INTERNATIONAL CARDIOVASCULAR FORUM JOURNAL

ISSN 2409-3424 (online) 2410-2636 (print)

SEPTEMBER 2019
ICFJ 2019 VOL 18
PAGES 1 - 40

INSIDE THIS ISSUE:

www.icfjournal.org

AFFILIATED WITH THE

MALTESE CARDIAC SOCIETY
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Part 2 of the special issues on
"Innovative Pharmacological Targets and Approaches in Heart Failure"

Contents

Review Articles

International Cardiovascular Forum Journal 18 (2019)
DOI: 10.17987/icfj.v18i0.609

sGC Stimulators and Activators

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Abstract

Nitric oxide (NO)-soluble guanylate cyclase(sGC)-cGMP signalling is impaired in HF syndromes, which could predispose to vascular oxidative stress. Nitrates directly stimulate cGMP, but are limited by tolerance. Therapeutic targets that aim at increasing cGMP concentrations have therefore been explored. Recently, two classes of drugs have been discovered, the sGC activators and the sGC stimulators, which target two different redox states of sGC: the NO-sensitive reduced (ferrous) sGC and NO-insensitive oxidized (ferric) sGC, respectively. Cinaciguat is an activator and riociguat and vericiguat are sGC stimulators. Vericiguat is the most advanced agent in its clinical trial programme with two completed phase IIb studies, SOCRATES -REDUCED in HFrEF and SOCRATES-PRESERVED in HFpEF, with mixed results on NT-proBNP. The ongoing VICTORIA trial in HFrEF will study 4,872 participants with a mortality/morbidity end-point and VITALITY HFpEF trial will study 735 participants, with a quality of life end-point.

Keywords: heart failure; sGC activators; sGC stimulators; vericiguat

Citation: Tolppanen H, Ponikowski P. sGC Stimulators and Activators. International Cardiovascular Forum Journal. 2019;18:609.2-6
DOI: 10.17987/icfj.v18i0.609

Introduction

The nitric oxide (NO)-soluble guanylate cyclase(sGC)-cGMP cascade is one of the key regulatory pathways in cardiovascular physiology. In heart failure (HF), the NO-sGC-cGMP signaling is impaired mainly due to reduced NO bioavailability and the altered redox state of sGC, making it unresponsive to NO. These changes might be a major source of vascular oxidative stress in the course of HF.

Nitrates, which have traditionally been used to treat acute and chronic HF, and angina, act through this cascade by increasing free NO by directly stimulating cGMP. However, this upstream stimulation of available NO is limited by tolerance, and it causes reactive oxygen species production and endothelial dysfunction. Therapeutic targets that aim at increasing cGMP concentrations have therefore been explored (Figure 1). Recently, two classes of drugs have been discovered, the sGC activators and sGC stimulators, which target two different redox states of sGC: the NO-sensitive reduced (ferrous) sGC and NO-insensitive oxidized (ferric) sGC, respectively (Table 1).[1] Phosphodiesterase type 5 inhibitors (PDE5, such as sildenafil) also act in the same regulatory pathway, but downstream of adenylate cyclase by inhibiting the degradation of cGMP. Cinaciguat, riociguat and vericiguat are direct sGC activators that act independently of nitric oxide.

Physiology of cGMP and the NO-sGC-cGMP signaling cascade

NO-sGC-cGMP signalling starts in the intact endothelium of blood vessels and the myocardium by hormonal and physical stimuli causing endothelial nitric oxide synthase (eNOS) to generate NO. NOS-derived NO diffuses to the neighbouring tissues, such as vascular smooth muscle cells or cardiomyocytes, where it binds to the cytosolic enzyme sGC. This NO-sGC binding catalyzes the conversion of guanosine triphosphate (GTP) to cGMP. cGMP activates protein kinase G (PKG), and these together lead to the decrease in intracellular free calcium resulting in the relaxation of vascular smooth muscle cells as one major physiological effect in the cardiovascular system.[2-4]

The best established role of GCs is within the vessel wall and the myocardium, as the receptors of NO signalling are in vascular smooth muscle and in the myocardium, where the sGC expression is at its highest. In vascular smooth muscle cells and cardiac myocytes with sGC-derived cGMP production NO generation from vascular, endocardial, and intramyocardial capillary endothelial cells stimulates sGC in coronary vessel walls as well as directly in cardiomyocytes.[1,5,6] Experiments performed in animal models have shown cGMP deficiency to play a crucial role in the development of diastolic dysfunction,

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ISSN: 2410-2636

Table 1. Characteristics of sGC stimulators and sGC activators

	sGC Stimulator	sGC activator
Defect	Upstream of sGC: insufficient sGC stimulation	sGC itself defective: sGC heme dissociation
Causative mechanism	Endothelial dysfunction = eNOS insufficiency e.g.; owing to oxidative stress, ADMA, inflammatory activation	Oxidative injury to the heme group of sGC
Role of NO	NO deficiency: Reduced eNOS-derived No bioavailability	NO resistance: Dysfunctional NO receptor: sGC low despite bioavailable NO
Molecular principle	NO-independent sGC stimulation by mimicking NO	NO-independent sGC activation by mimicking reduced heme + prolongation of sGC protein half-life under oxidative stress

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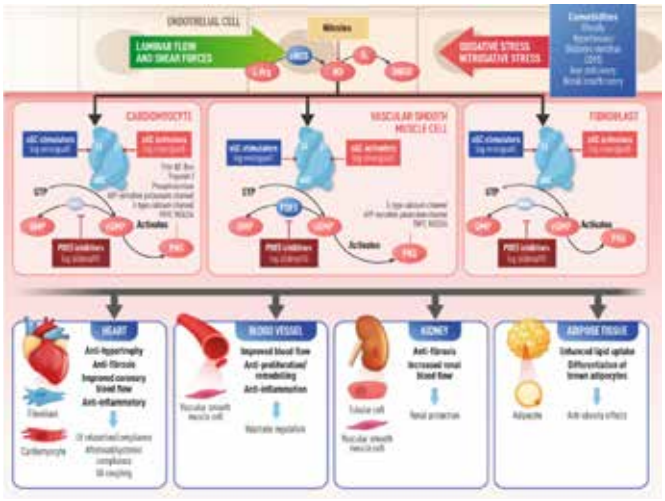

