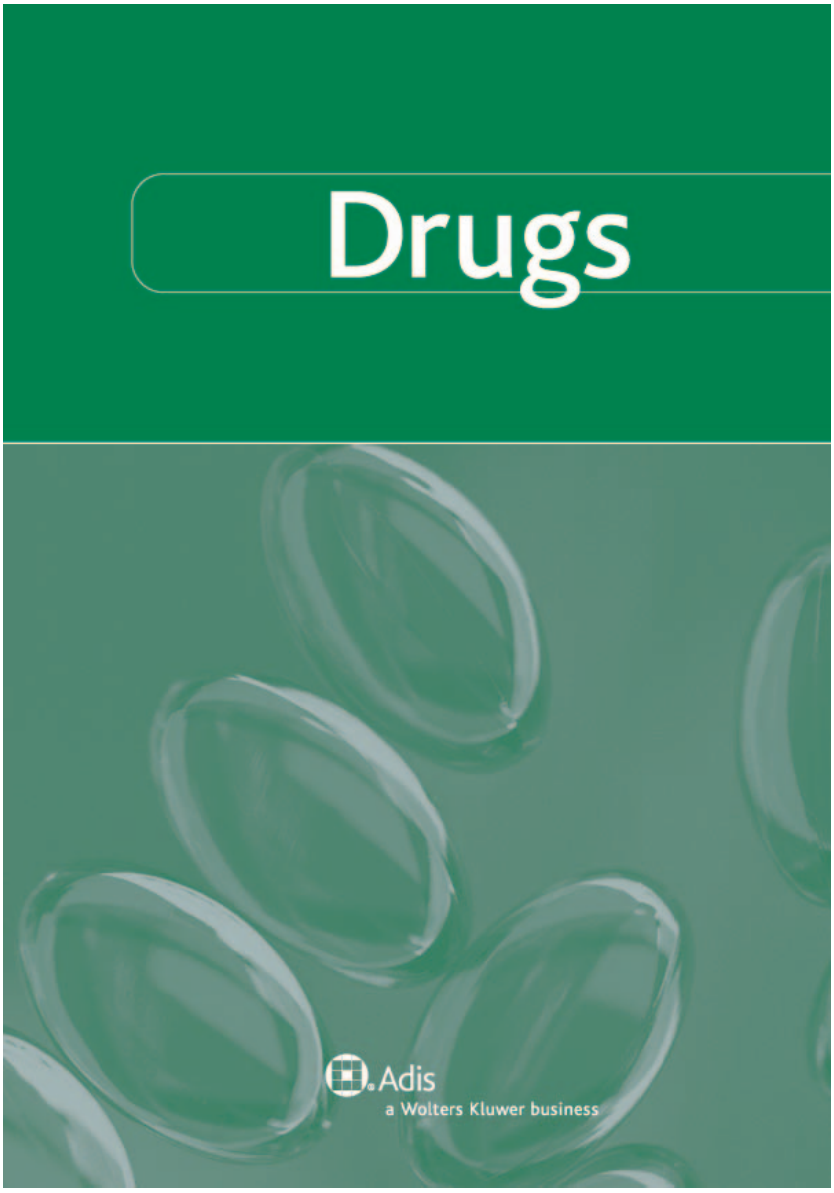

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Use of Inotropic Agents in Patients with Advanced Heart Failure

Lessons from Recent Trials and Hopes for New Agents

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Abstract

Abnormalities of cardiac function, with high intraventricular filling pressure and low cardiac output, play a central role in patients with heart failure. Agents with inotropic properties are potentially useful to correct these abnormalities. However, with the exception of digoxin, no inotropic agent has been associated with favourable effects on outcomes. This is likely related to the mechanism of action of current agents, which is based on an increase in intracellular cyclic adenosine monophosphate and calcium concentrations. Novel agents acting through different mechanisms, such as sarcoplasmic reticulum calcium uptake, cardiac myosin and myocardial metabolism, have the potential to improve myocardial efficiency and lower myocardial oxygen consumption. These characteristics might allow a haemodynamic improvement in the absence of untoward effects on the clinical course and prognosis of the patients.

