



Přehledový článek | Review article

Heart failure and inhibition of renin–angiotensin–aldosterone system

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Sacubitril/valsartan (LCZ696)

SOUHRN

Podán historický přehled mortalitních studií s inhibicí systému renin-angiotensin-aldosteron u nemocných s chronickým srdečním selháním. Od studie CONSENSUS po studii PARADIGM-HF je ukázáno, že zlatým standardem léčby jsou inhibitory angiotensin konvertujícího enzymu (ACE) / blokátory receptorů AT₁ pro angiotensin II – sartany, spolu s blokátory mineralokortikoidních receptorů. Přímý blokátor reninu aliskiren a duální blokátor enalapril s inhibicí neprilysinu se ukázaly neúčinnými, na druhé straně nový duální inhibitor receptoru AT₁ + inhibitor neprilysinu – sacubitril/valsartan – je novým léčebným přípravkem pro budoucnost léčby chronického srdečního selhání.

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ABSTRACT

A historical survey is presented of mortality clinical trials focussed on the inhibition of the renin–angiotensin–aldosterone system on different levels in patients with chronic heart failure. The first study, CONSENSUS, was published in 1987 and showed that the ACE-inhibitor enalapril clearly reduced mortality in severe heart failure compared with placebo. This was followed by studies with beta blockers, angiotensin II type 1 receptor blockers, blockers of mineralocorticoid receptors, and direct renin inhibitors.

A recent study, PARADIGM, comparing dual inhibitor of neprilysin and angiotensin II receptor (LCZ696) with enalapril, was terminated prematurely for a significant effect of inhibiting neprilysin and valsartan.

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Inhibition of the renin–angiotensin–aldosterone system (RAAS) has a firm place in the treatment of chronic heart failure (CHF) [1]. However, let us look at the inhibition of renin–angiotensin–aldosterone system in patients with heart failure as the time went on. We considered only large, mortality, randomized, double-blind trials that have been published in prestigious medical journals. We are not commenting the trials after myocardial infarction with reduced ejection fraction, the trials that have not monitored mortality or the trials that had only substitutive end-points – hemodynamic, echocardiographic and laboratory indicators. For the title of the article in the first trial we used the translation of CONSENSUS as a general agreement, and in the recent trial the translation of PARADIGM as a pattern of thinking.

ACE inhibitors

The ACE inhibitor enalapril has been used in the treatment of heart failure in mortality trial – CONSENSUS, which was published in 1987. It included 253 patients and evaluated the effect of enalapril (2×20 mg) added to a conventional treatment (digoxin and diuretics) in severe heart failure (NYHA IV). The trial had to be terminated prematurely after one year due to a completely clear decrease in mortality after the enalapril treatment. It is interesting that the number of patients was only 253, but the clear result of this trial ranked it obviously as the first mortality trial with ACE inhibitor in severe heart failure (Fig. 1) [2].

This was followed by two trials published in the same issue of NEJM, i.e. the trials SOLVD I and V-HeFT II. The trial SOLVD I (Treatment Trial) was to examine whether the enalapril treatment reduced the mortality and morbidity in chronic heart failure of functional class NYHA II–III with ejection fraction (EF) of the left ventricle below 0.35. The trial enrolled 2569 patients who, prior to treatment, had to tolerate the dose of minimum 2×2.5 mg of enalapril

followed by titration to the maximum dose of 2×10 mg vs. placebo; an average follow-up period was 41 months. The result was again clearly positive for enalapril, both as for the decline in mortality and the recurrence of impaired CHF (Fig. 2). However, similarly to the trial CONSENSUS, a sudden death was not affected [3].

The trial V-Heft II compared the effect of a combination of vasodilators: hydralazine (300 mg) with isosorbiddinitrate (160 mg) versus enalapril (2×10 mg). This trial engaged 804 men with chronic heart failure (left ventricular internal diameter in diastole of 2.7 cm/ m^2 or EF below 0.45) with reduced working tolerance, functional NYHA II–III; the average period of follow-up was 30 months. Very interesting were the overall results. Enalapril compared with hydralazine-isosorbiddinitrate decreased statistically significantly only the incidence of sudden death but did not reduce the terminal failure mortality. Hemodynamic indicators, ejection fraction and working capacity were more improved in the treatment with hydralazine-isosorbiddinitrate (Fig. 3) [4].

The second trial SOLVD II (Prevention Trial) monitored whether enalapril (2×2.5 – 10 mg) versus placebo reduces the morbidity and mortality in asymptomatic patients with impaired left ventricular function (NYHA I–II). It enrolled 4228 patients with ejection fraction below 0.35, who were not treated for chronic heart failure. However, diuretics to treat hypertension and digoxin to treat atrial fibrillation were allowed. A mean follow-up period was 37 months. Enalapril in patients with asymptomatic left ventricular dysfunction delayed the development of heart failure and reduced the number of hospitalisations. An insignificant decrease in fatalities was due to a mild heart failure (Fig. 4) [5].

Another two trials dealt with the size of the dose of ACE inhibitors in heart failure. The first trial NETWORK was to determine the relationship between different doses of enalapril and clinical indicators of heart failure (mortality, hospitalisation related to heart failure and disease progression). The trial encompassed 1532 patients

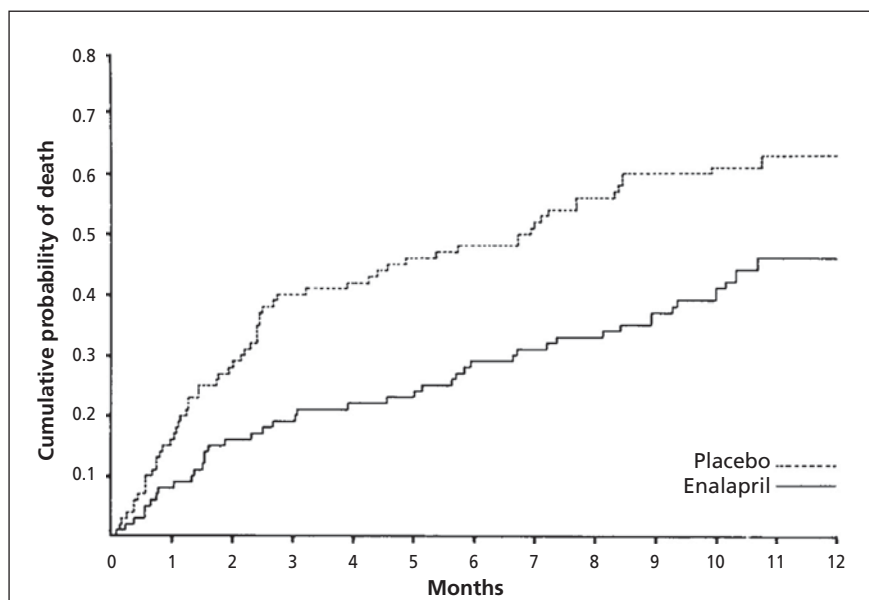


Fig. 1 – CONSENSUS.

