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Contemporary management of patients with left ventricular systolic dysfunction

Results from the Study of Patients Intolerant of Converting Enzyme Inhibitors (SPICE) Registry

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Aims The reported prevalence of angiotensin-converting enzyme (ACE) inhibitor use in patients with heart failure varies considerably. Recent reports suggest that many patients who could benefit from such therapy are not receiving ACE inhibitors. The Study of Patients Intolerant of Converting Enzyme Inhibitors (SPICE) Registry was established to understand better the demographics, characteristics, and contemporary use of ACE inhibitors in an international registry.

Methods and Results Between August 1996 and April 1997, each of 105 study centres from eight countries in North America and Europe was invited to review retrospectively the medical records of 100 consecutive patients with left ventricular ejection fractions $\leq 35\%$. The median age of the 9580 Registry patients was 66 years, 26% were women, the median ejection fraction was 27%, and the primary aetiology of left ventricular dysfunction was ischaemic (63%). Eighty percent of patients were receiving ACE inhibitors. The most common reason for non-use of ACE inhibitors was intolerance (9%).

Conclusion The SPICE Registry provides a contemporary description of the demographics and management of patients with documented left ventricular systolic dysfunction. The contemporary use of ACE inhibitors (80%) appears to be higher than previously reported and the main reason for non-use is perceived intolerance (9%).
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Key Words: Heart failure, ACE inhibitor, management, medication usage.

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Introduction

Congestive heart failure is an important public health problem associated with significant morbidity, mortality, and financial burden[1,2]. Treatment with angiotensin-converting enzyme (ACE) inhibitors in major trials reduces the combined end-point of total mortality or hospitalization for heart failure by 35%[3]. These important clinical benefits have prompted the universal recommendation that patients with left ventricular systolic dysfunction should be treated with ACE inhibitors[2,4,49,50].

Despite the proven benefits of ACE inhibitors, the reported prevalence of ACE inhibitor use among heart failure patients varies from 17% to 86%[5–13]. This suggests that a sizable population of patients who might

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benefit from ACE inhibitors are not receiving such agents.

Therefore, the purpose of the SPICE Registry is to describe the prevalence of ACE inhibitor use among a large, international, contemporary cohort of patients with documented left ventricular systolic dysfunction. Moreover, we sought to identify the reasons for non-use among those patients not treated with ACE inhibitors. This Registry also serves to define current management patterns in patients with left ventricular systolic dysfunction.

Methods

The SPICE programme is an international effort to assess the role of candesartan cilexitil (an angiotensin II receptor blocker) in the management of patients with heart failure and perceived intolerance to ACE inhibitors. A randomized, placebo-controlled trial was performed to assess the safety and tolerability of candesartan cilexitil in ACE inhibitor intolerant heart failure patients. The results of the treatment trial will be reported separately. This report of the SPICE Registry describes a parallel effort which was undertaken to determine the proportion of patients with left ventricular systolic dysfunction not receiving an ACE inhibitor due to perceived intolerance.

Between August 1996 and April 1997 the SPICE investigators identified patients with documented left ventricular systolic dysfunction for a Registry. These investigators, representing 105 study centres in eight countries (Canada, Germany, Italy, Poland, Sweden, Switzerland, United Kingdom, and the United States), retrospectively reviewed the medical records of consecutive patients with left ventricular systolic dysfunction (ejection fraction $\leq 35\%$ assessed by either radionuclide angiography, ventriculography, or echocardiography) seen at their place of clinical practice. Registry patients were identified according to methods best suited to each investigator's practice: invasive and non-invasive cardiology testing logsheets, or consecutive patient encounters (inpatient or outpatient). For example, study sites with an ability to query the results from their cardiac catheterization, echocardiography, and nuclear imaging laboratories could review cases retrospectively to include patients with qualifying ejection fractions in the Registry. Alternatively, study sites without such easy access to data from these imaging laboratories could identify patients by reviewing clinical contacts with heart failure patients (from outpatient clinics and inpatient wards) and confirming the presence of a qualifying ejection fraction by review of the medical record. Data collection was stopped at each site when 100 patients had been identified. In the absence of a quantitative estimate of ejection fraction, left ventricular function described as 'moderately' or 'severely' impaired was acceptable.

Study coordinators completed a data collection form recording demographics, clinical features and cardiovascular medications. Medications, laboratory values, and blood pressure were determined from each patient's medical record and reflected the most current information recorded. Reasons for non-use or discontinuation of ACE inhibitors were collected for patients not receiving ACE inhibitors.