Heart failure (HF) represents a major cause of morbidity and mortality. Use of neurohormonal antagonists, implantable cardiac defibrillators (ICDs), cardiac resynchronization therapy (CRT) and left ventricular (LV) assist devices has improved patient outcomes.[1-3] However, many patients still report severe symptoms and show a high rate of hospitalization.[4] Fluid overload and pulmonary congestion with elevated LV end-diastolic pressure and pulmonary wedge pressures are the main causes of patient hospitalization.[5-8] Reduced cardiac output and peripheral hypoperfusion are also important in some patients. These patients, whose prevalence can be estimated at approximately 10% of all patients admitted for acute HF, have low blood pressure (BP), signs of end-organ dysfunction, and severe LV systolic and diastolic dysfunction.[4,9] The administration of inotropic agents is potentially the only medical treatment that can improve their haemodynamic abnormalities and symptoms.[10-13] Accordingly, inotropic therapy is a major criterion for the indication of LV assist device implantation and/or urgent transplantation.[14] Unfortunately, most, if not all, of the inotropic agents have been associated with poor tolerance and untoward effects on outcomes. Thus, their administration may allow short-term improvement in haemodynamic parameters and symptoms with longer-term harm. Newer inotropic agents with a better benefit to risk ratio are needed.

In this review we summarize the main characteristics and limitations of current inotropic agents and review novel inotropic agents in various stages of development.

1. Current Indications

Inotropic agents are indicated for the treatment of patients with peripheral hypoperfusion and fluid overload secondary to cardiac dysfunction ('cold and wet patients').[8-12,14] Hypotension is the main sign of hypoperfusion and low cardiac output.[10,12,15] Other signs of hypoperfusion include cold, clammy skin, renal impairment, liver dysfunction and/or impaired mentation. For inotropic agents to be indicated, patients should also have dilated, hypokinetic ventricles at echocardiography. However, although echocardiography is ideal, it may not always be possible, and clinical assessment of signs of hypoperfusion may be sufficient when urgent therapy is needed. When indicated, inotropes should be administered as soon as possible and discontinued as soon as organ perfusion is restored and/or congestion is relieved.[11,16-18]

The European Society of Cardiology guidelines state that inotropic agents are indicated only for patients with low systolic BP (SBP) or a low measured cardiac index in the presence of signs of peripheral hypoperfusion or congestion.[16] These indications are in agreement with the current American College of Cardiology/American Heart Association (ACC/AHA)[17] and Heart Failure Society of America (HFSA)[18] guidelines. They state that inotropes are indicated to improve symptoms and end-organ function in patients with low output syndrome, LV systolic dysfunction and SBP <90 mmHg despite adequate LV filling pressure.

The HFSA guidelines expand the indications for inotropic agents to also include patients with evidence of fluid overload and lack of response to intravenous diuretics and/or with reduced or worsening renal function. Regarding safety, the HFSA guidelines state that the administration of inotropic agents should be accompanied by continuous monitoring of BP and cardiac rhythm, with drug withdrawal or dose reduction to be considered in patients with symptomatic hypotension or development of tachyarrhythmias.[18] Notably, inotropes may also be indicated as a bridge to heart transplantation or mechanical assist device implantation or as palliation for symptoms in end-stage HF.[19] Similarly, the ACC/AHA guidelines state that long-term use of an infusion of a positive inotropic drug may be considered only as palliation for patients with end-stage disease who cannot be stabilized with standard medical treatment.[17]

2. Use of Inotropes in Clinical Practice

Data from registries show a wide variation in the proportion of patients treated with inotropes. This ranges from 7% in the OPTIMIZE-HF (see table I for a list of trial acronyms) registry[9] to nearly 25% in the EHFS-II.[20] Notably, the administration of inotropic agents is often not based on current guidelines.[11,16,18] Although a low SBP is considered a major indication for inotropic agents, among the 48 612 patients enrolled in OPTIMIZE-HF, those treated with inotropic agents were 6.5%, 4.5% and 3.2%, respectively, of the patients with an SBP of 120–139, 140–160 and >161 mmHg.[9] In ADHERE, only 8% of the patients receiving inotropes had a SBP <90 mmHg, and the SBP on admission was 121 ± 27 mmHg and 124 ± 29 mmHg in the patients receiving dobutamine and milrinone,