Figure 1. sGC-derived cGMP generation in various cell types couples endothelial NO synthesis to function of organs including the heart and kidneys. cGMP is a second messenger of crucial importance to organ function. Reduced cGMP availability caused by NO deficiency due to endothelial dysfunction can be actively restored by sGC stimulation in smooth muscle cells, cardiomyocytes or fibroblasts, whereas PDE5 inhibition can only inhibit cGMP degradation. Restoration of cGMP signaling has beneficial effects in hearts, blood vessels, and kidneys and could also impact on adipose tissue. Legend: L-Arg = L-Arginine, O2 = peroxide, ONOO– = peroxynitrite, TRPC = transient receptor potential channels

reduced cardiac output and increased afterload.[4] In addition to the lusitropic effects of cGMP, it reveals also important anti-inflammatory and antifibrotic effects.[7]

The cGMP activity within the cell is regulated by both NO-dependent and by NO-independent pathways. The NO-dependent cGMP pool is regulated by NO availability and the activity of sGC. PDE5 inhibition (e.g. sildenafil) increases the cytoplasmic levels of cGMP by inhibiting its degradation. This process is limited to tissues, in which the PDE5 is up-regulated, such as the corpus cavernosum and pulmonary vasculature, and may be under-expressed in myocardium. The NO-independent regulatory pathways include natriuretic peptides, beta-adrenergic stimulation, prostacyclin-cAMP pathway and endothelial pathways.

Role of the NO-sGC-cGMP cascade in heart failure

The NO-sGC-cGMP signaling pathway plays a major role in protection against myocardial injury, ventricular remodeling, and the cardio-renal syndrome.[1] HF may be viewed as a syndrome in which NO deficiency results in an insufficient stimulation of sGC in the systemic, coronary, pulmonary, and renal vasculature, leading to the impaired protection against ischaemia/reperfusion injury, myocardial dysfunction, adverse left ventricular remodeling, and the cardio-renal syndrome.[1,8]

NO availability and functionality of sGC depends on the redox status. In HF the endogenous levels of NO are decreased due to various derangements in NO-sGC-cGMP signalling, such as a down-regulation of the endothelial NO synthase (eNOS), inactivation of NO by superoxide anions, increased plasma concentrations of an endogenous eNOS inhibitor, and an altered redox state of sGC due to oxidative stress.[1] All these abnormalities result in reduced levels of the NO-sensitive form of sGC. Neurohormonal activation and release of inflammatory mediators in HF may further reduce NO bioavailability, ultimately leading to an insufficient stimulation of the NO receptor, sGC, and subsequently the diminished production of its second messenger cGMP.[9,10] Reduced cGMP availability leads to endothelial dysfunction, vasoconstriction, vascular stiffness and adverse remodeling, and decreased renal and coronary blood flow with increasing impairment of respective organ function.[1,4,11] Dysregulation of the NO-cGMP-pathway by inflammation and oxidative stress resulting in endothelial dysfunction also negatively affects coronary perfusion[2,12] and promotes myocardial damage.[12]

In HFrEF, cGMP deficiency leads to impaired endothelium-dependent regulation of vessel tone, resulting in an increased afterload and impaired myocardial microcirculation. cGMP dependent PKG modulates pathological Ca2+ signalling involved in myocardial hypertrophy.[13] HFpEF, in particular, is an inflammatory condition accompanied in many patients by metabolic syndrome, obesity, diabetes mellitus (DM), arterial hypertension, and chronic obstructive pulmonary disease (COPD). The NO-sGC-cGMP axis plays a major role in the relaxation abnormalities that occur in HFpEF. Titin is a large cardiomyocyte cytoskeletal protein that modulates passive tension and stiffness of myocardial fibres. When titin is phosphorylated by cGMP-dependent protein kinase G (PKG), myocardial fibres stretch appropriately and allow ventricular relaxation and diastolic filling as well as recoil.[14,15] Indeed, hypophosphorylation of titin results in increased myocardial

International Cardiovascular Forum Journal 18 (2019)
DOI: 10.17987/icfj.v18i0.609

stiffness that leads to suboptimal ventricular filling and decreased cardiac output. Since dysfunction of the NO-sGC-cGMP axis also leads to vasoconstriction and vascular stiffness, the combination of impaired ventricular relaxation and increased afterload renders HF patients symptomatic during an increased demand, such as during exercise.[12] Indeed, impaired exercise-induced NO release may also contribute to reduced exercise capacity.[16] The increased myocardial stiffness in HFpEF patients was shown to be decreased after administration of PKG.[17] However, the results with the administration of PDE5 inhibitor (sildenafil) have been disappointing in this context in HFpEF patients.[18,19]

Secondary pulmonary hypertension (PH) in patients with left heart disease is an indicator of persistently increased LV filling pressures. As many as 33 to 48% of HFrEF and up to 83% of HFpEF patients may have secondary PH, and PH is associated with poor outcomes in these patients.[20,21] In addition to passive backward failure, a vasoreactive component may, in certain cases, aggravate the resulting PH.[22] The effects of riociguat and sildenafil were studied in an animal model with transverse aortic constriction-induced left ventricular hypertrophy and dysfunction, and secondary PH. Riociguat had a more pronounced effect on vascular remodeling compared to sildenafil. Treatment with riociguat and sildenafil maintained LV and RV function and decreased PVR and RV pressure, while in placebo treated animals LV and RV function deteriorated.[23] However, the clinical results for the PDE5 inhibitors came out negative, possibly due to lack of PDE5 overexpression and/or insufficient proximal sGC stimulation. In contrast, high sGC expression in the cardiac muscle and enhanced sGC-derived cGMP levels even in the absence of NO indicate a promising potential for sGC stimulators. In patients with PH associated with systolic left ventricular dysfunction, reduced PVR and SVR, improved stroke volume and cardiac index as well as improved quality of life (QoL) were seen when the treatment with riociguat was administered.[24]

Action of sGC stimulators and sGC activators

sGC consists of an α/β-heterodimeric protein with a prosthetic ferrous heme group. The heme group can exist in different redox states, which, in addition to its NO-sensing capability, may enable sGC to modulate intracellular redox homeostasis. The presence of a reduced Fe^{2+} (ferrous) heme group is crucial for NO-sensing and NO-dependent sGC stimulation. Oxidative stress favours heme-free sGC, which is unable to respond to NO, and can be regarded as a dysfunctional form of the enzyme. Oxidative stress may make sGC unresponsive to endogenous and exogenous NO either through reducing NO bioavailability or by altering the redox state of sGC.[25] In HF, endothelial dysfunction and an inflammatory state lead to increased formation of reactive oxygen species, reduced NO bioavailability, and shifts in sGC toward the oxidized and NO-unresponsive, heme-free form of sGC.[26] sGC stimulators target the heme-containing non-oxidized form of sGC by binding on the regulatory domain and triggering cGMP production. The sGC stimulators have a dual mode of action; they sensitize sGC to low levels of NO and can stimulate sGC directly in the absence of any endogenous NO. The sGC stimulators work NO-independently but their efficacy is further enhanced when endogenous NO is present, even at low concentrations. [1] By contrast, sGC activators specifically activate the NO-unresponsive, heme-free form of the enzyme irrespective of NO bioavailability.[25]

sGC activators: cinaciguat

Cinaciguat is a potent and selective sGC activator, which acts on sGC in its oxidized (Fe^{3+}) state and even the heme free form, independently of NO. The oxidation or absence of the heme moiety increases the effect of cinaciguat on the sGC causing a significant cGMP increase.[25,26] Animal studies with cinaciguat have shown arterial and venous vasodilatation and antihypertrophic and antifibrotic effects.

