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Anemia: An Independent Predictor Of Adverse Outcomes In Older Patients With Atrial Fibrillation

Ali N Ali, MBChB MSc MRCP(UK)[1] Nandkishor V Athavale, MBChB MD FRCP[2] Ahmed H Abdelhafiz, MBChB MSc MD FRCP[2]

[1]Stroke Unit, Sheffield Teaching Hospitals, Sheffield. [2]Department of Geriatric Medicine, Rotherham General Hospital, Rotherham, UK.

Abstract

Both anemia and atrial fibrillation are common in older people and their prevalence is age dependent which increases as population ages. Anemia, especially acute onset, predisposes to new onset atrial fibrillation which is likely to be mediated through inducing heart failure first and this predisposition seems to be potentiated by the presence of renal impairment. Anemia adds to the comorbidity burden of patients with atrial fibrillation and independently increases the risks of adverse outcomes such as increased hospitalization, mortality, bleeding and thromboembolic events. Early detection and correction of anemia in patients with atrial fibrillation may have a positive impact on reducing these adverse events.

Introduction

Anemia, defined as a reduced hemoglobin concentration or hematocrit value, is one of the most common disorders globally affecting about 24.8% of the overall world population.[1] The prevalence of anemia is higher in older people and seems to increase with aging and with increased comorbidity burden. For example, the prevalence of anemia is about 11% in men and 10.2% in women aged 65 years and about 25% in men and 20% in women above the age of 85 years.[2] In the frail older population living in care homes the anemia prevalence is even much higher reaching around 48% to 63% of the total residents reflecting their multiple comorbidities and advanced age.[3] Similarly, atrial fibrillation (AF), the most common sustained cardiac arrhythmia, is age dependent and its prevalence doubles with each decade of life from 0.55% at the age of 50 to 60 years reaching about 12% in those above the age of 75 years with an annual incidence of around 2%.[4] Therefore, AF appears to affect mainly older people with about 80% of the total AF population are 65 years of age or older and by the year 2050, this percentage will increase to around 88%.[5] Patients with AF have twice the mortality risk compared to those in sinus rhythm likely due to the associated comorbidities, including anemia, in AF patients.[6] Anemia commonly coexists with chronic conditions such as heart failure and diabetes mellitus and appears to be an independent predictor of adverse outcomes associated with these conditions.[7,8] AF, as a chronic condition, is not an exemption and this review explores the relationship between anemia and AF and its role as an independent predictor of adverse outcomes in patients with AF.

Key Words:
Anemia, Atrial Fibrillation, Adverse Outcomes.

Disclosures:
None.

Corresponding Author:
Ahmed H Abdelhafiz
Department of Geriatric Medicine
Rotherham General Hospital
Moorgate Road
Rotherham
S60 2UD.

Methods

We have performed a search of Medline and Embase from January 1969 to November 2015 using keywords relating to anemia, atrial fibrillation and adverse outcomes. Only English language articles were selected. Articles were reviewed for relevance by abstract. A manual review of citations in retrieved articles was performed in addition to the electronic literature search. The final list of cited references was chosen on the basis of scientific quality and relevance to the topic of review.

Does Anemia Precipitate New Onset AF?

The answer to this question is still not clear. It appears that the relationship between anemia and new onset AF is complex especially in the presence of comorbid chronic kidney disease (CKD) or heart failure. Recently, it has been shown that anemia, defined as a hemoglobin of <13 g/dL, was 1.5 times more likely to be associated with new onset AF in a Japanese 15-year prospective cohort study of 132,250 subjects aged 40 to 79 {hazard ratio (HR) 1.50, 95% confidence interval (CI) 1.24 to 1.83, p<0.0001} compared to normal hemoglobin level. CKD, defined as an estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73m^2, was 2.56 times more likely to be associated with new onset AF (2.56, 2.09 to 3.13, p<0.0001) compared to normal kidney function. The combination of CKD and

Box 1: Characteristics of patients with combined anemia and AF.* [13,14]

- Older
- More prevalence of:
  - Heart failure
  - Coronary artery disease
  - Acute coronary syndrome
  - Peripheral arterial disease
  - Chronic kidney disease
  - Diabetes mellitus
  - Stroke
- Higher scores in bleeding risk scales
- Higher history of major bleeding events especially gastrointestinal bleeding.
- Higher scores on thromboembolic risk scales
- Higher thromboembolic events
- Receive less oral anticoagulation therapy
- Higher rate of oral anticoagulation therapy discontinuation
- Higher mortality rate
- Higher hospitalization rate

