Use of Angiotensin-converting Enzyme Inhibitor Therapy and Dose-related Outcomes in Older Adults with New Heart Failure in the Community

Paula A. Rochon, MD, MPH, Kathy Sykora, MSc, Susan E. Bronskill, PhD, Muhammad Mamdani, PharmD, MA, MPH, Geoffrey M. Anderson, MD, PhD, Jerry H. Gurwitz, MD, Sudeep Gill, MD, Jack V. Tu, MD, MSc, PhD, Andreas Laupacis, MD

OBJECTIVE: To evaluate the dose-related benefit of angiotensin-converting enzyme (ACE) inhibitor therapy among older adults with heart failure and to evaluate whether low-dose ACE inhibitor therapy is better than none.

DESIGN: Observational cohort study.

SETTING: Community-dwelling older adults in Ontario, Canada.

PATIENTS/PARTICIPANTS: We identified 16,539 adults 66 years or older who survived 45 days following their first heart failure hospitalization discharge.

MEASUREMENT AND MAIN RESULTS: Multivariate techniques including propensity scores were used to study the association between the dose of ACE inhibitor therapy dispensed and 3 outcomes: survival, survival or heart failure rehospitalization, and survival or all-cause hospitalization at 1 year of follow-up. Logistic regression models explored the association between initial dose dispensed and subsequent dose reduction or drug cessation. Overall, 10,793 (65.3%) of patients were dispensed ACE inhibitor therapy, with more than a third (3,935; 36.5%) initiated on low-dose therapy. Relative to dispensing of low-dose ACE inhibitor therapy, nonuse was associated with increased mortality (hazard ratio [HR], 1.12; 95% confidence interval [CI], 1.02 to 1.22). Dispensing medium-dose therapy provided a benefit similar to low-dose (HR, 0.94; CI, 0.86 to 1.03) and dispensing of high-dose therapy was associated with improved survival benefit (HR, 0.76; CI, 0.68 to 0.85). Relative to dispensing of low-dose ACE inhibitor therapy, dispensing high-dose conferred a benefit (HR, 0.87; CI, 0.80 to 0.95) on the composite outcome of 1-year mortality or heart failure hospitalization and the composite outcome of 1-year mortality or all-cause hospitalization (HR, 0.87; CI, 0.81 to 0.93). Relative to those dispensed low-dose ACE inhibitor therapy, those initially dispensed high-dose therapy were twice as likely to have their subsequent dose reduced or the therapy discontinued (odds ratio, 2.36; CI, 2.07 to 2.69).

CONCLUSION: Our findings suggest that when possible, older adults should be titrated to the higher doses of ACE inhibitor therapy evaluated in clinical trials. If older adults cannot tolerate higher doses, then low-dose ACE inhibitor therapy is superior to none. High-dose ACE inhibitor therapy is not as well tolerated as lower doses.

KEY WORDS: angiotensin-converting enzyme inhibitors; heart failure; older adults; low dose.

J GEN INTERN MED 2004;19:676–683.

Angiotensin-converting enzyme (ACE) inhibitor therapy is recommended as first-line therapy for the management of all patients with heart failure due to left ventricular systolic dysfunction unless they have a contraindication.^{1,2} The major trials demonstrating the benefit of ACE inhibitor therapy in heart failure^{3–5} required upward titration of the ACE inhibitor therapy dose. Based on the intent of these randomized controlled trials (RCTs), heart failure guidelines^{1,6} suggest that ACE inhibitor therapy should be titrated upward. Few trials^{7–10} have studied the dose-related benefit of an ACE inhibitor. Two of these studies found a nonsignificant trend toward increased survival, one with high-dose lisinopril⁷ and the other with high-dose captopril therapy.¹⁰ The other two trials found no dose-related benefit. No study has evaluated whether low-dose ACE inhibitor therapy is better than none.

The vast majority of older adults receive ACE inhibitor therapy at doses lower than were suggested in clinical trials^{11–13} likely because of a reluctance to try higher doses or because the higher doses were not tolerated. Generally, ACE inhibitor-related adverse drug events are managed by decreasing the dose or discontinuing the therapy.⁷ It is important to determine whether low-dose ACE inhibitor therapy is beneficial, and the relative benefits of high- to lower-dose therapy in routine clinical practice. We assessed the dose-related benefits associated with use of ACE inhibitor therapies in a large population-based cohort of all older patients surviving a new heart failure hospitalization in Ontario, Canada.

METHODS

Sources of Data

The Canadian Institute for Health Information (CIHI) database collects and collates information on all acute care hospital discharges (discharges, transfers, or deaths)

Received from the Kunin-Lunenfeld Applied Research Unit (PAR, SG), Baycrest Centre for Geriatric Care; Departments of Medicine (PAR, SG) and Health Policy, Management, and Evaluation (PAR, SEB, MM, GMA, JVT), and Faculty of Pharmacy (MM), University of Toronto; Institute for Clinical Evaluative Sciences (PAR, KS, SEB, MM, GMA, JVT, AL); and Department of Medicine (JVT, AL), Sunnybrook and Womens College Health Science Centre, Toronto, Ontario, Canada; and Meyers Primary Care Institute (JHG), Fallon Healthcare System and University of Massachusetts Medical School, Worcester, Mass.

