and predispose to each other (Fig. 1). Both conditions experience similar consequences of a reduction in cardiac output, oxygen intake and peak work load [62]. Furthermore, emerging evidence suggests a significant role of inflammation in the pathogenesis of AF. For example, studies have shown heightened activity from lymphomononuclear cells, death of myocytes, elevated inflammatory markers and elevated neutrophil/lymphocyte ratios in patients with lone AF compared to control patients without AF [63]. Signalling pathways existent in inflammatory states can also inflict atrial remodeling and restrict atrial conduction through mediation of matrix metalloproteinases (MMP) 2 and MMP-9 [63]. Finally, anemia and iron-deficiency themselves can lead to significant myocardial hypertrophy and chamber dilatation, which can predispose to both heart failure and AF [64]. Thus, the interrelationship of AF, heart failure, and inflammation raise the strong possibility that associations of anemia and iron-deficiency in AF may be similar to that seen in heart failure.

Existing data on anemia and atrial fibrillation

To date, there are a limited number of studies evaluating the prevalence of anemia in AF patients (Table 1). A sub-study using the AFCAS registry found 30% of AF patients with available hemoglobin determinations undergoing coronary artery stenting to be anemic [65]. This prevalence rate was similar to another Danish registry study finding a prevalence rate of 34% in a cohort of over 18,000 AF patients [9]. In contrast, the prevalence was found to be 12% in another sample, suggesting there is some variation amongst different AF populations [11]. In a recent systematic review and meta-analysis of available data from 28 studies, we found the weighted proportion of AF patients with anemia to be 16% [8].

The AFCAS registry study found anemia to be an independent predictor for all-cause mortality, major adverse cardiac and cerebrovascular events [65]. The Danish registry study also showed anemia to be significantly associated with increased risks of major bleeding events, stroke, thromboembolic events and all-cause mortality compared to non-anemic AF patients [9]. Two analyses on individuals in different oral anticoagulant control trials also showed associations with anemia and increased risks in major bleeding and all-cause mortality [10, 11, 66]. In our recent meta-analysis, we found anemia to be associated with a 78% increased hazard of all-cause mortality, and every 1 g/dL decrease in hemoglobin associated with a 24% increased hazard [8]. Furthermore, anemia was associated with a 15% increased hazard of stroke or systemic thromboembolism, and 78% increased hazard of major bleeding. More recently, several cohort studies have also reported associations of anemia with greater risks of heart failure hospitalization [67–69]. Furthermore, at least one study has also suggested that anemia may be associated with clinical recurrence of AF [14]. In this large cohort, patients with anemia had greater post-ablation AF compared to patients without anemia. Although this association requires replication, it seems plausible that this could be due to an adverse effect of anemia on atrial remodeling. Despite these associations persisting after multivariate adjustment and being robust to a range of sensitivity analyses, it should be acknowledged that these studies are observational in nature, and as such, may be subject to residual or unmeasured confounding. Nonetheless, these studies on anemia in AF patients raise the potential relevance of anemia to subsequent complications. However, there are limited studies assessing anemia on other AF symptoms, such as functional capacity and exercise tolerance. One recent study reported quality of life using a validated questionnaire amongst AF patients with and without anemia. While baseline quality of life did not appear to differ, those with anemia did

Table 1 Studies reporting prevalence and associations of anemia or iron deficiency amongst individuals with AF

