Management of heart failure: evidence versus practice. Does current prescribing provide optimal treatment for heart failure patients?

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SUMMARY

Heart failure is an increasingly common and costly chronic disorder, with a rising prevalence of at least 2% in populations over the age of 45 years, mortality rates that are as poor as common solid cancers, and very high health care utilisation costs. Despite increased evidence supporting a range of effective interventions, predominantly therapeutic, there remain significant degrees of physician underperformance in terms of heart failure diagnosis and management.

Until the early 1990s, the management of heart failure was largely confined to the symptomatic relief of patients with well established heart failure in fluid overload. The introduction of angiotensin-converting enzyme (ACE) inhibitors provided the first treatments that beneficially altered the prognosis of patients with the most common expression of heart failure, namely established systolic dysfunction, whether symptomatic or asymptomatic. Evidence has now extended these benefits to delaying progression of heart failure and reducing hospitalisation. Much of our understanding of the pathophysiology of heart failure stems from these studies. More recent data has clarified the limited role of digoxin, the important benefits of beta-blockade and aldosterone blockers as adjuvants to ACE inhibition, and the emerging evidence on angiotensin II antagonists. There are, in contrast to these positive findings, reliable data from Europe and North America revealing significant underperformance of primary care and hospital physicians in heart failure diagnosis and management, with evidence of underuse and underdosing of evidence-based therapies. Limited qualitative data suggest the reasons for this underperformance are complex and relate to lack of access to objective testing of ventricular function and exaggerated concerns over treatment risks and side- effects.

Heart failure represents a complex cluster of aetiologies and risks that are not easy to correctly identify, even in specialist settings. Since there is now powerful evidence on how heart failure can be modified and improved, explicit guidance is needed for which suspected patients should be referred, for confirmation of diagnosis and advice on appropriate treatment regimes, and for which patients can be handled mainly within primary care but with enhanced access to objective non-invasive tests to improve diagnostic reliability and to stratify patients to evidence-based therapies. Current evidence suggests that in North America and Europe today primary care physicians do underperform in their management of patients with heart failure, often owing to factors outside of their immediate control.

Keywords: heart failure; primary care performance; Europe; North America.

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Introduction

HEART failure is a major and progressive cause of morbidity and mortality in most developed countries. This condition is common, occurring in 1% to 2% of the population,[1,2] with an annual incidence of new cases of approximately one to four per thousand,[3-5] rising to 30 per thousand in the 75 years and over age group.[6,7]

Most cardiovascular diseases have declined in the past 20 years in Western developed economies. The latter part of this period has coincided with the development of several effective drug therapies that substantially improve the management of hypertension and acute myocardial infarction. Despite these developments, the incidence of heart failure continues to rise.[8] Indeed, it is anticipated that with improved secondary preventative treatment leading to greater survival following acute myocardial infarction and an increasing elderly population in the developed world these increases will continue for the foreseeable future.

Impact of heart failure

Heart failure is directly responsible for 40 000 deaths per annum in the United States (US) and contributes to over 200 000 further deaths each year.[9] A five-year mortality rate of up to 50% is seen in patients with advanced heart failure,[1] who are also at a six- to nine-fold increased risk of sudden death compared with the general population,[10] and symptomatic heart failure (all grades combined) has a worse prognosis than breast or prostate cancer. In the period 1979 to 1993, deaths attributable to heart failure in the US increased by 110%, while during 1979 to 1994 the annual rate of US hospitalisation for heart failure rose by 132%.[11]

Heart failure is one of the most frequent causes of hospitalisation of the elderly in the US,[13] affecting an estimated three million Americans,[12] and it is thought that the financial impact on the US health care system of heart failure is over $8 billion per year.[13,14] Hospitalisation costs account for approximately 75% of this sum.[15] Surveys in the United Kingdom (UK) and Europe reveal health service burdens of similar proportion, with 5% of all hospital admissions in the UK relating to heart failure.[16-18]

In addition to facing a high risk of death or protracted hospitalisation, patients with heart failure also suffer from a grossly impaired quality of life,[19] with signs ranging from dyspnoea, abdominal pain, cough, and fatigue to adverse renal function with fluid overload and exacerbation of existing oedema.[20] Heart failure symptoms can eventually become sufficiently serious to prevent patients performing the least taxing of activities.

