Angiotensin-Converting Enzyme Inhibitors: Do We Utilize Our Knowledge in Heart Failure Patients?

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Angiotensin-Converting Enzyme Inhibitors: Do We Utilize Our Knowledge in Heart Failure Patients?

O. Sleiman, J. Murin, W. Ghanem

Recently, the problem of heart failure (HF) has become a topic of great interest. The use of angiotensin-converting enzyme inhibitors (ACEIs) in HF patients is considered nowadays as one of the important and necessary steps towards an optimal treatment of these patients. Even though most of the big studies have proved the great beneficial effects of these agents they are still underused and not applied in the recommended doses for HF patients. We have studied the use of ACEIs among HF patients in the 1st Internal department of the University Hospital of Bratislava. We observed that in the period between January–September 1997, 70 % of HF patients admitted to the department were treated with ACEIs. Only in 17 % of patients was there an acceptable reason for withholding the treatment. In most of patients who used ACEIs low doses had been prescribed, and in only 4 % of them recommended doses have been given. Just in 15 % of these patients was there a convincing reason for underdosing these agents. It seems prudent to emphasize that ACEIs should be administered in recommended doses in all HF patients unless there is a contraindication to their use. J Clin Basic Cardiol 2001; 4: 279–83.

Key words: Heart failure, angiotensin-converting enzyme inhibitors, remodelling, mortality.

Needless to stress the fact that the development of agents which inhibit the activity of angiotensin-converting enzyme represents a very important advance in the treatment of heart failure (HF). Such agents can be considered as a revolution in the present treatment of HF and with the recent and current studies it seems that we do not overestimate their benefits when we say that every HF patient is a candidate for their use unless he or she has a real and convincing contraindication.

Now we have a wide range of ACE inhibitors (ACEIs) in practice, ranging from those which have to be used frequently in divided doses such as captopril, to those which can be used once daily such as ramipril, perindopril, and trandolapril. Others such as enalapril can be adjusted according to individual cases (usually bid). Some other agents are used in clinical practice such as fosinopril, lisinopril, quinapril, and others.

Mechanism of Action of ACEIs

We can understand the importance of ACEIs when we take a look at their mechanism of action. Here are some of their recognized influences:

1. One of their basic actions is the inhibition of angiotensin-converting enzyme, which leads to inhibition of angiotensin II (ANG II) production, and this in turn causes:
   a) Removal of the vasoconstrictor action of ANG II, producing vasodilatation.
   b) Decreasing the stimulation of production of aldosterone leading to a decline in the reabsorption of sodium in addition to the avoidance of the direct effect of ANG II on the reabsorption of sodium from renal tubules [1].
   c) Avoidance of antidiuretic hormone release secondary to the stimulatory action of ANG II, so less water trapping.
   d) Inhibition of ANG II remodeling action so less ventricular hypertrophy to be expected, less extension of myocardial infarction lesion, and a decrease in the amount of deposited collagen.
   e) Attenuation of the effect of ANG II on the release of norepinephrine from the presynaptic nerve endings so less sympathetic activity to be expected.

2. ACE is like kininase, so by using ACEI the kinins level is expected to increase leading to:
   a) A beneficial vasodilatoritory action, improvement in endothelial dysfunction, inhibition of atherosclerosis, and a better exercise tolerance [1].
   b) Prevention of progressive loss of myocardial cells through kinins mediated synthesis of enzyme constitutive nitric oxide synthase (cNOS). Such influence of ACEI on remodelling is stronger through this mechanism than through its decrease in the level of ANG II.
   c) Improvement in the diastolic function of ventricles, which was found to be associated with higher levels of plasma kinins.

3. ACEIs exert antioxidant and antiproliferative activities in addition to stimulation of fibrinolytic system and decreasing insulin resistance.

4. ACEIs are thought to restore parasympathetic tone which is usually depressed in HF.

So, from the above points we realize that ACEIs are ideal drugs for HF patients by decreasing preload and afterload on heart muscles (by causing vasodilatation and diuresis without being considered as direct vasodilators or diuretics), improving systolic and diastolic dysfunction resulting in improvement in ejection fraction (EF), modulating both sympathetic and parasympathetic activities, and lastly their long term benefit of decreasing cardiac remodelling and prevention of cardiac hypertrophy.

