ORIGINAL ARTICLE

Underutilization of Angiotensin Converting Enzyme Inhibitors Among Heart Failure Patients

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SUMMARY

There are well-established guidelines regarding the use of Angiotensin converting enzyme inhibitors (ACEI) in the management of heart failure (HF). In-spite of that, many studies has documented underutilization of ACEI. Thus, this retrospective observational study aimed to evaluate the utilization of ACEI, to identify the pattern of ACEI use and the factors that might contribute to underutilization of ACEI. The target population was hospitalized HF patients in University Malaya Medical Centre (UMMC). Of 321 hospitalized HF patients, only 57% of them were treated with ACEI. 51.2% of the patients treated with ACEI received low dose (≤ 25% from target dose) at discharge. Factors that have significant association with the underutilization of ACEI included serum potassium and creatinine, chronic renal failure and other concurrent medications used (frusemide, aspirin, potassium chloride, calcium channel blockers and angiotensin receptor blockers). The findings indicated that the utilization of ACEI in the management of HF in UMMC is considerably low.

KEY WORDS:
Heart failure, Angiotensin converting enzyme inhibitors, Underutilization

INTRODUCTION

Heart failure (HF) is a complex clinical syndrome of the end stage of all heart diseases [1]. HF continues to be a fatal disease, with only 35% surviving 5 years after the first diagnosis [2]. Despite the clinical challenges with poor prognosis of HF, there are now evidence-based guidelines for the management of HF [3,4]. The introduction of Angiotensin converting enzyme inhibitors (ACEI) provides the first treatment that beneficially alters the prognosis of patients with HF. A lot of studies have shown that ACEI reduce mortality and hospitalization [5] and improve symptoms and quality of life [6].

In spite of the well-established evidence regarding the benefit of ACEI among HF patients, the practical use of ACEI in management of HF is still different from guidelines [7]. From the review done by Bungard and his associates [8], underutilization of ACEI in HF is still a major problem. Moreover, the dose used in practice is insufficient compared to target doses that have been proven efficacious in clinical trials [9].

Seeing the issue revolving the underutilization of ACEI in the management of HF patients, the aim of this study was to assess the utilization of ACEI in our local setting as currently there is lack of data to show whether the phenomenon does exist. Other objectives of this study were also to identify the pattern of ACEI use and to investigate the factors that might contribute to the underutilization of ACEI in hospitalized HF patients.

MATERIALS AND METHODS

This was a retrospective observational study conducted in a teaching hospital, University Malaya Medical Centre (UMMC), Kuala Lumpur, Malaysia. Subjects were identified using International Classification of Diseases, Tenth Revision (ICD-10th) under the coding of HF: I50.0, I50.1 and I50.9 from the electronic medical record database. Registration number (RN) obtained were then used to retrieve the patients' files from the medical record office.

A total of 351 medical records were reviewed to assess the eligibility of patients to be included in this study. All diagnosed adult HF patients admitted to UMMC from November 2005 to August 2006 were included. Patients who died during hospitalization, transferred to other institutions, with incomplete medical records were excluded.

Three hundred and twenty one patients fulfilled the eligibility criteria. The patient demographics, relevant clinical parameters as well as parameters pertaining to ACEI use and non-use were then recorded into data collection forms prepared.

Patients are considered to have contraindications to ACEI if they have valve stenosis, bilateral renal artery stenosis, anuric renal failure during previous exposure, pregnancy, hypotensive patients who are at immediate risk of cardiogenic shock and have experienced angioedema, allergy or life-threatening adverse reactions with ACEI before. For assessment of optimal ACEI dosages, the dose used was compared to target doses of ACEI used in HF stated in Malaysian Clinical Practice Guidelines of HF [10].

For all eligible patients, the number and percentage of patients receiving each type of ACEI were calculated to determine the proportion of HF patients who received ACEI therapy in UMMC admitted during that period of time. For the assessment of dose on hospitalization and discharge, the doses used were compared to the recommended target dose and presented in percentage of targeted dose. Factors associated with ACEI utilization in HF patients were also assessed. Besides, any documented contraindication and side effects, the reasons for not receiving ACEI were also reviewed.

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The data extracted were then analyzed using Statistical Package for Social Sciences (SPSS) software system, version 14.0 software (SPSS Inc., Chicago IL, USA). Data were numerically coded and entered into SPSS system. Descriptive statistic was used for all variables. The data were then tabulated and presented in the graphical form using Microsoft Excel and Word.

