New pharmacological agents have been developed during the last years, based on novel pathophysiologic concepts. Some are under investigation, while others such as levosimendan and neseritide are currently used in routine clinical practice.

Levosimendan is a calcium sensitisier and ATP-dependent potassium channel opener that has positive inotropic, vasodilatory and cardioprotective effects. This drug seems to be more effective than classical inotropes in improving cardiac mechanical efficiency and reducing congestion, without causing cardiomyocyte death or increasing myocardial oxygen uptake. Recent randomised trials, the second Randomized Multicenter Evaluation of Intravenous Levosimendan Efficacy (REVIVE II) and the Survival Of Patients With Acute Heart Failure In Need Of Intravenous Inotropic Support (SURVIVE) showed that levosimendan is not superior to placebo or dobutamine in improving one- and six-month mortality, although it caused a greater reduction of neurohormonal response. More data are needed regarding the optimum regimen and dosing of levosimendan before this treatment modality can become the first line therapy of acutely decompensated chronic heart failure patients.

One of the most promising categories of new drugs is vasopressin antagonists, which seem to represent a potentially beneficial therapeutic approach for both acute and chronic heart failure, especially in patients with congestion and low serum sodium. Conivaptan (a dual V1a/V2 receptor antagonist) and tolvaptan (a selective V2 receptor antagonist) are the most extensively studied vasopressin antagonists and both promote free water excretion without compromising renal function. The recently published Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST) trial demonstrated that oral tolvaptan in addition to standard therapy, including diuretics, improved many heart failure signs and symptoms associated with congestion, although the drug had neutral effect on mortality. Thus, vasopressin antagonists have the potential to assume an important role, in addition to, or instead of the current diuretic therapy for the management of acute heart failure, and are near to receiving approval from FDA.

A1-receptor antagonism by specific agents (e.g. BG9719) induces diuresis and natriuresis without exerting adverse effects on cardiac and renal functions, providing a potential therapeutic tool for acutely decompensated chronic heart failure. Research on Endothelin Antagonists in Chronic Heart failure (REACH UP) is an ongoing randomised trial that investigates the effects of an A1-receptor antagonist on renal function in patients with acute heart failure.
In the field of acute heart failure syndromes with low cardiac output, istaroxime is a novel agent that has both positive inotropic (inhibitor of Na-K ATPase) and lusitropic (SERCA 2a enhancer) properties. Experimental and small human studies have shown that istaroxime improves myocardial contractility, haemodynamics and diastolic relaxation without inducing proarrhythmic or ischaemic effects in the failing heart. Ongoing phase 2 trials (Hemodynamic Effects of Istaroxime, a Novel Lusitropic Agent, in Patients with Left Ventricular Systolic Dysfunction Hospitalized with Exacerbation of Chronic HF (HORIZON-HF) investigate the safety and efficacy of drug in the setting of acute heart failure syndromes.

Cardiac myocin activators, metabolic modulators (e.g. perhexilline), ularitide (a new natriuretic peptide of ANP family) and relaxin are also novel therapeutic agents with promising results in experimental models of heart failure or humans.

Although the use of these drugs is a challenging approach for the treatment of acute heart failure, no new agent has demonstrated a clear superiority in improving long-term prognosis compared to placebo or conventional therapies. Thus, more clinical data are needed in order to define the exact role of these novel agents in the management of acute heart failure syndromes.

REFERENCES
