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Underutilisation of ACE Inhibitors in Patients with Congestive Heart Failure

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Abstract

Congestive heart failure (CHF) is associated with substantial morbidity and mortality, and is the only major cardiovascular disease increasing in prevalence. Despite abundant evidence to support their efficacy and cost-effectiveness, angiotensin-converting enzyme (ACE) inhibitors are sub-optimally used in patients with CHF. This paper reviews the evidence for the sub-optimal use of ACE inhibitors in patients with CHF, the factors contributing to this, and its implications for health systems.

A systematic review of all articles assessing practice patterns (specifically the use of ACE inhibitors in CHF) identified by MEDLINE, search of bibliographies, and contact with content experts was undertaken.

37 studies have documented the use of ACE inhibitors in patients with CHF. Studies assessing use among all patients with CHF document 33% to 67% (median 51%) of all patients discharged from hospital and 10% to 36% (median 26%)

of community dwelling patients were prescribed ACE inhibitors. Rates of ACE inhibitor use range from 43% to 90% (median of 71%) amongst those discharged from hospital having known systolic dysfunction, and from 67% to 95% (median of 86%) for those monitored in specialty clinics. Moreover, the dosages used in the 'real world' are substantially lower than those proven efficacious in randomised, controlled trials, with evaluations reporting only a minority of patients achieving target doses and/or an overall mean dose achieved to be less than one-half of the target dose. Factors predicting the use and optimal dose administration of ACE inhibitors are identified, and include variables relating to the setting (previous hospitalisation, specialty clinic follow-up), the physician (cardiology specialty versus family practitioner or general internist, board certification), the patient (increased severity of symptoms, male, younger), and the drug (lower frequency of administration).

In light of the substantial evidence for reductions in morbidity and mortality, clearly, the prescription of ACE inhibitors is sub-optimal. Wide variability in ACE inhibitor use is noted, with higher rates consistently reported among patients having systolic dysfunction confirmed by an objective assessment – an apparent minority of the those having CHF. Optimisation of the prescription of proven efficacious therapies has the potential to confer a substantial reduction in the total cost of care for patients with CHF by reducing hospitalisations and lengths of hospital stays. It is likely that only multifaceted programs targeted toward the population at large will yield benefits to the healthcare system, given the widespread nature of the sub-optimal prescription of therapies proven effective in the management of patients with CHF.

Congestive heart failure (CHF) is associated with high mortality, and is the only major cardiovascular disease with an increasing prevalence.[1] Framingham data indicate the five-year survival rate for patients with CHF is 50%,[2] although more recent data suggest mortality rates may be as high as 40 to 50% at two years in the same subgroups.[1,3-5] In addition to a high death rate, CHF is the leading discharge diagnosis in the Medicare population in the US,[6] with as many as 40% of patients being admitted to hospital at least once within a year of diagnosis.[3,7,8]

Randomised, controlled trials (RCT) have conclusively demonstrated reductions in morbidity and mortality with the use of angiotensin-converting enzyme (ACE) inhibitors in patients with CHF,[9-12] and economic evaluations have consistently shown cost savings per life-year saved.[13-17] As such, the Agency for Healthcare Policy and Research, the American College of Cardiology/American Heart Association, the European Society of Cardiology, and the Canadian Cardiovascular Society Consensus Guidelines for the Management of CHF all recommend the use of ACE inhibitors for patients with systolic dysfunction.[8,18-21] Furthermore, these guidelines[8,18-21] recommend the use of ACE inhibitors at the dosages proven to reduce mortality, progression to overt heart failure, and rehospitalisation in the RCT (table I).[9-12] The efficacy of dosages below those used in the RCT are unknown.