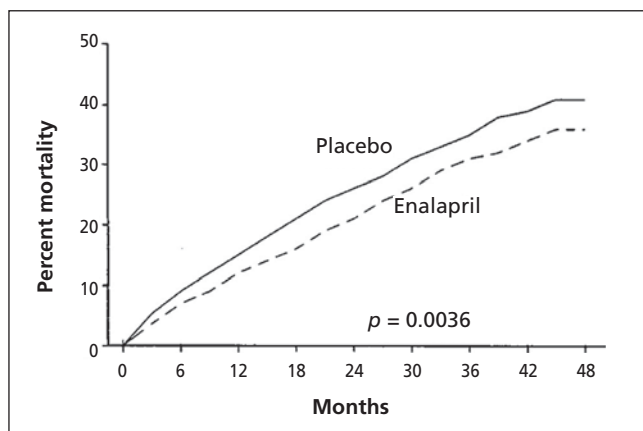


Fig. 2 – SOLVD I.

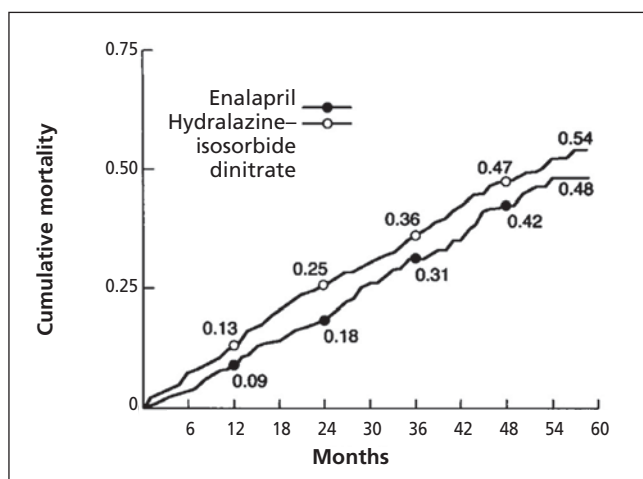


Fig. 3 – V-HEFT II.

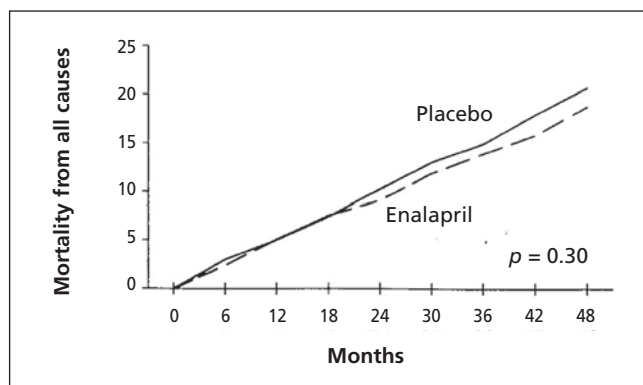


Fig. 4 – SOLVD II.

with symptomatic heart failure (NYHA II–IV). The follow up period was 6 months. Patients were randomized into 3 groups: enalapril 2.5 mg (group I), 5 mg (group II) and 10 mg (group III). The trial did not show that increasing the dose of enalapril from 2 × 2.5 mg to 2 × 10 mg resulted in a significant reduction of mortality and improvement of clinical findings (Fig. 5) [6].

Another trial – ATLAS – compared the effect of low and high doses of ACE inhibitor (lisinopril) in chronic heart fail-

ure on total cardiovascular mortality, number of hospitalisations, incidence of MI and hospitalisations for unstable AP. The trial covered 3164 patients with a moderate to severe heart failure. 1596 patients were administered with a low dose (2.5–5 mg/day) and 1568 patients with a high dose (32.5–35 mg/day). An average follow-up period was 48 months; the other treatment was standard – diuretics, digoxin, or beta-blockers. The conclusion of the trial was that a higher dose of lisinopril in treatment of heart failure had no effect on mortality, but was more effective than the lower dose in terms of reduced incidence of hospitalisations for impaired heart failure (Fig. 6) [7].

The CIBIS III trial asked a question with what to begin in the treatment of heart failure; whether to use the ACE inhibitor or beta-blocker and then to add a second drug. Randomization of 1010 patients with EF below 35% was initiated with either enalapril up to a target dose of 2 × 10 mg or with bisoprolol up to the dose of 10 mg. After 6 months, the second drug was titrated and the treatment continued with both agents. The primary end-point was mortality or hospitalisation. The conclusion of the trial is that it basically does not matter which drug group to begin with; it is important to administer both the ACE inhibitor and the beta-blocker simultaneously, as early as the clinical condition allows (Fig. 7) [8].

The trial with ACE inhibitor –perindopril – is devoted to patients with impaired diastolic function or heart failure with preserved left ventricular EF (heart failure with preserved ejection fraction HFpEF). The PEP-HF trial encompassed 850 patients older than 70 years. An HFpEF diagnosis was based on echocardiography with EF between 0.4–0.5. Patients were administered with either perindopril 4 mg or placebo. The primary end-point was mortality or hospitalisation for impaired chronic heart failure. After 12 months, the treatment with perindopril statistically insignificantly affected mortality, and it statistically marginally reduced the primary end-point – mortality and unplanned hospitalisations for heart failure, and it statistically significantly reduced unplanned hospitalisations for heart failure. However, after another 24 months of follow-up, the difference in achieving the primary end-point was not significant (Fig. 8) [9].

Angiotensin II type 1 receptor blockers (ARB, sartans)

Sartans were gradually seeking their place in the treatment of heart failure; the respective trials were largely those comparing sartans with ACE inhibitors. AT₁ receptors are responsible for the majority of clinically known effects of angiotensin II; according to the experimental trials they have more significant pharmacological effects than a mere inhibition of conversion of angiotensin I to angiotensin II by a converting enzyme, but this has not yet been clinically proved as shown in the following trials.