The first clinical trial with cinaciguat confirmed haemodynamic efficacy, with a reduction in post- and preload and a secondary increase in cardiac output, while preserving renal function. The COMPOSE trial compared multiple doses of cinaciguat in patients with acute HF with LVEF <40% and an elevated pulmonary capillary wedge pressure (PCWP) >18 mmHg.[27] High doses (50, 100 and 150 mcg / h) were associated with an excessive reduction in blood pressure, leading to premature discontinuation of the study. A parallel study included patients with chronic HF with elevated PCWP ≥18 mmHg, and the effects of cinaciguat were evaluated using invasive haemodynamic measurements.[28] In patients treated with cinaciguat, significant decreases in PCWP and right atrial pressure, systemic and pulmonary vascular resistance, and a significant increase in cardiac index were observed. A high rate of hypotension also led to the premature termination of this study. Subsequently, the study was criticized, as with other studies with vasodilators, because the baseline blood pressure was not high enough, ultimately biasing the estimate of the clinical potential of the molecule.[29]

Riociguat (sGS stimulator)

Riociguat is a novel potent sGC stimulator, which was mainly developed for primary pulmonary artery hypertension (PAH), but also for PAH caused by left-heart disease. Its use is currently approved in the treatment of primary PAH and inoperable chronic thromboembolic pulmonary hypertension (CTEPH).

Two trials have been published in patients with HF. The small phase IIa DILATE-1a study showed in 39 patients with HFpEF and PAH, that a single oral dose of riociguat decreased systolic blood pressure, increased systolic volume, but did not alter filling pressures or mean pulmonary arterial pressure.[29] The LEPHT trial then included approximately 200 patients with chronic HF with LVEF <45% with mean pulmonary arterial pressure ≥25 mmHg (confirmed by right heart catheterization).[30] Patients were randomized into four groups: placebo and three riociguat doses for 16 weeks. The primary outcome of decrease in mean pulmonary artery pressure was not significant, whereas significant improvements were observed in secondary end-points of increased cardiac index, and decreased systemic and pulmonary vascular resistance (invasive haemodynamic measurements).

Vericiguat (sGC stimulator)

The first experiences with an sGC stimulator in patients with HF and secondary PH encouraged the continued investigation of this novel drug class in HF at low doses. For further studies in HF, the

once daily compound vericiguat was chosen due to its optimized pharmacokinetic profile. Vericiguat was investigated in two phase IIb studies in HFrEF (SOCRATES -REDUCED) and HFpEF (SOCRATES-PRESERVED), in which patients were included during a hospitalization for acute HF, and the end-point was a decrease in circulating natriuretic peptides. The SOCRATES-PRESERVED randomized HFpEF patients (LVEF≥ 45%) into 5 parallel dose arms or placebo for 12 weeks to characterize safety, tolerability, and pharmacologic effects. The study was negative in its primary outcomes of decreasing levels of natriuretic peptides or reducing left atrial volume.[31] The SOCRATES-REDUCED showed a statistically positive effect on NT-proBNP only with the highest doses in secondary analysis[32], and the agent is currently being tested in a phase III study for HFrEF, the ongoing VICTORIA trial[33], with the primary hypothesis that vericiguat is superior to placebo in increasing the time to first occurrence of the composite of cardiovascular death or HF hospitalization in a planned 4,872 participants with HFrEF with results expected in 2020. The VITALITY-HFpEF trial plans to assess whether treatment with vericiguat 10 mg or 15 mg in patients with HFpEF improves the KCCQ PLS (Kansas City Cardiomyopathy Questionnaire Physical limitation score) compared to placebo after 24 weeks of treatment in a planned 735 participants, with results also expected in 2020.[34]

Conclusions

Experimental and preliminary clinical data suggest that sGC stimulators are promising molecules to be studied for a potential role in the future HF treatment strategy. The results of ongoing morbidity and mortality trial with vericiguat in patients HFrEF are expected.

Declarations of interest

The authors declare no conflict of interest.

Acknowledgements

The authors state that they abide by the authors' responsibilities and ethical publishing guidelines of the International Cardiovascular Forum Journal.

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DOI: 10.17987/icfj.v18i0.609

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Myosin Activators

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Abstract

Inotropes historically all increased intra-cellular calcium levels and they commonly caused intracellular Ca2+ overload and triggered malignant arrhythmias. The myosin activators, such as Omecamtiv Mecarbil (OM), increase myosin activity and function, and modify acto-myosin interaction through calcium-independent mechanisms. OM is a selective cardiac myosin activator that binds specifically the catalytic domain of cardiac myosin without any significant effect over other types of non-cardiac myosin. It increases the speed of ATP hydrolysis and, therefore, accelerates the transition rate to a strongly bound force-producing state, increases the number of myosin heads that interact with actin filaments and increases the proportion of time they are in a force producing state. OM decreases the inefficient use of non-contractile energy. OM has been studied in 4 phase II clinical trials with more than 1,300 patients with heart failure. The GALACTIC-HF trial is a nearly 8,000 patient HFrEF mortality/morbidity trial which started recruiting in January 2017 and should be completed soon.

Keywords: heart failure; myosin activators; omecamtiv mecarbil

Citation: Rosano GMC, Ponikowski P. Myosin Activators. International Cardiovascular Forum Journal. 2019;18:7-10. DOI: 10.17987/icfj.v18i0.611

Introduction

The term inotropes is used to describe all pharmacological agents that directly improve the contractile function of the heart.[1-3] Therefore, agents that alter cardiac performance by modifying the cardiac calcium ion (Ca^{2+}) balance and its flux into the cardiac myocyte are included under this definition.[4] These agents increase left ventricular systolic pressure generation per unit time (dP/dt) and thereby improve cardiac output and stroke volume. Some of these agents may also affect vascular tone and this effect may further improve their cardiac effects.