Association between the factors that might influence ACEI use was done using bivariate statistical techniques. For comparison of categorical variables, the assessment of significant patient sociodemographic and clinical characteristics associated with the use of ACEI was done using chi-square (χ^2) test for discrete variables (age, gender, race, categories of serum creatinine and potassium level, co-morbidities, concurrent medication). P value of less than 0.05 was considered to be statistically significant.

RESULTS

Patient Sociodemographic and Clinical Characteristics

Of 321 hospitalized HF patients, about half of them were within age 60 to 79 years old (49.6%) with a median at 65 years old. They were approximately equally distributed among Malays (32.4%), Chinese (35.5%) and Indians (31.2%). Most patients presented with other co-morbidites, eg: hypertension (65.1%), IHD (55.1%) and diabetes mellitus (54.5%).

A number of concurrent medications were used in HF patients during hospitalization; frusemide was the highest (89.1%) followed by aspirin (62.0%). The details of the sociodemographic and clinical characteristics of the patients are shown in Table I.

Pattern of ACEI Use

Only 183 (57%) of the total number of HF patients received ACEI during hospitalization. The most common ACEI use was perindopril (73.8%). Ramipril (1.1%) was least likely prescribed followed by enalapril (3.8%), lisinopril (4.9%) and captopril (16.4%). From 138 (43.0%) of HF patients who did not receive ACEI, only 4.3% was noted to have contraindications to ACEI, 95.7% of them were without documented reasons. Our study also showed 11.5% of the patients were given angiotensin receptor blockers (ARB) and this made up a total 68.5% of renin- angiotensin aldosteron system (RAAS) blockers use.

Each type of ACEI was used in a different range of dose and presented in Table II.

There was a further drop of ACEI use at hospital discharge, with 164 (51%) patients receiving ACEI due to modification of ACEI use during hospital stay. When the dose of ACEI used was compared with the recommended target dose of ACEI in Malaysian CPG on HF [10], the percentage of target dose received by patient was presented as in Figure 1. Only a total of 26 (15.9%) patients were on target dose of ACEI at discharge. The percentage of patients who received a lower dose ($\leq$25% of target dose) of ACEI dropped from 60.7% during hospitalization to 51.2% at discharge.

The percentages of dose achieved by different types of ACEI prescribed at discharge were further summarized in Figure 2. Half of the patients received lisinopril and ramipril at targeted level respectively. While for enalapril and perindopril, only around 15% of each achieved target dose. No single patient received captopril at target dose.

Most of the patients (71%) remained unchanged with the dose of ACEI therapy. 10.9% had dose increment while 2.7% had reduction of dose. Switching to another ACEI was found in 4 (2.2%) patients. It was also noted ACEI was withdrawn from 24 patients (13.1%) and only 9 of them were replaced with ARB. Reasons for withdrawal of ACEI were hypotension (4.9%), increase in serum creatinine (4.4%), cough (3.3%) and hyperkalemia (0.5%).

Factors Associated with the Underutilization of ACEI Use

With regards to the factors that influenced the utilization of ACEI during hospitalization, the demographic and clinical characteristic were assessed. It was found that serum creatinine, serum potassium, chronic renal failure, concurrent medications which were frusemide, aspirin, ARB, potassium chloride supplement and calcium channel blockers had significantly affected the use of ACEI during hospitalization. Other factors found to exceed the level of significance ($p > 0.05$) included gender, age, race, systolic BP, EF, co-morbidities (hypertension, diabetes mellitus, ischemic heart disease and myocardial infarct) and other concurrent medications (beta- blockers, digoxin, spironolactone, isosorbide dinitrate and hydrochlorothiazide). The results are shown in Table III and Table IV.

DISCUSSION

In UMMC, the type of ACEI most commonly prescribed for HF patients was perindopril. The result agreed with the local report of medication use from Malaysian Statistics on Medicine 2004 [11] where perindopril was the most common type of ACEI used. This is because perindopril is relatively cheap and has convenient daily dosing. Therefore, it is preferred in the management of HF in local settings.

Our findings showed the percentage of HF patients treated with ACEI during hospitalization was 57% which fell into the range of utilization rate of ACEI (33% to 67%) in the review of underutilization of ACEI in HF by Bungard *et al* [8]. Meanwhile the percentage of no apparent reason of ACEI underused was almost similar to the report of by Large State Peer Review Organization Consortium [12] as there was up to 25% of HF patients without contraindication were not treated with ACEI. Thus there was underutilization of ACEI in HF patients in UMMC.

In our study, it was observed that most HF patients were discharged at doses below recommended target dose of ACEI. The same conclusions were observed from several studies [8,13,14]. Most patients remained on low doses of ACEI used during hospitalization and even at discharge. Higher percentage of patients (51.2%) in this study received less than or equal to 25% of target dose compared to the finding in Lenzen *et al* [9] study where 40% to 50% of patients received minimum recommended dose.