*Compared to those with AF alone.

anemia conferred a synergistic threefold higher risk for new onset AF (3.22, 2.43 to 4.19, P<0.0003) which is higher than would have been expected from the individual effects of CKD or anemia alone. Borderline hemoglobin level increased the risk for new onset AF only in patients with CKD but not in patients with normal kidney function confirming the synergistic action between anemia and CKD in precipitating new onset AF. This may be due to the fact that the pathogenesis of both AF and CKD is associated with common risk factors such as advancing age, hypertension and diabetes mellitus in addition to the hemodynamic changes associated with anemia itself such as reduced oxygen carrying capacity which may contribute to the susceptibility of new onset AF development.[9] In another retrospective cohort study of Medicare patients without pre-existing AF or end stage renal disease who were followed up from 2006 to 2008, advanced CKD and anemia were independently associated with incident AF (HR 1.13, 95% CI 1.09 to 1.18, p<0.0001 and 1.05, 1.03 to 1.07, p<0.0001 respectively). No synergistic effect between renal function and anemia was investigated in this study.[10] The onset of anemia may be another determinant factor for the new onset AF precipitation. Chronic anemia alone was not directly associated with incident or prevalent AF in one study.[11] In a single center community based retrospective study of 3,867 patients over the age of 65 years, new onset AF was found in 7.5 % of the anemic patients and 5.5% of the non-anemic patients however, after the adjustment for comorbid conditions, chronic anemia was not associated with new onset AF (p=0.922). Chronic anemia seems to require other comorbid factors like heart failure to precipitate AF as suggested in this study cohort.[11] The cardiac effects of the acute onset may be different from the chronic onset anemia. Baseline cardiac status, severity and rapidity of the onset of anemia may affect cardiac hemodynamics. For example, in acute anemia hemodynamic stress occurs due to the acute drop in hemoglobin concentration leading to tachycardia, as a compensatory physiologic response, that may leave less time for the heart to adapt. On the other hand, the gradual decrease in hemoglobin levels in chronic anemia could allow the heart to adapt before heart failure or AF develops making chronic anemia better tolerated. Other factors specific to old age such as reduced muscle mass, reduced exercise capacity and reduced sympathetic responses may lead to reduced

Table 1: Studies on anemia as a predictor of mortality or hospitalization in patients with AF

Study	Population	Aim To	Main findings
Puurunen, 2014 [14]	861 patients with AF undergoing PCI	Analyse impact of anemia on outcome of patients with AF undergoing PCI	Anaemia predicted all cause mortality (HR 1.62, 95% CI 1.05 to 2.51, p=0.029)
Sharma, 2009 [15]	13,067 Medicare beneficiaries hospitalized with AF	Investigate the association of anemia with mortality and hospitalizations in patients with AF	Anemia predicted mortality (HR 1.66, 95% CI 1.28 to 2.17) and hospitalization (1.28, 1.15 to 1.43)
Lee, 2015 [16]	166 patients with AF	Investigate role of anemia in predicting CV outcome.	Anemia predicted mortality and hospitalization (HR 0.83, 95% CI 0.71 to 0.96, P=0.015).
Christiansen, 2013 [17]	729,088 patients with AF associated hospitalization	Examine the excess risk of hospitalization in patients with AF	Anemia increased risk of hospitalization (RR 3.8, 95% CI 3.7 to 3.8)
Suzuki, 2012 [18]	1942 patients with AF	Identify predictors of heart failure events in patients with AF	Anemia increased risk of mortality or hospitalization (HR 3.01, 95% CI 1.78 to 5.10, p<0.001)
Vidal-Perez, 2013 [19]	798 patients with AF in primary care.	Describe predictors of mortality or hospitalization.	Anemia predicted end points (HR 1.37, 95% CI 1.08 to 1.75, p=0.010)
Westenbrink, 2015 [20]	18,113 patients with AF in RE-LY study	Determine if anemia predicts CV events	Anemia predicted all cause mortality or myocardial infarction (HR 1.50, 95% CI 1.32 to 1.71)
Westenbrink, 2014 [21]	18,201 patients with AF in ARISTOTLE study	Test whether anemia predicts CV outcomes	Anemia predicted all cause mortality (HR 1.68, 95% CI 1.46 to 1.93, p<0.0001)
Takabayashi, 2014 [22]	3,821 patients with AF in Fushimi study	Test relationship between anemia and heart failure in patients with AF	Anemia predicted heart failure hospitalization (OR 1.6, 95% CI 1.00 to 2.36, p=0.049)

PCI= Percutaneous coronary intervention, CV=Cardiovascular, HR=Hazard ratio, CI=Confidence interval, RR=Relative risk, OR=Odds ratio.