The first mortality trial comparing ACE-I with ARB in chronic heart failure is known as ELITE II. A primary end-point of this trial was all-cause mortality and hospitalisation; the secondary end-point was mortality from sudden death. Input criteria were age > 60 years, NYHA II–IV, EF

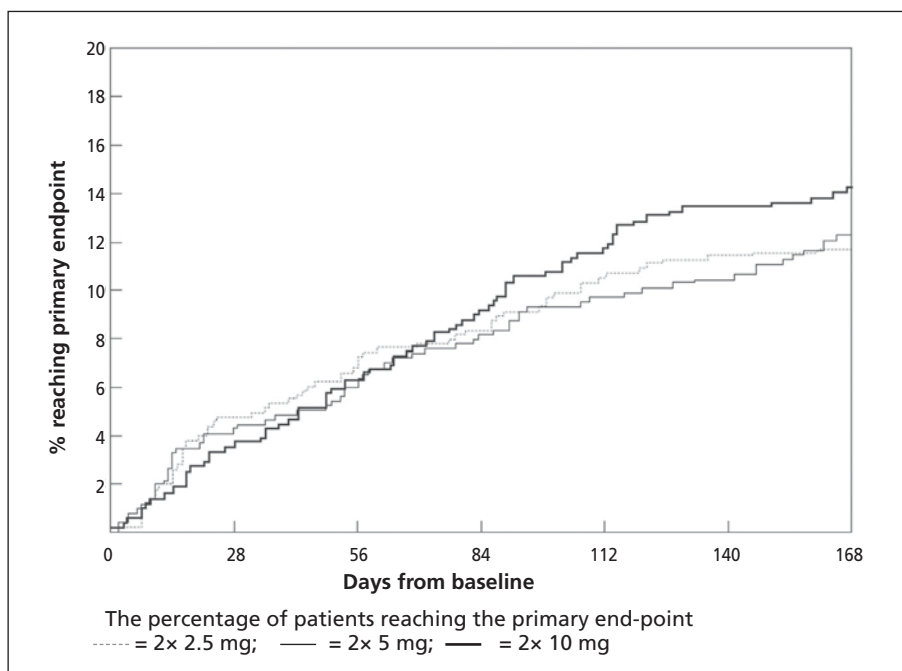


Fig. 5 – NETWORK.

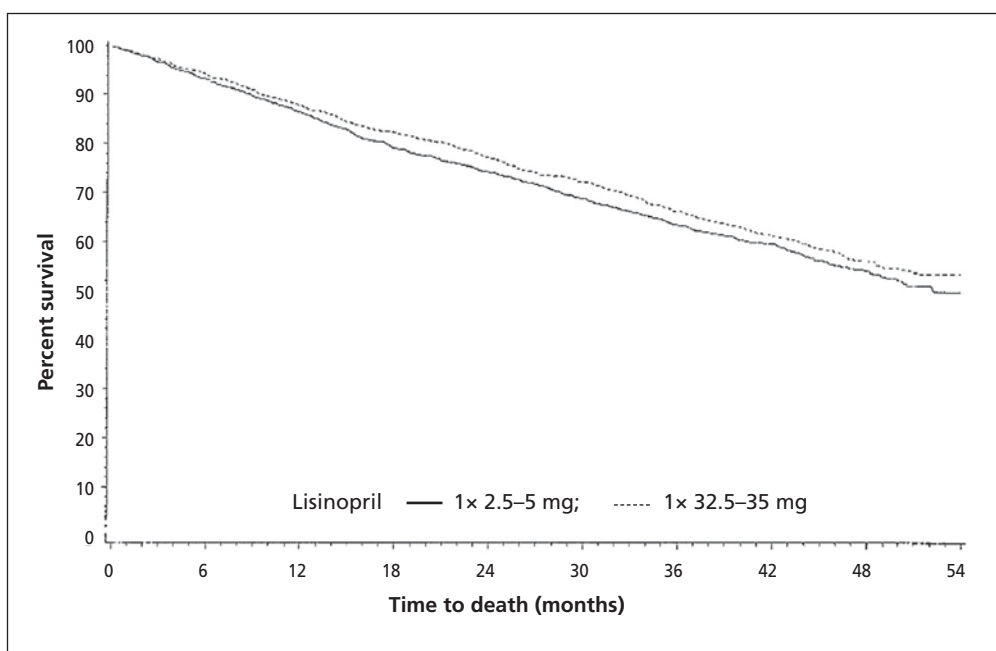


Fig. 6 – ATLAS.

<0.4, digitalis and/or diuretics were recommended, beta-blockers therapy was part of independent randomization, and generally beta-blockers were not expected to be administered in more than 25% of patients. For the treatment with captopril 3x 50 mg, 1574 patients were randomized, for the treatment with losartan 1x 50 mg 1578 patients and the mean follow-up period was 555 days. In the captopril group, 250 (15.9%) patients died; in the losartan group, it was 280 (17.7%) patients ($p = 0.16$).

A combined primary endpoint occurred in 707 (45%) of patients treated with captopril and 752 (48%) treated with losartan ($p = 0.21$) (Fig. 9). In terms of mortality and/or hospitalisations, losartan was not better than captopril. An incidence of cough confirms the previous data on a lower incidence of this adverse effect of losartan than that of captopril. The question is whether the neutral result would be the same if the dosage of losartan was also 150 mg as that of captopril [10].

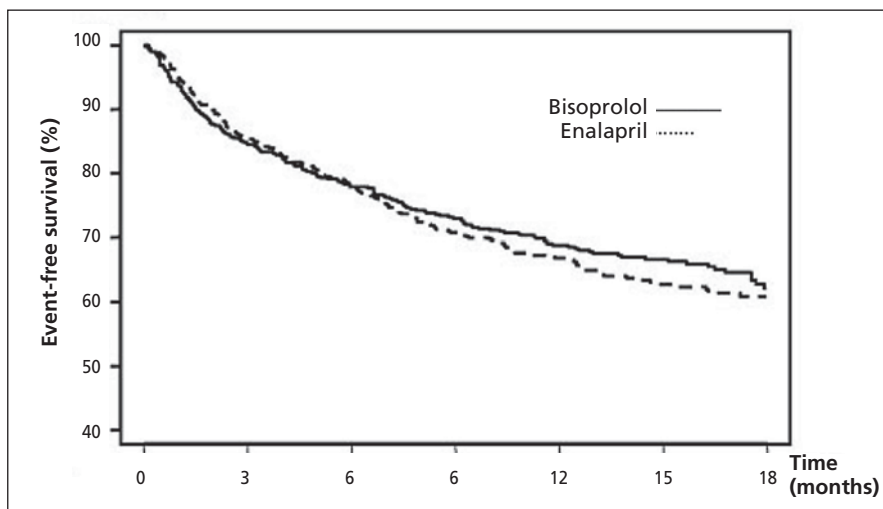


Fig. 7 – CIBIS III.

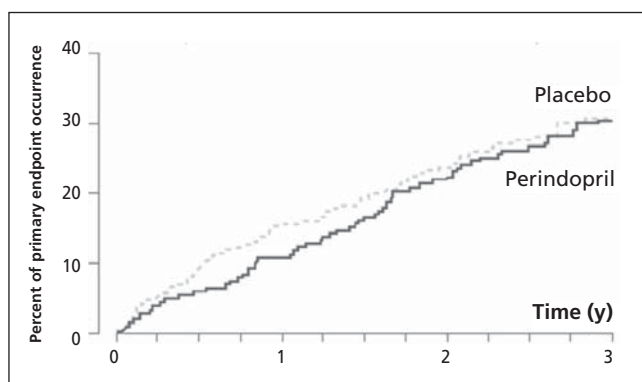


Fig. 8 – PEP-HF.

