Treatment with LCZ696 is likely to change first-line treatment of heart failure

LCZ696 – a promising new compound in heart failure treatment

Roger Hullin

Service de Cardiologie, CHUV, Lausanne, Switzerland

Summary

LCZ696 is an angiotensin receptor neprilysin inhibitor (ARNI) composed of the angiotensin receptor inhibitor valsartan and the neprilysin inhibitor AHU377. This compound molecule has proven efficiency in mild to moderate arterial hypertension and in heart failure patients with preserved ejection fraction, and has been shown to be superior to enalapril treatment in patients presenting with moderate to severe heart failure due to reduced left ventricular ejection fraction. The present overview will summarise pathophysiological and pharmacological aspects of this compound molecule, discuss results from clinical studies, and provide an outlook on the future role of this molecule in heart failure treatment.

Key words: LCZ696; chronic heart failure

Current treatment of heart failure with reduced ejection fraction

This section summarises current concepts of medical treatment in heart failure with reduced ejection fraction and provides the basis for discussion of the role of LCZ696.

The modern history of therapy for heart failure with reduced ejection fraction began in 1986 when the V-HeFT trial showed the favourable effect of vasodilation treatment [1]. In the following years, the CONSENSUS (1987) and SOLVD-treatment (1991) trials established the beneficial effect of angiotensin-converting enzyme (ACE) inhibition by enalapril by showing that this molecule reduces the absolute risk for mortality by 14.6% in severe heart failure and 4.5% in mild to moderate heart failure (number of patients needed to treat [NNT] to save one life 7 and 22, respectively) [2, 3]. In 1992, the SOLVD-prevention trial extended the benefit of enalapril treatment to asymptomatic patients with reduced left ventricular ejection fraction by evidencing a reduced rate for heart-failure-associated hospitalisation [4].

Angiotensin receptor blockers (ARBs) provide an alternative strategy for vasodilation in heart failure (fig. 1). These molecules interfere with the binding of angiotensin II at its type 1 receptor, whereas ACE inhibitors block conversion of angiotensin I to angiotensin II (see fig. 1). So far, ARBs remain recommended as alternative therapy in patients intolerant of an ACE inhibitor [5]. However, noninferiority of ARBs to ACE inhibition is apparent only with high-dose treatment [6]. Until the advent of the results of the EMPHASIS-HF trial, ARBs were considered to be the recommended first-choice add-on therapy in patients with heart failure and a left ventricular ejection fraction (EF) ≤40% and who remained symptomatic despite optimal treatment with an ACE inhibitor and beta-blocker. In the EMPHASIS-HF trial, however [7], eplerenone led to a larger reduction in the morbidity and mortality endpoint than was seen in the ARB "add-on" trials CHARM Added and Val-HeFT [8, 9]. Furthermore, mineralocorticoid-receptor antagonist (MRA) treatment reduced all-cause mortality both in EMPHASIS-HF (NNT: 51) and in the Randomized Aldactone Evaluation Study (RALES) (NNT for 2 years: 9) whereas ARB "add-on" treatment does not [4].

The other cornerstone of treatment in heart failure with reduced ejection fraction is down-regulation of increased sympathetic nervous system activity. Three key trials [10–12] randomised nearly 9,000 patients with mildly to severely symptomatic heart failure to placebo or beta-blocker treatment (bisoprolol, carvedilol, or metoprolol succinate CR/XL). Each of these three trials showed that, within 1 year of treatment start beta-blocker therapy reduces both mortality (NNT to save 1 life: 14–23) and the rate of heart failure hospitalisation when added to conventional therapy including ACE inhibition in >90% of the study patients. In addition, beta-blocker treatment improves self-reported patient well-being as shown in the MERIT-HF [13].