Descriptive statistics were used to summarize group characteristics. Medians and percentiles were used for all continuous and binomial variables, respectively. Multiple logistic regression was used to assess variables potentially associated with non-use of ACE inhibitors including: age, race, sex, aetiology of left ventricular dysfunction, New York Heart Association symptoms, ejection fraction, systolic blood pressure, continent (Europe vs North America), and serum concentrations of sodium, potassium, and creatinine. The authors recognize that the generalizability of all retrospective data to the true population of afflicted patients is limited.

Table 1. International representation, means of patient identification, and diagnostic tests used to assess left ventricular function in SPICE Registry patients

Identification of SPICE registry patients	SPICE Registry
Total enrollment	9580
Europe	4504 (47%)
North America	5076 (53%)
Enrollment period (months)*	4·1 (4·0,5·7)
Means of patient identification	
Invasive/non-invasive cardiac testing	3154 (33%)
Inpatient encounters	3028 (32%)
Outpatient encounters	3095 (33%)
Other	170 (2%)
Assessment of left ventricular function	
Radionuclide angiography	1483 (16%)
Ventriculography	1589 (17%)
Echocardiography	6283 (67%)

*Time elapsed between clinical contact with the first and last Registry patient at each site. Data presented are number of patients (%). Total percent and/or number of patients may not add up to 100% due to missing data.

Results

Identification of SPICE Registry patients

The data coordinating centre received 10 129 Registry forms, of which 549 were not included in the analysis because of missing data. Thus, 9580 patients were included in the final Registry for analysis. Information regarding the identification of Registry patients is presented in Table 1. The median enrollment period (time elapsed between clinical contact with the first and last Registry patient at each site) was 4·1 months. Patients from North America and Europe had nearly equal representation. Study sites identified Registry patients using cardiac testing logsheets, inpatient and outpatient encounters in equal proportions. Echocardiography was used to objectively assess left ventricular function in

Table 2. Clinical characteristics of SPICE Registry patients

Baseline clinical characteristics	SPICE Registry
Age (years)	66 (57,74)
Female	2513 (26%)
Ejection fraction (%)	27 (20,31)
Primary aetiology	
Ischaemic	5906 (63%)
Idiopathic	1592 (17%)
Valvular	488 (5%)
Hypertensive	416 (4%)
Other	408 (4%)
Unable to determine	534 (6%)
Atrial fibrillation	2459 (27%)
New York Heart Association Class	
I	964 (10%)
II	3538 (38%)
III	3228 (34%)
IV	853 (9%)
Unable to determine	830 (9%)

Data presented are number of patients (%) or medians (25th, 75th percentiles). Total percent and/or number of patients may not add up to 100% due to missing data.

Table 3. ACE inhibitor intolerance in all patients exposed to ACE inhibitors

Adverse event	Number (%)
Patients ever exposed to ACE inhibitors	8485
Patients withdrawn due to adverse event*	821 (9·7)
Cough	308 (3·6)
Renal insufficiency	188 (2·2)
Symptomatic hypotension	147 (1·7)
Hyperkalaemia	35 (0·4)
Rash/pruritis	25 (0·3)
Grastrointestinal upset	22 (0·3)
Anaphylaxis/angioedema	19 (0·2)
Taste disturbance	6 (0·1)
Neutropenia	1 (0·01)
Other	146 (2)

*The number of patients with adverse events exceeds the total number exposed to ACE inhibitors because some patients experienced more than one adverse event.

two-thirds of Registry patients while ventriculography and radionuclide angiography were performed in 17% and 16% of Registry patients, respectively. In total, 86% of Registry patients underwent quantitative assessment of left ventricular function; the remaining 14% had qualitative confirmation of 'moderate' or 'severe' left ventricular systolic dysfunction by echocardiogram.

Clinical characteristics

The clinical characteristics of Registry patients are shown in Table 2. The median age of Registry patients was 66 years, 26% were women, the median ejection fraction was 27%, and the primary aetiology of left ventricular systolic dysfunction was ischaemic cardiomyopathy (63%). Atrial fibrillation and New York Heart Association class III or IV heart failure symptoms were common (27% and 43%, respectively).