Study	Study type	Study size	Population type	Anemia, n (%)	Iron deficiency, n (%)	Outcomes studied
Shireman, 2006 [77]	Cohort study	26,345	Inpatient	2107 (8)	–	Bleeding
Sharma, 2009 [78]	Cohort study	13,067	Inpatient	7056 (54)	–	All-cause mortality
Park, 2011 [79]	Cohort study	488	Outpatient	–	–	All-cause mortality
Suzuki, 2012 [80]	Cohort study	1942	Inpatient	94 (5)	–	Mortality and hospitalization
Lip, 2012 [81]	Cohort study	7156	Inpatient	71 (1)	–	Bleeding
Friberg, 2012 [82]	Cohort study	90,490	Inpatients and outpatients	–	–	Bleeding
Manzano-Fernandez, 2012 [83]	Cohort study	285	Inpatient	105 (37)	–	Bleeding
Takabayashi, 2014 [84]	Cohort study	2774	Outpatient	471 (17)	–	Hospitalization and major bleeding
Puurunen, 2014 [65]	Cohort study	861	Inpatient	258 (30)	–	Bleeding and composite all-cause mortality, non-fatal MI, TIA, stroke, bleeding
Goodman, 2014 [85]	Secondary analysis of RCT	14,236	Anticoagulant trial	1976 (14)	–	Bleeding
Westenbrink, 2015 [10]	Secondary analysis of RCT	17,796	Anticoagulant trial	2223 (13)	–	Thromboembolism, all-cause mortality, MI, bleeding, stroke
Sherwood, 2015 [86]	Secondary analysis of RCT	14,236	Anticoagulant trial	1993 (14)	–	Bleeding
Lee, 2015 [87]	Cohort study	166	Outpatient	54 (33)	–	Mortality and hospitalization for heart failure
O'Brien, 2015 [88]	Cohort study	7411	Outpatient	2742 (37)	–	Bleeding
Dodson, 2016 [89]	Cross sectional study	31,951	Inpatients and outpatients	6514 (20)	–	Bleeding
Hori, 2016 [90]	Secondary analysis of RCT	1278	Anticoagulant trial	–	–	Bleeding
Kobayashi, 2016 [91]	Cohort	227	Inpatient	104 (46)	–	Bleeding
Li, 2016 [92]	Cohort	4632	Inpatients and outpatients	324 (7)	–	All-cause mortality
Westenbrink, 2017 [11]	Secondary analysis of RCT	18,103	Anticoagulant trial	2288 (12.5)	–	All-cause mortality, major bleeding, stroke, systemic embolism
Aisenberg, 2018 [93]	Secondary analysis of RCT	21,026	Anticoagulant trial	9885 (47)	–	Bleeding
Perera, 2018 [94]	Secondary analysis of RCT	7554	Anticoagulant trial	1888 (25)	–	All-cause mortality
Keskin, 2018 [73]	Cohort study	101	Outpatient	31 (30.7)	48 (47.5)	ID/Haematinic deficiencies compared to control group
Bonde, 2019 [9]	Cohort study	18,734	Inpatient	6358 (34)	–	Stroke, thromboembolism, major bleeding
An, 2019 [95]	Cohort study	4169	Outpatient	1547 (37)	–	Stroke, systemic embolism, bleeding, and mortality
Tiili, 2019 [96]	Cohort study	53,953	Outpatient	1619 (3)	–	Bleeding
Kuronuma, 2019 [97]	Cohort study	3237	Outpatient	–	–	All cause, cardiovascular and non-cardiovascular mortality
Fu, 2019 [98]	Cohort study	219	Inpatient	–	–	
Kodani, 2020 [99]	Cohort study	6536	Outpatient	1015 (16)	–	Thromboembolism, all-cause mortality

Table 1 (continued)

Study	Study type	Study size	Population type	Anemia, n (%)	Iron deficiency, n (%)	Outcomes studied
An, 2020 [69]	Cohort study	4169	Outpatient	1547 (37)	–	Thromboembolism, bleeding, heart failure
Krittayaphong, 2021 [67]	Cohort study	1562	Outpatient	518 (33)	–	Thromboembolism, bleeding, heart failure, mortality
Minhas, 2021 [68, 76, 100]	Cross-sectional	5,975,241	Inpatient	–	152,059 (3)	Length of stay, hospitalization costs, myocardial infarction, vasopressor use, mechanical ventilation, kidney injury, mortality
Al-Hussainy, 2021 [101]	Cohort study	41,321	Outpatient	11,812 (29)	–	Stroke, bleeding
Hashimoto, 2021 [68]	Cohort study	1677	Outpatient	378 (23)	–	Heart failure, bleeding, quality of life
Zhang, 2022 [100]	Cohort study	18,106	Outpatient	2500 (14)	–	Bleeding, cardiovascular and all-cause mortality

MI, myocardial infarction; TIA, transient ischemic attack, ID, iron-deficient, RCT, Randomised Control Trial

not demonstrate as much quality of life improvement at follow-up compared to non-anemic patients [68].

The aforementioned associations have biologic plausibility. For example, an effect of anemia on mortality could feasibly be mediated by established associations of anemia with other deleterious outcomes such as stroke, heart failure, and bleeding [70–72]. Conversely anemia may also be a marker of general frailty and the latter a potential confounder. However, given the magnitude of reported associations, we would argue that further investigation into the prognostic implications of anemia in AF, and whether treatment of this comorbidity may be beneficial, is warranted.