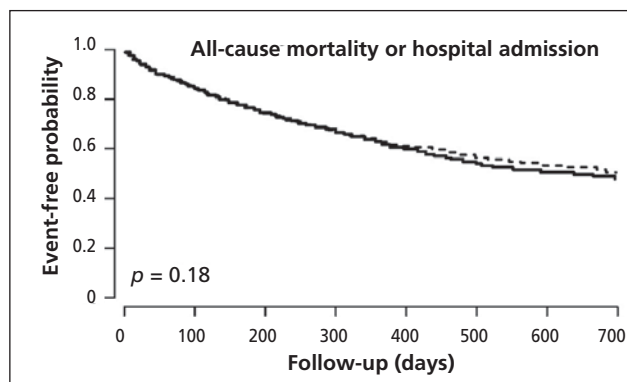


Fig. 9 – ELITE II.

The Val HeFT trial (Valsartan Heart Failure Trial) has so far been the largest trial of ARBs in heart failure, with 5010 enrolled patients and a mean follow-up period of 23 months. This trial evaluated a long-term effect of the receptor blocker for angiotensin II – valsartan – added to a standard therapy of heart failure, including ACE-I; i.e. not a comparison of ACE-I versus ARB, but their combination. Death from any cause was not affected by the addition of valsartan. However, the incidence of the combined endpoint – morbidity-mortality – was lower in the valsartan group (13.2%), mainly due to a reduction in the number of hospitalisations for heart failure. Valsartan administration compared with placebo resulted in a significant improvement in NYHA class, increase in the ejection fraction, alleviation of the symptoms of heart failure, and improvement of the quality of life. Nevertheless, in a post hoc analysis of subgroups, an undesirable effect was observed as of the combination of ACE inhibitor, beta-blocker and valsartan on the incidence of combined indicator of mortality and morbidity, which increased doubts about the safety of this particular triple. Therefore, for the treatment of heart failure, a combination of blocker of the renin–angiotensin–aldosterone system (ACE-I or

ARB) + beta-blocker is recommended. Provided that the patient does not tolerate the beta-blocker and also the blocker of mineralocorticoid receptors, it is possible to consider a combination of ACE-I + ARB, with careful clinical and laboratory monitoring [11].

Another large program with ARB, entitled CHARM, studied the effect of candesartan 32 mg vs placebo in patients with heart failure, and included three trials to determine whether the treatment with candesartan in patients with chronic heart failure could reduce mortality and morbidity. The first trial was to demonstrate whether in the patients who could not tolerate ACE inhibitors, the candesartan therapy could lead to improved clinical outcomes. The second trial monitored whether the addition of candesartan to the ACE inhibitor had a beneficial effect on the improvement of clinical prognosis. The last trial was to determine whether the addition of candesartan to the existing treatment of heart failure with preserved EF (HFpEF) could lead to improved clinical outcomes. It included a total of 7601 patients from three different groups: a) patients (n = 2028) with ejection fraction <40% not administered with the ACE inhibitor for its intolerance, b) patients (n = 2548) who were concurrently receiv-

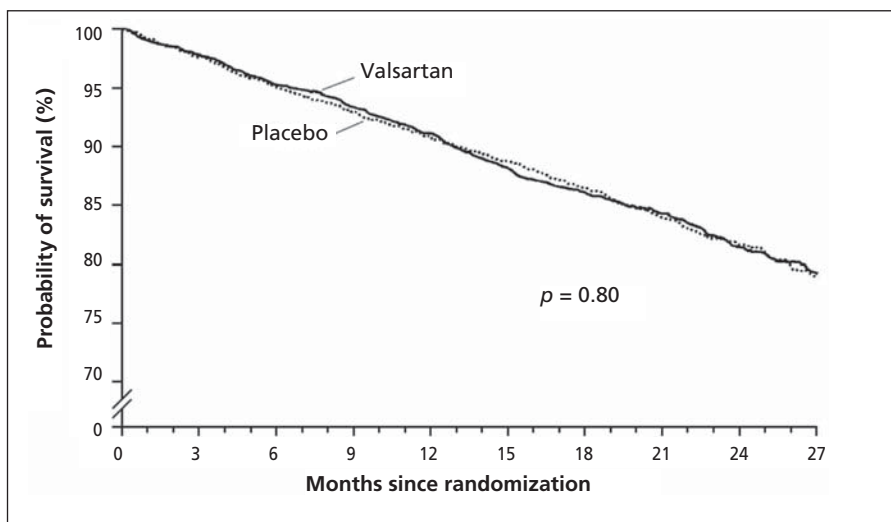


Fig. 10 – VAL-HEFT.

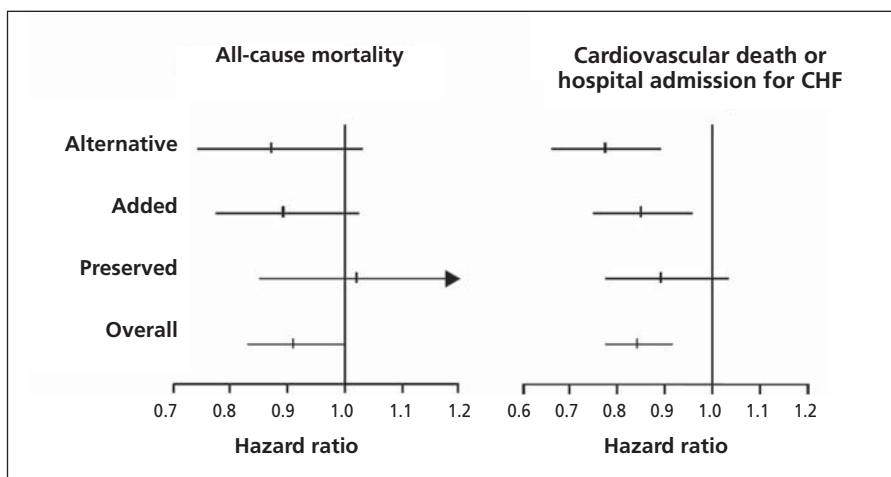


Fig. 11 – CHARM ALL.

ing the ACE inhibitor, c) patients ($n = 2028$) with ejection fraction > 0.4 . A mean follow-up period was 37.7 months, at least for 2 years. The conclusions of the individual trials were as follows:

1. Candesartan is very well tolerated in CHF patients, who cannot tolerate ACE inhibitors; it reduces cardiovascular morbidity and mortality.
2. Addition of candesartan to the existing treatment with ACE inhibitors leads to a further significant reduction in the incidence of cardiovascular events.
3. Candesartan in patients with heart failure and preserved ejection fraction more than 40% has a preventative effect on the number of hospitalisations for heart failure [12].