Use of ACE inhibitors

Eighty percent of Registry patients were receiving ACE inhibitors at the time of entry in the Registry (Fig. 1). Reasons for non-use of ACE inhibitors were: intolerance to ACE inhibitors (9%), perceived high risk for initiating therapy (2%), and newly diagnosed left ventricular systolic dysfunction/ACE inhibitors not yet started (3%). Investigators were unable to determine a reason for non-use of ACE inhibitors in 5% of the Registry patients. Cough was the most common adverse event experienced by Registry patients and led to the discontinuation of ACE inhibitors in 3·6% of patients (Table 3).

Variables independently associated with non-use of ACE inhibitors are shown in Table 4. Advancing age, female sex, ischaemic aetiology, higher ejection fraction, higher creatinine, and lower potassium were independent predictors for not being treated with ACE

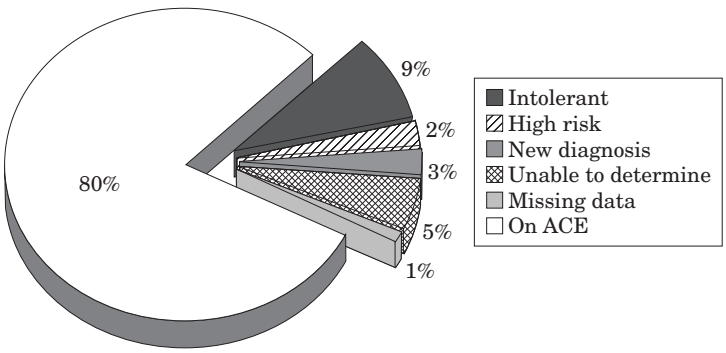

Figure 1. **Use of angiotensin-converting enzyme (ACE) inhibitors in SPICE Registry patients.**

Table 4. Factors associated with non-use of ACE inhibitors in SPICE Registry patients — results from a multiple logistic regression analysis

Clinical feature	Odds ratio	95% CI	*P* values
Older age	1·01	(1·006, 1·018)	0·0001
Race — white	1·021	(0·761, 1·370)	0·8901
Sex — female	1·240	(1·052, 1·462)	0·0105
Ischaemic aetiology	1·210	(1·034, 1·416)	0·0175
European	0·708	(0·608, 0·824)	0·0001
NYHA III or IV	0·983	(0·847, 1·140)	0·8170
Higher EF	1·024	(1·014, 1·034)	0·0001
Higher systolic BP	1·001	(0·998, 1·003)	0·6629
Higher sodium	0·988	(0·970, 1·007)	0·2053
Higher potassium	0·786	(0·677, 0·913)	0·0016
Higher creatinine	1·005	(1·004, 1·007)	0·0001

BP=blood pressure; EF=ejection fraction; NYHA=New York Heart Association. An odds ratio >1 indicates an increased likelihood of not receiving an ACE inhibitor and an odds ratio <1 indicates an increased likelihood of being treated with and ACE inhibitor.

inhibitors. Race, advanced heart failure symptoms (New York Heart Association class III–IV), systolic blood pressure, and serum sodium concentration had no independent predictive value. After correcting for important differences in baseline clinical characteristics, European patients were more likely than non-European patients to be treated with ACE inhibitors (odds ratio 0·708, 95% CI 0·608–0·824, $P=0·0001$).

Patterns of medication use

The common cardiovascular medications taken by Registry patients and their relationship to various clinical features are shown in Tables 5 and 6. Reduced ejection fraction was associated with increased use of ACE inhibitors, digoxin, diuretics, and warfarin; in contrast, aspirin and beta-blockers were used less frequently. Similarly, worsening heart failure symptoms (higher New York Heart Association class) were associated with increased use of digoxin, diuretics, nitrates and decreased use of beta-blockers. Patients with ischaemic cardiomyopathy were more likely to receive nitrates, aspirin, beta-blockers, and lipid lowering agents. A history of atrial fibrillation was associated with increased use of warfarin and antiarrhythmic agents.

Discussion

Use and non-use of ACE inhibitors

A larger than anticipated proportion of Registry patients (80%) were receiving ACE inhibitors. Results from the Large State Peer Review Organization Consortium suggest that heart failure patients with confirmed left ventricular systolic dysfunction are more likely to receive ACE inhibitors[11]. In this review of 6749 Medicare patients with a discharge diagnosis of heart failure, the overall prevalence of ACE inhibitor use was 55%. However, the proportion of patients treated with ACE inhibitors increased to 73% among 'ideal candidates' (patients with ejection fractions <40% and no obvious contraindications to ACE inhibitor therapy). Documented left ventricular dysfunction was a strong independent predictor of ACE inhibitor use (odds ratio 2·13, 95% confidence interval 1·92–2·38)[11]. Thus, the high rate of ACE inhibitor use among SPICE Registry patients may be related, in part, to the confirmed presence of left ventricular systolic dysfunction in the entire Registry population. Other studies describing lower rates of ACE inhibitor use included patients