When used chronically these drugs have a detrimental effect on myocardial energetics and decrease the adenosine triphosphate (ATP) to adenosine diphosphate (ADP) ratio. This, in turn, reduces the re-uptake of Ca^{2+} from the sarcoplasmic reticulum, causes intracellular Ca^{2+} overload and triggers malignant arrhythmias. [4} However, newer agents that improve myocardial performance and contraction by novel means have been developed. These agents may improve myocardial energetics and function through mechanisms of action that are distinct from conventional Ca^{2+}-acting medications.

Inotropic agents improve ventricular systolic performance by affecting the myocardial contractile apparatus. The three main components of this apparatus are the Ca^{2+} cycling elements responsible for the flow and uptake of myocardial Ca^{2+} and the contractile components. Myosin is the active enzyme of the myocardial sarcomere and converts the energy stored as high energy phosphates into contractile force. Myosin is constituted of head, neck and tail domains. The head domain binds the actin and moves along it, the neck binds the light chains while the tail regulates motor activity by interacting with cargo molecules and other myosin sub-units. Molecules of myosin aggregate to form thick filaments that are the core of the muscle contractile unit. They are inter-digitated with the thin filaments of actin on which they pull to mediate contraction.[5,6] Troponin and tropomyosin enable the intracellular Ca^{2+} status and other factors to regulate the myosin-actin interaction.

Myosin activators

Myosin has more recently become an attractive therapeutic target as it elicits myocardial contraction and is involved in the ATP hydrolysis outside of the myosin mechanochemical cycle. Newer therapeutic agents have been developed aimed at increasing myosin activity and function. Myosin activators are compounds that modify acto-myosin interaction through calcium-independent mechanisms. The first in class myosin activator omecamtiv mecarbil, that is currently completing its clinical development, is a small molecule that binds directly to the enzymatic domain of cardiac myosin and directly activates it in a calcium-independent manner by modulating its activity. [7] Omecamtiv mecarbil is a selective cardiac myosin activator that binds specifically the catalytic domain of cardiac myosin without any significant effect over other types of non-cardiac

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ISSN: 2410-2636

International Cardiovascular Forum Journal 18 (2019)
DOI: 10.17987/icfj.v18i0.611

myosin. The omecamtiv mecarbil binding site is the amino acid serine 148, which is about 6.5 ηm from the actin-binding interface. The conformational changes induced by omecamtiv mercabil increase the speed of ATP hydrolysis and, therefore, accelerate the transition rate to a strongly bound force-producing state. Omecamtiv mecarbil increases the number of myosin heads that interact, in the force producing activity, with actin filaments during depolarization (see figure 1). This compound increases the proportion of time the myosin head is tightly bound to actin in a force producing state. Binding to myosin it decreases the inefficient use of non-contractile energy.[7] Omecamtiv mecarbil does not increase the rate of force generation (dP/dt) but increases the total amount of time spent in a contraction state.

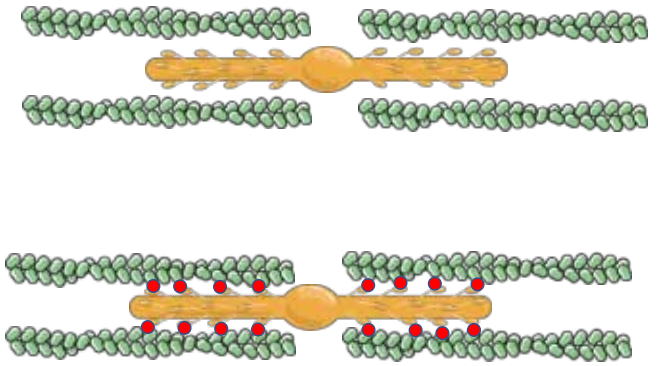

Figure 1. Omecamtiv mecarbil activates cardiac myosin and increases the ATP hydrolysis and accelerates the formation of a strong actin-myosin complex, linked to increased contractile force

Omecamtiv mecarbil

Omecamtiv mecarbil lengthens the total duration of systole by increasing the entry rate of myosin into a force-generating state. This effect entails more active cross-bridge formation and a consequently stronger cardiac contraction. Omecamtiv mecarbil infusion (bolus and 24-hour) induced a reduction of heart rate, vascular peripheral resistance and mean left atrial pressure, and left ventricular end diastolic pressure in two canine models of heart failure. These effects were associated with systolic wall thickening, and improvements in stroke volume (SV) and cardiac output (CO). Omecamtiv mecarbil increased systolic ejection time (SET) and cardiac myocyte fractional shortening without increasing left ventricular dP/dtmax, myocardial oxygen consumption nor myocyte intracellular calcium.

Omecamtiv mecarbil has been studied in nine phase I clinical trials including over 200 healthy volunteers and four phase II clinical trials with more than 1,300 patients with heart failure. The first-in-man phase I study in 34 healthy men aimed to establish the maximum tolerated dose and plasma concentrations after i.v. infusions of omecamtiv mecarbil (0.005–1 mg/kg/h).[8] This study reported a dose-dependent improvement of cardiac systolic function parameters including left ventricular fractional shortening (LVFS 8±1%), left ventricular ejection fraction (LVEF, 7±1%), systolic ejection time (SET, 85±5 ms), stroke volume (SV, 15±2 mL). These effects were not associated with any increase in heart rate. The study also found that the maximum tolerated dose was 0.5 mg/kg/h and that doses of 0.75 mg/kg/h or higher were associated with troponin elevation.

Cleland et al. assessed the effects of omecamtiv mecarbil on cardiac function in a double-blind, placebo-controlled, dose-ranging phase II study including 45 patients with heart failure with reduced ejection fraction (HFrEF).[9] Patients were divided into 5 cohorts of 8 to 10 patients and allocated to receive omecamtiv mecarbil infusion in escalating doses. Omecamtiv mecarbil plasma concentrations showed a significant direct relation with the change in SET and SV. Reductions in LV end-systolic volume and LV end-diastolic volume (LVEDV) were observed with higher plasma concentrations (>500 ηg/mL). Myocardial ischaemia was induced at very high concentrations (1750 and 1350 ηg/mL) in two patients.