The trial I PRESERVE tested the effect of irbesartan on the prognosis of patients with heart failure with preserved ejection fraction (HFpEF). This trial randomized

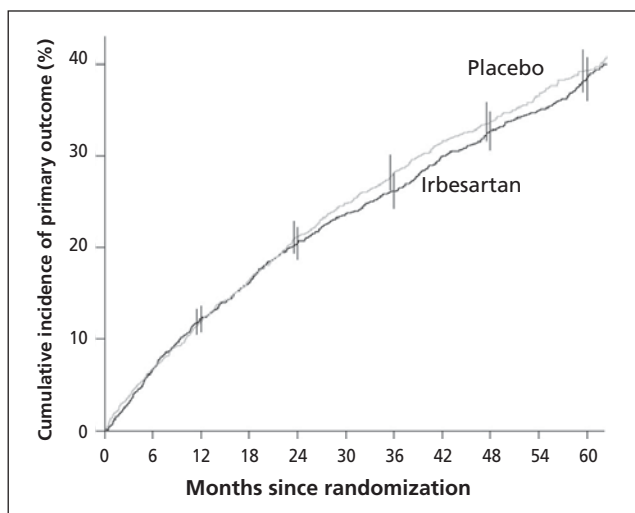


Fig. 12 – I-PRESERVE.

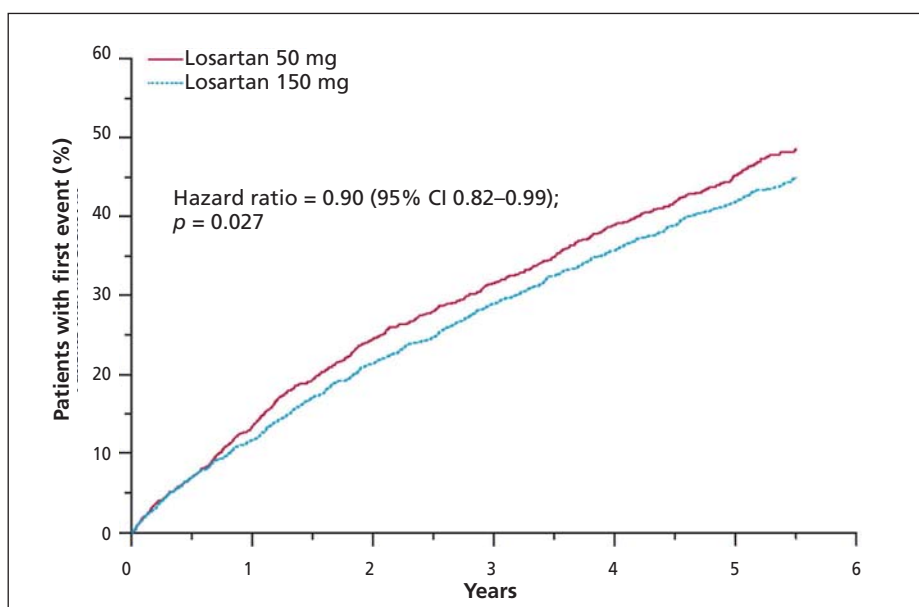


Fig. 13 – HEAAL.

4128 patients older than 60 years, functionally NYHA II–IV, with ejection fraction of 0.45 or higher. These patients were administered with either 300 mg of irbesartan or placebo. The primary end-point was the overall mortality or hospitalisation due to cardiovascular causes; the secondary endpoints were death, hospitalisation for heart failure, quality of life. The mean follow-up period was 50 months; the result was neutral in all indicators, i.e. irbesartan compared with placebo in patients with heart failure and preserved ejection fraction did not improve any of monitored end-points (Fig. 12) [13].

The last of mortality trials with sartans was the HEAAL trial, which, similarly to the ATLAS trial with lisinopril, monitored the dose size of losartan (small of 50 mg vs. large of 150 mg) affecting the clinical indicators in heart failure. This trial randomized 3846 patients with NYHA II–IV and EF of 0.4 or lower who were intolerant to ACE-I. The primary end-point was death or hospitalisation for heart failure. The result of the trial was that the higher dose of 150 mg of losartan was more beneficial in all monitored indicators than a lower dose of 50 mg. Adverse effects of hypotension, hyperkalemia and impaired renal function were more significant with a higher dose but without necessity to interrupt the trial [14].

None of the above trials demonstrated a significant beneficial effect on mortality in respect of ARBs (sartans) compared to ACE inhibitors and thus it did not clearly answer the question which drug group (ACE-I vs. ARB) is more beneficial for patients with impaired function of myocardium. It is evident that ARBs have a similar beneficial effect on mortality and morbidity as the ACE inhibitors. Therefore, in recommendations for the treatment of heart failure, ARBs (sartans) are indicated for the patients who do not tolerate ACE-I (cough, angioedema in history). A combination of ACE-I and ARB is not recommended mainly due to their adverse effects (decrease in blood pressure, impairment of renal function), although the

results of the above trials – Val-HeFT and CharmAdded – verified this combination as beneficial. The ARB dose should be the maximum one tolerated by the patient.

Mineralocorticoid-receptor antagonists

Another drug group monitored in heart failure are blockers of mineralocorticoid receptors (for aldosterone) – spironolactone and eplerenone. Aldosterone plays an important role in the pathophysiology of chronic heart failure, increases sodium retention, loss of magnesium, potassium, increases a sympathetic activity and decreases a parasympathetic activity, increases a myocardial and vascular fibrosis, and dysfunction of baroreceptors.

The first trial RALES, published as early as in 1999, evaluated the effectiveness of spironolactone on the morbidity and mortality in severe heart failure. This trial included 1663 patients, with the average age of 65 years, functional NYHA III–IV and EF below 0.35. At that time the patients received the standard therapy (ACE inhibitors, diuretics and digoxin) and were randomly assigned to either additional spironolactone of 25–50 mg/day or placebo. The trial was prematurely terminated after two years because the patients who received spironolactone had a better survival rate in comparison with placebo. The overall mortality was by 27% lower in the spironolactone group (Fig. 14). In addition, in the group of patients with spironolactone, a lower number of hospitalisations were observed. Gynecomastia occurred in 8.5% of patients receiving spironolactone vs. 1.5% of patients administered with placebo. Spironolactone added to the ACE inhibitors significantly reduced the mortality in severe heart failures [15].