Existing data on iron deficiency and atrial fibrillation

There is a paucity of data on iron deficiency in patients with AF (Table 1). One retrospective study in Turkey has been published that analysed data on iron deficiency in 101 patients with AF [73]. Using a diagnostic threshold of ferritin level less than 100 µg/L, or a combination of a ferritin level between 100 and 299 µg/L and transferrin saturation under 20%, these investigators found that 47.6% of individuals with AF had iron deficiency [73]. Furthermore, the prevalence appeared to be greater in patients with permanent AF compared to those with paroxysmal or persistent AF. Limitations include the small nature of the study and absence of medication data such as anti-coagulant use [74, 75]. More recently, a large analysis of the National Inpatient Sample was undertaken whereby 2.5% of hospitalized AF patients had a coded diagnosis of iron deficiency anemia [76]. In cross-sectional analyses,

iron deficiency anemia was associated with longer length of stay and worse inpatient outcomes (such as myocardial infarction, kidney injury, and vasopressor/ventilation requirement) but not mortality. Despite the significant size, the reported prevalence in this study is likely to be an underestimate due to the use of hospital coding data. Further studies in a variety of populations are warranted to better characterise the prevalence of iron deficiency and iron-deficiency, as does an assessment of the potential relevance of these conditions to AF symptoms and complications, as is the case in heart failure and other cardiovascular diseases.

Clinical implications and future directions

The available evidence to date suggests that there may be a significant prevalence of anemia and iron-deficiency in individuals with AF. Furthermore, anemia appears to be associated with worse clinical outcomes in patients with AF. Data on iron deficiency in AF is limited but preliminary findings raise the possibility that prevalence of iron deficiency may not be insignificant and might also be correlated with the AF severity and clinical outcomes.

Although there is clearly a paucity of reports in this area, and these limited data should be interpreted with caution at this point in time, these initial findings raise the strong possibility that anemia and iron deficiency may be a therapeutic target in patients with AF. Furthermore, this potential is underpinned by a close interrelationship between AF and heart failure, where the role and benefit of iron supplementation is now established.

Future observational studies should provide additional estimates of anemia and iron deficiency prevalence in

Table 2 Future research directions

Area	Goals
Incidence and prevalence	Additional studies on the incidence and prevalence of anemia and iron-deficiency in different AF subpopulations, including by age, gender, AF type, anticoagulation use, ethnicity, and setting (outpatient, inpatient)
Symptoms	Impact of anemia and iron deficiency on AF symptoms Impact of anemia and iron deficiency on exercise/functional capacity and peak oxygen consumption in patients with AF
Complications	Confirmation of reported associations of anemia, stroke, and bleeding in patients with AF Impact of iron deficiency on future complications such as stroke, bleeding, heart failure, and mortality
Pathophysiology	Assessment of iron-deficiency and other causes as contributors to anemia in patients with AF
Therapy	Evaluation of investigation and treatment of anemia and iron-deficiency in patients with AF

AF, atrial fibrillation

patients with AF, clarify associations of anemia and iron deficiency with clinical outcomes, and characterize any impact of anemia and iron deficiency on AF symptoms and functional capacity (Table 2). Importantly, these studies be done in patients with and without heart failure in order to provide some insight into the potential confounding effect of this condition. Should this line of investigation prove promising, clinical trials to correct iron deficiency may be worthwhile considering. If successful, this may lead to the routine screening and treatment of anemia and iron-deficiency in patients with AF, as has been evaluated in the heart failure sphere. Given the increasing burden of AF worldwide, anemia and iron deficiency may thus be a novel therapeutic strategy which future studies should evaluate.

Conclusion

Both anemia and iron deficiency appear to be highly prevalent amongst individuals with AF. Furthermore, anemia and iron-deficiency may be associated with worse symptoms and outcomes in patients with AF. Although these preliminary findings require confirmation, the limited data to date support the possibility that investigation and treatment of anemia and iron deficiency may have benefit in symptomatic patients with AF. Future studies are required to confirm the prevalence of anemia and iron deficiency across different populations with AF, better characterise associations with outcomes, and ultimately determine if correction of anemia and iron-deficiency is novel management strategy in patients with AF.

Abbreviations

AF: Atrial fibrillation; AFCAS: Atrial Fibrillation undergoing Coronary Artery Stenting; AFFIRM-AHF: Study to Compare Ferric Carboxymaltose With Placebo in Patients With Acute Heart Failure and Iron Deficiency; CONFIRM-HF: A Study to Compare the Use of Ferric Carboxymaltose with Placebo in Patients with Chronic Heart Failure and Iron Deficiency; EFFECT-HF: Effect of Ferric Carboxymaltose on Exercise Capacity in Patients with Iron Deficiency and Chronic Heart Failure; FAIR-HF: Ferric Carboxymaltose in Patients with Heart Failure and Iron Deficiency.

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Author contributions

CXW was responsible for conception and design of the work. NH, SJT and CXW were responsible for drafting of the work. NH, SJT, CG, ADE, DHL, PS and CXW were responsible for interpretation of the data and substantive revision. All authors read and approved the final manuscript.

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Availability of data and materials

Not applicable to this review article.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

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