Basic mechanisms for the development of heart failure and rationale for therapy

Left ventricular hypertrophy (LVH) is an important risk factor for angina, myocardial infarction or congestive heart disease.[21,22] Heart failure arises from LVH owing to structural changes, or

'remodelling,' of the heart caused by the stress of pressure and volume overload.[23,24] Remodelling is characterised by a change in the dimensions of the left ventricle and the ventricular wall, with associated or subsequent myocardial fibrosis, myocyte hypertrophy, slippage, elongation and necrosis,[25] and hypertrophy of coronary artery smooth muscle cells.[26] LVH results in impaired cardiac function in addition to an increased risk of ventricular arrhythmia[27] and coronary artery insufficiency owing to increased myocardial oxygen demand.[28] It has been suggested that remodelling is an adaptive response by local tissues stimulated by stretch receptors, which in turn mediate changes at the tissue level via angiotensin II (AT-II).[29] Moreover, it has been proposed that the reversal of these structural changes, known as cardioreparation, could be achieved by relief of the original causal stresses and inhibition of the renin angiotensin system. Intervention with angiotensin-converting enzyme (ACE) inhibitors, by restoring cardiac structure and function towards normal, might improve prognosis for heart failure patients.[25]

Despite compelling evidence of their value in the management of heart failure and recognition of the important role of the renin–angiotensin system in progression of heart failure, the condition remains poorly diagnosed and ACE inhibitor prescribing is still inadequate in terms of both underusage and underdosage, issues discussed in detail later. This review, drawing on current clinical trial data, prescribing patterns for ACE inhibitors, and recent guidelines for use in conjunction with other therapies, emphasises the need for more effective strategies to optimise this class of drug to improve treatment and management of the heart failure patient.

Guidelines for the management of heart failure

Recent guidelines for the evaluation and management of heart failure are established in both the US (ACC/AHA[30] and Consensus Recommendations[31]) and Europe (ESC[32]). These guidelines encompass the recent and significant evidence-based developments in therapy that offer benefits in the treatment of heart failure. Traditionally, therapy was primarily targeted at the relief of the symptoms of congestion (pulmonary and peripheral oedema) or increasing cardiac contractility (e.g. with diuretics and digoxin respectively). Current therapy strategies have been designed to additionally counter the progression of heart failure and to improve 'meaningful' survival. Within these guidelines ACE inhibitors are confirmed as a major mainstay of heart failure therapy.

ACE inhibitors as first-line treatment for heart failure

The Consensus guidelines recommend that all patients with heart failure owing to systolic dysfunction, symptomatic or asymptomatic, should receive an ACE inhibitor unless intolerant or contraindicated. Since the Captopril Multicenter Study[33] first highlighted the potential value of ACE inhibition in the treatment of heart failure, several large randomised controlled clinical trials have proven their efficacy in improved haemodynamic parameters, symptoms, functional status, mortality, and progression[34-36] (Table 1) as well as suggesting strategies to improve cost-effectiveness.[17]

A meta-analysis in a systematic review of 32 randomised trials up to the year 1994 summarised the effects of ACE inhibitors on mortality and morbidity in 7105 symptomatic heart failure patients.[37] Many of the endpoint analyses from this overview were consistent with outcomes from the major trials such as CONSENSUS[34] and SOLVD.[35] It showed that ACE inhibitors significantly reduce risks of total mortality, primarily deaths owing to progressive heart failure (OR = 24%, number needed to treat = 74), and reduce combined mortality and hospitalisation for heart failure. Although mortality endpoint reductions were similar for each of the patient subgroups analysed, patients with an ejection fraction of ≤25% appear to benefit most from ACE inhibitor therapy. ACE inhibitors were also associated with non-significant trends towards fewer fatal myocardial infarctions, sudden or presumed arrhythmic deaths, and fatal strokes.

If fluid retention is present, ACE inhibitors are used together with loop diuretics. While side-effects occur early with ACE inhibitors, symptomatic improvement may not be seen until later. Furthermore, disease progression may be reduced even if symptoms are not relieved. Preference should be given to the target doses of the specific ACE inhibitors evaluated in large-scale studies.