Clinical Studies Using ACEIs in HF Patients

The data and the results obtained from different studies made on ACEIs are so encouraging as to use them as basic agents in the treatment of heart failure patients.

The CONSENSUS Trial Study Group [2] published their results on the effects of enalapril on mortality in severe congestive HF in 1987, the patients were followed up for an average period of 188 days. The results showed 40 % reduction in mortality in these patients when compared with those who received placebo, but no difference was seen in the incidence of sudden cardiac death. Other positive results were that in
the enalapril group there was a significant improvement in NYHA classification together with a reduction in heart size and a reduced requirement for other medication for HF. It is interesting to notice that in only 17 cases enalapril was stopped in the enalapril group (which consisted of 127 patients) due to acceptable reasons (development of hypotension, increased serum creatinine level). The mean dose of enalapril used was 18.4 mg per day.

The SOLVD investigators enriched our information in the field of the use of ACEIs in HF by their results in 1991 showing the effects of enalapril on survival in patients with reduced left ventricular EFs and congestive HF (treatment arm of SOLVD). 1285 patients received doses of enalapril of 2.5 to 20 mg per day against 1284 patients who received placebo. They were followed up for an average period of 41.4 months. The results showed that there was a reduction in the risk of mortality by 16 % and a reduction in the risk of death or hospitalization for worsening HF by 26 % in the enalapril group compared with the placebo group advising to add this agent to the conventional therapy of HF patients [3].

This group of SOLVD investigators gave more valuable information when they directed their investigations towards the use of ACEIs in asymptomatic HF patients (preventive arm of SOLVD). The same ACEI (enalapril) was their tool. In a double-blind study the same as above doses of enalapril were used in 2111 patients and after a period of follow-up averaging 37.4 months the results were compared with the placebo group of 2117 patients. The outcome was 8 % reduction in the risk of death, a reduction of risk of death from cardiovascular causes by 12 %, 29 % reduction in the risk of development of obvious HF, and 20 % reduction in the risk of death or hospitalization for HF in the enalapril group compared with the placebo group [4].

Other information about the benefits of ACEIs came from the SAVE investigators [5], who published in 1992 a paper about the effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. In this study and within 3 to 16 days after myocardial infarction, 2231 patients with EF of 40 % or less but without overt HF or symptoms of myocardial ischaemia were randomly assigned to receive a double-blind treatment with either placebo (1116 patients) or captopril (1115 patients) and were followed up for an average of 42 months. The target dose of captopril was 50 mg three times daily. The results came to show that there was a reduction in mortality in the captopril group by 20 % as compared with the placebo group with a reduction in the incidence of fatal cardiovascular events by 21 % in the captopril group, 37 % for development of severe HF, 22 % for congestive HF requiring hospitalization, 25 % for recurrent myocardial infarction [5]. This study proved that long-term administration of captopril was associated with an improvement in survival and reduced morbidity and mortality due to major cardiovascular events in patients with asymptomatic left ventricular dysfunction.

The reduction of mortality rate by the use of ACEIs was also proved by the AIRE study [6] which used ramipril and showed a reduction of 27 % in mortality risk in patients with clinical signs of HF after myocardial infarction.

Trandolapril was the drug of interest of the TRACE Study Group in its published paper from Denmark in 1995. This study considered 1749 patients with ECHO evidence of left ventricular dysfunction (EF less or equal to 35 %) after myocardial infarction, they have been divided into two groups where one of them received trandolapril and the other received placebo [7]. The period of follow-up was 24 to 50 months after which the results showed a relative risk of death of 0.78 (22 % reduction) in the trandolapril group as compared with the placebo group. There was also a reduction in the risk of death from cardiovascular causes and sudden death in the trandolapril group (up to December 1995 this study was the first to show that ACEIs can reduce the risk of sudden death) but this study did not explain the mechanism of that reduction of sudden death. The progression to severe HF was less in the trandolapril group with a relative risk of 0.71 (29 % reduction), but in contrast the risk of recurrent myocardial infarction was not significantly reduced.