Table I: Patient sociodemographic and clinical characteristics

Characteristics		Number of patients (%) or Mean (±SD)
Gender	Male	179 (55.8)
	Female	142 (44.2)
Age (years old)	20-39	4 (1.2)
	40-59	111 (34.6)
	60-79	159 (49.6)
	80-99	47 (14.6)
Race	Malay	104 (32.4)
	Chinese	114 (35.5)
	Indian	100 (31.2)
	Others	3 (0.9)
Length of hospitalization (Days)	Hospital stay	6.5 ± 5.7
Co-morbidities (%)	Hypertension (HTN)	209 (65.1)
	Ischemic Heart Disease (IHD)	177 (55.1)
	Diabetes Mellitus (DM)	175 (54.5)
	Chronic Renal Failure (CRF)	63 (19.5)
	Myocardial Infarct (MI)	22 (6.9)
Concurrent medications (%)	Frusemide	286 (89.1)
	Hydrochlorothiazide	16 (5.0)
	Spironolactone	61 (19.0)
	Beta- blockers	123 (38.3)
	Calcium channel blockers	69 (21.5)
	Angiotensin receptor blockers	37 (11.5)
	Isosorbide dinitrate	49 (15.3)
	Aspirin	199 (62.0)
	Digoxin	108 (33.6)
	Potassium chloride	189 (58.9)
Ejection fraction (%)	< 40	115 (35.8)
	≥ 40	67 (20.9)
	undocumented	139 (43.3)
Blood pressure (BP) * (mmHg)	Systolic BP	137 ± 25
	Diastolic BP	79 ± 16
Renal function test *	Serum sodium (mmol/L)	137 ± 6
	Serum potassium (mmol/L)	4.4 ± 0.8
	Serum blood urea nitrogen (mmol/L)	9.9 ± 6.6
	Serum creatinine (μmol/L)	164 ±126

* reading upon admission

Table II: Dosage of different ACEI use during hospitalization

Types of ACEI	Range of daily dose used during hospitalization (mg)	Mean daily dose used during hospitalization (mg)
Captopril	6.25 – 75	22.71 ± 14.82
Enalapril	5 – 20	10.72 ± 4.50
Lisinopril	5 – 20	11.11 ± 5.46
Perindopril	2 – 8	3.24 ± 1.84
Ramipril	2.5 – 10	6.25 ± 5.30

Table III: Bivariate analysis of patient characteristics that were SIGNIFICANTLY associated with the use of ACEI (N =321)

Characteristic		Patient (n)	Received ACEI therapy n (%)		p- value
			Yes	No	
Serum potassium (mmol/L)	< 3.5	25	6 (24.0)	19 (76.0)	0.001
	3.5-5.0	243	152 (62.6)	91 (37.4)	
	5.1-5.4	25	13 (52.0)	12 (48.0)	
	≥ 5.5	28	12 (42.9)	16 (57.1)	
Serum creatinine (μmol/L)	< 133	183	118 (64.5)	65 (35.5)	0.001
	133-264	92	49 (53.3)	43 (46.7)	
	≥ 265	46	16 (34.8)	30 (65.2)	
Co- morbidities					
Chronic renal failure	Yes	63	23 (36.5)	40 (63.5)	<0.0001
	No	258	160 (62.0)	98 (38.0)	
Concurrent medications					
Frusemide	Yes	286	174 (60.8)	112 (39.2)	<0.0001
	No	35	9 (25.7)	26 (74.3)	
Aspirin	Yes	199	130 (65.3)	69 (34.7)	<0.0001
	No	122	53 (43.4)	69 (52.7)	
Potassium chloride	Yes	189	120 (63.5)	69 (36.5)	0.005
	No	132	63 (47.7)	69 (52.3)	
Calcium channel blockers	Yes	69	30 (43.5)	39 (56.5)	0.010
	No	252	153 (60.7)	99 (39.3)	
Angiotensin receptor blockers	Yes	37	0 (0)	37 (100)	<0.0001
	No	284	183 (64.4)	101 (35.6)	

Table IV: Bivariate analysis of patients characteristics that were NOT significantly associated with the use of ACEI (N=321)

