Original Research

Anaemia in heart failure patients: the prevalence of haematinic deficiencies and the role of ACE inhibitors and aspirin doses as risk factors

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Abstract

Background: Patients with heart failure often have comorbidities that alter the progression of heart failure and impact on prognosis. One such comorbidity is anaemia, and clinicians have started to appreciate the full gravity of its impact on heart failure patients. Yet, the extent of the problem is not fully understood, particularly the role of heart failure therapy itself as a risk factor for developing anaemia.

Objective: This study aimed to investigate the prevalence of anaemia in a cohort of heart failure patients. The impact of using different ACEIs and different doses of aspirin was also explored, together with the prevalence of haematinic deficiencies.

Methods: Medication lists and pathology results were examined to establish the prevalence of ACEIs use, and the use of aspirin at its most common doses of 100mg and 150mg, together with haematinic deficiencies. Multinomial logistic regression and the Student's t-test were utilised for the analysis of data. Statistical significance was pre-set at p<0.05.

Results: Ninety-six patients were eligible for analysis, with 26% having anaemia. The use of ACEIs had a RR of 17.4 for the presence of anaemia. Perindopril was associated with a RR of 20.8, while the use of ramipril was not significantly associated with such a high RR. Haematinic anaemia occurred only at a rate of 3.3%, but borderline deficiencies were found in more than a third of all patients. An aspirin dose of 150mg was associated with a higher risk for anaemia, compared to a dose of 100mg.

Conclusions: ACEIs are associated with the presence of anaemia, with perindopril posing more risk than ramipril when used in heart failure patients. The dose of aspirin may also be a factor in the development of anaemia, with lower doses being safer. Despite the lack of high prevalence of haematinic anaemia among this cohort of patients, borderline haematinic deficiencies were common.

Keywords

Anemia; Angiotensin-Converting Enzyme Inhibitors; Aspirin; Drug-Related Side Effects and Adverse Reactions; Heart Failure; Risk Assessment; Multivariate Analysis; Clinical Audit; Australia

INTRODUCTION

Anaemia in heart failure is an under-recognised problem, but it has a great impact on the prognosis of patients.[1] Even mild anaemia increases the risk of mortality; in fact, for every 1% decrease in haematocrit (HCT) the risk of mortality increases by 6%.[1] Anaemia is associated with increased hospitalisation, worse cardiac function, need for high diuretic doses, and poor quality of life.[2] Its prevalence of about 15-55% makes it almost a public health hazard.[3] Indeed, it is an independent risk factor for mortality in heart failure patients.[1,4]

Causes for anaemia in this cohort of patients are not fully understood, but speculations have been made with regards to haemodilution, worsening renal function, and the use of aspirin and ACE inhibitors (ACEIs).[5] It is difficult to imagine that all patients on ACEIs would eventually develop anaemia, as this will certainly depend on their starting haemoglobin (Hb) level. However, ACEIs are widely used in patients with cardiovascular disease, particularly in those with heart failure, and the prevalence of anaemia may be high enough. Thus, the role of regular monitoring is important, as is a clear guideline of when to commence active treatment.

Heart failure patients who have anaemia tend to benefit from treating their anaemia, as demonstrated by improved functional capacity, quality of life and exercise tolerance.[6,7] However, there is some contradicting evidence that shows a lack of clinically significant improvement.[8] A meta-analysis concluded that using erythropoietin to correct anaemia is in fact associated with increased mortality if high levels of Hb are achieved, probably due to elevated BP or increased propensity to thrombosis.[9] Yet, as the authors of that meta-analysis have alluded, it is unclear whether it was the level of Hb achieved or the means by which this level was achieved is the true risk for higher mortality. Mounting evidence shows improvements in New York Heart Association classification, Quality of Life, ventricular function, and hospitalisation rate when anaemia of heart failure is corrected appropriately.[5,10]

The challenge, therefore, seems to be the under-detection of anaemia and the less proactive role clinicians currently play in correcting this risk factor. The current study aimed to explore the prevalence of anaemia in heart failure patients who received pharmacist interventions during their attendance at outpatient heart failure clinics. It also aimed to provide an insight into the role of ACEIs and aspirin, and the extent of monitoring for haematinic anaemia in the management of heart failure patients.