Table 2: Studies on anemia as a predictor of bleeding or thromboembolic events in patients with AF

Study	Population	Aim To	Main findings
Puurunen, 2014 [14]	861 patients with AF undergoing PCI	Analyse impact of anemia on outcome of patients with AF undergoing PCI	Anemic patients had more thromboembolic events (29.1% vs 19.4%, p=0.002), stent thrombosis (3.9% vs 0.7%, p=0.002), minor (7.0% vs 3.3%, p=0.028) and total bleeding (25.2% vs 21.7%, p=0.059) events
Westenbrink, 2015 [20]	18,113 patients with AF in RE-LY study	Determine if anemia predicts thromboembolic or bleeding events	Anemia predicted stroke or systemic embolism (HR 1.41, 95% CI 1.12 to 1.78) and major bleeding (2.14, 1.87 to 2.46)
Westenbrink, 2014 [21]	18,201 patients with AF in ARISTOTLE study	Test whether anemia predicts major bleeding	Anemia predicted major bleeding (HR 1.92, 95% CI 1.62 to 2.28, p<0.0001)
Shireman, 2006 [23]	26,345 patients with AF on warfarin	Develop a bleeding risk model	Anemia predicted major bleeding (HR 2.36, 95% CI 1.76 to 3.17)
Katoh H, 2014 [25]	184 patients with AF on dabigatran	Determine risks of bleeding	Anemia was a predictor of major bleeding (β=0.457, p=0.02)
Goodman 2014 [26]	14,264 patients with AF on warfarin or rivaroxaban	Identify predictors of bleeding	Anemia predicted major bleeding (HR 1.88, 95% CI 1.59 to 2.22, p<0.0001)
Friberg, 2012 [27]	90,490 patients with AF	Investigate risks for bleeding	Anemia predicted major bleeding (HR 1.40, 95% CI 1.28 to 1.53)
Beyth, 1998 [28]	264 patients with AF on warfarin	Evaluate outpatient bleeding risk index	Anemia or other morbidity increased annual probabilty of bleeding from 11% to 44%
Gage, 2006 [29]	3791 patients with AF	Find a bleeding risk scheme	Anemia was validated as a part of the bleeding risk scheme
Fang, 2011 [30]	9,186 patients with AF	Develop a bleeding risk stratification score	anemia was validated as part of the bleeding risk scheme (HR 3.27)

PCI= Percutaneous coronary intervention, HR=Hazard ratio.

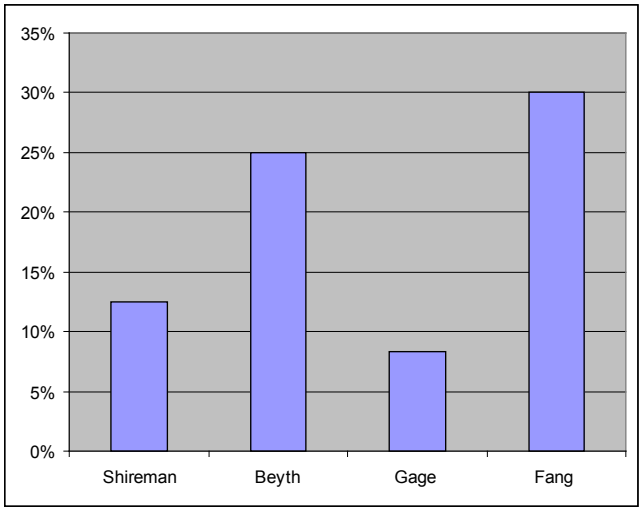

Figure 1: Weighting of anemia versus other risk factors for bleeding in 4 commonly used bleeding risk scores[23, 28-30]

oxygen demands and assist in the adaptation to the gradual decrease in hemoglobin levels in chronic anemia. It is possible that chronic anemia, if left untreated, may reach a threshold to precipitate heart failure first as an intermediate stage and subsequently precipitates AF. Therefore, patients with combined heart failure and anemia are likely to be at a higher risk for incident AF compared to those with anemia alone. In summary, anemia especially with acute onset appears to precipitate new onset AF mediated by inducing heart failure first and potentiated by the presence of renal impairment.