Characteristic		Patient (n)	Received ACEI therapy n (%)		p- value
			Yes	No	
Age	20-39	4	3 (75.0)	1 (25.0)	0.103
	40-59	111	73 (65.8)	38 (34.2)	
	60-79	159	83 (52.2)	76 (47.8)	
	80-99	47	24 (51.1)	23 (48.9)	
Gender	Male	179	103 (57.5)	76 (42.5)	0.829
	Female	142	80 (56.3)	62 (43.7)	
Race	Malay	104	63 (60.6)	41 (39.4)	0.411
	Chinese	114	59 (51.8)	55 (48.2)	
	Indian	100	60 (60.0)	40 (40.0)	
	Others	3	1 (33.3)	2 (66.7)	
Ejection fraction (n = 182)	< 40%	115	75 (65.2)	40 (34.8)	0.254
	≥ 40%	67	38 (56.7)	29 (43.3)	
Systolic blood pressure (mmHg)	90-119	90	54 (60.0)	36 (40.0)	0.715
	120-139	142	81 (57.0)	61 (43.0)	
	≥140	89	48 (53.9)	41 (46.1)	
Co- morbidities	Diabetes mellitus	175	97 (55.4)	78 (44.6)	0.531
	Hypertension	209	122 (58.4)	87 (41.6)	0.500
	Ischemic heart disease	177	104 (58.8)	73 (41.2)	0.48
	Myocardial infarct	22	16 (72.7)	6 (27.3)	0.123
Concurrent medications	Beta- blockers	123	77 (62.6)	46 (37.4)	0.111
	Digoxin	108	61 (56.5)	47 (43.5)	0.892
	Spirinolactone	61	39 (63.9)	22 (36.1)	0.225
	Isosorbide dinitrate	49	34 (69.4)	15 (30.6)	0.057
	Hydrochlorothiazide	16	6 (37.5)	10 (62.5)	0.106

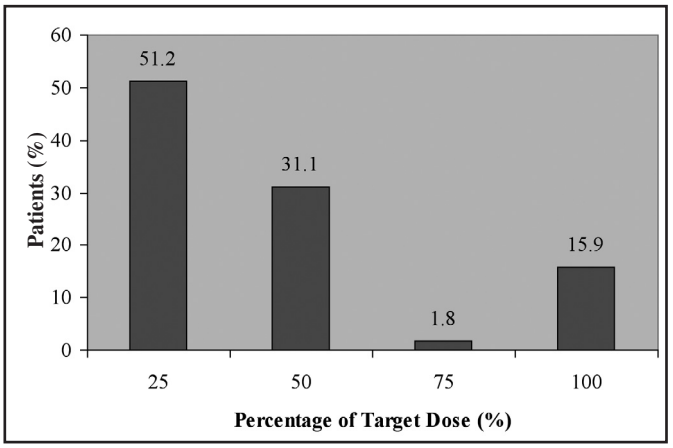

Fig. 1: The percentage of target dose of ACEI received at discharge

Patients who remained asymptomatic on therapy might be less likely to have upward titration of ACEI dose. Physicians also might continue previous dose and limit the dose below those dose used in randomized trials to avoid side effects [15]. Blood pressure and clinical response also determined the optimal usage of ACEI in clinical practice [16]. Echemann *et al* [17] reported that the titration of ACEI to target doses was based on the severity of HF and renal impairment. These might be the same reasons why ACEI were not given in high doses in our setting.

The low mean daily dose of ACEI used in HF might be due to mixed cases of new and old ACEI users in this study. Patients might receive greater daily doses of ACEI if they were already with ACEI therapy on admission. While for new users, the dose might be at initial dose. Practice guidelines recommend that dosing of ACEI has to be titrated upward over a period of 2 to 3 weeks[18]. This may explain why the target doses were not attained during the hospitalization period.