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METHODS

Design

This study is a retrospective audit of the data collected by pharmacists from patients who received pharmacist consultations while attending their heart failure outpatient appointments in an outpatient heart failure clinic at a major metropolitan hospital in Melbourne, Australia. The work described in this study was conducted according to institutional policies and guidelines, and in accordance with the Declaration of Helsinki.

Patients

Patients who attended their outpatient Heart Failure clinic were asked to be seen by the pharmacist, to review their medication regimens. This is a current practice, for pharmacists to see patients before they proceed with their cardiology appointments. The aim of this system is to optimise heart failure management, from a pharmacotherapeutic perspective and to ensure drug safety. Pathology results are always considered in conjunction with assessing patients' medications, so safety and efficacy of their pharmacotherapy is established and optimised. Advice and education are offered to patients, and liaison with their cardiologists occurs on an as-needed basis.

Intervention

Patients' medication lists were prepared, based on a review of their medical history, and an interview with the patient, after obtaining patient consent. Liaison with the patients' local pharmacies often occurred to confirm the medications or doses patients used, that may not be known to Heart Failure Clinic staff or the hospital. Pathology results were examined, e.g. renal function, full blood examination, etc. with the aim of monitoring the safety of the patients' therapy. Reference to the results of haematinic blood tests was made to investigate the prevalence and type of deficiencies among patients. Prepared medication lists were then consulted and the prevalence of ACEIs and aspirin use was tabulated for further analysis.

Outcome Measures were:

- Prevalence of anaemia among heart failure patients.
- Characterisation of the ACEIs used among the cohort of patients seen by pharmacists in the outpatient Heart Failure clinic.
- Relative Risk (RR) of ACEIs for the development of anaemia.
- RR of various aspirin doses for the development of anaemia.
- The prevalence of haematinic deficiencies and anaemia.

Statistical analysis

STATA/SE 10.1 was utilised to analyse the data. Multinomial logistic regression was used to establish the RR of independent variables known to cause anaemia including: age, gender, renal impairment, ACEIs use, and aspirin use. This statistical method was also used to

Table 1. Characterisation of angiotensin blockade in patients of the study.		
Angiotensin inhibition	**Number of patients (%)**	
	Non anaemic	**Anaemic**
ACEI	15 (15.6)	24 (25)
Perindopril	8 (8.3)	12 (12.5)
Ramipril	4 (4.2)	6 (6.3)
Other ACEI	3 (3.1)	6 (6.3)
A2RB (instead of ACEI)	6 (6.3)	1 (1.0)
Candesartan	3 (3.1)	
Irbesartan	5 (5.2)	
Other A2RB	0 (0)	
Not on any ACEI or A2RB	50 (52.1)	0 (0)
ACEI/A2RB combination	2 (2.1)	4 (4.2)
Proportion of patients who are on angiotensin inhibitory drugs and whether they had anaemia or not. ACEI: angiotensin-converting enzyme inhibitor; A2RB: angiotensin 2 receptor blocker.		

establish the RR of two of the ACEIs most used in our cohort of patients, namely perindopril and ramipril. Student's t-test (two tailed) was used to compare the Hb levels between patients on ACEIs and those who were not on ACEIs. A 2x2 contingency table was made to compare the RR of different aspirin doses. Statistical significance was declared at a P value of less than 0.05.

Power analysis of this study indicates that patient numbers were sufficient for its objective. The multiple logistic regression had five independent variables, and thus a patient number of 10-20 times this number of variables should be used.[11] This study included 96 patients, which is 19 times the number of variables.

RESULTS

Ninety-six patients were eligible for inclusion due to the availability of their data for analysis. The average age of patients was 65.3 years (95%CI 62.3-68.3). There were 68 males in the study, with 14 out of a total of 25 having a Hb level of less than 120g/L. ACEIs were used by all patients who had anaemia, while most patients in the non-anaemic group were not on any angiotensin blockade therapy, either ACEIs or angiotensin II receptor blockers (ARBs) (see Table 1).