Table I. Trial name acronyms

Acronym	Definition
ADHERE	Acute Decompensated Heart Failure National Registry
CUPID	Calcium Up-Regulation by Percutaneous Administration of Gene Therapy In Cardiac Disease
DIG	Digitalis Investigation Group
EHFS-II	European Heart Failure Survey-II
FIRST	Flolan International Randomized Survival Trial
HORIZON-HF	Hemodynamic, echocardiographic, and neurohormonal effects of istaroxime, a novel intravenous inotropic and lusitropic agent: a randomized controlled trial in patients hospitalized with heart failure
OPTIME-CHF	Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure
OPTIMIZE-HF	Organized Program to Facilitate Life-Saving Treatment in Hospitalized Patients with Heart Failure
REVIVE-II	Randomised multicentre evaluation of intravenous levosimendan efficacy versus placebo in the short term treatment of decompensated heart failure
SURVIVE	Survival of patients with acute heart failure in need of intravenous inotropic support trial

respectively.[21] Data from EHFS-II indicate that more than 4% of patients with hypertensive HF (with high BP defined as >180/100 mmHg) received dobutamine or dopamine.[20] Thus, intravenous inotropic agents are still administered to a significant proportion of patients admitted for acute HF, despite some patients likely not needing them.

3. Adverse Effects

A thorough description of the general mechanisms of action of inotropic agents goes beyond the aims of this review and has been discussed in detail in many previous reviews.[10-12,15,22] Their untoward effects are, however, important to point out as they still represent the main limitation to this otherwise probably beneficial class of agents.

The main adverse effects of inotropic agents are tachyarrhythmias, myocardial ischaemia and myocardial damage. These last two effects are favoured by the concomitant vasodilatory action of most of the traditional inotropic agents that may cause hypotension, coronary hypoperfusion, myocardial ischaemia and necrosis.[12,23] Further mechanisms are the increase in myocardial oxygen consumption caused by tachycardia and enhanced myocardial contractility.[24] These negative attributes may have differential effects depending on the underlying cardiac substrate. Thus, a retrospective analysis of the OPTIME-CHF trial has shown an increased mortality with milrinone administration in patients with ischaemic heart disease, but not in those with non-ischaemic cardiomyopathy.[25]

The adverse effects on outcomes of inotropic agents are related to their mechanisms of action, based on an increase in cyclic adenosine monophosphate (cAMP) and intracellular calcium. Thus, inotropic agents with different mechanisms of action may be better tolerated.

4. Digoxin, the First and Only Oral Inotropic Agent Currently Available

Digoxin is a cardiac glycoside acting through inhibition of the sarcolemmal Na^+/K^+ ATPase pump, hence increasing intracellular calcium. Its beneficial effects on LV function, symptoms and exercise tolerance were first shown by prospective controlled trials[26] as well as studies based on digoxin withdrawal.[27]

The effects of digoxin on outcomes were assessed in the DIG trial.[28] In this study, 6800 patients in sinus rhythm and with an LV ejection fraction (LVEF) ≤45% were randomized to placebo or digoxin (mean dose 0.25 mg/day) and followed for an average of 37 months. Most patients were on ACE inhibitors and diuretics. The primary endpoint, all-cause mortality, was unaffected. However, there was a trend to a lower mortality rate for worsening HF (risk ratio [RR] 0.88; 95% CI 0.77, 1.01; $p = 0.06$), and a reduction in HF hospitalizations (RR 0.72; 95% CI 0.66, 0.79; $p < 0.001$) and cardiovascular hospitalizations (RR 0.87; 95% CI 0.81, 0.93; $p < 0.001$), as well as in the combined endpoints of all-cause death and HF hospitalizations and of HF deaths or hospitalizations, in the digoxin versus the placebo group.[28] Further analyses from the DIG trial showed the importance of serum digoxin levels with respect to the effects of digoxin on outcomes. Compared with placebo, digoxin administration to patients with serum digoxin concentrations of 0.5–0.9 ng/mL was associated with lower mortality (29% vs 33% on placebo; adjusted RR 0.77; 95% CI 0.67, 0.89), all-cause hospitalizations (64% vs 67% placebo; adjusted RR 0.85; 95% CI 0.78, 0.92) and HF hospitalizations (23% vs 33% placebo; adjusted RR 0.62; 95% CI 0.54, 0.72). Patients with serum digoxin concentrations ≥1.0 ng/mL had lower HF hospitalizations (29% vs 33% placebo; adjusted RR 0.68; 95% CI 0.59, 0.79), without any difference in mortality, than patients on placebo.[29]