Address correspondence and requests for reprints to Dr. Rochon: Kunin-Lunenfeld Applied Research Unit, Baycrest Centre for Geriatric Care, 3560 Bathurst Street, Toronto, Ontario M6A 2E1, Canada (e-mail: paula.rochon@utoronto.ca).

in Ontario. Records for patients 66 years and older who were discharged alive after their first heart failure hospital admission were linked by encrypted patient identifiers to the Registered Persons Database (RPDB) to obtain demographic and survival information outside the hospital setting, and to the Ontario Drug Benefit Plan (ODB) database to track their use of ACE inhibitor therapy as well as use of other drug therapies. The ODB provides comprehensive drug coverage to older adults in the province of Ontario and provides information about the individual drug therapy and the strength dispensed. Additional information about the patients' characteristics and medical history were obtained using the CIHI, ODB, as well as Ontario Health Insurance Plan (OHIP) databases. The OHIP database contains records for all physician services billed in Ontario. These databases have been used to successfully study cardiovascular disease in a series of studies.¹⁴⁻²⁰

Study Cohort

Between January 1, 1998, and December 31, 1999, we identified 18,655 patients over the age of 66 who survived 45 days after discharge from an Ontario hospital following their first admission (no heart failure admission in the previous 3 years) with a primary diagnosis of heart failure (International Classification of Diseases, Ninth Revision [ICD-9] code 428). This code has been found to have an 88% positive predictive value for heart failure.²¹ The 45-day time point was chosen to identify patients who were likely stable outpatients. This approach is consistent with that taken in randomized control trials. Patients were excluded if they had an acute myocardial infarction on the same admission ($n = 843$ patients), were discharged to a chronic care hospital ($n = 432$ patients), had a length of stay of over 100 days (46 patients), or if we were unable to identify drug-related information ($n = 1$). In addition, we excluded the 794 patients dispensed angiotensin receptor blockers during the follow-up period, as this therapy has a similar indication as ACE inhibitor therapy. Our final cohort included 16,539 older adults.

Angiotensin-converting Enzyme Inhibitor Use and Dose Classification

Our cohort was classified into nonusers of ACE inhibitor therapy and those who were being dispensed the therapy at the index date (45 days following their heart failure discharge). Most (83%) of the group of older adults received their first outpatient ACE inhibitor therapy claim by this date. The ODB contains 3 fields relevant to dose calculation: the DIN (drug identification number), the quantity, and an estimate of the number of days supplied with the prescription. The DIN was linked to a drug list database containing details about each drug, including the strength of the active ingredient. The ACE inhibitor therapy dosages were calculated based on the drug strength and the number of days supplied. The daily dose, therefore, was estimated

Table 1. Classification of ACE Inhibitor Therapy Dose Range (mg/day)

ACE Inhibitor Therapy	Low	Medium	High
Benazepril HCl*	5	6 to 19	20
Captopril ^{†‡}	38	39 to 149	150
Cilazapril*	1.25	1.26 to 4	5
Enalapril maleate ^{†‡}	5	6 to 19	20
Fosinopril sodium*	5	6 to 19	20
Lisinopril [†]	5	6 to 19	20
Perindopril erbumine*	2	3 to 7	8
Quinapril HCl [†]	10	11 to 39	40
Ramipril*	2.5	2.6 to 9	10

* High doses based on the highest recommended maintenance dose in the *Compendium of Pharmaceuticals and Specialties*.²⁴

Analysis repeated for lisinopril high dose of 32.5 mg or greater and low dose 5 mg or less.

[†] High dose based on the ACE inhibitor target doses recommended by the Agency for Health Care Policy and Research for the management of heart failure.²³

[‡] High dose based on randomized controlled trial (RCT) evidence. ACE, angiotensin-converting enzyme.

by dividing the dosage dispensed by the days supplied. For example, a patient dispensed 30 days' supply of 10-mg tablets of enalapril and given 60 tablets would receive 600 mg of enalapril to be distributed over 30 days, or 20 mg/day. Based on the information included in Table 1, we classified this as a high-dose.

