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Peter A. McCullough

Keisha R. Sandberg
Henry Ford Health

Jerry Yee
Henry Ford Health, JYEE1@hfhs.org

Michael P. Hudson
Henry Ford Health

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Paper

Mortality benefit of angiotensin-converting enzyme inhibitors after cardiac events in patients with end-stage renal disease

Peter A McCullough, Keisha R Sandberg,† Jerry Yee,§ Michael P Hudson†*

Keywords: coronary care unit, end-stage renal disease, angiotensin-converting enzyme inhibitors, survival, arrhythmias, complications

* William Beaumont Hospital, Divisions of Cardiology, Nutrition and Preventive Medicine, Royal Oak, MI, Henry Ford Health System
† Henry Ford Heart and Vascular Institute
§ Henry Ford Hospital, Department of Internal Medicine, Division of Hypertension and Nephrology, Beaumont Health Center, 4949 Coolidge, Royal Oak, MI 48073, USA

Correspondence to:
Dr Peter A McCullough
Divisions of Cardiology, Nutrition and Preventive Medicine, William Beaumont Hospital, Beaumont Health Center, 4949 Coolidge, Royal Oak, MI 48073, USA
Tel: +1 248 655 5900
Fax: +1 248 655 5901
E-mail: pmc975@yahoo.com

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Abstract

Hypothesis/introduction

The risks and benefits of angiotensin-converting enzyme (ACE) inhibitors in patients with end-stage renal disease (ESRD) after cardiac events are unknown. We sought to determine the independent effect of ACE inhibitors (ACE-I) on long-term mortality in ESRD patients after cardiac events.

Materials and methods

We analysed a prospective coronary care unit registry and identified 527 ESRD patients, 368 with complete data on medications prescribed, over eight years at a single, tertiary centre.

Results

The overall mean age was 64.4±13.8 years with 54.9% men, and 59.2% African-American. A total of 143/386 (37.0%) were prescribed ACE-I during the hospital stay for cardiac reasons, including congestive heart failure (CHF) 52.8% and acute coronary syndromes (ACS) 47.2%. There were no significant differences in the rates of hypotension or arrhythmias in those who were treated with ACE-I versus those who were not. Survival analysis over three years, adjusted for known confounders, demonstrated a 37% reduction in all-cause mortality in those who received ACE-I, (p=0.0145).

Conclusions

In the setting of coronary care unit admission for CHF and ACS, ESRD patients selected for ACE-I, did not have increased rates of adverse haemodynamic or arrhythmic complications. The use of ACE-I conferred an independent mortality reduction over long-term follow-up.

Introduction

We and others have demonstrated that chronic kidney disease (CKD) including end-stage renal disease (ESRD) requiring renal-replacement therapy are independent risk factors for morbidity and mortality after a variety of cardiac events.[1-4] ESRD carries the highest risk of coronary heart disease death of any acquired medical condition.[2] Because CKD patients have been excluded from randomised trials of cardioprotective therapy, little is known about their risks and benefits in CKD, and in particular, in ESRD.[5] We sought to evaluate the short-term risks and benefits of angiotensin-converting enzyme (ACE) inhibitors in ESRD, given to patients in the coronary care unit after cardiac events.

Methods

Setting, data collection and follow-up

Henry Ford Hospital is a 903-bed tertiary care centre, located in the urban core of the Detroit metropolitan area, and receives patients whose care is provided primarily within the Henry Ford Health System, a vertically integrated, mixed-model managed care organisation with an advanced information technology infrastructure.[6-8] The Henry Ford Hospital Cardiac Intensive Care Unit Database characteristics have been published elsewhere.[1] Briefly, this was a registry in which every admission to this 16-bed unit had clinical data (~250 discrete elements) prospectively recorded on case report forms by trained research assistants. Data collected from 5/1/1990 to 8/22/1998 included baseline demographics, laboratory values, and events occurring during the unit stay, such as revascularisation and complications. The data collection period was stopped after discharge from the unit, either to another floor or to home. Mortality during the cardiac intensive care unit stay was recorded prospectively. Vital status was tracked on an annual basis using a multilayered approach. This approach called for ascertainment of future activity in the health system by the patient, confirmation of death by identification matching with the State of Michigan Death Certificate Registry, or record of a death on a later hospitalisation within the health system. Finally, for those not identified with any of the above means, the National Death Index was used to confirm death primarily in a state other than Michigan. These strategies yielded a 99% overall vital status ascertainment rate for patients followed after the first cardiac intensive care unit admission longitudinally over a mean of 36 months (minimum 0, maximum 100).