Dose of ACE inhibitor in heart failure

Despite the evidence, the preference of physicians is to prescribe doses of ACE inhibitors in heart disease treatment lower than doses demonstrated to be beneficial in mortality trials, possibly owing to the common, but unfounded, assumption that ACE inhibitor side-effects are dose-related. This assumption was tested in the Assessment of Treatment with Lisinopril and Survival (ATLAS) study,[38] based on a population, younger than in the SOLVD[35] and NETWORK[39] studies, with New York Heart Association (NYHA) class II–IV (77% class III) and major left ventricular systolic dysfunction. Three thousand, one hundred and sixty-four patients were randomised to either low-dose (2.5–5.0 mg daily) or high-dose (32.5–35 mg daily) lisinopril groups with background therapy with other drugs for heart failure. The study did not reach full power and no significant difference was observed in all-cause mortality between the dose groups (high dose group OR = 0.92, 95% CI = 0.82%–1.03%, $P = 0.128$). However, the high dose group had significant risk reductions in the pre-specified combined endpoint of all-cause mortality and repeat hospitalisation (OR = 0.88, 95% CI = 0.82%–0.96%, $P = 0.002$) and hospitalisations for heart failure (risk reduction [RR] = 24%, $P = 0.0002$). The higher lisinopril doses were tolerated as well as the lower doses, with a similar number of side-effect-related withdrawals in both groups. On the basis of ATLAS, heart failure patients should not remain on low doses of ACE inhibitors unless high doses are not tolerated.

In summary, ACE inhibitors are of proven clinical benefit in patients with symptomatic heart failure as well as asymptomatic patients with an ejection fraction of less than 35%. These agents are well tolerated and not only reduce mortality but also improve functional status and reduce the risk of hospitalisation for cardiac reasons.

Mechanisms of action of ACE inhibitors in heart failure: cardiac remodelling and cardioreparation

ACE inhibitor-mediated suppression of AT-II-related processes and stimulation of those processes arising from bradykinin would appear to be a logical strategy to be adopted in the reversal of remodelling, by tipping the balance in favour of collagen removal and away from collagen deposition and fibroblast differentiation.[25,40-42] Broadly speaking, ACE inhibitors halt the production of AT-II by antagonising ACE, thus reducing circulating concentrations of AT-II. In addition, ACE inhibitors also have a strong influence on the bradykinin and prostaglandin systems, most significantly inhibiting ACE-mediated bradykinin breakdown. In contrast, AT-II antagonists competitively bind at AT_1 sites and prevent access of AT-II to these receptors but have no similar effect on AT_2 receptors. There is also no known losartan blockade of antidiuretic hormone, bradykinin, renin or ACE.[43-46]

Table 1. Controlled clinical trials of ACE inhibitors and AT-II antagonists for patients with ventricular dysfunction.

Drug class (Study)	Drug treatment	Patients (n)	NYHA Class/EF[a]	Follow-up (months)	Outcome (RR)[b]	Comments
ACE inhibitors						
CONSENSUS	Enalapril 2.5–40 mg twice daily	253	IV	6	40% (6 months)	Owing to reduction in heart failure death
V-HeFT II	Enalapril 20 mg twice daily vs H + I	804	I–III EF<45%	30	28% (2 years)	Large reduction in sudden death
SOLVD (T)	Enalapril 2.5–20 mg twice daily	2569	II–III EF£35%	41	16%	Large reduction in heart failure
SOLVD (P)	Enalapril 2.5–10 mg twice daily	4228	I–II EF<35%	37	29% (combined death/heart failure development)	-
MHEART FAILURET	Captopril 25 mg twice daily vs placebo	170	I–III (mean = II)	-	Reduced progression heart failure	Largely owing to reduction in heart failure
NETWORK	Enalapril 2.5–5.0 mg or 10 mg twice daily	-	II–IV	-	Combined endpoint relative risk = 1.2	No dose response
ATLAS	Lisinopril 2.5–5.0 mg daily or 32.5–35 mg daily	3165	II–IV (77% III)	46	8% RR[a] = 12%	Reduction combined endpoint: mortality and hospitals
AT-II antagonists						
ELITE	Losartan 50 mg daily or Captopril 50 mg three times daily	722	II = IV EF<40%	48 weeks	Losartan (4.8%) mortality <captopril (8.7%)	Large reduction in sudden death
RESOLVD	Candesartan + Enalapril	769	Largely mild	-	-	Terminated owing to increased mortality on candesartan
ELITE II	Losartan 50 mg daily or Captopril 50 mg three times daily	3152	>60, HF grades II-IV vs EF<40%	2 years	Captopril/Losartan Hazard Ratio 95% CI = 0.88 (0.75–1.05) P = 0.16	Losartan significantly better tolerated, with 9.4% withdrawals compared with 14.5% on captopril, P<0.001