Anemia Increases The Comorbidity Burden Of Patients With AF

Patients with AF often have other cardiovascular comorbidities such as chronic heart failure, stroke, valvular heart disease, hypertension and diabetes mellitus.[12] The co-existence of anemia and AF further increases this comorbidity burden. For example, in the Fushimi-Japan AF Registry, patients with anemia and AF had higher prevalence of comorbidities compared to those with AF alone. They were older, mean (SD) age 79.6 (10.3) vs. 73.4 (10.5) years, p<0.001, had more prevalence of heart failure (43.1% vs. 25.8%, p<0.001), coronary artery disease (19.5% vs. 14.8%, p=0.006), peripheral arterial disease (6.2% vs. 4.2%, p=0.04), chronic kidney disease (52.5% vs. 22.3%, p<0.001) and history of major bleeding (4.2% vs. 1.5%, p<0.001). They tended to have a higher thromboembolic risk with greater mean (SD) CHA2DS2-VASc scores, 4.22 (1.64) vs. 3.35 (1.68), p<0.001, a higher prevalence of previous stroke (25.8% vs. 18.6% p<0.001) and received less oral anticoagulation therapy (44.4% vs. 52.4%, p<0.001).[13] In the prospective multicenter Atrial Fibrillation undergoing Coronary Artery Stenting (AFCAS) study, anemic patients with AF were older, more often had diabetes, CHA2DS2-VASc score >4, HAS-BLED score ≥3, prior history of heart failure, chronic renal impairment and acute coronary syndrome (p<0.05 for all) compared to those with AF alone.[14] Characteristics of patients with combined AF and anemia compared to those with AF alone are summarised in Box 1.

Anemia And Adverse Outcomes

Anemia is associated with chronic conditions and appears to increase the comorbidity burden of these conditions leading to adverse outcomes including increased mortality.[7, 8] AF, as a chronic condition, is not an exemption and patients with comorbid anemia and AF appear to have a worse outcomes compared to those with AF alone.

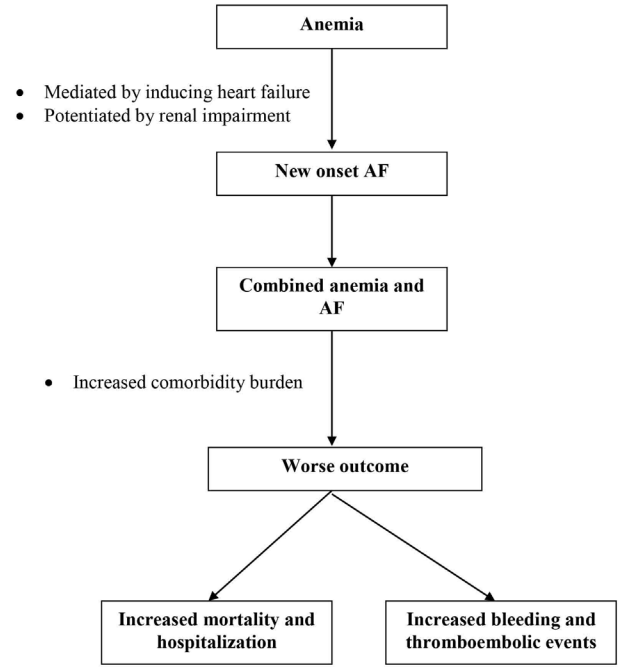

Figure 2: Relationship between anemia and AF: Anemia predisposes to new onset AF through inducing heart failure and potentiated by the presence of renal impairment. The coexistence of anemia and AF increases the comorbidity burden and worsens the overall outcome