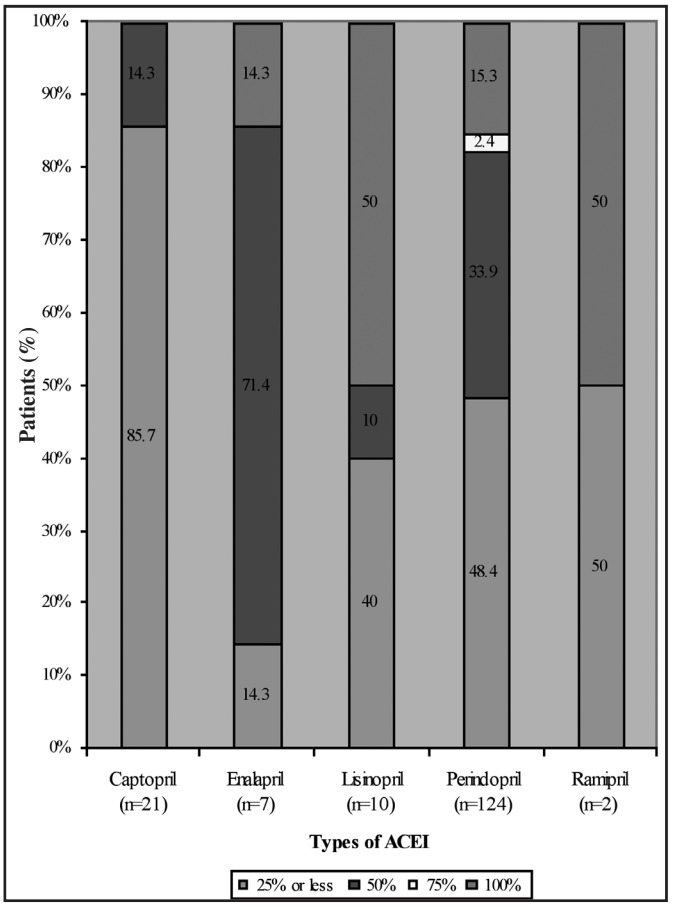

Fig. 2: Percentage of dose achieved by different types of ACEI at discharge

Of those HF patients who did not received ACEI, only 4.3% was documented to have contraindications to ACEI use which did not fill the shortfalls of ACEI utilization. The ongoing users were presumably able to tolerate ACEI therapy satisfactorily. Nevertheless patients might experience side effects that resulted in withdrawal of therapy during hospitalization. This was apparently true as adverse effects did lead to discontinuation of ACEI in HF patients [19], but the reported cases of side effects were considerably low to explain underutilization of ACEI in HF patients in this study.

Looking at the factors associated with the underutilization of ACEI, some studies [20,21,22] reported the overall rate of ACEI use was low in older hospitalized HF patients. Our study however had shown no apparent relationship of ACEI utilization with age. This might be due to no age limitation of ACEI use. ACEI are also effective and well-tolerated in young as well as elderly [4,23]. Nonetheless, there was unknown relationship on lower dose of ACEI use on elderly. Elderly patients are at greater risk of developing first-dose hypotension, hyperkalemia and renal function deterioration due to pre-existing risk factors [24].

With regards to the clinical features of HF patients, there was significant association of ACEI use with serum potassium and serum creatinine level identified in this study. This was apparently true since cautions were required in those with hyperkalemia and increase serum creatinine level [18]. This was further justified by Ahmad *et al* [24,25] in their reviews, where HF patients with higher serum creatinine and potassium level were not likely to be treated with ACEI. This might be explained by the consideration of potential deleterious effects of renal function with ACEI use. Nonetheless, no serum creatinine level is an absolute contraindication to ACEI use [26].

The studies by Komajda *et al* [13], Echemann *et al* [17] and Frances *et al* [27] recorded renal impairment influenced the outcome of whether HF patients received ACEI. Similarly, the results of this study had shown the presence of chronic renal failure was closely associated with failure of ACEI utilization. From The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines of ACEI use in chronic kidney disease [28], ACEI can be used safely in most patients with renal impairment. ACEI, in fact provide protection against deterioration of renal insufficiency [29]. Therefore, this should not be the reason that hinders ACEI use in chronic renal failure patients.

Simply switching from ACEI to ARB with no reason is not recommended as there is no evidence of ARB to be superior to the ACEI [18]. Our findings also showed there was no concurrent use of ARB and ACEI. However, there was significant association between ACEI use and the ARB prescribed to the patients and this is consistent with the study by Masoudi *et al* (2004) [7]. The reason might be that ARB was used as an alternative in those contraindicated or develop intolerance towards ACEI.

Our study serves a few limitations. First of all, the results did not represent the national practice of ACEI utilization in hospitalized HF patients. Generalization could not be made due to small sample size. Selection of HF patients using ICD-10th codes also could lead to errors as wrong coding of the diagnosis of patients may occur and the incomplete medical records hinder us to evaluate the reason of underutilization of ACEI. Thus, a larger, high-quality, prospective study should be performed to clearly evaluate the scenario of underutilization of ACEI in the management of HF in Malaysia.

CONCLUSION

In spite of ACEI being an agent which is class IA evidence in HF management, our study showed a low utilization of ACEI in our local setting. There was also lacked of documented reasons why patients did not received ACEI. Even for those treated with ACEI, most of them received low doses. Withholding this inexpensive treatment may deprive patients with HF of important clinical benefits of ACEI. Every effort should be made to increase the use of this cost effective agent in HF, not only in prescribing but also in optimizing the dose of ACEI for the survival benefit of HF patients. Interventions involving patients and all healthcare providers should be made to close the gap between clinical guidelines and practices in HF management.

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