The use of ACEIs for heart failure was associated with a RR of 17.4 for developing anaemia, compared to no ACEIs use (see Table 2). This is statistically significant (P=0.013). Multinomial logistic regression did not confirm that age older than 65 years, gender, renal impairment, or aspirin use were significant risk factors for the development of anaemia in the cohort of patients reported in this study. Furthermore, perindopril had a RR of 20.8, compared to ramipril which had a RR of 14.2 (see Table 2). However, statistical significance was achieved only for perindopril, not ramipril.

Patients who were using ACEIs had lower levels of Hb, almost 17g/L less than those who were not on ACEIs. This is a significant difference, with a P value of less than 0.0001 (see Table 3).

The prevalence of haematinic deficiencies was low, at only 3.3%. Only one folic acid test showed deficiency (see Table 4). However, when the lower limit of normal levels for these tests was raised, more patients were borderline

Table 2. Multinomial logistic regression analysis - the relative risk (RR) of various risk factors for the development of anaemia among patients with CHF.					
	RR	Std Err.	Z	P value	95% Confidence Interval
Relative risk (RR) of various risk factors for the development of anaemia among patients with CHF.					
ACEI	17.38	20.00	2.48	0.01	1.82 - 165.9
Aspirin	2.65	1.97	1.32	0.19	0.62 - 11.33
Renal impairment	2.16	1.57	1.06	0.29	0.52 - 8.95
65 years or more	0.96	0.77	-0.05	1.0	0.20 - 4.66
Gender	0.78	0.55	-0.35	0.73	0.20 - 3.13
Risk factors including perindopril.					
Perindopril	20.78	27.53	2.29	0.02	1.55 - 279.06
Aspirin	2.74	2.98	0.93	0.35	0.33 - 23.11
Renal impairment	2.26	2.62	0.70	0.48	0.23 - 21.95
65 years of more	0.98	0.04	-0.40	0.69	0.91 - 1.06
Gender	0.22	0.22	-1.51	0.13	0.03 - 1.57
Risk factors including ramipril.					
Ramipril	14.18	19.41	1.94	0.05	0.97 - 207.13
Aspirin	2.10	2.85	0.55	0.58	0.15 - 29.90
Renal impairment	1.74	2.43	0.40	0.69	0.11 - 26.99
65 years of more	0.96	0.04	-0.83	0.41	0.88 - 1.05
Gender	0.71	1.03	-0.22	0.82	0.05 - 11.65

deficient. Almost 37% may have haematinic anaemia. It was also found that the majority of heart failure patients did not have a haematinic test during the year of being seen by the pharmacist in their outpatient clinic attendance. The rate of testing was only less than 15%, for iron deficiency, and slightly over 8% for vitamin B12 and folic acid deficiencies.

Despite logistic regression not establishing aspirin as a risk factor for anaemia, a 2x2 contingency table showed that aspirin may indeed be a risk factor for anaemia. Compared to being on no aspirin, those who were using aspirin 100mg had a RR of 4.7, while this RR increased to 7.3 for those taking 150mg of aspirin (see Table 5).

DISCUSSION

ACEIs use

The current study confirms that ACEIs are associated with an increased risk of developing anaemia. The RR of anaemia in patients who used an ACEI was 17.4 (see Table 1). This is in line with previous evidence that strongly suggested ACEIs to be a risk factor for anaemia in heart failure.[12] What this study adds, though, is that different ACEIs may pose different levels of risk for causing anaemia. The study demonstrated that perindopril was associated with a RR of 20.7 (see Table 2), while ramipril was not associated with such a large risk, and it was insignificant (see Table 2). Previous studies have shown that ACEIs are more potent at lowering Hb than ARBs.[13] It is only plausible to expect variability within ACEIs as a drug class.

Angiotensin blockade has been observed to reversibly decrease HCT, as early as within a month of starting ACEI or ARB therapy; HCT reaches its nadir within 3 months.[12]

Losartan decreased Hb levels, with the largest decrease occurring after one year of treatment.[13,14] In the current study, users of ACEIs had significantly lower levels of Hb. The average difference between ACEIs users and non-users is about 17g/L, a Hb amount that may be the target of erythropoietin therapy in selected patients. This is congruent with previous studies that demonstrated the ability of ACEIs to reduce Hb, and their effective utilisation in treating erythrocytosis.[15,16] It is unclear from the current results, however, when Hb started to decrease after commencing angiotensin blockade therapy.