The prespecified long duration of follow-up in the DIG trial might have had an influence on the results. In a retrospective study, data were analysed after only 1 year of follow-up: digoxin had favourable effects on all the major endpoints with a reduction in 1-year all-cause mortality (hazard ratio [HR] 0.87; 95% CI 0.76, 0.995; $p = 0.043$), cardiovascular mortality (HR 0.87; 95% CI 0.75, 1.01; $p = 0.072$), HF mortality (HR 0.66; 95% CI 0.52, 0.85; $p = 0.001$) and all-cause hospitalization

(HR 0.89; 95% CI 0.83, 0.96; p = 0.002).[30] This 13% reduction in 1-year mortality matched the statistical significance requirements prespecified for the DIG trial, designed to enrol at least 7000 patients with an LVEF <0.45, to have 90% power to detect a 12% reduction in mortality by treatment. However, DIG was designed to assess events at 3 years.[31]

The data from the DIG trial cannot be considered as conclusive. High doses of digoxin were used in this trial, with 70% of the patients on digoxin 0.25 mg/day, whereas retrospective analyses have indicated the beneficial effects of lower doses of digoxin targeted to serum digoxin concentrations of 0.5–0.9 ng/mL.[29] In addition, patients with a recent hospitalization were not included in the DIG trial and this study was performed before the introduction of β-adrenergic receptor antagonists (β-blockers), ICDs and CRT in the treatment of HF. It is likely, but not proven, that these additional treatments may increase the beneficial effects of digoxin, i.e. β-blockers and devices should decrease the role of arrhythmias and sudden cardiac death, which were the main causes for concern for digoxin, versus placebo, in the DIG trial. Therefore, a new randomized controlled trial studying the effects of digoxin on outcomes is needed.[32]

5. Drugs Acting via an Increase in Cyclic Adenosine Monophosphate

Dobutamine is an agonist of β_1-adrenergic receptors, which mediate the increase in myocardial contractility and heart rate, and, to a lesser extent, of β_2- and α_1-adrenergic receptors.[33] It has beneficial short-term effects on haemodynamic variables, namely cardiac output and pulmonary wedge pressure, but it has generally been associated with poorer outcomes. One of the first studies was an analysis of 471 patients enrolled in FIRST, a randomized controlled trial of continuous intravenous epoprostenol plus conventional therapy of ACE inhibitors, diuretics and digoxin, versus conventional therapy alone, in patients with advanced HF. This study was prematurely terminated because of a strong trend towards decreased survival in the patients treated with epoprostenol. An analysis of the patients included in this trial showed that those on dobutamine infusion (mean dose 9 μg/kg/min, range 5–12 μg/kg/min, median duration 14 days) had a higher rate of adverse events (worsening HF, need for vasoactive medications, resuscitated cardiac arrest, myocardial infarction), higher total mortality (85.3% vs 64.5%; p = 0.0006) and higher mortality (70.5% vs 37.1%; p = 0.0001) than the others.[34] Subsequent analyses showed trends towards increased mortality in the patients on dobutamine versus the control groups and a meta-analysis confirmed the increased risk of death with dobutamine administration.[35]

Dopamine acts on dopaminergic, β- and α-adrenergic receptors. It is used to improve diuresis and renal blood flow in patients with acute HF or those at risk of acute renal failure. However, only data collected in small study groups, and generally not from controlled studies, support these indications.[11] A recent meta-analysis of 61 trials, including 3359 patients at risk of acute renal failure, has shown a 24% increase in diuresis during the first 24 hours of dopamine administration in the absence of any effect on serum creatinine levels, acute renal failure development and death.[36]