[a]Left ventricular ejection fraction; [b]risk reduction.

The precise mechanisms of both ACE inhibitors and AT-II antagonists in heart failure and left ventricular dysfunction are still poorly understood. Both classes of agents exert beneficial effects on cardiovascular and renal haemodynamics and can most likely modulate cellular hyperplasia[47,48] as well as hypertrophy.[49] The accumulation of bradykinin following ACE blockade of bradykinin degradation is likely to be an important factor not only in the development of cough but also in some of the beneficial effects of ACE inhibitors.[50,51] Data demonstrate that bradykinin accumulation is a key factor in the antihypertensive effect of ACE inhibition.[52] There is mounting evidence from human studies that ACE inhibitors exert a profound effect on remodelling and promote highly effective cardioreparation effects.[28,53-55]

Angiotensin II antagonists are also known to promote reversal of cardiovascular remodelling through their effects upon AT-II receptor binding but are unable to oppose collagen synthesis, presumably owing to a lack of inhibition of bradykinin degradation.[56] This supports the possible value of the bradykinin-PGE_2-nitric oxide system in the reverse remodelling effects of ACE inhibitors. ACE inhibition was more effective in the prevention of non-myocyte cellular proliferation and collagen deposition in the non-infarcted myocardium.

Beta-blockers in heart failure

The recent US Consensus guidelines recommend that all patients with stable NYHA class II or III heart failure owing to systolic dysfunction should receive a β-blocker unless contraindicated or intolerant. Beta-blockers are generally used together with diuretics and ACE inhibitors and are indicated for the long-term management of chronic heart failure. Side-effects may occur early but the drugs may reduce the risk of disease progression even in the absence of symptomatic improvement.

Contrary to traditional teaching that this class of drugs was relatively contraindicated in heart failure, recent studies and meta-analyses have suggested significant mortality benefits following treatment of heart failure patients with β-blockers.[57-59] Two recent studies, the Cardiac Insufficiency Bisoprolol Study II[60] and the Metoprolol Controlled and Extended Release, Randomised Intervention Trial in Congestive Heart Failure[61] were terminated prematurely owing to pronounced benefit in the treatment group. Relative risk reductions in mortality were 35% (P<0.001) and 34% (P = 0.006) respectively, with further significant reductions in hospitalisation. Carvedilol differs from these agents in its non-selective β-blockade, acting at both b_1 and b_2 receptor sites, and its capacity to induce vasodilatation by blockade at a_1 receptor sites. The results from recent carvedilol studies[57,62] showed even greater benefits, with mortality reductions at 65% (P = 0.001).

Beta-blockers have an effect greater than that of ACE inhibitors in heart failure, being most effectively and safely used in patients with milder symptoms to retard deterioration and increase the length and quality of life.[63]

Diuretics and digoxin in heart failure

Loop diuretics should be prescribed for all patients with symptoms of heart failure who have, or are predisposed to, fluid retention, as they are the only means of controlling fluid overload. Importantly however, diuretics may alter the efficacy and tolerability of other drugs used for the treatment of heart failure. Underdosing can lead to fluid retention, which may diminish the response to an ACE inhibitor and increase risks of treatment with β-blockers. Overdosing can lead to increased likelihood of hypotension and renal insufficiency with ACE inhibitors and other drugs. It is especially important to monitor renal function (creatinine) in patients treated with diuretics who are commenced on an ACE inhibitor. Furthermore, since ACE inhibitors retain potassium, potassium-sparing diuretics should be avoided with ACE inhibitor use. In severe heart failure patients with fluid retention despite loop diuretics, the addition of a thiazide has proven efficacy.