Although several short-term trials demonstrated a direct relationship between ACE inhibitor dosage and exercise capacity,[22-24] only two RCT have evaluated the impact of ACE inhibitor dosage on morbidity and mortality.[25,26] The Assessment of Treatment with Lisinopril and Survival (ATLAS) study was a double-blind, randomised trial comparing lisinopril 2.5 to 5mg with 32.5 to 35mg per day in 3164 patients.[25] Although the reduction in mortality with high-dose lisinopril (primary endpoint) was not statistically significant, there was a significant 12% relative reduction in the composite endpoint of death or hospitalisation for any reason, which remained significant after controlling for

Table I. Enalapril dose administration within randomised, controlled trials of patients with congestive heart failure

Trial	Initial dosage (mg/day)	Target dosage (mg/day)	Mean dosage achieved (mg/day)
CONSENSUS[10]	10	2.5-40	18.4
V-HeFT II[9]	10	20	15
SOLVD-Treatment[12]	5	2.5-20	16.6
SOLVD-Prevention[11]	5	2.5-20	12.7

CONSENSUS = Cooperative North Scandinavian Enalapril Survival Study; **SOLVD** = Studies of Left Ventricular Dysfunction; **V-HeFT** = Vasodilator Heart Failure Trial.

age, sex, left ventricular ejection fraction (LVEF), aetiology of CHF, and New York Heart Association (NYHA) functional class. The frequency of adverse events was similar between the high- and low-dose groups. The NETWORK (Clinical Outcomes with Enalapril in Symptomatic Chronic Heart Failure) study failed to demonstrate a dose-response relationship in terms of death, hospitalisation, or worsening heart failure in 1532 patients.[26] However, this was not surprising as the trial included predominantly patients with NYHA functional class II (71%) who were followed for only 24 weeks, and was probably under-powered.

Despite the publication of RCT, guidelines, consensus statements, and favourable economic evaluations supporting the use of ACE inhibitors in CHF,[8,18-21] several authors have suggested these agents may be used suboptimally in clinical practice.[6,7,27-61] Moreover, once patients are prescribed ACE inhibitors, the dosages used in clinical practice appear to be substantially lower than those proven to be effective in RCT.[30,34,36,40-44,46,48,54,57,58,62-65] The purpose of this paper is to review the evidence for the suboptimal use (defined as implementation of therapy and titration to optimal dosage) of ACE inhibitors in patients with CHF, analyse factors which contribute to this, and discuss the implications for health systems.

1. Literature Review

Articles published in English from 1966 to February 2000 were identified through MEDLINE by using the following keywords and MeSH headings: congestive heart failure; angiotensin-converting enzyme inhibitors; epidemiology; physician's practice patterns; ambulatory care; costs; and economic, medical. Bibliographies were reviewed for additional relevant articles and content experts were contacted to identify other articles. All articles assessing the use of ACE inhibitors in patients with CHF were included in this review. Because of the number of papers and wide range of results, rates of ACE inhibitor use are reported as medians throughout the paper.

1.1 Suboptimal Prescription of Angiotensin-Converting Enzyme (ACE) Inhibitors

Studies differ with respect to patient/physician demographics, the pathophysiological classification of CHF (systolic dysfunction versus diastolic dysfunction), and the setting (hospital versus community, academic versus nonacademic). The vast majority of these evaluations have been undertaken in the hospital setting, with only a few evaluating the use of ACE inhibitors in the community.

1.1.1 Unselected Patients with Heart Failure

Studies assessing the use of ACE inhibitors amongst all patients with heart failure document that, between 1986 and 1996, 37% of patients were prescribed ACE inhibitors upon presentation to hospital,[27,34,35,47,48,50-52] and 53% were taking them at discharge (table II).[27,35,36,41,44,46,47,50-52] No difference in the use of ACE inhibitors was apparent between academic and nonacademic institutions, despite the presumption that practitioners affiliated with academic institutions may be more familiar with current practice guidelines. Although the utilisation rates improved over time, almost half of patients were not receiving this therapy even in the most recent studies.