Hospitalization And Mortality Risks

Anemia is an independent predictor of mortality and hospitalizations in older people with AF independent of the demographic factors, comorbid conditions or the use of cardiovascular medications. In a retrospective study of 13,067 Medicare beneficiaries in the US, mean age 79.8 years, hospitalized with AF, Hematocrit (Hct) was significantly (P <0.0001) associated with increased risk of death and re-hospitalisation. Patients in the lowest Hct category (<25%) had the worst survival, whereas patients with Hct's of 40% to 44.9% or 45% to 49.9% had the most favorable survival. The trend was of an increasing risk of mortality with a decreasing Hct value. In comparison to Hct of 40% to 44.9%, the adjusted HRs for all cause mortality were 1.66 for Hct <25%, 1.50 for 25% to 29.9%, 1.28 for 30% to 34.9% and 1.07 for 35% to 39.9%. The risk of re-hospitalization was 1.28 fold higher in the Hct category 25% to 29.9% (adjusted HR 1.28, 95% CI 1.15 to 1.43) compared to the category 40% to 44.9% after one year of follow up.[15] In another prospective study of 166 patients, mean (SD) age 71.0 (10.0) years, with persistent AF referred for echocardiographic examination in Taiwan, low hemoglobin concentration was also a predictor of cardiovascular events (mortality and hospitalization). Fifty four patients had anemia, mean (SD) hemoglobin 11.0 (1.4) g/dl compared to 112 non anemic subjects, mean (SD) hemoglobin 14.6 (1.2) g/dl, p=0.001. In the multivariate analysis hemoglobin was independently associated with increased cardiac events (HR 0.83, 95% CI 0.71 to 0.96, P = 0.015) after an average of 20 months follow up. The addition of hemoglobin to the clinical and echocardiographic data significantly improved the prediction of adverse cardiac events (P = 0.010).[16] In a Danish nationwide retrospective study, patients with AF were more likely to be admitted to hospital compared to those in sinus rhythm. When adjusted for age, sex and time period, patients with AF had a relative risk of 8.6 (95%CI 8.5 to 8.6) for cardiovascular related

admissions and 4.0 (95% CI 4.0 to 4.0) for non-cardiovascular related admissions. Anemia was identified as an independent predictor of hospital admissions increasing hospitalization by almost 4 folds in patients with compared to those without AF {Relative risk (RR) 3.8, 95% CI 3.7 to 3.8} and was also associated with a longer mean length of hospital stay (6.3 vs 5.6days).[17] Heart failure events defined as an increased mortality or hospitalization were independently increased by the presence of anemia in a prospective Japanese study of 1942 patients (HR 3.01, 95% CI 1.78 to 5.10, p<0.001). Anemia diagnosis formed a part of a risk score to identify patients with AF who are at risk for the incidence of new hospitalization or death with a diagnosis of heart failure (the H2ARDD score: 2 points for heart diseases, 1 point for anemia, 1 point for renal dysfunction, 1 point for diabetes and 1 point for diuretic use).[18] In the primary care, anemia was also identified as a risk factor for hospitalisation or mortality (HR 1.37, 95% CI 1.08 to 1.75, p=0.01) in a cohort of 798 patients with AF followed up for a mean (SD) of 2.8 (0.7) years.[19] The presence of anemia was associated with the composite endpoint of all-cause mortality or myocardial infarction (adjusted HR 1.50, 95% CI 1.32 to 1.71) in a retrospective analysis of the RE-LY study, all-cause mortality (adjusted HR 1.68, 95% CI 1.46 to 1.93, p<0.0001) in the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial and of all-cause mortality at 12-month follow-up (HR 1.62, 95% CI 1.05 to 2.51, p=0.029) in the AFCAS study.[20, 21, 14] Anemia likely to increase hospitalization through increasing adverse events. For example, after one year of follow up of the Fushimi-Japan AF Registry, patients with anemia had more heart failure related (7.4% vs 3.7%, p<0.01) and more major bleeding related hospitalisation (3.2% vs 1.3%, 0.01) and in a national registry study of 26,345 patients with AF, anemia was an independent risk factor for major bleeding that led to hospitalisation (HR 2.36, 95% CI 1.76 to 3.17).[22, 23] (Table 1)