Natriuretic peptides and the renin-angiotensin system

Atrial and B-type natriuretic peptides (ANP, BNP) are hormones that play an important role in fluid homeostasis. Both peptides are secreted in response to an increase in wall tension, with ANP predominantly

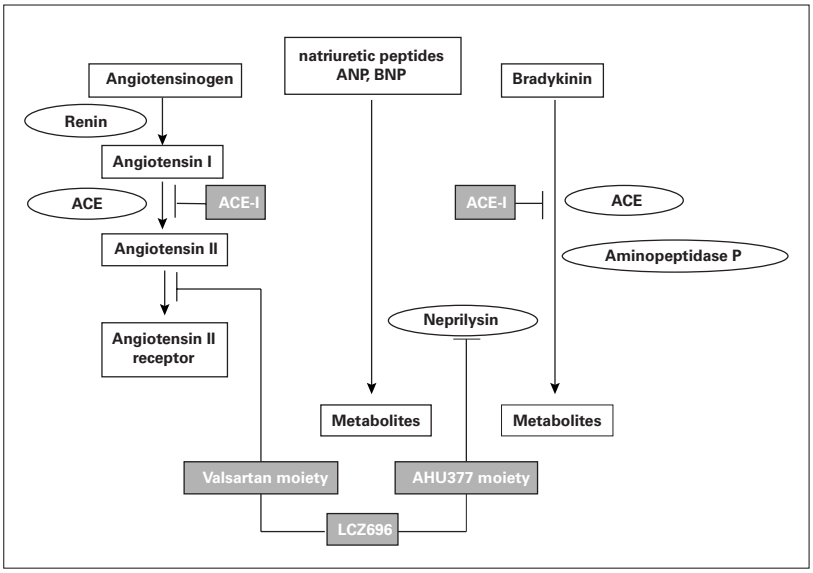

Figure 1: Mechanism of action LCZ696 on the renin-angiotensin system and natriuretic peptides. Adapted from Waeber B, Feihl F. Lancet. 2010;375:1228–9.
ACE = angiotensin-converting enzyme; ACE-I = ACE inhibitor; ANP = atrial natriuretic peptide; BNP = B-type natriuretic peptide.

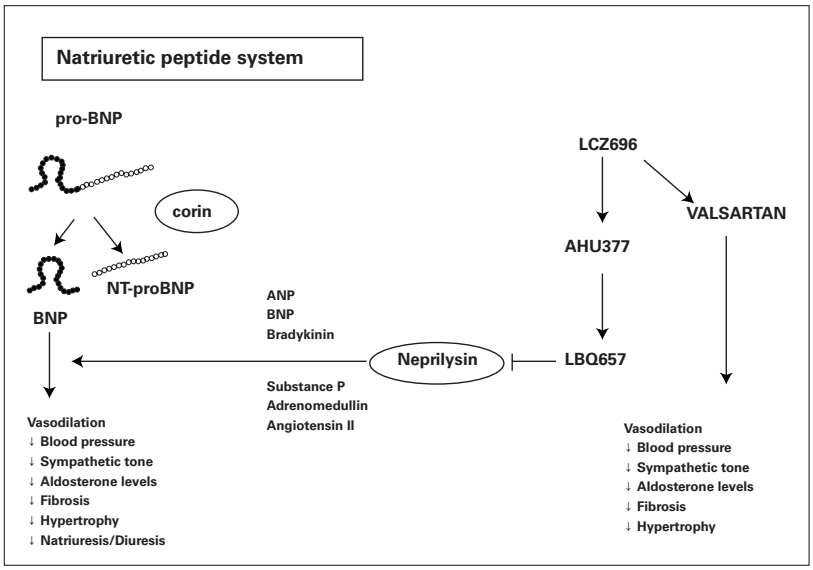

Figure 2: Pharmacological action and mechanisms of action of the AHU377 moiety of the ARNI LCZ696.
ARNI = angiotensin receptor neprilysin inhibitor; BNP = B-type natriuretic peptide; NT-proBNP = N-terminal of proBNP; proBNP = BNP prohormone.

synthesised and secreted in the atria whereas BNP is released from the ventricles. Both natriuretic peptides promote natriuresis and diuresis, induce vasodilation, and oppose acute effects of volume overload by inhibition of the renin-angiotensin-aldosterone system and the sympathetic nervous system (fig. 2). Because of these effects, the natriuretic peptide system has been a target of potential therapeutic strategy in heart failure. Since results from trials investigating the effect of exogenous administration of natriuretic peptides in heart failure are inconsistent, pharmacological inhibition of natriuretic peptide degradation has been a focus of clinical research in recent years.