Ramipril again appeared in one study published at the beginning of the year 2000 by the Heart Outcomes Prevention Evaluation Study Investigators who studied the effects of ramipril on cardiovascular events in high-risk patients (with preserved systolic function) and showed a reduction in the rate of death from cardiovascular causes, decrease in the incidence of myocardial infarction, lower rates of cardiac arrest, and a lower incidence of HF [8].

The ability of ACEIs to reduce mortality has been confirmed using various ACEIs and was greater than those achieved with non-specific vasodilators [9]. Captopril, which is believed to have an anti-platelet activity, was also found to reduce the frequency of ventricular arrhythmias induced by experimental coronary reperfusion, in part because of the drug’s ability to decrease the outpouring of myocardial catecholamines that are responsible for the creation of arrhythmogenic state [1]. One paper was published in 1998 showing the significant benefits of ACEIs compared to other modalities of treatment, the results are shown in Table 1 [10]. A lot of trials were interested in assessing the effect of ACEIs on exercise capacity. Narang et al. [11] summarized that work as: 35 published, double-blind, randomized placebo-controlled trials, involving 3411 patients compared the effect of ACEIs and placebo on exercise capacity in patients with symptomatic chronic HF. Exercise duration improved in 23 of the trials with a noticed high concordance (82 %) between the effect on symptoms and exercise capacity in the majority of them. It was also stated in this review that exercise duration increased progressively on serial assessment, at least until 12 weeks but long term follow-up did not show the same positive results in two of the three trials that had a follow-up of greater than 11 months. Another point of interest was that of the four studies that compared dosing regimes, only one suggested that higher or more frequent doses were more effective.

These are some of the studies, which helped us to have an idea about the benefits of ACEIs. From these we can conclude that ACEIs, being used in patients with HF, can reduce

<p>| Table 1. Benefits of ACEI in the treatment of HF compared with other treatment modalities |</p>
<table>
<thead>
<tr>
<th>Treatment</th>
<th>Events prevented per 1000 patient-years of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuretics / β-blockers for HTN</td>
<td>1–2 strokes</td>
</tr>
<tr>
<td>Aspirin after MI</td>
<td>16 deaths / MIs / strokes</td>
</tr>
<tr>
<td>Oral β-blockers after MI</td>
<td>13 deaths / 15 Mls</td>
</tr>
<tr>
<td>HMG-CoA reductase inhib. after MI</td>
<td>6 deaths / 12 Mls / 4 HF / 11 revascularization</td>
</tr>
<tr>
<td>ACE after MI</td>
<td>12 deaths / 9 Mls / 16 HF / 10 revascularization</td>
</tr>
<tr>
<td>ACEI for severe HF</td>
<td>160 deaths</td>
</tr>
<tr>
<td>ACEI for mild / moderate HF</td>
<td>16 deaths / 3 Mls / 116 hospitalization</td>
</tr>
</tbody>
</table>
ACE Inhibitors in Heart Failure

J Clin Basic Cardiol 2001; 4: 281

Table 2. Recommended ACEI maintenance doses per day

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initiating dose</th>
<th>Maintenance dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Captopril</td>
<td>6.25 mg (3 × 1)</td>
<td>150 mg (50 mg × 3)</td>
</tr>
<tr>
<td>Enalapril</td>
<td>2.5 mg</td>
<td>20 mg (10 mg × 2)</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>2.5 mg</td>
<td>20–30 mg (OD)</td>
</tr>
<tr>
<td>Perindopril</td>
<td>2 mg</td>
<td>4 mg (OD)</td>
</tr>
<tr>
<td>Ramipril</td>
<td>1.25–2.5 mg</td>
<td>5–10 mg (OD, 5 mg × 2)</td>
</tr>
<tr>
<td>Trandolapril</td>
<td>0.5 mg</td>
<td>2–4 mg (OD, 2 mg × 2)</td>
</tr>
</tbody>
</table>

the mortality and morbidity even in asymptomatic cases, with the benefit being more marked in patients who are suffering from more advanced HF than milder ones, those who are on diuretic treatment, patients with anterior MI (ISIS-IV) [12], older patients (SAVE, AIRE, and GISSI-III [13]), in women (AIRE, GISSI-III), hypertensives (AIRE), diabetics, patients with elevated heart rate, and those with a previous MI. The benefit is also seen in patients with or without coronary artery disease, and in patients who are and are not receiving digoxin [2–4].