Spironolactone

Potassium-sparing diuretics, such as spironolactone, have been previously contraindicated in treatment of heart failure patients already receiving an ACE inhibitor, owing to fears of hyperkalaemia. However, a recent study has prompted a revival of interest in spironolactone, a competitive aldosterone antagonist. The Randomised Aldactone Evaluation Study[64] was stopped prematurely owing to reduced mortality in the treatment group. The study examined the effect of spironolactone added to ACE inhibition and loop diuretic in patients with moderate to severe heart failure. Mortality was reduced by 27% (P = 0.0001) in the spironolactone group compared with placebo and there was a significant reduction in hospitalisation. Hyperkalaemia was not considered to be a problem, although 15% of patients required dose reductions.

Digoxin

Digoxin is recommended to improve the clinical status of patients with heart failure owing to left ventricular systolic dysfunction and should be used in conjunction with diuretics, ACE inhibitors, and β-blockers. Digoxin can improve symptoms and reduce hospitalisations but has no effect on survival. It is generally well tolerated by most patients with heart failure, with a particular role in patients with rapid atrial fibrillation. (However, since digoxin only limits resting heart rate, β-blockers may be advantageous in active atrial fibrillation patients, since they further limit heart rate rises during exercise.) A substudy of the Digitalis Investigation Group trial[65] showed no detrimental effects of digoxin on survival in patients with left ventricular diastolic dysfunction. However, since effects on hospitalisation are modest (6% absolute risk reduction, 26.8% versus 34.7% RR = 0.72, P<0.001), and there is no documented survival benefit, digoxin use in patients in sinus rhythm should only occur after diuretics, ACE inhibitors, and â-blockers have been initiated.

AT_1 receptor blockers — the evidence in heart failure

Angiotensin II (type 1) receptor blockers (AT_1 receptor blockers), the most recently developed major class of antihypertensives, are emerging as a possible therapeutic option in the treatment of heart failure. However, the US Consensus recommendations, prepared by the Advisory Council to Improve Outcomes Nationwide in Heart Failure, commented on the role of AT_1 receptor blockers as follows: 'there is no persuasive evidence that AT_1 receptor blockers are equivalent or superior to ACE inhibitors in the treatment of heart failure',[31] a view endorsed by the European Society of Cardiology Working Party on Heart Failure.[32]

Conflicting results of AT_1 receptor blockers on exercise tolerance,[66-68] heart failure progression,[69] and mortality outcome[70,71] (Table 1), were resolved by recently presented ELITE II data confirming losartan has similar benefits to captopril in clinical endpoints (captopril group OR = 0.88, 95% CI = 0.75%–1.05%, P = 0.16), though with significantly greater tolerability with losartan (9.4% withdrawals compared with 14.5%, P<0.001). AT_1 receptor blockers for heart failure would therefore appear to be indicated only when ACE inhibition is contraindicated or not tolerated.[72,73] Ongoing trials with AT_1 receptor blockers are likely to prove them complementary, if not synergistic, in combination with ACE inhibitors in heart failure.

Physician prescribing patterns for ACE inhibitors: evidence of underuse and underdosing

The strong evidence base for the ACE inhibitors, allied with recommendations in key US and European guidelines, should have resulted in their widespread acceptance in the treatment of heart failure. However, there is persisting evidence of physician underuse and underdosing of these effective drugs in hospital and primary care practice.

US prescribing

In a review of treatment records of Medicare patients admitted to acute care hospitals in the US between 1993 and 1994, only 35% of heart failure patients were taking ACE inhibitors at the time of admission.[9] In the oldest age group (85 years), this percentage was as low as 31%. At discharge, prescription of ACE inhibitors had risen to 55% of all study patients, ranging from 48% to 57% across 10 US states. Among defined patient subgroups, the highest use of ACE inhibitors (79%) was found in those with cardiac ejection fraction records and the lowest quantitative ejection fractions (≤25%), i.e. the more established the diagnosis, the more likely that ACE inhibitors were prescribed. At time of admission, only 2.5% of records indicated any intolerance or allergy to ACE inhibitors. On discharge, up to a quarter of suitable patients with no clear contraindications were not prescribed ACE inhibitors. It was also noted that a substantial additional number without documented ejection fraction records would also have benefited from ACE inhibitors.