Neprilysin is a neutral endopeptidase that catalyses the degradation of ANP and BNP. The AHU377 moiety of LCZ696 targets neprilysin and interferes with the catalytic breakdown of ANP and BNP. However, inhibition of neprilysin will not only augment the naturally occurring natriuretic peptides but also increase the levels of circulating bradykinin, substance P, adrenomedullin, endothelin and angiotensin II. The latter is a potent vasoconstrictor which provides the rationale for a compound molecule with dual action, on neprilysin as well as the renin-angiotensin system. In any case, neprilysin plays no role in the breakdown of the N-terminal of BNP prohormone (NT-proBNP), therefore NT-proBNP levels remain representative for the amount of secreted pro-BNP (fig. 2).

Omapatrilat was the first molecule simultaneously acting both on the renin-angiotensin and the natriuretic peptide system by blocking enzymatic activity of the angiotensin-converting enzyme and of the vasopeptidases neprilysin and aminopeptidase. This compound drug made it into clinical trials because of superior effects in experimental studies to either approach alone [14, 15]. Beneficial effects were present in patients with hypertension [16], and in initial studies in patients with heart failure [17]. However, an outcomes trial comparing omapatrilat 40 mg with enalapril 10 mg twice per day did not demonstrate benefit from omapatrilat in reducing the combined risk of death or hospitalisation in patients with moderate to severe heart failure [18]. In addition, the 0.8% incidence of angioedema in the heart failure outcome trial prompted withdrawal of omapatrilat from regulatory consideration. In fact, all three enzymes targeted by omapatrilat are involved in the inactivation of bradykinin, which is considered as the predominant mediator of angioedema [19].

LCZ696 is the first molecule of new class of compound molecules blocking simultaneously the renin–angiotensin system via its ARB (valsartan) moiety and slowing the degradation of natriuretic peptides via its AHU377 moiety that interferes with the vasopeptidase neprilysin. Because of this dual action this new class of pharmacological agents is called angiotensin receptor neprilysin inhibitors (ARNIs). After ingestion, LCZ696 is broken into two components, the neprilysin prodrug AHU377 and valsartan (fig. 2), and AHU377 is subsequently metabo-

lised to the active neprilysin inhibitor LBQ657. With respect to pharmacokinetics, the plasma half-life of the valsartan moiety averages at 17.5 h. AHU377 has an average plasma half-life of 1.7 h owing to its rapid conversion into the active metabolite LBQ657 (fig. 2), which explains the rapid onset of biological activity of LCZ696.

Clinical studies with LCZ696

Mild to moderate arterial hypertension

In mild to moderate hypertension, LCZ696 with its dual action leads to more efficient lowering of diastolic blood pressure in patients with mild to moderate arterial hypertension when compared with an equivalent dose of valsartan [20]. The average reduction in mean sitting diastolic blood pressure was –2.97 mm Hg (p = 0.0023) for 200 mg LCZ696 versus 160 mg valsartan, and –2.7 mm Hg (p = 0.0055) for 400 mg LCZ696 versus 320 mg valsartan. LCZ696 was well tolerated in this study and no cases of angioedema were reported; only three serious adverse events occurred during the 8-week treatment period, of which none was related to the study drug, and no patients died.

PARAMOUNT

PARAMOUNT was a phase II, randomised, parallel-group, double-blind multicentre trial in heart failure patients with preserved left ventricular ejection fraction (≥45%), in New York Heart Association (NYHA) class II–III and with a NT-proBNP concentration of >400 pg/ml [21]. Participants were randomly assigned (1:1) to LCZ696 titrated to 200 mg twice daily or valsartan titrated to 160 mg twice daily; treatment duration was 36 weeks. The primary endpoint was change in left ventricular wall stress measured as NT-proBNP level at baseline and 12 weeks. NT-proBNP was significantly reduced at 12 weeks in the LCZ696 group compared with the valsartan group. After 36 weeks of treatment, there was likewise a significant reduction in the left atrial volume (p = 0.003) and in left atrial dimension (p = 0.034) in the LCZ696 group, with the most apparent reduction present in patients without atrial fibrillation at baseline. LCZ696 was well tolerated with adverse effects similar to those of valsartan; 22 patients (15%) on LCZ696 and 30 (20%) on valsartan (p = 0.14) had one or more serious adverse events. Whether the reduction in left ventricular wall stress and the structural changes translate into improved outcomes will be tested prospectively in the PARAGON study, which is starting enrolment in autumn 2014.