Bleeding And Thromboembolic Risks

Anemia has been shown to be associated with an increased risk of thromboembolic and bleeding events in anticoagulated patients with AF. A retrospective analysis of 17,796 patients with available hemoglobin results in the RE-LY study showed that anemia was present in 12% of the population at baseline and the presence of anemia was associated with stroke or systemic embolism (adjusted HR 1.41, 95% CI 1.12 to 1.78). Anemia was also associated with a higher risk of major bleeding complications (adjusted HR 2.14, 95% CI 1.87 to 2.46) and discontinuation of the anticoagulant therapy (adjusted HR 1.40, 95% CI 1.28 to1.79). The association between anemia or hemoglobin and the different cardiovascular endpoints did not differ according to gender, major comorbidities, treatment allocation, eGFR, aspirin use or prior use of warfarin. The incidence of events was lower in patients with transient anemia than in patients with chronic anemia (adjusted HR 0.66, 95% CI 0.49 to 0.91). Anemia remained a predictor of bleeding complications, even after adjustment for the HAS-BLED score. During the course of the study, patients with anemia spent more time below the therapeutic range than those without anemia (26% vs. 22%, P < 0.0001), whereas the times above the therapeutic range were comparable.[20] In the AFCAS study of 861 patients, anemia was common affecting 30% of AF patients and was associated with major adverse cardiac and cerebrovascular thrombotic events (29.1% vs 19.4%, p=0.002) and minor bleeding events (7.0% vs 3.3%, p=0.028) compared to those without anemia. The incidence of stent thrombosis was also significantly higher in anemic versus non-anaemic patients (3.9% vs 0.7%, p=0.002).[14] The thromboembolic events associated with anemia seem to also affect the functional outcome. In the Acute STroke Registry and Analysis of Lausanne (ASTRAL) study, AF was more common in patients with compared to those without anemia (33.5% vs 25.2%, p<0.001) and the presence of anemia was a predictor of worse stroke functional outcomes as well as short and long term mortality.[24] In the ARISTOTLE trial anemia predicted major bleeding (adjusted HR 1.92, 95% CI 1.62 to 2.28, p<0.0001). Patients with anemia were older (median 73 vs. 69 years), had higher mean CHADS2 score (2.4 vs. 2.1), and were more likely to have experienced previous bleeding events (mean 20.1% vs. 16.2%) compared to those without anemia.[21] Pre-existing anemia was associated with major bleeding (β=0.457, p=0.02) in a retrospective Japanese study of 184 patients with AF on dabigatran treatment after a mean (SD) follow up of 383 (190) days. The baseline hemoglobin concentration also correlated negatively (r=-0.160, p=0.03) with the development of major bleeding.[25] In the Rivaroxaban Once-daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial (ROCKET) in Atrial Fibrillation, anemia at baseline was independently associated with major bleeding risk in both rivaroxaban and warfarin arms (HR 1.88, 95% CI 1.59 to 2.22, p<0.0001).[26] In 90,490 patients of the Swedish AF cohort study without anticoagulant treatment, anaemia a significant predictor of major bleeding (HR 1.40, 95% CI 1.28 to 1.53).[27] Anemia is also highly scored as an independent risk factor for bleeding in several commonly used risk stratification schemes validated to assess the risk of bleeding in patients with AF before initiating oral anticoagulation therapy.[23, 28-30] (Figure 1) Anemia appears to be an independent risk for bleeding regardless of the duration of oral anticoagulation. In a prospective cohort study to investigate the significance of anemia as a risk factor for bleeding in patients with AF newly started compared to those on long term oral anticoagulation, anemia remained a significant risk factor (HR 2.21, 95% CI 1.53 to 3.18, p<0.001) irrespective of the timing of initiation of anticoagulation therapy.[31] (Table 2)

Discussion

The coexistence of anemia and chronic conditions not only further adds to the comorbidity burden but it appears to be a detrimental factor in worsening the outcomes.[7, 8] AF is not an exemption to this observation. In AF population anemia clearly predicts adverse outcomes including increased mortality, bleeding, thromboembolic events and hospitalization. (Figure 2)