The use of ACE inhibitors in community settings is very poor, with only 26% receiving the

Table II. Hospital and community evaluations of ACE inhibitor use

Study	Patient selection	Heart failure severity	Country	Time frame	All patients		Patients with systolic dysfunction	
					No.	ACEI use	No.	ACEI use
Hospital evaluations: academic								
McDermott et al.[44]	Consecutive patients with a principal diagnosis of heart failure	N/A	US	1986 1994	140 294	33%[a] 46%[a]	63 82	43%[a] 71%[a]
Bourassa et al.[29][b]	Consecutive patients admitted with heart failure or left ventricular dysfunction	Mean EF 30% (±SD 9.2%)	US	1988-89			6,273	30%[a]
Rich et al.[54]	Retrospective record review of patients with a primary discharge diagnosis of heart failure	N/A	US	1990 1995			47 108	78.7%[a] 89.8%[a]
Bart et al.[28]	Admissions with a principal diagnosis of heart failure	46.3% NYHA class IV	US	1992-93			242	76%[a]
McDermott et al.[46]	Consecutive medical record review of patients with a principal diagnosis of heart failure	N/A	US	1992-93	387	48%[a]	102	74%[a]
Hillis et al.[36]	Medical record review of all patients with diagnosis of CHF, left ventricular failure, or heart failure	64.9% (1992) and 68.9% (1995) were NYHA class III or IV	UK	1992 1995	325 265	40%[a] 55%[a]		
Chin & Goldman[7]	Elective & non-elective admissions for CHF	Lowest EF was ≤20% in 16% patients, 21-35% in 22% patients, 36-49% in 17% patients, ≥50% in 44% patients	US	1993-94			108	63% PTA
Luzier et al.[41]	Retrospective cohort of patients readmitted twice with a principal diagnosis of CHF in a 36 month period	N/A	US	1993-95	209	67%[a]		
Missouris & MacGregor[47]	Consecutive patients with a primary discharge diagnosis of CHF	N/A	UK	1994	249	37% PTA, 58%[a]		
Rich et al.[53]	Patients aged >70y admitted with diagnosis of heart failure (+ a history of heart failure, >4 hospitalisations in past 5y, or CHF precipitated by MI or uncontrolled HTN)	Mean NYHA class 2.4	US	NA[c]			282	58.9%[a]
Reis et al.[52]	Consecutive patients with a primary discharge diagnosis of CHF	66.4% NYHA class III or IV at admission	US	1995	298	37% PTA, 51%[a]		
Ferreira et al.[34]	Consecutive patients admitted with decompensated heart failure	Mean NYHA class at admission 3.1 (± 0.77)	Portugal	1995-96	355	58.6% PTA, 80.6%[d]		
Hospital evaluations: academic and nonacademic								
McDermott et al.[45]	Record review of patients with a primary discharge diagnosis of CHF	N/A	US	1991-92			206	65%[a]
CQINI[32]	Record review of consecutive patients admitted with a primary, secondary, most responsible, or complicating diagnosis of CHF	N/A	Canada	1992-93	4606	53%[d]		