The trial EMPHASIS HF enrolled 2 737 patients with heart failure and EF below 0.35, functional class NYHA II. These patients were randomized to treatment with by eplerenone (25–50 mg) or placebo added to the standard

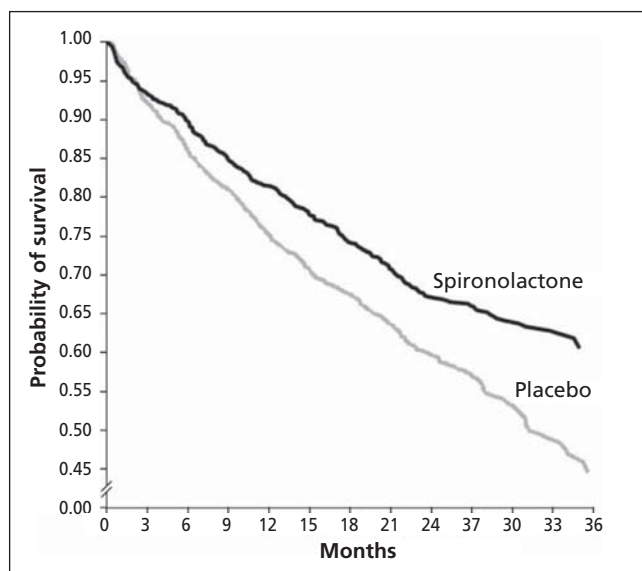


Fig. 14 – RALES.

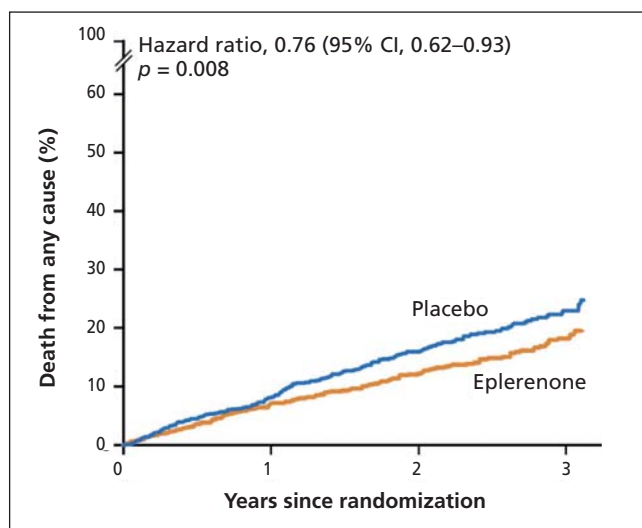


Fig. 15 – EMPHASIS HF.

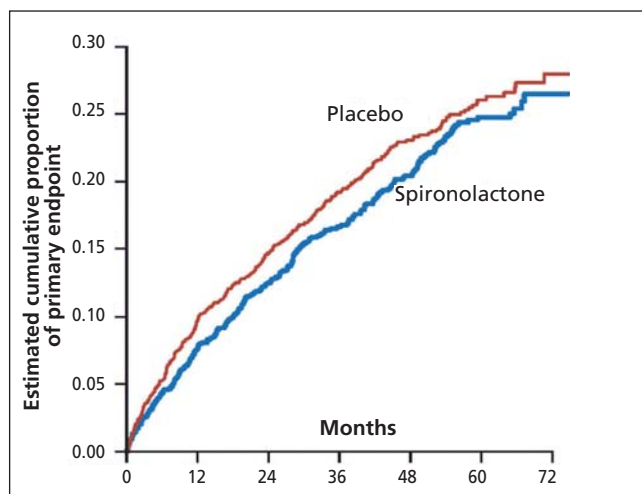


Fig. 16 – TOP-CAT.

treatment of CHF. A primary end-point was to monitor the cardiovascular death or hospitalisation for heart failure. Again, the trial was terminated prematurely after 21 months for a clearly positive effect of eplerenone, a reduction in the primary end-point compared with placebo (18.3% vs. 25.9%). The trial clearly showed a beneficial effect of blockade of mineralocorticoid receptors by eplerenone in patients with mild heart failure (Fig. 15) [16].

The trial TOPCAT was devoted to patients with heart failure and preserved ejection fraction above 45%. 3445 patients were enrolled to receive either spironolactone (15–45 mg) or placebo. The primary end-point was again composed of (composite) death from CV causes, cardiac arrest or hospitalisation for impaired heart failure. A mean follow-up period was 40 months, and all indicators of this composite end-point were similar after the intervention of spironolactone or placebo, and only marginally significant ($p < 0.04$) was a reduction of hospitalisations for heart failure after spironolactone. A conclusion of the trial was that spironolactone did not affect the primary end-point, increased potassium levels and reduced hospitalisations for heart failure [17].

Direct renin inhibitor

Another potential therapeutic step based on pathophysiological grounds of activation of the RAA system was a hypothesis of blockade of renin that cleaves angiotensinogen into angiotensin I and the renin inhibition prevents the formation of angiotensin II.

The examined therapeutic agent was aliskiren (direct renin blocker) in the trial ASTRONAUT in patients with heart failure with EF below 0.4 or elevated levels of natriuretic peptides (BNP or NT-proBNP) and signs of fluid overload. 1639 patients were randomized to be administered with aliskiren (150–300 mg) or placebo added to the standard treatment. The primary end-point was a composite of CV deaths or hospitalisations for impaired heart failure after 6 and 12 months (Fig. 17). The conclusion of the trial was such that aliskiren compared to placebo did not affect the primary end-point or the other CV indicators and therefore it is not recommended for the treatment of heart failure [18].

Dual inhibitors of the RAA system and neprilysin

The last monitored therapeutic group, which affects not only the RAA system but also blocks neprilysin – neutral endopeptidase, which cleaves endogenous vasodilator peptides. Neprilysin inhibition increases vasodilation. The first major trial was conducted in 2002 with omapatrilate (enalapril with neprilysin inhibition) entitled OVERTURE. In this trial, omapatrilat (1× 10–20 mg) and enalapril (2× 2.5–5 mg) were compared in 5770 patients with heart failure with EF below 0.3 and the functional class NYHA II–IV. The follow-up period was on average 14 months, the primary endpoint was a composite of all-cause mortality and hospitalisation for heart failure. The primary end-point was recorded in 973 patients tre-

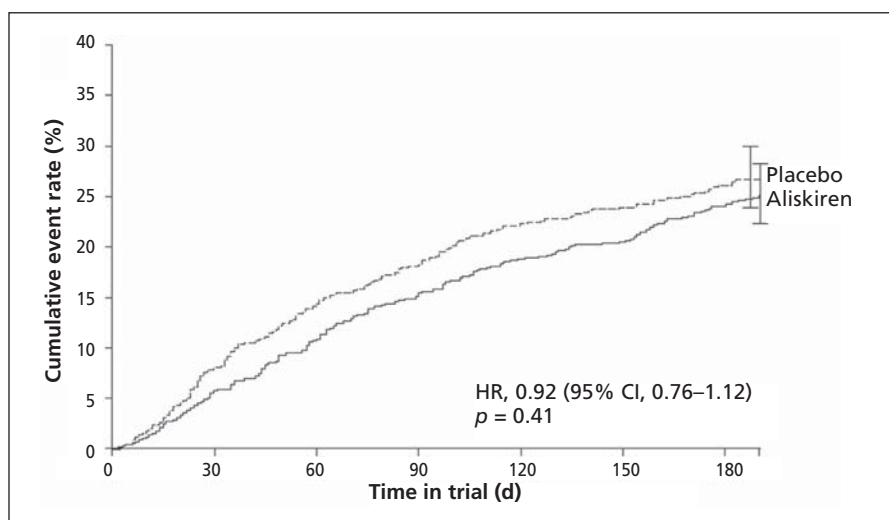


Fig. 17 – ASTRONAUT.