ACE inhibitor therapy dose was classified into 4 mutually exclusive groups: nonusers, and those dispensed low- (25% or less of trial dose), medium- (25% to 99% of trial dose), or high-dose (trial dose or higher) using the approach described by Barron et al.²² where the doses are a percentage of the targeted dose (Table 1). For example, for enalapril, where the high dose was 20 mg per day, low-dose therapy would be a dose of 5 mg or less per day. ACE inhibitor doses were calculated for both the initial dose (first dose dispensed) and the final dose (last dose dispensed at end of 1-year follow-up). The high-dose level of the ACE inhibitor therapy was determined using 3 sources. The target doses for captopril, enalapril, lisinopril, and quinapril were identified using the ACE inhibitor target doses recommended by the Agency for Healthcare Research and Quality (AHRQ) for the management of heart failure.²³ These doses were consistent with those recommended in the captopril,⁵ and enalapril,³ in trials. The target trial dose for lisinopril recommended by the AHRQ guidelines (20 mg) is lower than the target dose of 32.5 mg published in a more recent trial.⁷ This trial was published in December 1999 (end of our study period) and would not have influenced the prescribing patterns in our data. Irrespective, we repeated our analyses using lisinopril at the low dose of 5 mg or less and the high dose of 32.5 mg evaluated in this trial.⁷ High doses for benazepril, cilazapril, fosinopril, perindopril, and ramipril were determined based on the highest listed dose in the usual maintenance dosage

category that was recommended in the Compendium of Pharmaceuticals and Specialties 1998.²⁴

Change of ACE Inhibitor Therapy Dose

We identified all patients who changed from their initial ACE inhibitor therapy dose assignment during the 1-year follow-up. Specifically, we identified patients who had their ACE inhibitor therapy titrated from one dose category to another (e.g., initiated on low-dose therapy and increased to medium- or a high-dose category). As well, we identified those who were initiated on ACE inhibitor therapy after the index date or had their therapy discontinued. To identify cessation of drug therapy, we identified all older adults who failed to obtain a new ACE inhibitor drug therapy claim at the time that they were 20% over the amount of days of therapy provided using the “days supplied” variable of the pharmacy claims database. For example, if an older adult was dispensed a drug therapy for 60 days, and the drug was not dispensed again at day 60, they were allowed a 20% grace period on the previous days’ supply to refill the next prescription. If they did not refill their prescription for the study drug within this subsequent time window, they were deemed to have discontinued the drug.

Older adults were identified as having a dose reduction within any dose category if their initial ACE inhibitor therapy dose decreased by 50% or more. For example, if a patient was initially dispensed a low dose of enalapril therapy (5 mg) and their final dispensed dose was 2.5 mg, they would be classified as having a dose reduction.

Potential Contraindications to ACE Inhibitor Therapy

Potential contraindications to ACE inhibitor therapy were prespecified using a definition similar to that provided in guidelines for the management of heart failure⁶ and identified using claims from the 365 days prior to the hospital admission. CIHI discharge abstracts were reviewed to identify hospitalizations with a diagnosis (primary or other) of angioneurotic edema (ICD-9 995.1), hyperkalemia (ICD-9 276.7), hypotension (ICD-9 458), or renal impairment (ICD-9 codes 580-583, 584.6-584.9, 585-588, 589.1, 589.9, 590.0, 591, 593.7, and 593.8). Hyperkalemia was additionally identified by searching the ODB database for claims for potassium-removing resins, used for the management of hyperkalemia. Renal impairment was also identified by searching the OHIP database for related diagnostic codes (403, 446, 580, 581, 584, 585, 590, 591, 593, 753).

Heart Failure Severity

We used US national consensus recommendations for the management of chronic heart failure⁶ guidelines to identify use of other drugs recommended for the treatment of heart failure (i.e., beta-blockers, digoxin, isosorbide dinitrate with hydralazine, loop, or other diuretics). Patients requiring

multiple drug therapies recommended for the treatment of heart failure likely had more severe heart failure. We identified patients’ use of these drugs in the ODB database, based on the 45-day period between the discharge from the heart failure episode of care and the entry into the study.

Patient Characteristics

Patients were classified into 3 age groups: 66 to 74 years; 75 to 84 years; and 85 years and older.²⁵ Comorbidity was measured using the Charlson Index²⁶ adapted by Deyo²⁷ for computerized databases, collapsing the diagnostic information on the discharge abstracts for the index episode of care. The Charlson comorbidity scores were categorized as 0 to 1, 2, or greater than 2.

Outcomes

Benefit of ACE Inhibitor Therapy. We evaluated the relation between ACE inhibitor dose and 3 outcomes during 1 year of follow-up: mortality, the composite outcomes of mortality or rehospitalization with heart failure, and mortality or all-cause rehospitalization.

Statistical Analyses. Descriptive and simple univariate statistics (χ^2 for categorical and one-way ANOVA for continuous variables) were used to compare characteristics of older Ontarians in our cohort who were nonusers or were dispensed, low, medium, or high doses of ACE inhibitor therapy prior to the index date for our cohort.

We used a Cox proportional-hazards model²⁸ to evaluate ACE inhibitor therapy and its relation to the outcomes in the 1 year following study entry. Patients who changed from one dose category to another were censored and therefore no longer followed at the time of the dose change. For example, if a patient was initially classified as a nonuser but was subsequently initiated on an ACE inhibitor therapy, the patient would be censored at the time of the ACE inhibitor therapy initiation. Similarly, if a patient was initially classified as being in a low-dose ACE inhibitor therapy group and was later increased to a high-dose category, they would be censored at the time the dose was increased.