Type 3 phospodiesterase inhibitors (milrinone, enoximone) inhibit cAMP hydrolysis and increase its concentrations in the cardiomyocytes and smooth muscle vascular cells, with an improvement in myocardial contractility, diastolic function and peripheral vasodilation.[37] Phosphodiesterase inhibitors have similar effects and limitations to sympathomimetic amines (namely, dobutamine) with, as the main difference, a greater peripheral and pulmonary vasodilating activity. In contrast to sympathomimetic amines, because their site of action is downstream from the β-adrenergic receptor, they also maintain their effects when the patient is on β-blockers.[38]

As in the case of dobutamine, the use of phosphodiesterase inhibitors has also been limited by the increased mortality associated with their administration. This is mainly based on retrospective analyses of trials and registries consistently showing an increase in mortality in the patients receiving intravenous phosphodies-

terase inhibitors.[20,21,25,35,39] In the only prospective randomized trial comparing intravenous milrinone with placebo, which included 951 patients with acutely decompensated HF, milrinone administration did not improve any of the prespecified outcomes and was associated with a higher rate of sustained hypotension requiring intervention (10.7% vs 3.2%; $p < 0.001$) and new atrial arrhythmias (4.6% vs 1.5%; $p = 0.004$).[40]

An increase in mortality in the patients receiving phosphodiesterase inhibitors has been consistently shown in long-term studies with the oral agents.[41-43] However, these data were collected before the introduction of β-blockers in HF treatment and there were data suggesting that lower doses of these agents might have had a better benefit to risk ratio. More recently, the effects on outcomes of low doses of oral enoximone has been assessed in 1854 patients with advanced HF on current medical treatment with β-blockers and ACE inhibitors.[44] Enoximone did not affect mortality, hospitalizations, symptoms or exercise capacity, assessed by the 6-minute walk test, compared with placebo.[44]

6. Other Mechanisms: The Case of Levosimendan

Levosimendan acts through sensitizing contractile proteins to calcium and opening ATP-dependent potassium channels;[45] the opening of potassium channels causes peripheral vasodilation. Levosimendan also has some degree of type 3 phosphodiesterase inhibitor activity, which can cause an increase in intracellular cAMP and calcium concentrations.

The two larger randomized controlled trials with levosimendan were the REVIVE-II trial and the SURVIVE trial, which compared levosimendan with placebo and dobutamine, respectively.[46] The primary endpoint of REVIVE-II was an improvement in the signs and symptoms of HF at 24 hours, 48 hours and 5 days. Levosimendan treatment was associated with a favourable effect on the primary endpoint ($p = 0.015$), with a larger decline in plasma B natriuretic peptide (BNP) levels and a shorter (2 days) duration of hospital stay. No difference in 90-day mortality was found (35 deaths on placebo [12%] vs 45 deaths [15%] with levosimendan; $p = 0.210$). Moreover, treatment with levosimendan was associated with a higher rate of adverse effects than placebo: hypotension (50% vs 36%), ventricular tachycardia (24% vs 17%) and atrial fibrillation (8% vs 2%).[46]

In the SURVIVE trial, 1327 patients with acute HF needing inotropic support were randomized to levosimendan or dobutamine.[47] Mortality at 180 days (primary endpoint) was similar between the two study groups (26% with levosimendan vs 28% with dobutamine; $p = 0.40$). The BNP decrease was larger in the patients assigned to levosimendan and the rate of worsening HF was greater in the dobutamine group, whereas the rate of new-onset atrial fibrillation was greater in the levosimendan group.[47]

Peripheral vasodilation and hypotension are the most likely causes of the lack of beneficial effects on survival of levosimendan compared with dobutamine.[12,23] The likelihood of hypotensive episodes was likely favoured by the study protocol as an insufficient response to diuretics and/or vasodilators was an inclusion criterion so that patients were already on maximal doses of these agents at the time of entry into the trial. In addition, a relatively high-dose 12 μg/kg intravenous bolus had to be administered before continuous infusion at 0.1 μg/kg/min. SURVIVE also suggested a greater efficacy of levosimendan compared with dobutamine in the patients on concomitant β-blocker therapy.[48] In these patients, mortality at day 5 was lower in the group treated with levosimendan than in those on dobutamine (1.5% vs 5.1%; RR 0.29; 95% CI 0.11, 0.78; $p = 0.01$). However, no difference was found at 14 and 31 days.[48]