PARADIGM-HF

In this double-blind trial, 8,442 patients in class II–IV heart failure with a left ventricular ejection fraction ≤40% were randomised to receive either LCZ696 (at a dose of 200 mg twice daily) or enalapril (at a dose of 10 mg twice daily), in addition to standard therapy. The primary outcome was a composite of death from cardiovascular causes or hospitalisation for heart failure. Moreover, the trial was powered to detect a difference in the rates of cardiovascular death. After a median follow-up of 27 months the trial was stopped prematurely because of an overwhelming benefit with LCZ696. At the time of study closure, the primary outcome had occurred in 914 patients (21.8%) in the LCZ696 group and 1,117 patients (26.5%) in the enalapril group (hazard ratio [HR] in the LCZ696 group 0.80; p <0.001) corresponding to a 20% reduction in the primary endpoint in the LCZ696 treatment group. All-cause mortality was observed in 711 patients (17.0%) receiving LCZ696 and 835 patients (19.8%) receiving enalapril (p <0.001); of these patients, 558 (13.3%) and 693 (16.5%), respectively, died from cardiovascular causes (HR 0.80; p <0.001) corresponding to a 20% reduction in the rate of cardiovascular death in the LCZ696 treatment group. As compared with enalapril, LCZ696 also reduced the risk of hospitalisation for heart failure by 21% (p <0.001); likewise, the symptoms and physical limitations of heart failure were decreased (p = 0.001).

Patients in the LCZ696 group had higher proportions of events with hypotension; however, the total number of patients discontinuing the study drug was higher in the enalapril group (table 1). Lower proportions of patients in the LCZ696 treatment group presented with renal impairment, hyperkalaemia, and cough (table 1) [22]. The incidence of angioedema was not significantly increased in patients with LCZ696 treatment (LCZ696 vs enalapril: 19 vs 10 cases; 0.45 vs 0.24%). Overall, the incidence of angioedema reported for the enalapril treatment group in the PARADIGM-HF study compares to the incidence of 0.5 and 0.3% observed in the OVERTURE study [18] and ONTARGET [23], respectively. This suggests that the study population of the PARADIGM-HF study is representative with respect to the risk of angioedema, whereas the higher proportion of patients with cough, hypotension, renal impairment is compatible with characteristics of a heart failure population (table 1).

Table 1: Adverse events during randomized treatment comparing study groups from the ONTARGET and the PARADIGM-HF trial.

	ONTARGET	ONTARGET	PARADIGM-HF	PARADIGM-HF
	Ramipril	Telmisartan	LCZ696	Enalapril
	(n = 8,576)	(n = 8,542)	(n = 4,187)	(n = 4,212)
Variable				
Discontinuation (n, %)	2,099 (24.5%)	1,962 (23%)	977 (23.3%)	1,094 (26%)
Hypotension (n, %)	149 (1.7%)	229 (2.7%)	700 (16.7%)	447 (10.6%)
Cough (n, %)	360 (4.2%)	93 (1.1%)	474 (11.3%)	601 (14.3%)
Angioedema (n, %)	25 (0.3%)	10 (0.1%)	19 (0.4%)	10 (0.3%)
Hyperkalaemia (n, %)	283 (3.2%)	287 (3.4%)	855 (20.4%)	960 (22.9%)

Future role of LCZ696

In the PARADIGM-HF trial, the mean (± standard deviation) doses in the LCZ696 and enalapril groups were 375 ± 71 mg and 18.9 ± 3.4 mg, respectively, with the latter dose being above the dose shown to reduce mortality in severe and mild to moderate heart failure (16.6 mg and 18.4 mg, respectively, for CONSENSUS, and SOLVD). LCZ696 was superior to enalapril in reducing the primary endpoint and the secondary endpoint of cardiovascular death; therefore, LCZ696 has the potential to replace ACE inhibitor treatment as first-line treatment in heart failure, all the more so as many patients with heart failure receive low (and potentially subtherapeutic) doses of ACE inhibitors and ARBs [24].