The Cochran-Armitage Trend Test²⁹ was used to determine whether there was a dose-related trend between increasing dose of ACE inhibitor therapy and death or the composite outcomes.

The models controlled for age, gender, Charlson comorbidity scores, history of renal disease, acute myocardial infarctions, diabetes, previous use of ACE inhibitors, presence of potential contraindications to ACE inhibitor, other medications recommended for the management of heart failure (angiotensin receptor blocker [ARB], beta-blocker therapy, digoxin, diuretic therapy, or isosorbide dinitrate and hydralazine).

Analysis using propensity scores has been suggested as a method to control for the effects of observed covariates.³⁰ The analyses were repeated using a propensity score

approach that compared low-dose ACE inhibitor therapy to none, and separately, high- to low-dose ACE inhibitor therapy for each of the 3 outcomes.

Among those patients dispensed ACE inhibitor therapy, we used logistic regression to evaluate initial ACE inhibitor dose dispensed (low, medium, or high) and its relation to subsequent dose reduction or cessation. Logistic regression was used because we could identify when a therapy was not renewed but we could not identify the exact date when the therapy was stopped.

We conducted two sensitivity analyses to further explore the association between ACE inhibitor dose and the survival-related outcomes. First, we repeated our analyses using an intention-to-treat approach. At the index date of our cohort, patients were assigned to 1 of our 4 drug categories and patients were not censored if they changed to a different category. Next, we repeated the analyses using a time-dependent approach where patients who changed from one drug category to another were reassigned (rather than being censored) to the new drug category until the end of the follow-up period.

RESULTS

Characteristics of the Cohort

Table 2 describes the cohort. Of the 16,539 heart failure 45-day survivors, the mean ($\pm$ standard deviation)

age of the group was 79.1 ± 7.4 years. The majority (8,854; 53.5%) were women. Many patients were frail, with 1,476 (8.9%) having Charlson comorbidity scores > 2 . During the 1-year follow-up period 4,186 (25.3%) died, 6,179 (37.4%) either died or were rehospitalized with heart failure, and 10,092 (61.0%) either died or had a hospitalization for any cause. Almost a quarter (3,502; 21.2%) of the older adults had a previous history of hyperkalemia, hypotension, or renal impairment.

Overall, 10,793 (65.3%) patients were taking an ACE inhibitor therapy at 45 days following their heart failure hospitalization. Of these, 4,582 (42.5%) were dispensed enalapril, 1,998 (18.5%) lisinopril, and 1,641 (15.2%) ramipril. As expected, many patients (3,935; 36.5%) were given a low dose of ACE inhibitor therapy. Among the 3,935 patients dispensed low-dose therapy, only 349 (8.9%) were titrated to a high dose. Among the 4,316 patients dispensed medium-dose therapy, 830 (19.2%) were titrated to a high dose. Of those dispensed the high-dose therapy, 79.8% remained on the high-dose therapy. At the end of 1 year, the vast majority of users (9,176; 85.0%) were dispensed doses lower than those targeted in trials.

Survival and Composite Outcomes

Dispensing of ACE inhibitor therapy was associated with improved survival. Table 2 describes crude mortality at 1 year by the dose of ACE inhibitor therapy dispensed

Table 2. Characteristics of all 16,539 Older Adults Surviving 45 days After a Heart Failure Admission Between January 1, 1998, and December 31, 1999 by the Initial ACE Inhibitor Dose Dispensed

	Total (N = 16,539)	Initial Dose Dispensed			
		Nonuser (N = 5,746)	Low (N = 3,935)	Medium (N = 4,316)	High (N = 2,542)
Mean age, $y \pm SD$	79.13 ± 7.39	79.30 ± 7.44	80.24 ± 7.53	78.96 ± 7.23	77.33 ± 6.99
Charlson Index, mean $\pm SD$	0.94 ± 1.15	1.02 ± 1.23	0.84 ± 1.11	0.92 ± 1.12	0.94 ± 1.06
0–1, n (%)	12,686 (76.7)	4,232 (73.7)	3,136 (79.7)	3,350 (77.6)	1,968 (77.4)
2, n (%)	2,377 (14.4)	874 (15.2)	497 (12.6)	627 (14.5)	379 (14.9)
>2 , n (%)	1,476 (8.9)	640 (11.1)	302 (7.7)	339 (7.9)	195 (7.7)
Female gender, n (%)	8,854 (53.5)	3,093 (53.8)	2,216 (56.3)	2,237 (51.8)	1,308 (51.5)
Potential Contraindications to ACE Inhibitor Therapy, n (%)					
History of hypotension	353 (2.1)	131 (2.3)	100 (2.5)	82 (1.9)	40 (1.6)
History of hyperkalemia	260 (1.6)	117 (2.0)	56 (1.4)	60 (1.4)	27 (1.1)
History of renal impairment	3,160 (19.1)	1,423 (24.8)	672 (17.1)	663 (15.4)	402 (15.8)
Any of the above	3,502 (21.2)	1,537 (26.7)	768 (19.5)	755 (17.5)	442 (17.4)
Use of Additional Heart Failure Therapies, n (%)					
Beta-blockers	3,282 (19.8)	1,033 (18.0)	689 (17.5)	908 (21.0)	652 (25.6)
Digoxin	6,682 (40.4)	1,845 (32.1)	1,705 (43.3)	1,944 (45.0)	1,188 (46.7)
Diuretic therapy	13,900 (84.0)	4,267 (74.3)	3,489 (88.7)	3,850 (89.2)	2,294 (90.2)
Isosorbide dinitrate with hydralazine	36 (0.2)	30 (0.5)	3 (0.1)	0 (0.0)	3 (0.1)
Crude Outcomes, n (%)					
Death	4,186 (25.3)	1,606 (27.9)	995 (25.3)	1,061 (24.6)	524 (20.6)
Death or heart failure rehospitalization	6,179 (37.4)	2,267 (39.5)	1,424 (36.2)	1,583 (36.7)	905 (35.6)
Death or all-cause hospitalization	10,092 (61.0)	3,675 (64.0)	2,343 (59.5)	2,585 (59.9)	1,489 (58.6)