Given the suggestion of a possible precipitation of myocardial ischaemia at very high doses, the safety and tolerability of omecamtiv mecarbil during exercise was studied in 94 heart failure patients with ischaemic cardiomyopathy. All patients had angina and entered a double-blind, randomised, placebo-controlled trial.[10] Patients were randomised to receive omecamtiv mecarbil or placebo at escalating doses previously shown to improve systolic function. The study included 2 exercise treadmill tests at baseline and one before the end of the 20-hour omecamtiv mecarbil infusion. Omecamtiv mecarbil was dosed to target different plasma levels in the two cohort studied (~295 ηg/mL and ~550 ηg/mL). Patients who tolerated IV infusion continued with oral omecamtiv mecarbil or placebo for 7 days. No patients receiving omecamtiv mercabil and one patient in the placebo arm developed limiting angina during the exercise test. The results of this study showed that in heart failure patients with ischaemic cardiomyopathy and angina omecamtiv mecarbil is well tolerated and there is no evidence that it may induce myocardial ischaemia.

ATOMIC-AHF trial.

The ATOMIC-AHF (Acute Treatment with Omecamtiv Mecarbil to Increase Contractility in Acute Heart Failure)[12] was a phase IIb double-blind, randomised, placebo-controlled sequential cohort study aimed at investigating the pharmacokinetics/pharmacodynamics, safety, and efficacy of omecamtiv mecarbil infusion in hospitalised patients with acute heart failure. The primary end-point of the study was improvement in dyspnoea assessed using the Likert scale. The study included 606 patients who were treated in three sequential cohorts with a 48-hour omecamtiv mecarbil infusion in escalating dose regimens targeting a mean plasma concentration of 115, 230 and 310 ηg/mL.

The response rates of dyspnoea relief throughout the 48 hours did not differ between placebo groups and the three treatment cohorts (p=0.316). A greater relief of dyspnoea was noted in the high-dose omecamtiv mecarbil cohort compared with placebo. Although more patients receiving omecamtiv mecarbil had elevated troponins compared to placebo, no clear relationship to omecamtiv mecarbil concentrations was found. The echocardiographic sub-study patients receiving omecamtiv mecarbil were found to have a significantly greater reduction in LVESD ($p<0.05$) and a significantly greater plasma concentration-dependent increase in SET ($p<0.0001$).

A similar occurrence of serious adverse events was observed in the placebo and omecamtiv mecarbil groups at 30 days [placebo n=70 (23%), omecamtiv mecarbil n=66 (22%)]. All-cause and heart failure rehospitalisation as well as occurrence of cardiovascular deaths were similar between placebo and omecamtiv mecarbil groups. This study, therefore showed that i.v. omecamtiv mecarbil did not improve dyspnoea, although an improvement in the high-dose group was observed. However, omecamtiv mercabil increased SET, decreased LVESD and was well tolerated, thereby supporting its further investigation in a phase III mortality/morbidity study.

COSMIC-HF trial

The Chronic Oral Study of Myosin Activation to Increase Contractility in Heart Failure (COSMIC-HF trial) was a phase II, randomised, parallel-group, double-blind, placebo-controlled study conducted in 448 patients with chronic HFrEF with LVEF less than or equal to 40%.[12] The primary end-point was based on pharmacokinetics and was to dose titrate omecamtiv mecarbil to a targeted plasma concentration range for the duration of the study.

The study included patients with NYHA class II or III chronic heart failure who had received an optimal heart failure treatment for at least 4 weeks. The 448 patients were randomised 1:1:1 to receive oral placebo or omecamtiv mecarbil in either a fixed-dose (25 mg twice daily) or with pharmacokinetic [PK]-titration (25 mg with up-titration to 50 mg b.d., according to omecamtiv mecarbil plasma concentration).

A significant improvement compared to placebo was observed with omecamtiv mecarbil in SET (fixed-dose group: +11 ms, p=0.007; PK-titration group: +25 ms, p<0.001) and SV (fixed-dose group: +5 mL, p=0.0036; PK-titration group: + 4 mL, p=0.0217). The PK-titration group showed significantly reduced LVESD (–1.8 mm, p=0.0027) and LVEDD (–1.3 mm, p=0.0128) and heart rate (–3 beats per minute, p=0.0070). Similarly, a reduction in LVESV, LVEDV and an improvement in LVFS were found in the omecamtiv mercabil groups. LVEF was significantly improved in the fixed-dose group (p=0.025) but only reached a positive trend towards improvement in the PK-titration group (p=0.063). Plasma concentrations of NT-proBNP were reduced in both omecamtiv mecarbil groups at 20 weeks and this effect persisted after discontinuation of omecamtiv mecarbil. Adverse events and rates of deaths were comparable between omecamtiv mecarbil and placebo. Cardiac and noncardiac adverse events were also similar between the placebo and the two treatment groups. Cardiac troponin levels at week 20 increased in the omecamtiv mercabil groups compared with placebo (0.001 ηg/mL in the fixed-dose and by 0.006 ηg/mL in the PK-titration group). Therefore, the results of COSMIC-HF confirmed the improvement in cardiac function and the reduction of ventricular dimensions with omecamtiv mercabil compared to placebo.

GALACTIC-HF

The Global Approach to Lowering Adverse Cardiac Outcomes Through Improving Contractility in Heart Failure is a phase III, double-blind, randomised, placebo-controlled multicentre clinical trial conceived to compare omecamtiv mecarbil with placebo added to guideline-recommended heart failure treatment in nearly 8000 patients with chronic HFrEF. The primary endpoint of the study is the composite end-point of time-to-cardiovascular death or first heart-failure event, whichever occurs first. Secondary endpoints include time to first heart-failure hospitalization, time to all-cause death and measurement of patient-reported quality of life measured with the Kansas City Cardiomyopathy Questionnaire, KCCQ.

The study started its recruitment in January 2017 and should be completed by early 2021.[13] Included in the study will be those with LVEF ≤35%, NYHA II–IV, and elevated BNP or NT-proBNP levels. Patients will be randomised to placebo or oral omecamtiv mecarbil at a starting dose of 25 mg twice daily followed by a PK-guided dose optimisation up to one of three target doses (25, 37.5 or 50 mg twice daily). It is an event-driven study.

Conclusions

Omecamtiv mecarbil is a cardiac myosin activator that increases the speed of ATP hydrolysis, and accelerates the production of a strong actin-myosin complex leading to increased contractile force production. Animal and human studies have shown that it causes dose-dependent increases in SET, SV, ejection fraction and fractional shortening. The GALACTIC-HF is currently investigating the prognostic effect of omecamtiv mecarbil compared to placebo when added to guideline-recommended heart failure treatment in patients with chronic heart failure and reduced ejection fraction and it is expected to be completed in by early 2021.

Declarations of interest

The authors declare no conflict of interest.