In an analysis of US physician office visits by heart failure patients between 1989 and 1994, the use of ACE inhibitors rose from 24% in 1989 to 31% in 1994,[74] a figure close to the admission percentage noted in the above review.[9] Office visits by heart failure patients rose from 4.7 million to 5.7 million. Use of ACE inhibitors was found to be more likely in visits to cardiologists (46% versus 22% for all other physicians), in white patients (27% versus 21% in non-white patients), in privately insured patients (31% versus 24% in all others), and in men (29% versus 23% in women). Higher ACE inhibitor prescribing among cardiologists and general internists could be owing to case-mix (patients with severe heart failure preferentially visiting specialists). The inclusion of asymptomatic and mildly symptomatic patients in the study sample may have accounted for at least part of the large proportion (23%) of patients who received no medication indicated for heart failure.

These US trends have been confirmed by many other sources,[75,76] In a retrospective single hospital review of heart failure patient records,[77] ACE inhibitor prescriptions had increased from 43% (between 1986 and 1987) to 71% (between 1992 and 1993) in patients with systolic dysfunction. But, despite contraindication in only 2% of patients, more than 25% were dis-

charged without an ACE inhibitor.

UK and European prescribing

United Kingdom prescribing patterns are similar to the US, with the proportion of patients prior to 1994 who might have benefited from receiving ACE inhibitors being in the range 10% to 20%.[78-80] Despite strong advice to prescribe ACE inhibitors to all patients with left ventricular systolic dysfunction regardless of symptoms, many physicians have regarded ACE inhibitors as 'second-line' therapy in a role as an adjunct to diuretics.[81]

More recently, reviews of prescribing activity for heart failure within primary care show little progress has been made.[82,83] Against a background of extensive prescribing of ACE inhibitors for hypertension by general practitioners in Northern Ireland,[84] the same doctors were prescribing ACE inhibitors in only 18% of their heart failure patients, and at doses considerably below recommended doses.[77,85]

The most recent information regarding perception and practice in European primary care physicians is the Euro-HF study, a qualitative study among a random sample of primary care physicians in six European countries.[86] It reveals that although most doctors (more than 90%) believe there is strong evidence for the mortality benefits of ACE inhibitors and that a larger majority claim to prescribe ACE inhibitors in heart failure, only between 47% (Spain) and 62% (Germany and Italy) actually do so.

Physicians also prescribe at doses below recommended levels in between 65% and 73% of cases. In the US, the average dose of captopril given to heart failure patients is estimated to be 42mg and that of enalapril 9 mg.[73] In large, randomised ACE inhibitor trials, the dose of captopril was 50 mg three times daily[36] and that of enalapril was 10 mg to 20 mg twice daily.[34,35,87] Upon discharge from a Scottish hospital between 1991 and 1992, 76% of cardiac failure patients were on maintenance doses of ACE inhibitors below those used in the major trials.

Prescribing low doses of ACE inhibitors is most likely owing to the (invalid) perception of clinicians that lower doses retain full efficacy but with reduced side-effects.[74] In the light of the ATLAS study results,[38] this is a false perception. An additional problem is that of patient concordance, with estimates that elderly concordance with digoxin may be as low as 10%.[88] Since non-concordance directly affects treatment benefits and hospital readmission rates,[89] this is of particular concern in ACE inhibitor therapy in heart failure.[90]

Why do physicians underuse treatments in heart failure?