ACE, angiotensin-converting enzyme; SD, standard deviation.

Table 3. Association Between Dose of ACE Inhibitor Therapy Dispensed and the Outcomes During One Year of Follow-up for the 16,539 Older Adults Surviving 45 days Past a New Heart Failure Admission Between January 1, 1998, and December 31, 1999

Dose (Day 45)	Hazard Ratio (CI)		
	Death	Death / Heart Failure Hospitalization	Death / All Hospitalization
None (N = 5,746)	1.12 (1.02 to 1.22)	1.08 (1.00 to 1.16)	1.04 (0.98 to 1.10)
Low* (N = 3,935)	1.00	1.00	1.00
Medium (N = 4,316)	0.94 (0.86 to 1.03)	0.95 (0.88 to 1.02)	0.95 (0.89 to 1.00)
High (N = 2,542)	0.76 (0.68 to 0.85)	0.87 (0.80 to 0.95)	0.87 (0.81 to 0.93)

Adjusted for age, gender, comorbidity, medical history (hyperkalemia, renal disease, hypotension, edema, diabetes, AMI), as well as concomitant use of other heart failure drug therapies (beta-blockers, angiotensin-receptor blockers, ASA, calcium channel blockers, spironolactone, potassium supplements, digoxin, and diuretics).

* Reference category.

ACE, angiotensin-converting enzyme; CI, confidence interval; AMI, acute myocardial infarction; ASA, acetyl salicylic acid.

(nonuser or low-, medium-, or high-dose). Changing the low- and high-dose classification for lisinopril did not change our results. Multivariate adjusted models suggest that relative to dispensing of low-dose ACE inhibitor therapy, not being dispensed ACE inhibitor therapy was associated with a significant increase in mortality, dispensing of medium-dose therapy provided a similar mortality benefit, and dispensing of high-dose therapy was associated with a significantly improved survival benefit (Table 3).

Dispensing of ACE inhibitor therapy was also beneficial with regard to the composite outcome of 1-year mortality or heart failure rehospitalization (Table 3). Relative to dispensing of low-dose ACE inhibitor therapy, not being dispensed ACE inhibitor therapy was associated with a significantly greater risk of death or a heart failure rehospitalization, dispensing medium-dose provided similar benefit, and dispensing high-dose conferred a significant benefit. Dispensing of higher doses of ACE inhibitor therapy was beneficial with regard to the composite outcome of 1-year mortality or all cause hospitalization (Table 3). Relative to

dispensing of low-dose ACE inhibitor therapy, nonusers were at a similar risk for 1-year mortality or heart failure rehospitalization, dispensing medium-dose provided some benefit, and dispensing of high-dose therapy was associated with a significant reduction in mortality or all-cause hospitalization.

Using the Cochran-Armitage Trend Test,²⁹ we found a dose-related association of ACE inhibitor therapy prescription and subsequent death with the composite outcomes of death or heart failure rehospitalization, and death or all-cause hospitalization (all $P < .001$).

The analyses reported in this paper used the traditional risk adjustment approach. Analyses using propensity scores produced very similar results (details of the analysis available upon request).

Table 4 outlines the results of the two sensitivity analyses we conducted to further explore the association between ACE inhibitor dose and the survival-related outcomes. Our results continued to show an association between the use of ACE inhibitor therapy and improved outcomes.