Outcome validation

Arrhythmic, haemodynamic, and fatal outcomes were selected for validation with blinded chart abstraction. A random sample, n=20, from each outcome category was chosen and each record was compared against chart abstraction for the development of the outcome during the coronary care unit stay. Agreement statistics were computed for each outcome and then averaged over the

Table 1 Baseline characteristics of ESRD patients admitted to a coronary care unit treated with or without ACE-I.

Characteristic	ACE-I (n=143)	No ACE-I (n=225)	p-value
Age	64.0±14.3	65.4±13.0	0.34
Male	75 (52.4)	137 (60.9)	0.11
Female	68 (47.6)	88 (39.1)	0.11
African-American	81 (56.6)	137 (60.9)	0.41
Caucasian	57 (39.9)	82 (36.4)	0.51
Other race	5 (3.5)	6 (2.7)	0.89
Hypertension	122 (85.3)	179 (79.6)	0.16
Diabetes	76 (53.1)	123 (54.7)	0.78
Smoking	76 (53.1)	91 (40.4)	0.02
Prior cardiac revascularisation	34 (23.8)	30 (13.3)	0.01
History of CHF	94 (65.7)	89 (39.6)	<0.0001
Chronic medications			
ACE-I	86 (62.8)	38 (17.6)	<0.0001
Beta-blocker	24 (18.8)	33 (15.2)	0.39
Discharge diagnoses			
UA/NSTEMI	29 (20.3)	103 (45.7)	<0.0001
STEMI	15 (10.5)	17 (7.6)	0.33
CHF	99 (69.2)	105 (46.7)	<0.0001

ACE-I = angiotensin-converting enzyme inhibitor, UA/NSTEMI = unstable angina/non-ST-elevation myocardial infarction, STEMI = ST-elevation myocardial infarction, CHF = congestive heart failure.

Table 2 In-hospital complications according to ACE-I use. Hypotension = sustained systolic blood pressure <90 mmHg with signs of hypoperfusion, hypertension = sustained systolic blood pressure >180 mmHg.

Complication	ACE-I (n=143)	No ACE-I (n=225)	p-value
Hypotension	31 (21.7)	54 (24.0)	0.61
Hypertension	41 (28.7)	42 (18.7)	0.03
Atrial fibrillation/flutter	23 (16.1)	41 (18.2)	0.60
Ventricular tachycardia	5 (3.5)	14 (6.2)	0.24
Ventricular fibrillation	8 (5.6)	7 (3.1)	0.24
In-hospital death	6 (4.2)	12 (5.3)	0.62

12 categories. The mean percent agreement was 92.7% across the eleven outcomes.

Statistical analysis

Baseline characteristics are reported with means±standard deviation (SD) or proportions with 95% confidence intervals (CI), as appropriate, with exclusion of missing data points. Univariate comparisons were carried out using analysis of variance, or Chi-square as appropriate. Cox proportional hazards model was used to derive the independent predictors of time to cumulative death as the primary outcome. All models were tested for interactions and none were found. The log-rank test was used to evaluate the independent differences in survival across the strata. All p-values are two-tailed and considered significant at α <0.05.