Prescribing factors

The underuse and underdosing of ACE inhibitors in heart failure may in part be owing to a lack of familiarity on the part of physicians with this drug class[91] and caution regarding known side-effects of this treatment.[92-94] However, the Euro-HF study revealed high primary care physician knowledge of the benefits of ACE inhibitors in heart failure.[84] Those side-effects of most concern to physicians are largely first-dose hypotension, renal failure, and cough.[11,84,88] However, clinical trial data show the incidence of first-dose hypotension is low and can be predicted by monitoring of systolic blood pressure. The risk can be further minimised by withholding diuretic administration several days prior to ACE inhibitor therapy, gradually titrating the ACE inhibitor dose up to an optimum level, and monitoring the patient for a short period after first dose. Only in cases of renal insufficiency is particular caution needed. It is, however, safe to prescribe ACE inhibitors in patients with a serum creatinine level less than 2.5 mg/dl, with close follow-up. In summary, if treatment is initiated as recommended, the incidence of such serious problems is low.[95]

Cough is another side-effect associated with ACE inhibitors that concerns physicians. Cough is most common in the elderly and in Asian patients[96] and may occur independent of ACE inhibitor dose.[38,97] Up to 20% to 30% of heart failure patients on long-term ACE inhibitor therapy can develop cough,[98] of whom half may need to be withdrawn from treatment. In many patients, cough has a delayed onset, with over 40% of patients not affected until at least six months.[99]

Cough is regarded as a class effect and is only rarely resolved with a change in ACE inhibitor.[100] However, before discontinuation, in light of the common occurrence of cough among placebo patients in the SOLVD study,[35] doctors should consider whether ACE inhibitor therapy or heart failure symptoms are the actual cause of cough. Patients need to consider whether the inconvenience outweighs the progression and mortality benefits of the ACE inhibitor, especially since spontaneous disappearance of cough is reported in over half of patients.[101]

Diagnostic issues leading to underprescribing

A final factor contributing to ACE inhibitor underuse may be diagnostic issues. Diagnoses of heart failure made in primary care are often not accurate,[102] especially in the absence of cardiographic evidence.[78] Physicians may suspect that a proportion of patients labelled with heart failure on clinical grounds will be suffering less morbid conditions, such as dependent oedema. Doctors may therefore be comfortable with prescribing a diuretic for symptoms but be unhappy with prescribing medication, perceived as more potent, for mortality benefits. This 'low-key' approach to heart failure management,[84] while a pragmatic necessity to most primary care physicians with limited or no access to appropriate diagnostic tests, is unacceptable. Since accurate diagnoses and better categorisation of patients is likely to improve prescribing in heart failure, widespread access to reliable echocardiography is essential.[77,84]

The disparity in ACE inhibitor prescribing between primary care physicians and specialists suggests that underuse of these agents requires further education in this therapeutic area. It appears on the evidence to date that primary care physicians especially tend to consider risk before benefit. Indeed, the Euro-HF study demonstrated that underuse of ACE inhibitors was not because primary care physicians were unaware of the evidence for ACE inhibitor treatment benefits. Increased use of ACE inhibitors has often coincided with the publication of large, convincing studies.[72] However, a lack of substantial studies demonstrating safety of ACE inhibitor therapy in primary care is at least partially responsible for 'fear of side-effects'.[103] Wider and improved dissemination of trial data through clinical guidelines, stressing prevention rather than treatment of symptoms, could provide at least a partial solution. A re-emphasis of the accumulated evidence that failure to administer ACE inhibitors (and now β-blockers) may expose the patient to an increased risk of recurrent heart failure or death is essential.

Conclusion

Recent guidelines are based upon the overwhelming evidence for treatment benefits in heart failure but recent surveys of practice in many fields show a low level of implementation. Responding to these data on underperformance requires positive action in a number of areas of physician practice. Enhanced access to diagnostic tests, especially echocardiography, is essential. However, there is an imperative that primary care physicians upgrade their perceptions as to the importance of heart failure. Not only should

they more actively suspect the disease in patients at most risk (post-myocardial infarction, hypertension, diabetes) but, once confirmed, the condition should be aggressively case managed. The aims of treatment are improving not just symptoms but also overall morbidity and mortality. In heart failure patients with left ventricular dysfunction, this treatment should include an ACE inhibitor, and at a high dose. If we re-interpret heart failure as a condition with analogous prognosis to a serious malignancy, then our management would be more urgent and more appropriate.

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Conflict of interests
FDRH is a member of the European Society of Cardiology Working Party on Heart Faliure and Board of the British Society of Heart Faliure. He has received support for travel and fees for talks at major symposia from companies that market cardiovascular products.

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