Table 4. Association Between Dose of ACE Inhibitor Therapy Dispensed and the Outcomes During One Year of Follow-up for the 15,539 Older Adults Surviving 45 Days Past a New Heart Failure Admission Between January 1, 1998, and December 31, 1999, Using Two Sensitivity Analyses

	Hazard Ratio (95% CI)			
	None	Low	Medium	High
Mortality				
Intention-to-treat	1.40 (1.29 to 1.52)	1.00	0.94 (0.86 to 1.02)	0.69 (0.63 to 0.76)
Time-dependent	1.50 (1.38 to 1.63)	1.00	1.05 (0.97 to 1.14)	0.77 (0.70 to 0.84)
Mortality/Heart Failure Hospitalization				
Intention-to-treat	1.13 (1.05 to 1.22)	1.00	0.99 (0.93 to 1.06)	0.86 (0.80 to 0.92)
Time-dependent	1.14 (1.06 to 1.22)	1.00	0.99 (0.93 to 1.06)	0.86 (0.80 to 0.93)
Mortality/All Hospitalization				
Intention-to-treat	1.01 (0.95 to 1.07)	1.00	0.96 (0.91 to 1.01)	0.85 (0.80 to 0.90)
Time-dependent	1.00 (0.94 to 1.05)	1.00	0.92 (0.88 to 0.97)	0.83 (0.79 to 0.88)

Low dose was the reference dose for all categories.

ACE, angiotensin-converting enzyme; CI, confidence interval.

Table 5. Association Between Initial Dose of ACE Inhibitor Therapy Dispensed and Subsequent Dose Reduction or Cessation of Therapy

Dose on Day 45	Patients Who Reduced or Stopped ACE Number (%)	Odds Ratio (95% CI)	P Value
Low (N = 3,935)	516 (13.1)	1.00	
Medium (N = 4,316)	809 (18.7)	1.57 (1.39 to 1.77)	< .001
High (N = 2,542)	645 (25.4)	2.36 (2.07 to 2.69)	< .001

ACE, angiotensin-converting enzyme; CI, confidence interval.

Decreasing Dose or Stopping Therapy

We explored the association between the dose of ACE inhibitor therapy dispensed during the 45 days following discharge and the subsequent dose reduction (50% or more) during the follow-up as outlined in Table 5. Using logistic regression and controlling for all the covariates used in the outcomes analysis, we found that, relative to those dispensed low-dose ACE inhibitor therapy, those dispensed medium-dose therapy (odds ratio [OR], 1.57; confidence interval [CI], 1.39 to 1.77) or a high-dose therapy (OR, 2.36; CI, 2.07 to 2.69) were significantly more likely to have their dose reduced by 50% or more.

DISCUSSION

Our study demonstrates that in clinical practice few older heart failure patients receive high-dose ACE inhibitor therapy, but those who do have an improved survival benefit compared to those on low-dose therapy. Our findings of a dose-related survival benefit may encourage physicians to slowly titrate up the ACE inhibitor dose as tolerated. The major trials³⁻⁵ that evaluated the benefit of ACE inhibitor therapy in heart failure had protocols that required that patients have their doses titrated upward to the target dose of the trial. Guidelines for the management of heart failure consistently recommend that, where possible, the dose of ACE inhibitor therapy be titrated to the high dose tolerated in the trials. Despite this imperative, no study has demonstrated the survival benefit of high- relative to low-dose ACE inhibitor therapy. Packer et al.⁷ explored the dose-related benefit of the ACE inhibitor lisinopril in a group of relatively young older adults (mean age 64) who were predominately men (80%). In this trial, 3,164 patients were randomly assigned to receive either low (mean 4.5 mg) or high doses (mean 33.2 mg) of lisinopril. Relative to those in the low-dose group, older adults dispensed high-dose therapy had a trend (non-statistically significant) toward a survival benefit. Adults in our cohort are on average more than 10 years older than those in the lisinopril trial and the

majority are women. Accordingly, our study is among the first to provide a measure of the effectiveness of increasing doses of ACE inhibitor therapy, as our data were obtained from older adults with heart failure living in the community. These individuals are likely much more representative of people with heart failure in clinical practice than are subjects selected for inclusion in clinical trials evaluating drug therapy for the management of heart failure.

We demonstrated a mortality reduction of more than 20% for older adults dispensed high-dose ACE inhibitor therapy relative to those dispensed the low-dose therapy. This survival benefit persisted for the combined outcomes. Our results are in keeping with the results of the CONSENSUS Trial Study Group,⁴ one of the key trials to demonstrate the benefit of ACE inhibitor therapy in heart failure. Patients enrolled in this study had severe heart failure and were dispensed high-dose enalapril (up to 40 mg per day). Relative to those dispensed placebo, those dispensed ACE inhibitor therapy had a 31% mortality reduction at 1 year. By comparison, the unadjusted reduction in mortality for older adults with heart failure dispensed high-dose ACE inhibitor therapy in our study population was 26%. This suggests that our results are consistent with those reported in previous trials.

Our study suggests that low-dose ACE inhibitor therapy does provide a survival benefit to older patients compared to not receiving any ACE inhibitor therapy. Packer et al.⁷ in their evaluation of the dose-related benefit of lisinopril did not include a placebo group and therefore could not compare survival among those randomized to low-dose lisinopril therapy to those who were not treated.