Table 5. Use of cardiovascular medications

Medication	Number (%)
Specific heart failure therapies	
ACE inhibitor	7664 (80)
Digoxin	5573 (59)
Diuretic	7439 (78)
Nitrate	3726 (40)
Angiotensin II receptor blocker	561 (6)*
Intravenous inotrope	170 (2)
Hydralazine	242 (3)†
Antithrombotic therapies	
Antiplatelet agent	4827 (51)
Warfarin	3056 (32)
Beta-blocker	2452 (26)
Lipid lowering agent	1728 (18)
Calcium channel antagonist	1404 (15)‡
Antiarrhythmics	1488 (16)§
Combination therapy	
ACE inhibitor, digoxin, diuretic	4118 (43%)
Digoxin, diuretic	769 (8%)
ACE inhibitor, diuretic	2005 (37%)

*14% of patients not treated with ACE inhibitors were receiving angiotensin II receptor blockers.
†7% of patients not treated with ACE inhibitors were receiving hydralazine.
‡2% of patients received short acting calcium channel antagonists.
§11% of patients received amiodarone.

Table 6. Relationship of cardiovascular medications to clinical features

Clinical feature	ACEI	Digoxin	Diuretic	Nitrate	Aspirin	Beta-blocker	Ca-antag	Antiarr	Warfarin	X-lipid
EF										
31–35%	78	49	69	42	58	32	17	14	25	20
21–30%	80	61	79	39	50	26	16	17	33	19
11–20%	84	71	88	39	46	21	12	19	39	16
≥10%	87	77	92	39	30	20	10	26	54	12
NYHA										
I	76	41	55	27	55	32	15	13	29	23
II	81	54	74	28	54	30	15	15	31	21
III	82	69	89	44	48	21	16	18	37	16
IV	78	74	92	48	44	16	13	20	31	11
Aetiology										
Ischaemic	79	53	76	49	62	29	17	17	28	24
Non-ischaemic	82	69	82	24	33	21	12	16	39	9
Atrial fibrillation										
Present	78	76	84	35	37	21	15	27	53	13
None	81	52	76	41	56	28	15	12	24	20

Values represent percent of patients with each clinical feature receiving treatment.
ACEI=angiotensin-converting enzyme inhibitor; Antiarr=antiarrhythmic agent; Ca-antag=calcium channel antagonist; EF=ejection fraction; Non-ischaemic=non-ischaemic cardiomyopathy; NYHA=New York Heart Association; X-lipid=lipid lowering agent.

without documented left ventricular systolic dysfunction or failed to separate patients with preserved function from those with systolic dysfunction[13–18].

Another factor possibly contributing to the high prevalence of ACE inhibitor use in the SPICE Registry was the expertise of the SPICE investigators. However, we attempted to minimize this effect by including all qualifying patients from each investigator's hospital in the Registry (i.e. the Registry is not entirely comprised of the investigators' personal patients).

Age and sex were independent predictors of not receiving ACE inhibitor therapy. Other investigators have described age and sex-related practice variations, indicating that there may be biases in the management of patients with cardiovascular disease[19–21]. The unexpected finding that North American residence was an independent predictor of not receiving an ACE inhibitor suggests that there may be important international differences in the management of left ventricular dysfunction[22,23].

Previously documented intolerance was the most common reason for non-use of ACE inhibitors and occurred in 9% of Registry patients — a rate similar to that reported in other studies[7,11,24]. Six percent of patients included in the Large State Peer Review Organization Consortium study had an allergy to ACE inhibitors or were treated with such drugs and subsequently had them withdrawn prior to discharge[11]. Bart *et al.*[7], reviewed the charts of 242 patients with documented ejection fractions ≤45% who were admitted to a tertiary care medical centre with the primary or secondary discharge diagnosis of heart failure. Previously established intolerance to ACE inhibitors was the reason for non-use in 5·4% of the study patients. An additional 9·9%= did not receive ACE inhibitor therapy because of perceived contraindications including renal artery stenosis, symptomatic hypotension, and renal insufficiency. No reason for withholding ACE inhibitor therapy could be determined in 8·3% of patients. Hillis *et al.* reviewed the medical records of 265 patients with the discharge diagnosis of heart failure[24]. At the time of discharge, 9.8% of patients were not receiving ACE inhibitors due to ACE intolerance or contraindications, 26·7% had no clear reason for non-use.