Keeping in mind that ACEIs are still one of the most cost-effective treatments available [14], there is no excuse for limiting their use by considering them to be a costly treatment.

It is interesting that the addition of angiotensin II blockers (AT1) to the basic standard treatment of HF (including ACEIs) brings up more benefits to these patients as was proved by the ValHeFT study [15]. In this study 5000 patients were included, the angiotensin II blocker (valsartan) when it was added to the standard treatment of HF patients, caused a significant reduction in hospitalisation rate, a significant reduction in cardiovascular events, improvement in NYHA class with a better compensation of HF, a better quality of life, some improvement in ejection fraction and a little increase in the incidence of side effects.

Who is a Candidate for Receiving an ACEI?

It was noticed that both volume expansion and deteriorated renal function independently attenuate the haemodynamic response to ACEIs [1]. Volume expansion should be corrected with diuretics in particular if oedema is present.

So, the patients with HF have to receive ACEIs as a long-term treatment even if a symptomatic improvement was not noticed early, this is because the benefit from ACEIs is mainly the favourable alteration of the natural history of HF which needs a long-term treatment with these agents.

It has to be mentioned here that a lot of patients who are at a high risk of side effects can benefit from long-term therapy with ACEIs. It has to be emphasized that patients with a mild increase in serum creatinine or a slight fall in systolic blood pressure after the first ACEI dose should not be denied receipt of these drugs at increasing doses (ATLAS study) [16].

When to Start Using an ACEI?

When the diagnosis of HF is made, an ACEI can be prescribed for long-term treatment.

A lot of research was made about the use of ACEIs in patients after myocardial infarction [17–19]. In one Italian study [17] the ACEI was given to patients within 24–36 hours of their infarctions where the 30-day mortality was reduced from 7.6 % to 7 %. Furthermore, the incidence of non-fatal congestive HF was also reduced by ACEIs from 15.2 % to 14.6 %, the survival benefit seen at six weeks was still present after four years. One very important finding was that more than 80 % of the lives saved in the early intervention trials were saved during the first week, indicating that unnecessary delay in initiating ACEI treatment should therefore be avoided [17], and this is in contrast to the previous impression of no clinically significant difference if the treatment with an ACEI is delayed to the day 3–16 after MI [18].

The later studies [18] in which the ACEI was administered early after MI as in GISSI-III [13] and ISIS-IV [12] or in those where it was administered late as SAVE, AIRE and TRACE showed a reduction in mortality and a reduction in the development of persistent HF, but in those where the ACEI was administered very early after MI as in CATS [20], CAPTIN [21], and CONSENSUS II there was a high incidence of hypotension and no survival benefit was observed.

So, in general it is recommended that for a greater benefit from the use of ACEIs they should be given within 24–36 hours of myocardial infarction after the administration of other recommended therapies, such as aspirin, beta-blockers and reperfusion therapy in order not to miss the period of the greatest rate of infarct expansion and risk of death, and at the same time to avoid the risk of hypotension which is associated with a worse prognosis if it is induced by an ACEI [18, 19]. The administration of an ACEI can be delayed in patients with continuing chest pain or haemodynamic instability.

Which ACEI to be Used?

No clinically important differences between the effectiveness of the various ACEIs have been reported although most evidence is derived from randomised trials of enalapril [14]. So if the diagnosis of chronic HF has already been made, any ACEI preparation can be administered. However, if an ACEI is indicated after an acute MI it is prudent to follow the recommendations of the SAVE (captopril), AIRE (ramipril) and TRACE (trandolapril) trials. Moreover, the findings of the PRACTICAL study suggest that enalapril may be superior to captopril in this setting [22].

Recommended Doses of ACEIs in HF

Treatment with ACEIs is started with small doses that are rapidly increased to reach therapeutic doses within 1–4 weeks.

Recommended dosage should be attempted in all patients to achieve the maximum benefit from these drugs. Importantly, one double-blind study has shown that suboptimal dosages of enalapril (5 mg bid) may result in less clinical benefit than high dosages [23, 24]. Subsequently, the findings from the ATLAS trial confirmed that a suboptimal dose of lisinopril (5 mg OD) does not prevent progression of the disease (by hospitalisation rate) to the same extent as a high lisinopril dose (35 mg OD). It was recently shown in a data base study that in patients listed for heart transplantation the use of high ACEI dosages predicts survival [25].