Krumholz et al.[39]	Medicare beneficiaries aged ≥65y with a principal diagnosis of myocardial infarction	N/A	US	1992-93			1228[e] 549[f]	45%[a] 57%[a]
Ackman et al.[27]	Medical record review of patients with CHF	N/A	Canada	1992-93	1040	34% PTA, 50%[a]		
				1994-95	1131	42% PTA, 48%[a]		
Ghali et al.[35]	Record review of medicare patients aged ≥65y with principal discharge diagnosis of CHF	N/A	US	1993	1212	34% PTA, 52%[a]	278	64%[a]
LSPROC[6]	Record review of medicare patients aged ≥65y admitted with a principal diagnosis of heart failure	N/A	US	1993-94	6749	35% PTA, 55%[a]	1,893[g]	42.5% PTA, 73%[a]
Krumholz et al.[40]	Record review of patients having a principal discharge diagnosis of heart failure	N/A	US	1994			401	86%[a]
Tsuyuki et al.[61]	Record review of consecutive patients admitted with a primary, secondary, most responsible, or complicating diagnosis of CHF	N/A	Canada	1994-95	3191	55%[d]		
Hospital evaluations: nonacademic								
Parameshwar et al.[48]	Consecutive admissions of patients with heart failure to a district hospital	N/A	UK	1987-88	140	24% PTA[d]		
Philbin[50]	Patients with a primary discharge diagnosis of CHF and shock – decompensated heart failure	89% NYHA class III or IV	US	1992	520	33% PTA, 51%[a]		
Philbin et al.[51]	Principal diagnosis of CHF and shock in 10 acute care community hospitals	88% NYHA class III or IV at admission	US	1995	987	42% PTA, 64%[a]		
Ambulatory evaluations: academic and nonacademic								
Smith et al.[58]	Prospective observational study in 4 communities of those aged ≥65y with heart failure having annual examinations	N/A	US	1989-90 1994-95	250 431	26% 36%		
Croft et al.[33][h]	National Ambulatory Medical Care Survey of physician office visits in those >65y	N/A	US	1991-92	16 968	30%		
Stafford et al.[59][h]	National Ambulatory Medical Care Survey of physician office visits in those with heart failure	N/A	US	1989 1990 1991 1992 1993 1994	[i]	24.2% 20.8% 23.4% 31.1% 24.5% 30.6%		
Ambulatory evaluations: nonacademic								
Parameshwar et al.[49]	All patients with heart failure in 3 general practices in North West London	N/A	UK	1988	117	10%		
Clarke et al.[31]	Survey of all patients receiving loop diuretics in general practices in Nottingham Health District	N/A	UK	NA[j]	281	17%		

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Table II. Contd

Study	Patient selection	Heart failure severity	Country	Time frame	All patients		Patients with systolic dysfunction	
					No.	ACEI use	No.	ACEI use
Mair et al.[42]	Retrospective record review of 2 general practices of all patients with a diagnosis of heart failure in Liverpool	N/A	UK	1994	266	33%		
Ambulatory evaluations: specialty clinics/academic								
Kornowski et al.[38]	Patients aged ≥65y completing 1y of home surveillance	NYHA class III and IV	Israel	1992			42	67%
Stevenson et al.[60]	Patients discharged following evaluation for heart transplantation and optimisation of medical therapy, followed for at least 1y by a medical team	54% NYHA IV	US	1991-93			266	86%
Senni et al.[55]	Patients awaiting heart transplantation in the community setting exposed to a comprehensive heart failure programme	44% NYHA III, 56% NYHA IV	US	1991-94 before evaluation			214	77%
				after evaluation			214	95%
Smith et al.[57]	Patients awaiting heart transplantation in the community setting exposed to a comprehensive heart failure programme	44% NYHA III, 56% NYHA IV	US	1994-95			21	95%
Shah et al.[56]	Patients with heart failure	63% NYHA III or IV	US	1994-95			27	89%
McAlister et al.[43]	Consecutive patients referred to clinic	35% NYHA II, 38% III	Canada	1989-95	566	83%	441	86%
Chin et al.[30]	All patients with heart failure seen at cardiology, general internal medicine and geriatrics clinics	Moderate to severe systolic dysfunction (fractional shortening <24%)	US	1994-96			214	75%
Houghton & Cowley[37]	All referred with confirmed systolic dysfunction in Nottingham Health District	EF <40%	UK	1994-95			41	80%

a ACEI use at hospital discharge.

b SOLVD Registry Database.

c Published Nov 2, 1995.

d ACEI use at any point during hospitalisation.

e Krumholz 'ideal' post-myocardial infarction with CHF, LVEF ≤40%, no contraindication to ACEI therapy.

f Krumholz 'very ideal' post-myocardial infarction with LVEF <40% and no contraindication to ACEI therapy.

g Large state 'ideal candidate' has an EF <40%, serum creatinine <265 μmol/L, serum potassium <5.5 mEq/L, systolic blood pressure >90mm Hg, and no contraindications or intolerance to ACEI therapy.

h Reported on a per-visit basis and not a per-patient basis.

i 1529 office visits throughout 1989 to 1994.

j Accepted for publication Dec 13, 1993.