Prespecified subgroup analysis in the PARADIGM-HF showed a nominally significant interaction between NYHA class at randomisation and the effect on the primary endpoint (p = 0.03). However, no such interaction was observed between NYHA class and the secondary endpoint death from cardiovascular cause (p = 0.76). Separation of NYHA classes into patients with NYHA I/II and III/IV, suggests favourable interaction of LCZ696 with NYHA class I/II patients for the primary and secondary endpoint, whereas no interaction was obvious for patients in NYHA class III and IV. The absence of a significant interaction of LCZ696 with severe heart failure resembles results from clinical trials in which exogenous natriuretic peptides were administered [25] and requires further investigation. There was also no interaction between enalapril treatment and NYHA class III and IV with respect to the primary endpoint and cardiovascular death, despite of a strong and consistent interaction of this ACE inhibitor with mortality in the CONSENSUS trial and many other ACE inhibitor trials performed in patients with heart failure [26]. It remains to be shown whether this observation is due to contemporary heart failure treatment with a beta-blocker (≥92.9%) and treatment with mineralcorticoid receptor antagonist (≥54%).

It is important to note that a total 12% of patients did not complete the run-in period because of adverse events (most frequently cough, hyperkalaemia, renal dysfunction or hypotension). Overall, the incidence of adverse events was higher for patients receiving enalapril than for those receiving LCZ696 (table 1). Altogether, the safety profile suggests that LCZ696 administration should be applicable to a broad spectrum of patients with heart failure, including those who are currently taking an ACE inhibitor or ARB, or who are likely to be able to take such an agent without having unaccepted side effects.

Conclusion

Heart failure affects nearly 150,000 individuals in Switzerland, and its prevalence is increasing progressively owing to an aging population. Current heart failure treatment has already achieved large improvement in the reduction of morbidity and mortality. Based on the results of the PARADIGM-HF study, treatment with LCZ696 is likely to change first-line treatment of heart failure because of significant improvement of survival and reduced rehospitalisation rates. Nevertheless, even in the intervention arm of PARADIGM-HF, the mortality rate among patients with heart failure remains about 20% over 2 years, highlighting the reality that this newest entry hardly concludes the compelling story of heart-failure treatment.

Correspondence:
Roger Hullin,
M.D. Ph.D. eMBA FH
Head Division of Severe Heart Failure and Heart Transplantation
Service de Cardiologie
Rue du Bugnon 46
1011 Lausanne
Switzerland
Roger.Hullin[at]chuv.ch

Disclosures
The author receives financial support from Swiss National Fund (320030–147121/1), Swiss Heart Foundation, Swiss Transplant Cohort Study, the Fondation Muschamps, and NOVARTIS for a clinical research project.

References
The full reference list is available in the on-line version of this article.