However NETWORK study [26] did not prove that, and showed that increasing the enalapril dose from 2.5mg bid to 10mg bid did not result in better clinical outcome in patients with HF (this could be due to the short period of follow up).

Table 2 shows recommended doses of some ACEIs [27].

Here we have to stress an interesting point related to the treatment with ACEIs, which is the concomitant use of aspirin with these agents, because it has been proved in large multicenter trials that this combination was associated with a loss of the survival benefits of captopril and enalapril and caused marked attenuation of the benefits of these drugs on cardiovascular morbidity [1].
The preliminary results of the WASH study comparing the effect of aspirin 300 mg/day, warfarin (INR 2.5) or no antithrombotic in patients with left ventricular systolic dysfunction showed that mortality was higher in the aspirin group (30 %) compared to warfarin group (25 %) and no-antithrombotic-therapy group (21 %) [28]. However the trend to less benefit from ACEIs in those taking aspirin was not significant in AIRE, even greater benefit was noticed from this combination in SAVE. Very recently a paper appeared, which did not find evidence of interaction between ACEIs and low-dose aspirin (160 mg/d and 75 mg/d) in patients with reduced left ventricular function after acute myocardial infarction [29].

These data together with the lack of data supporting the use of aspirin suggest that physicians should reevaluate the use of aspirin in all patients who are receiving ACEIs, until the time when some studies guide us to the dose of aspirin which could be used concomitantly with ACEIs without attenuating their maximum benefits. It is possible to use only a low aspirin dose (75–160 mg/d) or to use other anti-aggregant drugs instead of aspirin in HF patients, such as ticlopidin. In routine clinical practice we usually neglect the “negative” influence of aspirin on ACE inhibitor’s action.

Due to the great valuable benefits of ACEIs, guidelines for the initiation of ACEI therapy in primary care of congestive HF were made in 1999 as it is shown in Table 3 [30].

The procedures for starting an ACEI recommended by the European Society of Cardiology are shown in Table 4 [27].

**Side Effects of ACEIs in HF**

In general the side effects of ACEIs can be divided into two main groups:

**A. Side effects related to the decrease in the production of ANG II**

1. Hypotension: a decrease in blood pressure is seen in nearly every patient but a significant hypotension which requires our attention is that which is associated with dizziness, blurred vision, or syncope. Such a deterioration of blood pressure, if it happens, is most likely to take place in the first 24 hours of therapy, and this is more to be expected in those patients with marked hyponatraemia or those of a recent rapid diuresis [1]. To avoid such complications it seems prudent to start the ACEI in low doses (as 6.25 mg in case of captopril), or in certain cases to withhold diuretic treatment for 1–2 days. It was found that even with symptomatic hypotension, which could affect certain patients they are still candidates for long-term treatment with ACEIs if appropriate measures are taken to prevent or minimize hypotensive reactions.

2. Functional renal insufficiency: this is explained by the fact that renal perfusion in some patients is maintained by the effect of ANG II on efferent arterioles where it produces vasoconstriction and elevation of intraglomerular pressure. Such action can be abolished by using an ACEI resulting in azotemia. This adverse reaction can be seen in 25–50 % of HF patients within NYHA class IV, and in about 5–15 % of class II–III but in general, increases in serum creatinine are small even in severe HF (up to 10–15 %), as are changes in serum potassium.

3. Hyperkalaemia: this side effect may happen with the use of ACEI especially if the patient is taking potassium supplement or he is on potassium sparing diuretics, with the risk being greater in diabetics.

**B. Side effects related to kinin accumulation:**

1. Cough: nonproductive cough may occur in about 5–25 % of patients treated with ACEIs and disappears within 1–2 weeks of withdrawal. It has been noticed that most of cough episodes during the treatment with ACEIs are due to reasons other than the use of ACEI itself, so before the withdrawal of the ACEI one has to exclude other causes of cough. In case of persistant cough due to the ACEI use, an angiotensin II receptor inhibitor (AT1 receptor) can be an alternative.

2. Angioneurotic edema: occurs in about 1 % of patients receiving an ACEI with a greater incidence in blacks. This side effect is potentially life-threatening and necessitates the permanent withdrawal of any ACEI.