ACEI = angiotensin-converting enzyme inhibitors; **CHF** = congestive heart failure; **CQINI** = Clinical Quality Improvement Network Investigators; **EF** = ejection fraction; **HTN** = hypertension; **LSPROC** = Large State Peer Review Organization Consortium; **MI** = myocardial infarction; **NA** = not available; **NYHA** = New York Heart Association; **PTA** = prior to admission; **SOLVD** = Studies of Left Ventricular Function.

therapy.[31,33,42,49,58,59] Two of these evaluations of ACE inhibitor use in the community have evaluated the temporal trend over six years, one found an absolute increase in use of 10% ($p < 0.01$),[58] whereas the other found a fluctuating trend toward increased rates of ACE inhibitor use (ranging from 20.8 to 31.1%) [$p < 0.02$].[59] As reported in hospital evaluations, the increased use of ACE inhibitors with time, while statistically significant, seems minor in relation to the proportion of patients that could derive benefit from ACE inhibition.

1.1.2 Patients with Known Systolic Dysfunction

Several studies evaluated the use of ACE inhibitors in only those patients with confirmed systolic dysfunction, and report higher use of ACE inhibitors; with 53% taking ACE inhibitors at hospital admission[6,7] and 71% at discharge (table II).[6,29,35,39,40,44-46,53,54] Irrespective of the institution's academic affiliation, confirmation of systolic dysfunction dramatically increases the likelihood of the prescription of ACE inhibitors.

Similar overall trends are apparent in the community setting (table II). However, studies restricted to patients with systolic dysfunction in an ambulatory setting have only been undertaken in academic, specialty clinics (i.e. heart failure clinics) or under similar circumstances (i.e. planned home-based interventions).[30,37,38,43,57,60,62] Typically, in this setting patients receive continuous, long-term support in the community that includes the optimisation of medical therapy, patient education and the implementation of a support structure.[66,67] These clinics consistently demonstrate superior usage of ACE inhibitors, in the order of 86%.[30,37,38,43,57,60,65]

1.2 Suboptimal Dose Administration of ACE Inhibitors

Considerable evidence indicates that dosages used in clinical practice are often substantially lower than those proven to be efficacious in RCT (table III).[30,34,36,40-44,46,48,57,58,60,62-65]

Although specialty clinics/programmes demonstrate considerable variation in the proportions of patients reaching target dosages (11 to 68%),[30,43,57,62,64,65] they do document superior dose administration (dosing) relative to general practice and hospital evaluations.[34,36,40-42,44,46,48,54,58,63] Three studies evaluated drug administration over six months and all reported a statistically significant improvement, highlighting the potential to titrate ACE inhibitor dosages over time.[57,62,65]

1.3 Factors Associated with ACE inhibitor Use and Optimal Dose Administration

The prescription of ACE inhibitors has been used as a quality-of-care indicator for patients with CHF.[40] Indeed, it has been observed that patients prescribed an ACE inhibitor are more likely to be taking other drugs appropriate for the treatment of CHF.[34,51,59] Factors associated with the use of ACE inhibitors can be broadly classified into those pertaining to the setting, physician, patient, and drug.

1.3.1 Setting

Patients seeking medical attention at hospitals for CHF are more likely to receive ACE inhibitor therapy than those in the community (with the exception of patients referred to specialty clinics). Indeed, the majority of patients identified in the community setting taking ACE inhibitors have had a previous hospital admission.[34,40] However, the vast majority of patients with CHF (78%) are cared for by primary-care physicians outside the hospital setting.[33]

The community setting affords clinicians the ability to titrate dosages of ACE inhibitors over time. In contrast, hospital-based assessments of dosages are often limited by the acuity of patients being admitted, concomitant conditions, and the short length of stays for many of these patients (i.e. not allowing enough time for titration of doses).