The most common reason for ACE intolerance in the SPICE Registry was cough followed by symptomatic hypotension, progressive azotaemia, and hyperkalaemia. The prevalence and clinical features of ACE intolerance in the SPICE Registry are similar to those reported in other trials[25–28].

Demographics of Registry patients

The median age of patients in the SPICE Registry (66 years) is older than that of patients enrolled in several large heart failure trials[25,29–34], but not as old as that reported in population-based studies[15,16]. These age differences probably represent a bias introduced by requiring objective evidence of left ventricular systolic dysfunction for inclusion in the Registry — older patients may be less likely to undergo testing to assess left ventricular function and have a higher incidence of diastolic dysfunction (heart failure with relatively preserved left ventricular systolic function)[35,36].

Despite the similar prevalence of heart failure among men and women in the general population[14,15], the majority of patients in the SPICE Registry (74%) were men. Similar findings have been published in other reports[6,30–32,37]. The high representation of men in this

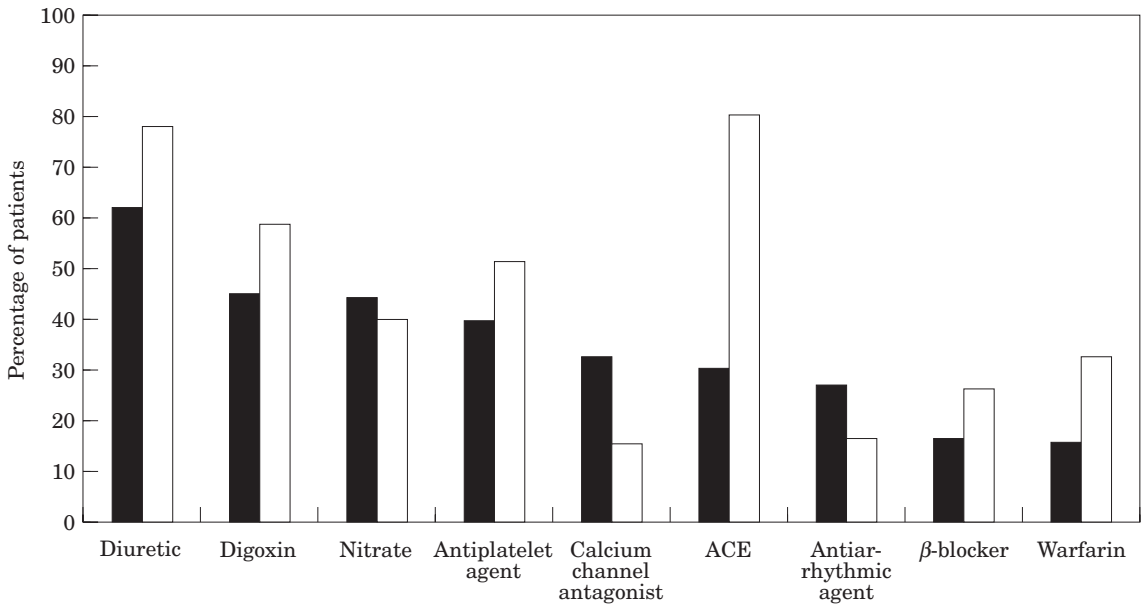

Figure 2. **Use of cardiovascular medications in SPICE (□) and SOLVD (■) Registry patients (n=9580 and 5999, respectively). ACE=angiotensin-converting enzyme inhibitor.**

study and others may reflect sex-related differences in the pathophysiology of heart failure — women may have a higher incidence of diastolic dysfunction than men[38]. Excluding patients with relatively preserved systolic function may preferentially select for men.

Ischaemic cardiomyopathy was the most common aetiology of left ventricular systolic dysfunction in Registry patients. This is consistent with other reports[30–32,37] and highlights the important role coronary artery disease plays in the pathogenesis of cardiomyopathy. The median ejection fraction and the prevalence of advanced heart failure symptoms (New York Heart Association Class III or IV) in the SPICE Registry were similar to other studies[29,31,32,37,39].

Atrial fibrillation was present in 27% of Registry patients. This is higher than the rate reported in other studies[31,39] and may reflect the older age of patients in the SPICE Registry. Another possible explanation is that there may be a selection bias against enrolling patients with atrial fibrillation in heart failure trials — such patients were excluded from the Digitalis Investigation Group (DIG) Trial[32].