Mechanism Of Adverse Outcomes

Anemia may increase mortality through increasing the risk of coronary ischemic events. This may be due to the fact that anemia may predispose to left ventricular hypertrophy and subsequently to heart failure. Anemia is associated with cardiovascular compensatory changes including high cardiac output, low systemic vascular resistance and sodium and water retention increasing the cardiac workload.[32] In patients with established atherosclerosis, anemia appears to be a direct risk factor for myocardial ischemia and increased mortality.[33] In a meta-analysis of 27 studies, anemia was associated with increased mortality risk in patients with acute coronary syndrome.[34] The increased risk of bleeding induced by anemia may be explained by the fact that in the normal conditions, with normal red blood cell count, the flow and number of erythrocytes force the platelets centrifugally towards the endothelial lining. This facilitates the contact of

the platelets to the vessel wall. Therefore, platelet adhesion and aggregation occurs to reduce any bleeding when the vascular integrity is disrupted by injury. In patients with anemia and reduced red blood cell count this relationship is compromised with more luminally rather than marginally placed platelets impairing the process of platelet aggregation and adhesion increasing the risk of bleeding.[35] Anemia also decreases the amount of adenosine diphosphate that is available to contribute to collagen induced platelet aggregation at the site of injury.[36] The thromboembolic events precipitated by anemia may be due to the fact that anemia may aggravate myocardial ischaemia and unveil significant coronary obstruction in patients with established atherosclerosis. The hemodynamic changes associated with anemia such as increased heart rate and cardiac output lead to myocardial hypertrophy increasing myocardial oxygen demands and exaggerating the imbalance between myocardial oxygen demand and supply.[37] The duality of anemia to predict both bleeding and thromboembolic events is not unusual as it is shared by the other risk factors for ischemic stroke such as age or hypertension. Increased hospitalization risk is likely to be due to the increased adverse outcomes induced by anemia as stated above.

Implications For Clinical Practice

The relationship of anemia with adverse outcomes could be due to the possibility that anemia acts as a mediator of adverse outcomes and therefore correction of anemia may improve outcomes. The other possibility is that anemia may merely act as a marker for persons with worse prognosis related to their underlying complex condition and comorbidity burden. However, in the Randomized Etanercept North American Strategy to Study Antagonism of Cytokines (RENAISSANCE) trial, correction of anemia improved the outcome. For each one g/dL increase in the hemoglobin concentration there was an improvement in the left ventricular hypertrophy with a 4.1 g/m2 decrease in left ventricular muscle mass and a 15.8% reduction in mortality risk after 24 weeks of follow up.[38] Anemia appears to identify patients with AF who are at increased risk for thromboembolic events who could benefit most from oral anticoagulation therapy and who are also at risk for bleeding complications. These findings suggest that close monitoring of oral anticoagulation is important in patients with combined AF and anemia. Anemia enhances the performance of the bleeding risk scales and is already included as an independent predictor in four of them. However, anemia may not enhance the performance of the thromboembolic risk scales such as CHA2DS2-VASc as older people (≥75 years) are likely to benefit from oral anticoagulation therapy regardless of their risk stratification.[39]

Physicians may under estimate the magnitude of the bleeding risk of anemia in patients with AF. In a study to describe physicians' assessment of patient's risk of bleeding using data from national clinical registry of AF, anemia was the most significantly associated with physician-assigned bleeding risk being lower than empirically calculated bleeding risk (adjusted estimate, 1.36, 95% CI, 1.30 to 1.42).[40] The bleeding risk predicted by anemia, especially gastrointestinal bleeding, could be limited by the inability to account for the effects of antiplatelets or nonsteroidal anti-inflammatory drugs used over the counter. Another factor is whether the use of oral anticoagulation may have a confounding effect on calculating the bleeding risk. However, in the Loire valley AF project, anemia was an independent risk factor for bleeding in 7156 patients with AF whether on vitamin K antagonist or not (HR 2.49, 95% CI 1.27 to 4.88).[41] Anemia therefore appears to be a modifiable risk factor, which suggests that prevention or treatment of anemia could improve the prognosis in patients with AF.

Conclusions

Anemia is common in patients with AF, increasing their comorbidity burden and independently associated with increased risks of adverse outcomes. The early detection and treatment of anemia may have a positive effect in improving the outcomes however future research is needed to confirm that anemia is a modifiable risk factor in patients with AF.

Key points

- The prevalence of anemia and atrial fibrillation is age dependent.
- Anemia predisposes to new onset atrial fibrillation especially when renal impairment is present.
- The coexistence of anemia and atrial fibrillation increases the comorbidity burden and is associated with increased risk of adverse events.
- Early detection and treatment of anemia may improve the clinical outcomes in patients with atrial fibrillation.

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