1.3.2 Physician Factors

Family practitioners and general internists use ACE inhibitors for CHF less frequently than cardiologists,[30,33,59,68] particularly for patients with less severe symptoms.[30,52] This may be partially attributable to the fact that cardiologists are more likely to order diagnostic tests than general practi-

Table III. Summary of evaluations reporting ACE inhibitor dosages

Evaluation	Date	Dosage endpoint reported
Hospital evaluations		
Academic[44]	1986	Average dosages: enalapril 8.8 mg/day, captopril 20 mg/day
	1994	Average dosages: enalapril 7.7 mg/day, captopril 21 mg/day
Academic[54]	1990	24% reached 'optimal dosing'[a]
	1995	60% reached 'optimal dosing'[a]
Academic[46]	1992-93	18% reached 'optimal dosing'[a] with enalapril and captopril
Academic[41]	1993-95	Mean enalapril dosage of 11.4 mg/day; 22% reached ≥20 mg/day, 41% ≤5 mg/day
Academic[48]	1994	17%[b]; mean captopril dosage 42 ± 25 mg/day (n = 6 od, n = 53 bid, n = 33 tid), enalapril 17 ± 15 mg/day (n = 26 od, n = 21 bid, n = 1 tid), lisinopril 14 ± 8 mg/day (n = 4 od)
Academic and nonacademic[40]	1994	14%[b] met target doses suggested by the randomised, controlled trials
Academic[36]	1992	76% received dosages < captopril 75 mg/day or enalapril 20 mg/day or equivalent
	1995	55% received dosages < captopril 75 mg/day or enalapril 20 mg/day or equivalent
Academic[34]	1995-96	Average dosages: captopril 37.7 mg/day, enalapril 13.3 mg/day, lisinopril 12.7 mg/day
Ambulatory evaluations		
Academic and nonacademic[58]	1989-1995	Mean daily doses of captopril 54.2mg, enalapril 8.9mg, and lisinopril 11.7mg
Academic[43]	1989-95	Mean daily doses of captopril 62.1mg, enalapril 10.7mg, lisinopril 10.3mg
Academic[62]	1991-94	Before evaluation daily dose of captopril or equivalent was 95 ± 120mg, after 6 month evaluation was 183 ± 143mg
Academic and nonacademic[42]	1994	Median daily doses: enalapril 10mg, captopril 37.5mg, lisinopril 5mg
Academic[65]	1994-95	Mean daily dose before evaluation: lisinopril 17 ± 12 mg, after 6 month evaluation: 23 ± 12mg (p = 0.0004) –82% increase in dose; captopril before 67 ± 22mg after 100 ± 56mg (p = 0.04)
Academic[57]	1994-95	Mean quinapril dose at baseline was 20mg, increased to 40mg od after 6 month clinic follow up (p = 0.005)
Academic[30]	1994-96	Overall, 60% of dosages proven effective in randomised clinical trials[c]; specifically 46% captopril, 58% enalapril, and 82% lisinopril
Academic[63]	1996	≤74 years old: 68.8% at target[b] (mean dose of captopril 112.5, enalapril 18.75 mg/day) aged ≥74y: 21.4% at target[b] (mean dosage of captopril 75 mg/day, enalapril 10 mg/day)
Academic[64][d]	1999	11% taking doses proven effective in randomised clinical trials

a 'Optimal dosing' defined as: captopril ≥150 mg/day, enalapril ≥20 mg/day, lisinopril ≥20 mg/day, fosinopril ≥20 mg/day, benazepril ≥20 mg/day, quinapril ≥20 mg/day, or ramipril ≥10 mg/day.

b Please refer to table I (dosages used in randomised, controlled trials).

c Captopril 50mg tid, enalapril 10mg bid, lisinopril 10mg od, ramipril 5mg bid, benazepril 20mg od, fosinopril 20mg od, and quinapril 10mg bid.

d Published in 1999, abstract only.

bid = twice daily; **od** = once daily; **tid** = three times daily.

tioners (since patients with known systolic dysfunction are more likely to be prescribed ACE inhibitors).[31,36,52,69]

Despite this discrepancy between specialty groups, the vast majority of family/general practitioners, internists and cardiologists indicate an awareness of trials demonstrating improved survival with ACE inhibitor therapy in CHF when surveyed.[69,70] Recently trained general physicians report practice patterns closer to specialists than their older peers.[30,69] Board certification was independently associated with more frequent use of echocardiograms,[69] and greater use of ACE inhibitors as initial and maintenance therapy.[30,69] Some studies have demonstrated differences in ACE inhibitor use by geographical location,[6,51] although data is sparse.