References

1 Cohn JN, Archibald DG, Ziesche S, Franciosa JA, Harston WE, Tristani FE, et al. Effect of vasodilator therapy on mortality in congestive heart failure. Results of a veterans administration cooperative study. N Engl J Med. 1986;314:1547–52.
2 The CONSENSUS Trial Study Group. Effects of enalapril on mortality in se- vere congestive HF: results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). N Engl J Med. 1987;316:1429–35.
3 The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive HF. N Engl J Med. 1991;325:293–302.
4 McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Boehm M, Dickstein K, et al. The Task Force for the Diagnosis and Treatment of Acute and Chronic HF 2012 of the European Society of Cardiology. Developed in collaboration with the HF Association (HFA) of the ESC. Eur Heart J. 2012; 33:1787–1847.
5 Maggioni AP, Anand I, Gottlieb SO, Latini R, Tognoni G, Cohn JN. Effects of valsartan on morbidity and mortality in patients with HF not receiving angiotensin-converting enzyme inhibitors. J Am Coll Cardiol. 2002;40:1414–21.
6 Konstam MA, Neaton JD, Dickstein K, Drexler H, Komajda M, Martinez FA, et al. Effects of high- dose versus low-dose losartan on clinical outcomes in patients with HF (HEAAL study): a randomised, double-blind trial. Lancet. 2009; 74:1840–8.
7 Zannad F, McMurray JJ, Krum H, van Veldhuisen DJ, Swedberg K, Shi H, for the EMPHASIS-HF Study Group. Eplerenone in Patients with Systolic Heart Failure and Mild Symptoms. N Engl J Med. 2011;364:11–21.
8 Cohn JN, Tognoni G. A randomized trial of the angiotensin-receptor blocker valsartan in heart failure. N Engl J Med. 2001; 5:293–301.
9 McMurray JJ, Ostergren J, Swedberg K, Granger CB, Held P, Michelson EL; CHARM Investigators and Committees. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial. Lancet. 2003 Sep 6;362:767–71.
10 The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomized trial. Lancet. 1999;353:9–13.
11 Packer M, Coats AJ, Fowler MB, Katus HA, Krum H, Mohacsi P, et al. Effect of carvedilol on survival in severe chronic HF. N Engl J Med. 2001;344: 1651–8.
12 Effect of metoprolol CR/XL in chronic HF: Metoprolol CR/XL Rando- mised Intervention Trial in Congestive HF (MERIT-HF). Lancet. 1999;353:2001–7.
13 Hjalmarson A, Goldstein S, Fagerberg B, Wedel H, Waagstein F, Kjekshus J, et al. Effects of controlled-release metoprolol on total mortality, hospitalizations, and well-being in patients with HF: the Metoprolol CR/XL Randomized Intervention Trial in congestive HF (MERIT-HF). MERIT-HF Study Group. JAMA 2000;283:1295–302.
14 Rademaker MT, Charles CJ, Espiner EA, Nicholls MG, Richards AM, Kosoglou T. Combined neutral endopeptidase and angiotensin-converting enzyme inhibition in HF: role of natriuretic peptides and angiotensin II. J Cardiovasc Pharmacol. 1998;31:116–25.
15 Trippodo NC, Fox M, Monticello TM, Panchal BC, Asaad MM. Vasopeptidase inhibition with omapatrilat improves car- diac geometry and survival in cardiomyopathic hamsters more than does ACE inhibition with captopril. J Cardiovasc Pharmacol. 1999;34:782–90.
16 Campese VM, Lasseter KC, Ferrario CM, et al. Omapatrilat versus lisinopril: efficacy and neurohormonal profile in salt-sensitive hypertensive patients. Hypertension. 2001;38:1342–8.
17 Rouleau JL, Pfeffer MA, Stewart DJ, et al. Comparison of vasopeptidase inhibitor, omapatrilat, and lisinopril on exercise tolerance and morbidity in patients with HF: IMPRESS randomised trial. Lancet. 2000;356:615–20.
18 Packer M, Califf RM, Konstam MA, Krum H, McMurray JJ, Rouleau JL, et al. Comparison of omapatrilat and enalapril in patients with chronic HF: the Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events (OVERTURE). Circulation. 2002;106:920–6.
19 Fryer RM, Segreti J, Banfor PN, Widomski DL, Backes BJ, Lin CW, et al. Effect of bradykinin metabolism inhibitors on evoked hypotension in rats: rank efficacy of enzymes associated with bradykinin-mediated angioedema. Br J Pharmacol. 2008;153:947–55.
20 Ruilope LM, Dukat A, Böhm M, Lacourcière Y, Gong J, Lefkowitz MP. Blood-pressure reduction with LCZ696, a novel dual-acting inhibitor of the angiotensin II receptor and neprilysin:
a randomised, double-blind, placebo-controlled, active comparator study. Lancet. 2010;375:1255–66.
21 Solomon SD, Zile M, Pieske B, Voors A, Shah A, Kraigher-Krainer E, et al. for the Prospective comparison of ARNI with ARB on Management of heart failure with preserved ejection fraction (PARAMOUNT) Investigators. Lancet. 2012;380:1387–95.
22 McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, for the PARADIGM-HF Investigators and Committees. Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure. N Engl J Med. 2014 Sep 11;371(11):993-1004. DOI: 10.1056/NEJMoa1409077.
23 The ONTARGET investigators. Telmisartan, ramipril, or both in patients at high risk for cardiovascular events. N Engl J Med. 2008;358:1547–59.
24 Maggioni AP, Anker SD, Dahlström U, Filippatos G, Ponikowski P, Zannad F, et al. Are hospitalized or ambulatory patients with HF treated in accordance with European Society of Cardiology guidelines? Evidence from 12,440 patients of the ESC HF Long-Term Registry. Eur J Heart Fail. 2013;15:1173–84.
25 Colucci WS, Elkayam U, Horton DP, Abraham WT, Bourge RC, Johnson AD, et al. intravenous nesiritide, a natriuretic peptide, in the treatment of decompensated congestive heart failure. N Engl J Heart Fail. 2000;343:246–53.
26 Garg R, Yusuf S, for the Collaborative group on ACE inhibitor trials. Overview of randomized trials on angiotensin converting enzyme inhibitors on mortality and morbidity in patients with heart failure. JAMA. 1995;273:1450–6.