Acknowledgements

The authors state that they abide by the authors' responsibilities and ethical publishing guidelines of the International Cardiovascular Forum Journal.[14]

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Adenosine Receptor Agonists

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Abstract

Adenosine is a purine nucleoside that binds to adenosine cell surface receptors, which are widely expressed in heart and blood vessel cells as well as in the brain, kidney and adipose tissue. There are 4 subtypes of P1 (adenosine) G protein-coupled receptors (GPCR), named A_1, A_{2A}, A_{2B}, and A_3, which mediate a variety of cardioprotective and regenerative effects. In the heart, these effects are predominantly mediated through A1 receptors (A1R), which are expressed in atrial and ventricular cardiomyocytes and smooth muscle cells. Pre-clinical studies have reported multiple potential benefits achievable by modulation of adenyl cyclase with beneficial effects in a variety of pre-clinical models of cardiovascular disease including chronic heart failure (HF). A1R blockade (e.g. rolofylline) was however not successful in the PROTECT trial, where 2033 patients with acute HF and renal dysfunction were randomized to rolofylline or placebo, showed no benefit on renal function, symptoms, rehospitalization, or mortality. Following this attention turned to partial adenosine agonists, capadenoson and neladenoson bialanate hydrochloride, which has two phase II studies underway, PANACHE (HFpEF) and PANTHEON (HFrEF).

Keywords: heart failure; adenosine receptor agonists

Citation: Wallner M, Ponikowski P. Adenosine Receptor Agonists. International Cardiovascular Forum Journal. 2019;18:11-14. DOI: 10.17987/icfj.v18i0.613

Introduction

Advances in the management of acute coronary syndrome[1] and improvements in heart failure (HF) treatment have led to significant reductions in both morbidity and mortality.[2-4] Such changes are thought to be responsible for an increase in the prevalence of HF as patients with cardiovascular disorders are living longer and the world population is ageing. Thus, HF has become one of the most prevalent cardiovascular (CV) diseases in the Western world[5], with a mortality exceeding that of many types of cancer.

Although several early therapeutic breakthroughs (for example neurohumoral inhibition) have significantly improved mortality and morbidity in patients with HF with reduced ejection fraction (HFrEF) from the 1980's to the first decade of the millenium, relatively fewer successes have been reported during the past decade.[6] A purported reason for the failure of recent HFrEF treatment trials may be that the addition of yet more haemodynamically active (usually vasodilatory) agents to the standard treatment of care may cause adverse effects such as hypotension or bradyarrhythmias, and thus, incremental improvements may be unattainable with these agents.[7] Data from the ESC Heart Failure Long-Term Registry have demonstrated that desirable target doses for RAAS-blockers, MRAs, and ß-blockers were only achieved in about 30% of patients with chronic HF.[8] These safety concerns have guided the field of research, and there is now a focus on developing novel treatment strategies directly targeting intrinsic myocardial properties, without significantly affecting haemodynamics.[9,10] This shift in focus has led to the development of partial adenosine receptor agonists[11], a group of agents which are thought to be haemodynamically neutral.

Adenosine Receptor Signalling

Adenosine is a purine nucleoside that binds to adenosine cell surface receptors, which are widely expressed in heart and blood vessel cells as well as in the brain, kidney and adipose tissue.[12,13] There are 4 subtypes of P1 (adenosine) G protein-coupled receptors (GPCR), named A_1, A_{2A}, A_{2B}, and A_3, which mediate a variety of cardioprotective and regenerative effects.[14,15] In the heart, these effects are predominantly mediated through A1 receptors (A1R)[11], which are expressed in atrial and ventricular cardiomyocytes[16] and smooth muscle cells.[17] Activation of A1R reduces the intracellular levels of cyclic adenosine monophosphate (cAMP) by inhibiting adenyl cyclase[18], modulating protein kinase C, and opening ATP-sensitive potassium channels (Figure 1).[19]

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ISSN: 2410-2636

International Cardiovascular Forum Journal 18 (2019)
DOI: 10.17987/icfj.v18i0.613

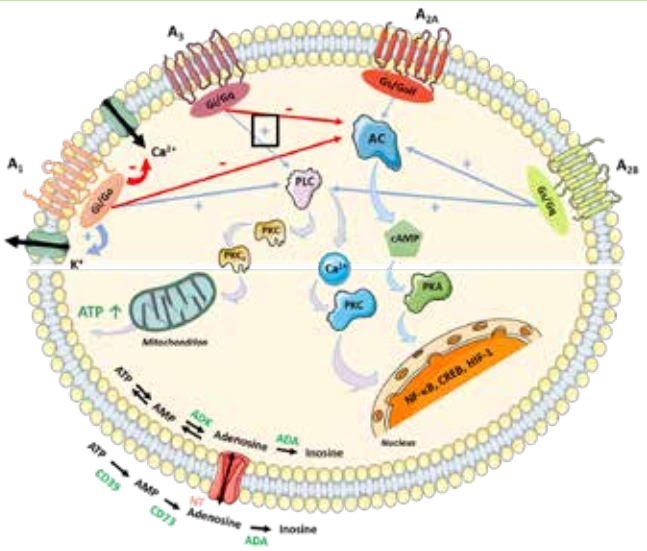

Figure 13.1. Adenosine metabolism and signaling Adenosine can be produced intracellularly via hydrolysis of AMP by 5´- nucleotidase. Extracellular synthesis of adenosine occurs via ATP dephosphorylation by ectonucleoside triphosphate diphosphohydrolase CD39 and 5ß-nucleotidase CD73. Adenosine can be degraded to inosine by ADA or phosphorylated to AMP by ADK, both intracellular. Signaling pathways of adenosine receptor subtypes (A_1, A_{2A}, A_{2B}, A_3). AC, adenylyl cyclase; ADA, adenosine deaminase; ADK, adenosine kinase; cAMP, cyclic AMP; CREB, cAMP response element-binding protein; HIF-1, hypoxia-inducible factor; NF-κB, nuclear factor κB; NT, nucleoside transporter; PKA, protein kinase A; PKC, protein kinase C; PLC, phospholipase C.