Board-certified physicians have been found to use higher dosages of ACE inhibitors.[69] Amongst physician specialties, cardiologists prescribe high-

er dosages relative to family/general practitioners[69,71] in all but one study.[30] The majority of internists and generalists reported using the lowest dose to produce an adequate symptom response, whereas the majority of cardiologists advocated increasing doses unless intolerance developed.[69,71] In a survey of cardiologists, investigators found that heart failure specialists use these agents more aggressively than other cardiologists, with 75 versus 31% ($p < 0.001$) titrating to high dosages (captopril >75 mg/day, enalapril >15 mg/day) regardless of symptomatic response.[72]

1.3.3 Patient Factors

Studies evaluating the use of ACE inhibitors amongst patient subgroups consistently report an increase in their prescription as the severity of CHF symptoms increases.[7,29,34,35,58] Females[7,32,34,50,59] and the elderly[6,7,30,32,35,50,51,58] are less likely to receive ACE inhibitors. Two of three studies reporting ACE inhibitor use among different races reported them to be more commonly used in Caucasians.[7,35,59]

Specific patient populations may receive higher dosages of ACE inhibitors. African Americans, a population believed to be less responsive to ACE inhibitors, have received higher dosages relative to Caucasians. Gattis and colleagues[63] report that only 21.4% of their elderly patients (≥75 years of age) are receiving optimal dosages, compared with 68.8% of those ≤74 years of age, suggesting an age-related barrier for dosage titration,[63] although this may be a reflection of altered pharmacokinetics in older patients. Patients with lower blood pressure[34,46] or more advanced CHF[34] have been reported to receive lower dosages of ACE inhibitors.

1.3.4 Drug Factors

Physicians who perceive higher rates of adverse effects from ACE inhibitors are less likely to prescribe these agents.[30,70] In particular, physicians are most concerned about hypotension[30,34,70] and renal dysfunction,[30,34,69,70] with general practitioners being most likely to cite adverse effects as a reason for not initiating ACE inhibitor therapy.[30,69,70] While RCT suggest that adverse effect and withdrawal rates are the same in placebo- and ACE inhibitor-treated patients,[19,10,12] trial participants are often healthier and followed more closely than usual-care patients. Practice audits document 5 to 24% of patients have a contraindication and/or intolerance to ACE inhibitors.[6,28,40,42,47,54]

A few studies reported dosage titration with specific ACE inhibitors.[30,34,42,44,48,58] Consistent across most studies is that as the frequency of daily dose administration increased, the percentage of patients reaching target doses declined.[30,34,42,43,48,58,63,65] For example, in one study 82, 58 and 46% reached target doses with lisinopril (taken once daily), enalapril (twice daily) and captopril (three times daily), respectively.[30]

2. Limitations of the Available Data

It should be noted that all but a few[7,35,48] of the hospital-based evaluations retrospectively evaluated the health records of admitted patients.[6,27,28,32,36,39,40,44,46,47,50,51,52,54,61] Therefore, these studies are limited by documentation and subject to measurement bias. In addition, many of these studies were prone to selection bias as subgroups of patients that may have been eligible for ACE inhibitor therapy were excluded: for example, 27 to 72% were excluded because of lack of an objective assessment of ventricular function in several studies.[6,30-32,34-36,39,40,42,44-49]