Results

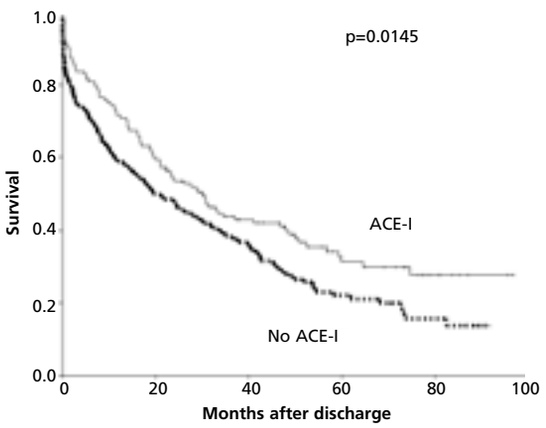
Baseline characteristics

The overall mean age was 64.4±13.8, range 20 to 93 years. Baseline characteristics according to use of ACE-I are given in Table 1. A total of 143/386 (37.0%) were prescribed ACE-I during the hospital stay for cardiac reasons, including congestive heart failure (CHF) 52.8% and acute coronary syndromes (ACS) 47.2%. More patients in the ACE-I group were receiving ACE-I prior to their hospital admission. Also, the majority (69.2%) of patients who received ACE-I were admitted for CHF. Overall, 54.1% had a history of diabetes, and presumably, had diabetic nephropathy as the aetiology of ESRD. The duration on dialysis was not recorded on the case report form. The admission serum potassium level was 4.5±1.0 and 4.7±1.1 mmol/L for those treated with and without ACE-I, respectively, (p=0.14). The admission haemoglobin was 11.3±2.2 and 10.1±2.5 g/dl for those treated with and without ACE-I, respectively, p<0.0001.

In-hospital complications

In-hospital complications are given in Table 2. There were no differences in the rates of hypotension or arrhythmias. Hypotension was defined as

Figure 1 Long-term survival in 368 patients with ESRD treated with angiotensin-converting enzyme inhibitor (ACE-I) after a cardiac event.



a sustained systolic blood pressure <90 mmHg, with signs of hypoperfusion. The development of hypertension was more common among those treated with ACE-I and may reflect an indication for ACE-I treatment. The complications of angioedema, cough, and hyperkalaemia were not recorded on the case report form. There was no difference between the rates of in-hospital mortality, 4.2% *vs*. 5.3%, p=0.62, for those prescribed ACE-I versus not.

Long-term survival

Figure 1 displays survival over long-term follow-up. The mean and median survival was 43.2±3.3 and 30.0±3.9, and 32.4±2.3 and 19.5±3.5 months for those treated with and without ACE-I, respectively. Cox proportional hazards regression revealed the independent reduction in the hazard for death for ACE-I was RR=0.63, 95% CI 0.47–0.83, p=0.001. A history of CHF was found to be a significant adverse predictor of death, RR=1.52, 95% CI 1.16–1.99, p=0.002. Factors not found to be significant in the model included age, sex, race, β-blocker use, and diabetes. When the model was restricted to either ACS patients alone or CHF patients alone, the overall relative risk reduction for ACE-I remained the same. However, all variables in the model became insignificant due to a lack of stability from too few endpoints.

Discussion

Our study has demonstrated an independent, 37% reduction in all-cause mortality after hospitalisation for cardiac events, primarily ACS and CHF, with the use of ACE-I. Although the overall survival with ESRD patients after cardiac events was poor, the relative risk reduction observed with ACE-I is on par with the 20–40% reduction in death seen in the general population in the treatment of acute myocardial infarction (MI) and CHF.[9] Although we did not record additional events, we would expect that rates of recurrent MI, hospitalisation for CHF, and sudden death would also be reduced with ACE-I.[9]

Robson originally reported the first clinical trial of ACE-I in ESRD in a 107-patient randomised, factorial design.[10] This trial evaluated cerivastatin (10 mg per day) and enalapril (2.5–5 mg per day) in ESRD patients on haemo- or peritoneal dialysis. The enalapril arm of this trial was stopped early because of an excessive incidence of hypotension. In a recent prospective study of 11 ESRD patients, Agarwal and co-workers demonstrated that lisinopril, 40 mg once a day, three times a week, can be used safely in ESRD with considerable reductions in systolic and diastolic blood pressure, 22 and 11 mmHg, respectively.[11] We observed that patients in our study, if anything, tended to be hypertensive during their stay, and it is quite possible that the ACE-I was used in addition to other drugs with the primary intent of controlling hypertension.