Table 1. Adenosine receptor signaling. Beneficial effects of partial A1R agonists in heart failure

Energy Metabolism
Fatty acid oxidation ↑
Glut-1 and Glut-4 expression ↑
LV Anti-Remodeling Effects
LV hypertrophy ↑
Interstitial fibrosis ↑
Preserves myocardial capillary density
Preserves oxygen diffusion distances
End-systolic volume ↑
Mitochondrial Function
ROS production ↑
Opening rate of mitochondrial permeability transition pores ↑
Apoptosis ↑
ATP production ↑
Efficiency of electron transport chain ↑
Mitochondrial uncoupling proteins ↑
Cardioprotective Effects
Catecholamine release ↑
SERCA2a activity ↑
Protection from calcium overload

Pre-clinical studies have reported that modulation of adenyl cyclase attenuates sympathetic over-activation and stimulates a release of atrial natriuretic peptide.[20] Furthermore, it has been shown that an adenosine activation of A1R improves mitochondrial function[21,22], attenuates cardiac hypertrophy and fibrosis[23], modulates derangements in cardiac metabolic profile[24], and exerts cardioprotective effects by maintaining intracellular calcium homeostasis and preventing ischaemia. Due to this broad spectrum of mechanisms, adenosine A1R activation has been shown to exert beneficial effects in a variety of pre-clinical models of cardiovascular disease associated with ischaemia/reperfusion (I/R), arrhythmogenesis, myocardial stunning, ventricular dysfunction, acute myocardial infarction, apoptosis, and chronic heart failure (Table 1).[25-27]

Concept of Adenosine A1R Blockade

Several complex effects of adenosine on the kidney, such as sodium reabsorption in the proximal tubules, vasoconstriction of afferent renal arterioles, and enhanced tubuloglomerular feedback in the macula densa have been described, which all lead to fluid overload and decreased glomerular filtration rate.[28,29] Approximately 50% of chronic HF patients and 2/3 of patients with acute HF have renal dysfunction, therefore adenosine-related renal effects are highly undesired and raise major safety concerns.[30] These renal effects raise the question whether adenosine A1R blockade may be potentially beneficial in HF and this led to large-scale drug development programs with adenosine A1R antagonists (e.g. rolofylline).

Two smaller randomized, controlled clinical trials reported positive effects of rolofylline on renal function in patients with acute and chronic HF.[31,32] However, a subsequent larger phase 3 study did not confirm these findings. In the **PROTECT** trial, 2033 patients with acute HF and renal dysfunction were randomized to receive either rolofylline, an adenosine A1R antagonist, or placebo. Treatment with rolofylline showed no benefit on renal function, symptoms, rehospitalization, or mortality during the follow-up of 60 days[33], but increased rates of seizures and stroke were reported in this group. However, no temporal relation to rolofylline infusion and no specific stroke subtype which predicted stroke in the rolofylline group was reported.[34]

Full vs Partial Adenosine A1R Agonists

The neutral results of the PROTECT trial indirectly influenced the continued development of adenosine A1R agonists. Given the fact that adenosine receptors are expressed on the vast majority of cells, it became obvious that full adenosine agonists activated not only the desired target cells, but also activated cells involved in a variety of diverse physiological processes.[35] Due to the widespread distribution and diverse function of A1R, the cardioprotective effects may have been counteracted by various unintended off-target effects, such as atrioventricular block, bradycardia, and negative inotropic and dromotropic effects.[11,12,36] Therefore, partial adenosine A1R agonists have been designed to exert cardioprotective and anti-remodelling effects, while maximizing safety by limiting negative side effects. In general, partial agonists are low efficacy ligands that elicit only submaximal effects compared to full agonists.[35] Therefore,

partial A1R agonists exert tissue and functional selectivity by acting as a semi-potent agonist or weak antagonist depending on the specific tissue receptor activity.[37] Furthermore, receptor desensitization may be less of a problem with partial A1R agonists compared to full agonists, which may be particularly beneficial for long-term treatment strategies.[38,39]

VCP28, an adenosine-like A1R agonist, was found to have cardioprotective effects in experimental models of ischaemia/reperfusion (I/R).[27] Although promising results have been reported for these adenosine-like A1R agonists, the short half-life and low bioavailability significantly limit their use for chronic oral therapy.

Capadenoson, a non-adenosine-like partial A1R agonist that elicits improved pharmacokinetics, was reported to significantly reduce infarct size in a dose-dependent manner in a pre-clinical I/R model.[39] In a canine model of HF, oral capadenoson treatment for 12 weeks improved LV function and exerted anti-remodeling effects.[21] In addition in a phase II, randomized, placebo-controlled trial, capadenoson showed improved total exercise time in male patients with stable angina.[40] Although capadenoson did not cause ECG alterations, the potency for A1R may have be too high, as central effects such as vertigo were reported.

This finding led to the development of **neladenoson bialanate hydrochloride**, a partial A1R agonist with improved solubility and an optimized therapeutic window compared to capadenoson.[41] Two small clinical trials evaluated the safety and tolerability of neladenoson bialanate in patients with HFrEF.[42] The **β-Blocker Interaction Study**, a single-centre, single-blind, placebo-controlled study, showed that a single-dose of neladenoson bialanate is safe in patients with HFrEF treated with β-blockers. The second, the **PARSIFAL** pilot study was a double-blind, placebo-controlled trial that showed no atrioventricular conduction disorders or neurological side effects in HFrEF patients treated with β-blockers and a 7-day course of neladenoson bialanate. However, no significant changes in cardiac function were reported.[42]

Two larger clinical, randomized, controlled, dose-finding phase II studies assessing the efficacy and safety of neladenoson bialanate are currently ongoing. The **PANACHE** trial randomized 305 patients with HF with preserved ejection fraction (HFpEF) to either neladenoson or placebo treatment. The primary endpoint is the absolute change from baseline in 6-minute walking distance after 20 weeks of treatment. The **PANTHEON** trial has a similar design to PANACHE, but enrolled 427 patients with HFrEF. The primary endpoint is absolute change from baseline in LVEF after 20 weeks of treatment.

Conclusions

While there have been 3 decades of experimental research supporting the idea that adenosine receptor signaling is advantageous in a variety of cardiovascular pathologies, there is currently insufficient evidence supporting the clinical efficacy of AR agonists in patients with cardiovascular diseases. However, with encouraging preclinical data and strong biological rationale, adenosine signaling holds promise as a potential treatment for the ever-growing HF population. The results of PANCHE and PANTHEON will provide new evidence for the role of partial adenosine A1R agonists in heart failure therapy.

Declarations of interest

The authors declare no conflict of interest.

Acknowledgements

The authors state that they abide by the authors' responsibilities and ethical publishing guidelines of the International Cardiovascular Forum Journal.[43]

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Beta-3 Receptor Agonists

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Abstract

Beta-3 adrenergic receptors (β3-AR) have a more widespread tissue distribution in the human body as compared to beta1- and beta2 (β1/2)-adrenergic receptors, including in the bladder, brain, adipose tissue and cardiovascular system. Thus, β3- AR are potential drug targets for a wide range of therapeutic areas, both cardiovascular and non-cardiovascular including overactive bladder (OAB), depression, metabolic syndrome, obesity and heart failure (HF). β3-AR agonists that are selective to the β3-AR include CL 316,243, amibegron (SR58611A), mirabegron (YM-178) and vibegron (RVT-901). However, in HF, study results regarding a possible inotropic effect of β3-AR agonists remain equivocal and some authors report a negative inotropic effect in HF and β3-AR antagonists are also under study.