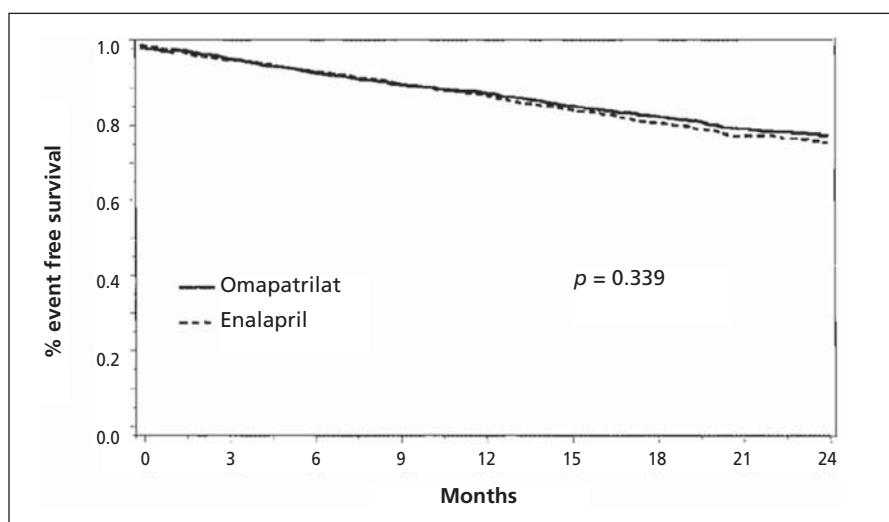


Fig. 18 – OVERTURE.

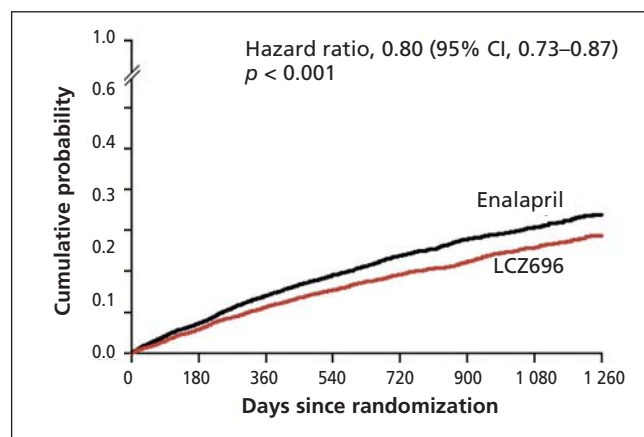


Fig. 19 – PARADIGM-HF.

ated with enalapril and 914 patients treated with omapatrilate (Fig. 18) ($p = 0.187$). Angioedema occurred in 24 (0.8%) patients after omapatrilate and in 14 (0.5%) patients after enalapril. Compared to the treatment

with ACE inhibitors, omapatrilat reduced the number of deaths and rehospitalisation for heart failure but did not reduce the all-cause mortality and the risk of primary clinical events. For higher incidence of angioedema after omapatrilate, it was not recommended for the treatment of chronic heart failure [19].

The latest trial, which was presented at 2014 at the Congress of European Society of Cardiology, tested a new dual inhibitor of neprilysin (sacubitril) and valsartan so far marked as LCZ696 (Entresto) with enalapril in patients with heart failure and reduced ejection fraction. It was a double-blind trial PARADIGM-HF in 8442 patients with heart failure of NYHA class II, III and IV and ejection fraction below 0.4. Patients received sacubitril/valsartan (2×200 mg) or enalapril (2×10 mg) added to the standard therapy. The primary end-point was a composite – cardiovascular death and hospitalisation for the first heart failure. The trial was prematurely terminated according to the set rules at an average follow-up period of 27 months showing a clear benefit from the LCZ696 therapy. At the time of termination, the primary end-point occurred in

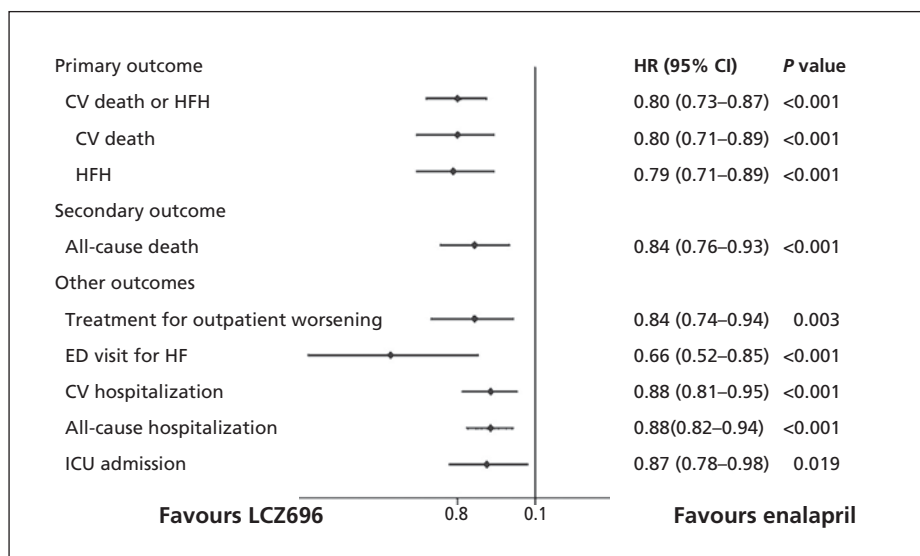


Fig. 20 – Key clinical outcomes in PARADIGM-HF.

914 patients (21.8%) in the group of LCZ696 and in 1117 patients (26.5%) in the group treated with enalapril (Fig. 19) ($p < 0.001$). LCZ696 compared to enalapril reduced the risk of hospitalisation for heart failure by 21% ($p < 0.001$) and decreased the symptoms of heart failure ($p = 0.001$) (Fig. 20). In the group treated with LCZ696, more hypotension and minor angioedema was reported, but a lower incidence of renal failure, hyperkalemia, and cough than in the group treated with enalapril. LCZ696 was significantly more effective than enalapril in reducing the risk of cardio-vascular deaths and hospitalisations for heart failure [20].