One of the benefits of ACE-I in ESRD is a predictable reduction in left ventricular (LV) mass index. Regression of LV hypertrophy is a leading mechanism by which ACE-I modify the natural history of cardiac disease, in particular CHF and sudden death.[12] Dyadyk and co-workers demonstrated a 20% reduction in LV mass index over 12 months in ESRD patients treated with either captopril or enalapril.[13] There have been no clinical trials of treatment for ACS or CHF in patients with ESRD. We have recently shown that CKD patients, including ESRD, in the setting of ST-segment elevation MI (STEMI), significantly benefit from the use of aspirin and β-blockers.[14] Our data from the present study, confirm that ACE-I are cardioprotective for ESRD patients across a variety of cardiac events, including ACS (with a small subgroup of STEMI) and CHF. Although these analyses cannot stand in the place of clinical trials, they do suggest that those patients selected for these therapies, whether due to the effect of the drug, or to the characteristics of the patients, have improved survival over those not prescribed these agents.

One of the concerns regarding the use of ACE-I in ESRD is the worsening of anaemia related to erythropoietin deficiency.[15-16] However, in a recent crossover trial of 51 patients with ESRD, ACE-I were not shown to be related to the level of haemoglobin or to the need for increasing erythropoietin dosage.[17] Our study was not designed to address this issue; however, we did note that those selected for ACE-I had higher haemoglobin levels than those not selected for ACE-I. While the ACE-I-erythropoietin interaction remains controversial, it is prudent to closely monitor the haemoglobin level and to adjust erythropoietin doses accordingly if ACE-I are going to be used in ESRD.

Study limitations

Our study has many of the limitations that are common to retrospective analyses of prospectively collected data. First and most importantly, we could not control for selection bias. That is, clinicians chose to use ACE-I based on clinical scenarios and perceived benefit to the patient. The most common condition driving the choice of ACE-I was CHF. However, we controlled for CHF in the multivariate modelling and found ACE-I to have

conferred benefit. Unfortunately we did not have the specific ACE-I or dosage used. This is important, due to the different rates of renal clearance within the ACE-I class.[18] Also very importantly, we did not have medication use data collected over the long term, and made the assumption that the in-hospital course of therapy set the outpatient management programme. Lack of adherence to ACE-I, or changes to other non-ACE-I drugs by outpatient physicians, would have if anything, caused bias to the null hypothesis. Lastly, we did not track ACE-I specific adverse events in the case report form, such as angioedema, cough, and the development of hyperkalaemia. These events almost certainly dictated, in some cases, who received an ACE-I and who did not.

Although heavily confounded and influenced by selection bias, our data suggest that those individuals with ESRD selected for ACE-I on admission for cardiac events have considerable opportunity for cardioprotection. The survival benefit we observed should be validated in two prospective, double-blind randomised trials, one in ACS and one in CHF. Such trials should carefully assess for adverse events, including hypotension, angioedema, cough and, importantly, hyperkalaemia – all of which we could not completely account for in our data. It is only through a clinical trials programme in ESRD that inroads will be made with this subgroup, which has the highest cardiac death rate recognised today.[19]

Conclusions

We observed that ACE-I were used in 39% of ESRD patients admitted to a coronary care unit primarily for ACS and CHF. For those patients selected for ACE-I, there were no adverse haemodynamic or arrhythmic complications. The use of ACE-I conferred an independent, 37% mortality reduction over long-term follow-up.

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