There is biological evidence to support our finding of the benefit of low-dose therapy. Lisinopril in the low-dose range (2.5 to 5 mg) has favorable hemodynamic effects. Uretsky et al.³¹ evaluated 55 patients with heart failure and found that lisinopril at doses of 2.5, 5, and 10 mg produced changes in a range of cardiovascular measures (increase in cardiac index, reduction in pulmonary capillary wedge, right atrial, pulmonary arterial and systemic arterial pressure, and systemic vascular resistance). Further, these changes were dose related.

The finding of the benefit of low-dose ACE inhibitor therapy is important for two reasons. First, higher doses of ACE inhibitor therapy may not be tolerated by many older adults. Our findings may encourage physicians to maintain their patients on the low-dose therapy when it may otherwise be discontinued. Second, some adults with heart failure and without obvious contraindications to ACE inhibitor therapy are not being treated. Our findings may encourage physicians to initiate ACE inhibitor therapy at low doses to these patients and to titrate upward as tolerated.

Our findings also demonstrate that patients initiated on high-dose therapy were twice as likely to have their subsequent dose reduced relative to those initiated on a low dose of ACE inhibitor therapy. This finding is consistent with trial evidence. In the lisinopril trial,⁷ participants were evaluated in a prerandomization period and those that

could not tolerate at least a medium-level dose of lisinopril were excluded. Even among patients who successfully passed the screening process, close to 10% of the enrolled subjects could not be titrated to the target dose of lisinopril. Finding the right balance between benefit and tolerability of the therapy is particularly important when prescribing for frail older people who are particularly vulnerable to the development of a dose-related adverse event.

Limitations

Our study has important limitations. Ideally, one would develop a series of RCTs to evaluate the drug-specific and dose-related benefit associated with the use of ACE inhibitor. However, the large sample size required, the increased cost associated with including frailer individuals in trials, and the difficulty of having frailer individuals continue with trial protocols make this approach an unlikely option for obtaining comprehensive information about older heart failure patients in the near future. Using our database, we explored dose-related drug benefit in older adults in Ontario, not just those traditionally recruited into an RCT.

Our study is observational and relies on administrative data. Accordingly, there may have been residual confounding by indication. We have taken a number of steps to control for confounding. We used statistical techniques to control for key variables that might be related to selection bias. These factors included age, gender, comorbidity, and the use of additional drug therapies recommended for heart failure. We do not have access to clinical data such as ejection fraction or the New York Heart Association class to include in our model. We repeated our analyses using propensity score analysis and found that our results remained consistent. Examination of the propensity score quintiles indicated that the measured covariates were balanced within the quintiles.

We estimated the dose dispensed based on the defined daily dose information provided in our database. As with all trial designs, we do not actually know the adherence to the recommended therapy. We did not report ACE inhibitor dose-related adverse events severe enough to require hospitalization. These are likely infrequent. We did report decreasing of the ACE inhibitor dose or the discontinuation of therapy, which are likely markers for adverse events.

Conclusions

We demonstrated a dose-related benefit of ACE inhibitor therapy associated with improved survival and the reduction of heart failure and all-cause rehospitalization in older adults. Our findings suggest that when possible, older adults should be titrated to the higher doses of ACE inhibitor therapy evaluated in clinical trials. If older adults cannot tolerate higher doses, then low-dose ACE inhibitor therapy is superior to none. High-dose ACE inhibitor therapy is less well tolerated than lower doses, supporting the need to start low and go slow.

Dr. Rochon was supported by an Investigator Award, Drs. Mamdani and Bronskill by New Investigator Awards, Dr. Gill by a Post-doctoral Award, Dr. Tu by a Canada Research Chair in Health Services Research, and Dr. Laupacis by a Senior Investigator Award, all from the Canadian Institutes for Health Research (CIHR).

This work was supported by the CIHR Chronic Disease New Emerging Team program (NET—54010) and the Physicians Services of Ontario. The NET program receives joint sponsorship from the Canadian Diabetes Association, the Kidney Foundation of Canada, the Heart and Stroke Foundation of Canada, and the CIHR Institutes of Nutrition, Metabolism, and Diabetes, and Circulatory and Respiratory Health.