ACEIs have been found to not only inhibit the production of erythropoietin, and thus reduce its circulating level, but also to inhibit its action.[17] Other proposed mechanisms of action include the inhibition of Interleukin 12 (IL-12) and insulin-like growth factor-1 (IGF-1), with both having significant roles in erythropoietin production.[13,18] ACEIs can also inhibit the angiotensin II-induced stimulation of erythroid progenitor cell growth, and stimulate a stem cell regulator known as Ac-SDKP that inhibits erythroid growth.[19] Captopril was found to cause myelosuppression by inhibiting haematopoietic cell proliferation of progenitor and stem cells.[20] Enalapril had the same effect that explains its use in post-transplant erythrocytosis (PTE).[15,16] The detrimental actions of ACEIs are not unopposed, as this phenomenon is associated with higher doses of ACEIs. As such, they could be overcome by administering exogenous erythropoietin, or increasing its dose.[18] The current study did not investigate the impact of ACEI dosing on the development of anaemia.

The use of erythropoietin in anaemic patients adds another dimension to their management, and certainly would be the last resort after taking rather preventive measures to reduce the risk of anaemia. Whether there is a benefit in

Table 3. Significant difference in Hb levels between users and nonusers of ACEIs.				
	ACEI users	95% Confidence Interval	Non ACEI users	95% Confidence Interval
Mean	122.69	116.87 - 128.52	139.23	135.51 - 142.94
Standard deviation	17.96		14.00	
Standard error of mean	2.88		1.85	
Number of patients	39		57	
The two-tailed P value is less than 0.0001, t=5.06, df=94				

Table 4. Results of haematinic tests and the observed Hb levels in the tested patients.

Anaemia Status	Ferritin (microg/L)		Vitamin B12 (pmol/L)		Folic acid (nmol/L)	
	< 15	<50*	<150	<200*	<7.6	<8.5*
Hb <120g/L (anaemia)	0	6	0	2	1	2
Hb > 120g/L	0	3	0	6	0	5
Total Tested	14		8		8	
Testing Rate in study ample (%)	14.6%		8.3%		8.3%	
* Arbitrarily chosen borderline lower levels to establish the prevalence of borderline deficiencies.						

using ARBs instead of ACEIs, or substituting ACEIs, in heart failure patients who are at risk of developing anaemia is a question still unanswered. Further studies are needed to understand whether ARBs should replace ACEIs as the first line therapy for heart failure, or whether ramipril should be used in place of perindopril in those at risk of anaemia.

Haematinic anaemia

Haematinic deficiencies do not seem to be the main cause of anaemia observed in patients with heart failure. In one study, vitamin B12 deficiency was encountered in only 6% of patients, while folate deficiency was found in 8% of them.[3] Iron deficiency anaemia was seen in 13% of patients of that study. This low prevalence of haematinic anaemia is consistent with the results of the current study. The underlying cause of these deficiencies is of some interest, because cytokines were found to inhibit the absorption of iron and its release from iron stores.[2] This may explain why this study demonstrated a relatively high prevalence of borderline haematinic anaemia, including iron deficiency anaemia.

In the population of this study, there was a total of 30 haematinic tests requested, 14 for ferritin, and 8 for each of vitamin B12 and folic acid (see Table 2). Only one test showed frank haematinic deficiency, a folic acid test. The rate of detecting a deficiency on haematinic tests was only 3.3%. However, when higher borderline cut-off points were considered for these tests, this rate increased to 37%. The cut off points were only borderline, i.e. ferritin <50 microg/L (normal range: 30-300 microg/L), vitamin B12 <200 pmol/L (normal range: 148-590 pmol/L) and folate <8.5 nmol/L (normal range: 5.7-45.3 nmol/L).[21] This demonstrates that many heart failure patients with anaemia may have a haematinic predisposition, and are indeed borderline haematinic deficient.

