VIA MEDICA

EDITORIAL

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Functioning in chronic disease — a key factor determining adherence to heart failure treatment

Patients with heart failure require long-term medical treatment [1, 2]. Non-adherence to medication is the main factor limiting treatment efficacy due to increased morbidity and mortality [3–9]. Therefore, knowledge of the true adherence level and understanding the causes of non-adherence is pivotal [10–12]. Asking patients is the simplest and most frequently used method of adherence assessment. However, it has been shown that the data obtained in this way have limited credibility [13]. The application of dedicated questionnaires to assess the risk of low adherence may help detect non-adherence problems [14–19]. The impact of medication on the severity of heart failure symptoms as well as the occurrence of side effects have been shown to strongly influence the overall functioning of the patient with chronic disease [20–23]. On the other hand, the patient's perception of the disease and acceptance of treatment is determined by functioning in the disease, including the quality of life [24–26]. Therefore, medication efficacy and tolerability are both equally important [27].

Several ground-breaking trials have formed the basis of current guidelines for the treatment of patients with heart failure [28–33]. According to the new 2021 ESC guidelines for the diagnosis and treatment of acute and chronic HF, the first-line therapy should include four elements: angiotensin-converting enzyme inhibitors (ACE-I) or an angiotensin receptor-neprilysin inhibitor (ARNI), beta-blockers (BB), mineralocorticoid receptor antagonists (MRA), and sodium-glucose co-transporter 2 inhibitor (SGLT2i) dapagliflozin or empagliflozin, unless the drugs are contraindicated or not tolerated [1]. All these medications are proven to be effective but also shown to differ concerning tolerability.

The SOLVD trial was the first randomized clinical study showing reduced mortality and hospitalizations with ACE-I and enalapril in patients with chronic congestive heart failure and reduced ejection fractions (HFrEF). However, a significantly higher proportion of participants assigned to enalapril (28.1%) than those to placebo (16%) developed side effects ($p < 0.0001$). This resulted in the discontinuation of blinded therapy in 15.2% and 8.6% ($p < 0.0001$) of participants respectively [28]. The CIBIS-II study was the first large, randomized study demonstrating a dramatic reduction in mortality and hospitalization rate with a beta-blocking agent — bisoprolol in comparison to a placebo in HFrEF patients. Nevertheless, in patients with a heart rate < 72 beats/min at inclusion, the risk of permanent bisoprolol withdrawal was 1.97 (1.38–2.80) [29]. The RALES study was the first to show that the blockade of aldosterone receptors by spironolactone, in addition to standard therapy, substantially reduces the risk of both morbidity and mortality in patients with HFrEF. However, gynecomastia or breast pain was reported by 10% of the men in the spironolactone group and 1% of the men in the placebo group ($p < 0.001$), causing more patients in the spironolactone group than in the placebo group to discontinue treatment (10% *vs.* 1%, $p = 0.006$) [30]. Similarly, eplerenone, as compared with placebo, reduced both the risk of death and the risk of hospitalization among patients with HFrEF, as shown in the EMPHASIS-HF Study [31]. In contrast to aldosterone, treatment with eplerenone was associated with a slightly lower incidence of adverse events leading to study drug withdrawal in comparison to placebo (13.8% *vs.* 16.2%; $p = 0.09$), albeit hyperkalaemia occurred more often in patients receiving eplerenone

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(8.0% *vs.* 3.7%; p < 0.001) [31]. In the PARADIGM-HF trial, sacubitril/valsartan (ARNI) reduced morbidity and mortality compared to enalapril in patients with chronic HFrEF [32]. As such, ARNI has been recommended as a more effective alternative to an ACE-I inhibitor to be used in conjunction with other evidence-based treatments for this type of heart failure. Slightly fewer patients in the sacubitril/valsartan group than in the enalapril (previously shown to be poorly tolerated) group stopped their study medication because of an adverse event (10.7% *vs.* 12.3%, p = 0.03) or because of renal impairment (0.7% *vs.* 1.4%, p = 0.002), but yet patients in the sacubitril/valsartan group were more likely than those in the enalapril group to have symptomatic hypotension [32].

Two randomized clinical trials testing SGLT2 inhibitors, dapagliflozin (DAPA-HF) and empagliflozin (EMPEROR – Reduced) in comparison to the placebo, both shown to improve clinical outcomes reducing the risks of death and hospitalization for heart failure in patients with HFrEF [33–35]. Both of these studies consistently showed that the incidence of side effects and the rate of therapy discontinuation were lower in patients receiving SGLT2i compared to placebo, although the differences were not statistically significant [33, 34]. Moreover, treatment with dapagliflozin as well as with empagliflozin was associated with improvement in HF-related symptoms, function, and quality of life [33–38].

The impact of the disease essentially covers all areas of human functioning, including physical activity, the emotional and spiritual sphere, and functioning in society. The functioning limitation of patients with heart failure results in lower self-value perception, deterioration in well-being, and an increase in anxiety and uncertainty about the future. Therefore, a comprehensive assessment of the effectiveness of therapy in patients with HFrEF should include a comprehensive assessment of functioning in chronic disease [39–41].

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