Few data are available about oral levosimendan. In a recent randomized, double-blind, multicentre trial, 307 HF patients (New York Heart Association [NYHA] class IIIB–IV, LVEF ≤30%) on ACE inhibitors and β-blockers were randomized to placebo or oral levosimendan (1 mg once or twice daily for at least 180 days). There were no differences between levosimendan and placebo in symptoms and episodes of worsening

HF ($p = 0.567$), but there was an improvement in the Minnesota Living with Heart Failure quality-of-life score ($p < 0.001$) and a decrease in N-terminal proBNP (NT-proBNP, −30–40%; $p < 0.001$) in the levosimendan group.[49]

7. Novel Agents with Inotropic Effects

7.1 Istaroxime

Istaroxime is a new agent with inotropic and lusitropic effects. It acts through the stimulation of the sarcoplasmic reticulum (SR) calcium ATPase isoform-2 (SERCA2), which enhances calcium reuptake by the SR during diastole with the subsequent release of a greater amount during systole and an improvement in LV diastolic and systolic function. Istaroxime also inhibits the sarcolemmal Na^+/K^+ ATPase with an increase in intracellular calcium.[50]

The HORIZON-HF study assessed the haemodynamic effects of istaroxime in 120 patients admitted for acute HF with an LVEF ≤35% (mean 27% ± 7%) and a SBP between 90 and 150 mmHg (mean 116 ± 3 mmHg). Patients were randomized 3 : 1 to a 6-hour continuous infusion of three different doses of istaroxime (0.5, 1.0 or 1.5 μg/kg/min) or placebo. Compared with placebo, istaroxime was associated with a reduction in the pulmonary capillary wedge pressure (primary endpoint; $p < 0.05$ for all three doses), and with a decreased heart rate and increased SBP. The cardiac index increased and LV end-diastolic volume decreased significantly with istaroxime 1.5 μg/kg/min.[51] With respect to changes in LV diastolic function, istaroxime was associated with a dose-dependent increase in E′ velocity, E-wave deceleration time and a decreased E/E′ ratio. LV pressure-volume analysis showed a decrease in LV end-diastolic elastance after istaroxime administration.[52] There were no changes in neurohormones, renal function or troponin I.

These studies have shown a unique profile of haemodynamic effects for istaroxime compared with the other previously mentioned inotropic agents. Similar to the other inotropic agents, istaroxime is associated with a decrease in LV filling pressure and a tendency to greater cardiac output. However, in contrast to the other inotropic agents, istaroxime decreases heart rate and increases SBP. These effects are potentially useful in patients with low cardiac output and hypotension as the increase in BP might increase coronary and end-organ perfusion pressure, whereas the decrease in heart rate may allow a longer diastolic filling time, better coronary perfusion and decreased myocardial oxygen consumption.[23] In addition, this agent has a direct effect on LV diastolic function. However, further studies are needed.[53]

7.2 Cardiac Myosin Activators

Cardiac myosin activators are new agents that accelerate the transition of the actin-myosin complex from a weakly bound to a strongly bound configuration, thus increasing the number of myosin heads interacting with the actin filament while at the same time reducing the rate of nonproductive ATP hydrolysis. They increase the duration of systole and, hence, stroke volume in the absence of any change in intracellular calcium concentrations and in the rate of contraction so that the improvement in myocardial systolic function may occur in the absence of arrhythmogenesis and increased oxygen consumption.[13,54]

The administration of omecamtiv mecarbil (formerly called CK-1827452) in two different experimental models of HF with LV systolic dysfunction was associated with a sustained increase, without desensitization, in LV wall thickening, stroke volume (by 44 ± 6.5%) and cardiac output (22 ± 2.8%), with a decrease in LV end-diastolic pressure and in heart rate (−15 ± 3.0%) and no effect on BP. In contrast to catecholamines, omecamtiv mecarbil did not increase the rate of rise of LV pressure (dP/dt) but increased LV systolic ejection time (+26 ± 2.9%) and did not change myocardial oxygen consumption.[55]