We have tried to give a brief overview of mortality trials of blockade of the renin angiotensin aldosterone system published over the last 30 years [21].

What conclusions can we take from this?

1. ACE still remain the gold standard of treatment of chronic heart failure ranging from the asymptomatic left ventricular dysfunction up to the severe heart failure (NYHA class I to IV) and should be combined with beta-blockers.

2. In the case of intolerance to ACE-I, blockers of AT₁ receptors of angiotensin 2 (sartans) should be used; they provide only slightly less evidence than ACE-I, but are equally effective in the treatment of heart failure.

3. Both therapeutic groups – ACE inhibitors and sartans – should be titrated up to the maximum tolerated doses and should be mutually combined only in exceptional situations.

4. Mineralocorticoid receptor blockers are clearly indicated for moderate to severe heart failure (NYHA II–IV) along with ACE inhibitors or sartans and beta-blockers for laboratory check-ups of potassium levels and renal functions.

5. All the trials dealing with heart failure and preserved ejection fraction (HFpEF) did not prove that the RAAS inhibition compared to placebo would be more beneficial for the prognosis of patients with CHF.

6. A direct renin inhibitor – aliskiren – is not more effective than placebo.

7. Dual inhibitors of RAAS and neutral peptidases had different results. While omapatrilate (enalapril and inhibition of neprilysin) had neutral results with a higher incidence of angioedema and it was not recommended for the treatment of heart failure, a new therapeutic agent LCZ696 dual inhibitor of neprilysin (sacubitril) and valsartan was significantly more effective than enalapril and raises the question of whether in the future it will not replace ACE inhibitors. However this path is not easy – it requires further randomized mortality trials and economic balance sheet.

Conflict of interest

None declared.

Ethical statement

Authors state that the research was conducted according to ethical standards.

Funding body

None.

References

- [1] J.J. McMurray, CONSENSUS to EMPHASIS: the overwhelming evidence which makes blockade of the renin–angiotensin–aldosterone system the corner-stone of therapy for systolic heart failure, *European Journal of Heart Failure* 13 (2011) 929–936.
- [2] The CONSENSUS Trial Study Group, Effects of enalapril on mortality in severe congestive heart failure, *New England Journal of Medicine* 316 (1987) 1429–1435.
- [3] The SOLVD investigators, Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure, *New England Journal of Medicine* 325 (1991) 293–302.
- [4] J.N. Cohn, G. Johnson, S. Zeishe, et al., A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure, *New England Journal of Medicine* 325 (1991) 303–310.

- [5] The SOLVD investigators, Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions, *New England Journal of Medicine* 327 (1992) 685–691.
- [6] The NETWORK investigators, Clinical outcome with enalapril in symptomatic chronic heart failure: a dose comparison, *European Heart Journal* 19 (1998) 481–489.
- [7] M. Packer, P.A. Poole-Wilson, P.W. Armstrong, et al., on behalf of the ATLAS Study Group, The assessment of treatment with lisinopril and survival. Comparative effects of low and high doses of the angiotensin-converting enzyme inhibitor, lisinopril, on morbidity and mortality in chronic heart failure, *Circulation* 100 (1999) 2312–2318.
- [8] R. Willenheimer, D.J. van Veldhuisen, B. Silke, et al., Effect on survival and hospitalization of initiating treatment for chronic heart failure with bisoprolol followed by enalapril, as compared with the opposite sequence. Results of the randomized Cardiac Insufficiency Bisoprolol Study (CIBIS) III, *Circulation* 112 (2005) 2426–2435.
- [9] J.G. Cleland, M. Tendera, J. Adamus, et al., on behalf of PEP-CHF Investigators, The perindopril in elderly people with chronic heart failure (PEP-CHF) study, *European Heart Journal* 27 (2006) 2338–2345.
- [10] B. Pitt, P.A. Poole-Wilson, R. Segal, et al., on behalf of the ELITE II Investigators, Effect of losartan compared with captopril on mortality in patients with symptomatic heart failure: randomised trial—the Losartan Heart Failure Survival Study ELITE II, *Lancet* 355 (2000) 1582–1587.
- [11] J.N. Cohn, G.A. Tognoni, For Valsartan Heart Failure Trial Investigators, A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure, *New England Journal of Medicine* 345 (2001) 1667–1675.
- [12] M.A. Pfeffer, K. Swedberger, C.B. Granger, et al., for the CHARM Investigators and Committees, Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall programme, *Lancet* 362 (2003) 759–766.
- [13] B.M. Massie, P.E. Carson, J.V. McMurray, et al., for the I-PRESERVE Investigators, Irbesartan in patients with heart failure and preserved ejection fraction, *New England Journal of Medicine* 359 (2008) 2456–2467.
- [14] M.A. Konstam, J.D. Neaton, K. Dickstein, et al., for the HEAAL Investigators, Effects of high-dose versus low-dose losartan on clinical outcomes in patients with heart failure (HEAAL study): HEAAL study, *Lancet* 374 (2009) 1840–1848.
- [15] B. Pitt, F. Zannad, W.J. Remme, et al., For The Randomized Aldactone Evaluation Study Investigators, The effects of Spironolactone on morbidity and mortality in patients with severe heart failure, *New England Journal of Medicine* 341 (1999) 709–717.
- [16] F. Zannad, J.J. McMurray, H. Krum, et al., for the EMPHASIS-HF Study Group, Eplerenone in patients with systolic heart failure and mild symptoms, *New England Journal of Medicine* 364 (2011) 11–21.
- [17] B. Pitt, M.A. Pfeffer, F.A. Assmann, et al., for the TOPCAT Investigators, Spironolactone for heart failure with preserved ejection fraction, *New England Journal of Medicine* 370 (2014) 1383–1392.
- [18] M. Gheorghiade, M. Böhm, S.J. Greene, et al., for the ASTRONAUT Investigators and Coordinators, Effect of Aliskiren on postdischarge mortality and heart failure readmissions among patients hospitalized for heart failure, *JAMA* 309 (2013) 1125–1135.
- [19] M. Packer, R.M. Califf, M.A. Konstam, et al., for the OVERTURE Study Group, Comparison of omapatrilat and enalapril in patients with chronic heart failure: the Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events (OVERTURE), *Circulation* 106 (2002) 920–926.
- [20] J.J. McMurray, M. Packer, A.S. Desai, et al., for the PARADIGM-HF Investigators and Committees, Angiotensin–neprilysin inhibition versus enalapril in heart failure, *New England Journal of Medicine* 371 (2014) 993–1004.
- [21] H. Burnett, A. Earley, A.A. Voors, et al., Thirty years of evidence on the efficacy of drug treatments for chronic heart failure with reduced ejection fraction. A network meta-analysis, *Circulation: Heart Failure* 10 (2017) e003529, <http://dx.doi.org/10.1161/CIRCHEARTFAILURE.116.003529>.