3. Implications

3.1 Clinical

Overall, it appears that many patients with CHF are not prescribed ACE inhibitors; of those that are, most are not prescribed them at dosages shown to be efficacious. Our review documents a wide range of use, with population-derived data in the community setting showing only one-third of patients with CHF being prescribed ACE inhibitors[33,58,59] versus over 80% of patients seen in specialty clinics.[43,56,57,60,62,65] Through the provision of a focused, coordinated approach, observational studies suggest that heart failure clinics im-

proved the accuracy of diagnosis[37] and the application of proven efficacious therapies for CHF.[37,38,43,56,57,60] Subsequently, the frequency of hospitalisations[38,53,56,57,62,65,73,74] and emergency room visits[57,65,74] for CHF may be reduced, resulting in cost-savings to healthcare systems.[62,75] Indeed, a recent meta-analysis of 11 trials involving over 2000 patients managed with multidisciplinary teams has shown improved processes of care and outcomes.[76]

Although these specialty clinics/programmes have dramatically improved the use of ACE inhibitors in CHF, they are limited in that they only serve a minority of the population with CHF. On the horizon are studies assessing internet-based disease management for CHF.[77] Multifaceted programs with the ability to serve the population at large seem most promising in optimising the medical management of patients with CHF, thereby improving patient outcomes and the use of healthcare resources.

3.2 Economic

In the case of CHF, the suboptimal application of RCT evidence into clinical practice has significant detrimental implications for the healthcare system.[78,79] Cost-of-illness estimates indicate the economic impact of CHF is considerable, with hospital admissions accounting for 60 to 75% of the total cost of care in CHF.[17,80,81] Many of these hospitalisations are re-admissions (with approximately 33% of patients with CHF being re-admitted within one year), and it appears that those having frequent hospitalisations for CHF have prolonged lengths of stay.[15] It seems intuitive that healthcare costs increase in conjunction with the severity of CHF, with patients in NYHA Functional Class IV having healthcare costs up to 30 times greater than patients in NYHA Class II.[78]

While drug treatment represents only a small portion (2 to 7.5%) of the total cost of care for CHF,[17,80,81] it is difficult to determine what an optimal level of spending for drug therapy in CHF might be. Several economic evaluations of ACE inhibitors (based largely on the RCT)[19,10,12] have been performed.[13-17] Given that all of these evaluations have shown cost savings per life-year saved, a re-allocation of resources may be in order. On the basis of the results of the RCT and the published economic evaluations, optimisation of the prescription of ACE inhibitors may lead to an important incremental reduction in the total cost of care for patients with CHF.

As an example, Glick et al.[14] estimated that the expected cost of care for patients within the Studies of Left Ventricular Dysfunction (SOLVD) trial (including costs of hospitalisation, enalapril, ambulatory care, and death during the first 48 months of follow-up) was [in 1992 US dollars ($US)] $US11 840 and $US12 557, for each patient randomised to enalapril or placebo, respectively.[14] The majority of these costs were attributable to hospitalisation, accounting for $US9683 and $US11 134 among the enalapril- and placebo-treated patients, respectively. Trial patients treated with enalapril were hospitalised less frequently than those given placebo (rates of 53 and 75%, respectively) and had shorter lengths of stay. As such, if the use of ACE inhibitors were increased from 55 to 80% amongst all patients with CHF, a cost-savings of $US615 per patient would result, primarily as a result of reduced hospitalisations. Although this may seem minimal on a per-patient basis, extrapolation of these savings to the population with CHF (4.8 million Americans) are impressive.[20] These estimates provide an indication of the economic benefit that can be achieved with the optimal prescribing of proven efficacious therapies.

4. Conclusion

Despite conclusive evidence establishing the efficacy of ACE inhibitors in patients with CHF (particularly those with systolic dysfunction), the application of this evidence in clinical practice is suboptimal both in terms of the frequency of ACE inhibitor use and the dosages reached. Observational studies of heart-failure clinics document the most favourable rates of ACE inhibitor use (typically greater than 80%), but are limited by the number of patients they are able to serve. Future inter-

ventions are necessary to optimise the management of CHF, and focused, multidisciplinary disease-management programmes have the highest likelihood of success. In a setting of limited resources for healthcare, therapies with conclusive evidence should be used to benefit as many individuals as possible. In fact, the wider application of underutilised yet proven therapies may actually have a greater overall impact on health than any single new treatment itself.

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