**C. Other side effects**

Including rash and dysgeusia seen in about 5 % of patients, such adverse effects may disappear while continuing the drug administration. Very rare side effects including proteinuria and leukopenia may occur in certain patients ailing from other diseases such as, for example, collagen disorders [1].

Even with the stress on the extensive use of ACEIs, it was shown in certain studies that only 30 % of HF patients received ACEIs [14], and notably the doses lower than those shown to be effective in clinical trials [31]. Other studies in the U.K. showed that approximately 58–81 % of eligible hospitalized patients receive ACEIs. The doses used were only 25–50 % of target doses used in clinical studies [31].

In our department (1st Internal Department) at the University Hospital of Bratislava, we studied the use of ACEIs among our heart failure patients. We found that 100 heart failure patients were admitted to the department in the period between January and September 1997. 70 % of them (70 patients) were treated with ACEIs. Only in about 17 % (5 patients) of those who were not on ACEI therapy was there an acceptable reason for withholding the treatment. This reason was one of the following reasons: development of hypotension in (40 %; 2 patients), deterioration in renal function (40 %;

| **Table 4. Recommended procedures for starting an ACEI** |
| 1. Avoid excessive diuresis before treatment. Stop diuretics for 24 h |
| 2. Better start treatment in the evening when supine; if started in the morning check BP for several hours |
| 3. Start with low doses and build up to reach effective doses of large trials |
| 4. Monitor renal function tests during drug titration every 3 months and subsequently at 6-monthly intervals, if renal function deteriorates beyond a threshold of 3 mg/100 mg serum creatinine interrupt ACEI treatment for symptomatic measures and diagnostic procedures (renal artery stenosis) |
| 5. Avoid potassium-sparing diuretics during initation of therapy. Hyperkalaemia (threshold 5.5 mEq/l) is a contraindication to their use |
| 6. Avoid NSAIDs |
| 7. Check BP 1–2 weeks after each dose increment |

**Table 3. The “five Ms” for the initiation of ACEI therapy**

| 1. Maximum tolerable doses of ACEI |
| 2. Manage concomitant diuretic treatment |
| 3. Monitor renal function |
| 4. Minimise co-prescribing (particularly of NSAIDs) |
| 5. May take several months for apparent improvement |
Table 5. ACEIs used in our department and their doses per day

<table>
<thead>
<tr>
<th>ACEI used</th>
<th>Number of pts.</th>
<th>Average dose per day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Captopril</td>
<td>4</td>
<td>44 mg</td>
</tr>
<tr>
<td>Enalapril</td>
<td>29</td>
<td>8.5 mg</td>
</tr>
<tr>
<td>Perindopril</td>
<td>2</td>
<td>2 mg</td>
</tr>
<tr>
<td>Ramipril</td>
<td>31</td>
<td>2 mg</td>
</tr>
<tr>
<td>Trandolapril</td>
<td>4</td>
<td>1.5 mg</td>
</tr>
</tbody>
</table>

2 patients; serum creatinine did not reach a level of 3 mg/100 ml and no case of acute renal failure necessitating dialysis was recorded), or cough (20 %; 1 patient). When cough appeared as a side effect of the use of ACEIs, no (AT1) receptor inhibitor replaced them.

The use of low doses of ACEIs was the rule in our department as shown in Table 5. We found that only 4 % (4 patients) were put on recommended doses of ACEIs for heart failure patients, and only in 15 % (15 patients) was there a convincing reason for underdosing these agents. The development of renal deterioration was noticed in 9 patients whereas 6 patients developed hypotension.

There are some explanations for the failure of physicians to prescribe these agents optimally such as: failure to recognize that HF is an important public health problem worthy of treatment, failure to appreciate fully the magnitude of the clinical benefits of ACEIs in HF, failure to understand that the clinical benefits of ACEIs fully justify the cost of these drugs, concern that the adverse effects of ACEIs outweigh their clinical benefits, and the belief that the benefits observed in clinical trials do not translate into clinical practice [10].

Finally we hope that with the increased stress on the benefits of ACEIs in the course of life of heart failure patients, they will be used more frequently and in the recommended doses to achieve the maximum benefits.

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