These results in animal models have been confirmed by preliminary findings in patients with chronic HF and low LVEF, with a concentration-dependent increase in LV systolic ejection time, stroke volume and cardiac output, and a reduction in heart rate after omecamtiv mecarbil administration.[54] These agents may

potentially lower the threshold of myocardial ischaemia in patients with coronary artery disease as they increase systolic time at the expense of diastole with potential limitations to coronary perfusion and filling. However, no untoward effects on exercise tolerance have been shown after omecamtiv mecarbil administration to patients with ischaemic cardiomyopathy.[56] Therefore, omecamtiv mecarbil could be a promising agent for the treatment of HF patients. A programme of clinical studies is ongoing.[55]

7.3 Urocortin

The urocortin peptides Ucn1, Ucn2 and Ucn3 are recently isolated members of the corticotropin-releasing factor (CRF) family. These peptides act through the two G protein-coupled CRF receptors CRF_1 (localized almost exclusively in the central nervous system) and CRF_2 (present in both brain and peripheral tissues, including the myocardium and blood vessels, where it is strongly expressed). In contrast to Ucn1, which binds similarly to both receptor subtypes, Ucn2 and Ucn3 are selective for the CRF_2 receptors.[57,58] The administration of urocortins, namely Ucn2 or Ucn3, in experimental models of HF has been associated with an increase in cardiac output and a fall in peripheral resistance, left atrial pressure and mean arterial pressure. It has induced a persistent, dose-dependent decrease in plasma vasopressin, renin activity, aldosterone, natriuretic peptides and endothelin-1 plasma levels, with an acute rise in adrenocorticotrophic hormone (corticotrophin) and cortisol levels. Lastly, a dose-dependent, sustained increase in diuresis, natriuresis and creatinine clearance was found.[58-60] A favourable interaction with diuretic treatment that leads to increased diuretic responsiveness and blunting of furosemide-induced renin increase has also been described.[61] Ucn3 (stresscopin) is now undergoing further assessment in larger clinical trials in patients with HF.

7.4 Metabolic Modulators

The mechanism of action of metabolic modulators is mainly based on a shift in energy utilization from free fatty acids (FFAs) to glucose. FFAs are the preferred metabolic substrate used by the heart to produce energy. This is primarily due to the fact that FFA oxidation generates a greater amount of ATP than the glycolytic pathway, although a greater amount of oxygen is required and, hence, myocardial efficiency, i.e. the ATP production to oxygen consumption ratio, is lower.[62,63] Moreover, high levels of FFA derivatives may inhibit pyruvate dehydrogenase and glucose oxidation, resulting in increased conversion of pyruvate to lactate, tissue acidosis and impaired myocyte contractility. Metabolic modulators were initially developed for patients with recurrent angina pectoris and/or with diabetes mellitus but their mechanisms of action also make them potentially useful for the treatment of HF.[64,65]

Perhexiline is an inhibitor of carnitine palmitoyl transferase-1, an enzyme critical to mitochondrial FFA uptake. Its inhibition causes the shift of myocardial substrate from FFAs to carbohydrates. Early trials demonstrated that perhexiline used at doses of 100 to 200 mg twice daily effectively relieves anginal symptoms and improves exercise tolerance, but later studies demonstrated that perhexiline has a narrow therapeutic index with an increased risk of hepatotoxicity and peripheral neuropathy. Toxicity is a result of phospholipid accumulation mediated by carnitine palmitoyl transferase inhibition, which mainly occurs in patients with slowed hepatic metabolism (cytochrome P450 [CYP]2D6) of perhexiline. Further studies demonstrated that cautious dose titration to maintain plasma concentrations within a relatively narrow range may avoid serious adverse effects.[66] However, further studies are needed, especially given the safety concerns of this agent.

One small, short-term trial has suggested a significant benefit of perhexiline in patients with chronic HF.[67] Fifty-six patients with HF (LVEF ≤40%, NYHA class II/III) were randomized to perhexiline or placebo with serial measurements of blood perhexiline levels to prevent toxicity. Eight weeks of perhexiline administration was associated with improvements in peak oxygen uptake ($\dot{V}O_2$) [from 16.1 ± 0.6 to 18.8 ± 1.1 mL/kg/min; $p < 0.001$], the Minnesota Living with Heart Failure quality-of-life score and LVEF (24 ± 1% to 34 ± 2%; $p < 0.001$), with no significant adverse effects.