Management of heart failure

Prior to the SPICE Registry, the largest and most detailed heart failure database was that established by the SOLVD investigators in the late 1980s[39,40]. Comparing the SOLVD and SPICE Registries may provide insight into how the management of heart failure has evolved over the past 10 years.

The use of commonly prescribed cardiovascular medications in the SOLVD and SPICE registries are described in Fig. 2[41]. The difference in the prevalence of ACE inhibitor use is the most striking finding in this comparison (30% vs 80% in the SOLVD and SPICE registries, respectively). This change is not surprising since the SOLVD treatment trial was one of the major trials that proved the value of ACE inhibitor therapy and led to the widespread use of these agents[2,4].

There are other descriptive differences in the use of cardiovascular medications worth mentioning. The higher use of diuretics among SPICE Registry patients may reflect more advanced heart failure symptoms; the prevalence of New York Heart Association class III or IV symptoms in the SPICE Registry was 43% compared to 32% in the SOLVD treatment trial[31] and 17% in the SOLVD Registry substudy[40]. The increase in the use of beta-blockers may be explained, in part, by growing recognition and acceptance of the role beta-blockers play in modulating neurohormonal activation in patients with heart failure[30,42,43].

The increase in the use of digoxin and warfarin in the SPICE Registry most likely reflects the higher prevalence of atrial fibrillation in the SPICE Registry (27%) compared to that in SOLVD Registry patients (14%).

The use of calcium channel antagonists and antiarrhythmic drugs in the SPICE Registry is lower than that in the SOLVD Registry. The change in the use of antiarrhythmics is not surprising given the results of the Coronary Arrhythmia Suppression Trial which showed increased mortality in post-myocardial infarction patients with left ventricular dysfunction treated with class IC drugs[44]. The decrease in the use of calcium channel antagonists probably reflects awareness that some calcium channel antagonists (especially short acting dihydropyridines) may increase mortality in patients with left ventricular dysfunction[45,46].

The contemporary nature of the SPICE Registry places it in a unique position to describe the current demographics and management of patients with left ventricular systolic dysfunction. Differences in the use of cardiovascular medications, as outlined in this review of the SPICE and SOLVD Registries, suggest that evidence-based medicine has had a major impact on clinical practice patterns[47].

Strengths and limitations

Much of what is known about the clinical features and prognosis of heart failure is based on well designed clinical trials. However, eligibility requirements and the necessity of obtaining informed consent significantly impair the generalizability of such trials[38,40,48]. One important feature that distinguishes the SPICE Registry from other cohorts of heart failure patients is that Registry patients represent consecutive clinical encounters — not patients who agreed to participate in clinical trials.

While there are limitations with retrospectively acquired data, the size and broad cross-section of patients and study centres represented in the SPICE Registry may compensate for many of these limitations. The main strengths of this Registry are related to its precisely defined cohort, multiple sites, international scope, large size, consecutiveness, significant representation of outpatients, and temporal relevance. However, the design of this investigation introduces certain study population biases. First, patients enrolled in the Registry may not be fully representative of heart failure patients in the general population because of referral bias and the specialized interests of the SPICE investigators. We attempted to limit the influence of these potential biases by including a large number of study sites in geographically diverse locations. Additionally, Registry patients reflect consecutive clinical encounters at the investigators' institution — not from their individual practices. Second, there are substantial selection biases introduced by including only those patients with objective evidence of left ventricular systolic dysfunction in the Registry. Heart failure patients with preserved systolic function or without any objective assessment of ventricular function probably represent a different population. Third, SPICE study investigators may have presented the coordinating centre with a 'convenience sample' of heart failure patients, preferentially including ACE inhibitor intolerant patients. Thus, an investigator wishing to give the false impression that recruitment for a large clinical trial would be easy, might be tempted to 'save-up' such patients and include them preferentially in the Registry. This scenario seems unlikely. Preferential inclusion of ACE inhibitor intolerant patients would have the effect of falsely increasing the reported prevalence of ACE inhibitor intolerance. Since 80% of the Registry patients were receiving ACE inhibitors (a suprisingly large percentage), it seems unlikely that many investigators were 'saving-up' ACE inhibitor intolerant patients to any significant degree.

Summary

The SPICE Registry describes the contemporary demographics and management of patients with documented left ventricular systolic dysfunction. The use of ACE inhibitors in this international Registry was 80% and the main reason for non-use of such agents was intolerance, which occurred in 9% of the total patient population.

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Appendix

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