REFERENCES

1. Hunt SA, Baker DW, Chin MH, et al. ACC/AHA Guidelines for the Evaluation and Management of Chronic Heart Failure in the Adult: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1995 Guidelines for the Evaluation and Management of Heart Failure); 2001. American College of Cardiology Website. Available at: http://www.acc.org/clinical/guidelines/failure/hf_index.htm. Accessed November 24, 2003.
2. American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Evaluation and Management of Heart Failure). Guidelines for the evaluation and management of heart failure. *J Am Coll Cardiol*. 1995;26:1376–98.
3. SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med*. 1991;325:293–302.
4. CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). *N Engl J Med*. 1987;316:1429–34.
5. Captopril-Digoxin Multicenter Research Group. Comparative effects of therapy with captopril and digoxin in patients with mild to moderate heart failure. *JAMA*. 1988;259:539–44.
6. Advisory Council to Improve Outcomes Nationwide in Heart Failure. Consensus recommendations for the management of heart failure. *Am J Cardiol*. 1999;83(2A):1A–38A.
7. Packer M, Poole-Wilson PA, Armstrong PW, et al. Comparative effects of low and high doses of the angiotensin-converting enzyme inhibitor, lisinopril, on morbidity and mortality in chronic heart failure. *Circulation*. 1999;100:2312–8.
8. Nanas JN, Alexopoulos G, Anastasiou-Nana MI, et al. Outcome of patients with congestive heart failure treated with standard versus high doses of enalapril: a multicenter study. *J Am Coll Cardiol*. 2000;36:2090–5.
9. Network Investigators. Clinical outcome with enalapril in symptomatic chronic heart failure: a dose comparison. *Eur Heart J*. 1998;19:481–9.
10. Clement DL, De Buyzere M, Tomas M, Vanavermaete G, on behalf of the CHIPS investigators. Long-term effects of clinical outcome with low and high dose in the Captopril in Heart Insufficient Patients Study (CHIPS). *Acta Cardiol*. 1999;55:1–7.
11. Krumholz HM, Wang Y, Parent EM, Mocalis J, Petrillo M, Radford MJ. Quality of care for elderly patients hospitalized with heart failure. *Arch Intern Med*. 1997;157:2242–7.
12. Forman DE, Chander RB, Lapane KL, Shah P, Stoukides J. Evaluating the use of angiotensin-converting enzyme inhibitors for older nursing home residents with chronic heart failure. *J Am Geriatr Soc*. 1998;46:1550–4.
13. Chin MH, Wang JC, Zhang JZ, Lang RM. Utilization and dosing of angiotensin-converting enzyme inhibitors for heart failure: effect of physician specialty and patient characteristics. *J Gen Intern Med*. 1997;12:563–6.

14. Alter DA, Naylor CD, Austin P, Tu JV. Effects of socioeconomic status on access to invasive cardiac procedures and on mortality after acute myocardial infarction. *N Engl J Med*. 1999;341:1359–67.
15. Rochon PA, Anderson GM, Tu JV, et al. Age- and gender-related use of low-dose drug therapy: the need to manufacture low-dose therapy and evaluate the minimum effective dose. *J Am Geriatr Soc*. 1999;47:954–9.
16. Rochon PA, Anderson GM, Tu JV, et al. Use of beta-blocker therapy in the elderly following acute myocardial infarction. *Can Med Assoc J*. 1999;161:1403–8.
17. Naylor CD, Slaughter P. Cardiovascular Health and Services in Ontario. Toronto, Ontario: Institute for Clinical Evaluative Sciences (ICES); 1999.
18. Tu JV, Pashos CL, Naylor CD, et al. Use of cardiac procedures and outcomes in elderly patients with myocardial infarction in the United States and Canada. *N Engl J Med*. 1997;336:1500–5.
19. Tu J, Hannan EL, Anderson GM, et al. The fall and rise of carotid endarterectomy in the United States and Canada. *N Engl J Med*. 1998;339:1441–7.
20. Rochon PA, Tu JV, Anderson GM, et al. Rate of heart failure and 1-year survival for older people receiving low-dose beta-blocker therapy after myocardial infarction. *Lancet*. 2000;356:639–44.
21. Quan H, Parsons GA, Ghali WA. Validity of information on comorbidity derived from ICD-9-CCM administrative data. *Med Care*. 2002;40:675–85.
22. Barron HV, Viskin S, Lundstrom RJ, et al. Beta-blocker dosages and mortality after myocardial infarction: data from a large health maintenance organization. *Arch Intern Med*. 1998;158:449–53.
23. Konstam M, Dracup K, Baker D. Heart failure: evaluation and care of patients with left-ventricular systolic dysfunction. Rockville, Md: Agency for Health Care Policy and Research, Public Health Service, U.S. Department of Health and Human Services; 1994.
24. Canadian Pharmacists Association. Compendium of pharmaceuticals and specialties. 33rd ed. Ottawa, Ontario: Canadian Pharmacists Association; 1998.
25. Rochon PA, Fortin PR, Dear KBG, Minaker KL, Chalmers TC. Reporting of age data in clinical trials of arthritis: deficiencies and solutions. *Arch Intern Med*. 1993;153:243–8.
26. Charlson ME, Pompei PA, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40:373–83.
27. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol*. 1992;45:613–9.
28. Hosmer DW, Lemeshow S. Applied Survival Analysis. New York, NY: John Wiley and Sons; 1999.
29. Argenti A. Categorical Data Analysis. New York, NY: John Wiley and Sons; 1990.
30. Rubin D. Estimating causal effects from large data sets using propensity scores. *Ann Intern Med*. 1997;127(8S):757–63.
31. Uretsky BF, Shaver JA, Liang C et al. Modulation of hemodynamic effects with a converting enzyme inhibitor, lisinopril, with observations on long-term clinical, functional, and biochemical responses. *Am Heart J*. 1988;116:480–8.