Furthermore, haematinic abnormalities could, after all, be responsible, at least partially, for their anaemia. Should such abnormalities be treated? Further research is required to answer this question. However, given the multifaceted nature of anaemia in CHF, different causes of anaemia may be present in different patients. It seems only plausible that treating haematinic anaemia, or deficiency, should be sought in those who are known to be at risk. It might be a safer clinical practice to treat a deficiency suspected of causing the anaemia, rather than risk a poorer heart failure prognosis if left untreated.

Aspirin dose

Aspirin has been shown to contribute to anaemia in heart failure, which the results of this study support. Compared to non-aspirin-users, patients who used aspirin have a relatively higher risk of developing anaemia. An interesting finding of this study, however, is that aspirin dose may have a role in the development of anaemia. A 2x2 contingency table demonstrated that the use of aspirin 100mg had a relative risk of 4.7, while using aspirin 150mg had a RR of 7.3 (see Table 3). Compared to aspirin 100mg, the use of aspirin 150mg had a relative risk of 1.55. This poses the question of whether it is safer to use a lower dose of aspirin in heart failure patients. The antiplatelet action is still maintained, but there would be a reduced RR with a lower dose of aspirin. The study was not large enough to detect the relative risk of even lower antiplatelet doses of aspirin, i.e. 50-75mg.

This dose-related effect is a phenomenon consistent with that reported in previous studies that looked at various doses of the ACEIs. It seems that anaemia in heart failure is related to the doses of the medications used, i.e. ACEIs and aspirin, not only their class. Although reducing the aspirin dose from 150mg to 100mg may not be a problem, reducing the dose of an ACEI may pose a challenging clinical dilemma. Down-titration of ACEI doses is not the current trend in heart failure management, and may be related to worse outcomes. However, since anaemia is also related to worse outcomes, further studies are required to well define the doses that are considered safer in those at risk of anaemia. The use of the maximum tolerated doses of ACEIs may not be safest option in this cohort of patients.

Drug utilisation and pathology monitoring

This study demonstrates that among all patients considered for data analysis, only 48% of them had been on either an ACEI or an ARB. The reason for this relatively low uptake of angiotensin inhibition among this cohort is beyond the scope of the current study. However, it demonstrates that should more patients have been on angiotensin blockade, many more may have been diagnosed with anaemia, and the results providing a clearer picture of the role of ACEIs and aspirin dosing in the development of anaemia.

Another observation from this study is the low rate of screening for haematinic deficiencies. Only 14.6% of patients had haematinic anaemia assessed, during the year when the pharmacist saw them, while 43% of those

Table 5. Contingency table showing the use of aspirin to be associated with a higher risk of anaemia, which seems to be aspirin-dose dependent.

	Anaemia present	Anaemia absent	Relative risk	95% Confidence Interval
Aspirin 100mg	11	9	4.7	2.24 - 9.76
Aspirin 150mg	6	1	7.3	3.21 - 16.54
No aspirin	8	60	RR compared to "no aspirin"	
Compared to aspirin 100mg, aspirin 150mg confers a RR of 1.56.				

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suspected of haematinic anaemia had only one type of haematinic test, i.e. vitamin B12, folic acid or iron study, but not all three tests. More than half of all tested patients had only one test. The rate of haematinic deficiencies may have been higher, and thus the prevalence of haematinic anaemia higher, if the levels of folate, B12 and ferritin were all tested for all patients. The reason for this low level of screening could be that clinicians tested patients some years earlier and decided there were no anaemias or deficiencies to be concerned about. They may have determined that further screening was unwarranted. This study, however, shows that there is some merit in frequent regular screening to actively detect and monitor haematinic deficiencies and anaemia of heart failure.

CONCLUSIONS

The current study demonstrates that anaemia is common among patients who have heart failure. One possible cause is the use of ACEIs, but it seems that some ACEIs are less likely to cause anaemia than others. The level of Hb among ACEIs users is significantly lower than that observed in non-ACEIs users. Moreover, the dose of aspirin may have a role in the development of anaemia, as has been previously established with the dose of ACEIs. Furthermore, haematinic deficiencies are common in heart failure patients and should be monitored regularly. Although patients may not be "diagnosed" with haematinic anaemia, many would have deficiencies that could compromise their heart failure management, and worsen their prognosis.

CONFLICT OF INTEREST

There are no potential conflicts of interest.

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