Other available carnitine palmitoyl transferase-1 inhibitors include trimetazidine, ranolazine and etomoxir. Etomoxir is no longer studied because of its adverse effects. In contrast, preliminary data from small studies have shown encouraging results with trimetazidine and ranolazine.

Trimetazidine has been associated with an improvement in NYHA functional class, a reduction in LV end-systolic volume and an increase in LVEF, compared with conventional therapy, in patients with HF caused by LV systolic dysfunction.[68-70] An improvement in exercise tolerance and outcomes has also been shown in a small, retrospective study.[71] Changes in LV function after trimetazidine are associated with an increase in the phosphocreatine to adenosine triphosphate (PCr/ATP) ratio, assessed by ^{31}P-magnetic resonance spectroscopy,[72] and by reduced FFA oxidation and unchanged myocardial oxidative rate, implying increased glucose oxidation.[70] These data suggest that a drug-induced change in myocardial metabolism, with an increase in glucose compared with FFA oxidation, may have beneficial effects on myocardial function.

Ranolazine is a new drug that acts through the inhibition of the late sodium channel current, hence preventing intracellular calcium overload during myocardial ischaemia, and through the inhibition of FFA oxidation. It is now indicated for the treatment of angina. However, beneficial effects on LV diastolic function, likely mediated by the prevention of intracellular calcium overload, [73,74] and on LV remodelling and myocardial fibrosis have also been shown in experimental models.[75]

Glucagon-like peptide (GLP)-1 and its analogues are new antidiabetic agents. Beneficial effects of GLP-1 on LVEF and exercise tolerance have been shown in patients with HF in some,[76,77] but not all,[78] of the studies. As with the previous compounds, a larger, controlled trial with clinical endpoints is needed.

7.5 Agents Acting on SERCA2a

Calcium reuptake into the SR occurs by a calcium-dependent ATPase (SERCA2a), which is downregulated in HF. This deficiency in SERCA2a has many consequences: (i) reduced and slower calcium reuptake during cell relaxation causing impaired LV diastolic function; (ii) increased free intracytoplasmatic calcium in the cardiomyocytes, a mechanism that favours cardiac dysfunction and tachyarrhythmias; and (iii) reduced calcium accumulation within the SR, with a reduction in the amount of calcium released by the SR during systole and, hence, reduced myocardial contractility.[79]

SERCA2a is a major target for treatment of HF. In addition to istaroxime, another agent under development is an adenovirus-associated vector (AAV) carrying the gene for SERCA2a (AAV1/SERCA2). In the CUPID trial,[80] AAV1/SERCA2 was administered as a single intracoronary infusion to nine patients with end-stage HF (NYHA class III/IV, LVEF ≤30%, peak $\dot{V}O_2$ <16 mL/kg/min). Several of these patients showed an improvement from baseline in parameters related to HF severity (NYHA class, Minnesota Living with Heart Failure Questionnaire, 6-minute walk test, peak $\dot{V}O_2$, NT-proBNP, LVEF and end-systolic volume). Two patients who failed to improve had pre-existing anti-AAV1-neutralizing antibodies. No serious adverse events occurred. These data supported the initiation of a larger phase II trial.[80]

In addition to gene therapy, a class of novel small molecules, acting as allosteric compounds, is under development and has been found to modulate SERCA2a activity and increase myocardial contractility without increasing energy utilization in preclinical models.[13] Other studies of gene therapy of HF are based on the inhibition of G protein-coupled receptor kinase 2 (GRK2), an enzyme that is upregulated in HF causing β-adrenergic pathway dysfunction.[81] These agents would be expected, however, to cause increased cardiac sympathetic drive, with the potential adverse effects of sympathetic stimulation.

8. Conclusions

A fraction of patients with acutely decompensated HF and signs of peripheral hypoperfusion and fluid overload may need treatment with agents with inotropic properties. Current inotropic

agents have been associated with poorer outcomes, but no alternative medical treatments are available to improve the abnormal haemodynamics and end-organ perfusion of patients with low cardiac output. New agents with different mechanisms of action, including sarcolemma and SR ion currents, LV systole duration and myocardial metabolism, seem promising and are associated with a lower likelihood of untoward effects. However, larger studies are needed to prove this hypothesis.

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