Keywords: heart failure, beta-3 adrenergic receptors,; mirabegron

Citation: Bachus E, Ponikowski P. Beta-3 Receptor Agonists. International Cardiovascular Forum Journal. 2019;18:15-18. DOI: 10.17987/icfj.v18i0.615

Introduction

Beta-3 adrenergic receptors (β3-AR) belong to the superfamily of G protein-coupled receptors and show a more widespread tissue distribution in the human body as compared to beta1- and beta2 (β1/2)-adrenergic receptors. For example β3-AR have been described to be present in the bladder, brain, adipose tissue and cardiovascular system, among other tissues. Thus, β3-AR are potential drug targets for a wide range of therapeutic areas, both cardiovascular and non-cardiovascular including overactive bladder (OAB), depression, metabolic syndrome, obesity and heart failure (HF).[1]

Selective beta-3 adrenergic agonists

β3-AR agonists that are selective to the β3-AR include CL 316,243, amibegron (SR58611A), mirabegron (YM-178) and vibegron (RVT-901). These β3-AR agonists have different profiles. For example, CL 316,243 has anti-obesity and anti-diabetic properties and amibegron has antidepressant effects in animal models. Mirabegron is approved for the treatment of OAB syndrome, and vibegron is currently under development in human clinical trials also for the treatment of that condition. Newer β3-selective compounds showing interesting profiles as potential drugs for the treatment of obesity and non-insulin-dependent diabetes have recently been reported.[1]

Cardiovascular/metabolic properties and therapeutic concepts

Adipose tissue and diabetes. β3-AR mediate lipolysis in white adipose tissue and thermogenesis in brown adipose tissue.[2-4] The presence of the Arg64 allele in the first intracellular loop of the β3-AR gene may predispose subjects to abdominal obesity, which may in turn predispose them to insulin resistance and the earlier onset of type 2 diabetes mellitus.[5] β3-AR agonists appear to be of significance not only for the treatment of obesity, but also in terms of the risks of cardiovascular disorders related to visceral obesity, the form of obesity, which is more directly linked to augmented β3-AR activity.[6,7]

Vascular smooth muscles. β3-AR produce the sustained peripheral vasodilation, which is predominant in skin and fat.[8,9] Studies have shown that the relaxation of rat thoracic aorta was caused by selective β3-AR agonists.[10-13] A β3-AR-mediated vasorelaxation was also observed in the canine pulmonary artery.[14] The presence of β3-AR has also been reported in veins of rats.[15] Also in rats, it was demonstrated that β3-AR stimulation causes a vasodilation of microvessels in the islets of Langerhans.[7,16]

Endothelium. In human vessels, β3-AR vasorelaxation was found to be mediated partly through the production of nitric oxide (NO) [17], which may be caused by the functional coupling of β3-AR agonists to NO production.[7,18,19]

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ISSN: 2410-2636

International Cardiovascular Forum Journal 18 (2019)
DOI: 10.17987/icfj.v18i0.615

Cardiac effects. β3-AR stimulation of the human cardiac muscle, in contrast with β1-AR and β2-AR stimulation, results in a profound dose-dependent negative inotropic effect, which has been shown in different animal models. These findings may suggest that β3-AR may participate in the pathophysiology of HF.[20] Functional β3-AR stimulation, which occurs in the normal left ventricle, causes a direct inhibition on calcium (Ca2+) channels and produces a negative inotropic action.[21] It has been found that β3-AR activation inhibits the L-type Ca2+-channel in both normal and HF rat myocytes. In HF, β3-AR stimulation-induced inhibition of Ca2+-channels was enhanced, which was responsible for the reduced inotropic response[7,22], and an increased activity of the sympathetic nervous system led to the downregulation of cardiac β1- and β2-AR in HF.[20] Reduced β1- and β2-AR expression leads to a decrease in the contractile response to β-AR agonists.[23] Contrary to β1- and β2-AR, the abundance of the negatively inotropic β3-AR increases in the failing myocardium.[18] β3-AR lack the phosphorylation sites for cAMP-dependent protein kinase or β-AR kinase[23], and thus may not be downregulated in HF. Accordingly, the high adrenoceptor tone during HF may alter the cardiac contractile activity as a result of unmasked β3-AR stimulation in the presence of reduced β1- and β2-AR.[24] Overstimulation of the relatively desensitization-resistant β3-AR[25] after increased sympathetic tone and norepinephrine release in the setting of HF in humans may further decrease cardiac inotropy.[18] The levels of β3-AR mRNA and proteins show an increase in the failing heart compared with the nonfailing heart. If the levels of β3-AR are too high, they might contribute to the loss of cardiac function and be the foundation of the functional degradation in HF.[26] These study results may suggest the treatment options with specific antagonists of the human cardiac β3-AR for correcting the disordered adrenergic regulation of the failing heart.

Contrary to the aforementioned evidence, it has been reported that increased intracellular myocyte sodium (Na+) levels represent a key adverse pathophysiological feature of HF, and that the β3-AR mediates the stimulation of the only export route for Na+, the sodium-potassium (Na+-K+)-pump. The upregulation of the β3-AR may thereby represent a useful compensatory mechanism. Thus β3-AR *agonists* may be a potential therapeutic option for the treatment of HF.[27]

However, study results regarding the inotropic effect of β3-AR agonists remain equivocal. As mentioned above, some authors conclude that there is a negative inotropic effect (mainly in HF models)[21,28], whereas others do not agree.[29,30] The reasons for this discrepancy probably include the type and dose of the agonist used (with high doses of non-specific agonists producing opposing positive inotropic effects) and the control systems mediating for reflex orthosympathetic reactions leading to intense peripheral vasodilatation.[29]

Data from experimental models (summarised in table 1; but by no means exhaustive) have shown promising effects on cardiac function in HF and relevant co-morbidities.[30] These include beneficial effects on oxidative stress[31], augmentation in left ventricular contractility[32], diabetes-induced cardiac dysfunction[33], cardiac arrhythmia control after myocardial infarction[34], pulmonary hypertension[35-37] and erectile function (ED).[38]

Table 1. Involvement of β3-AR signalling in the pathophysiology of listed pathologies and involved tissues in different animal models.

Effect/medical condition	Organ/ tissue	Species	Reference
Heart failure	Heart	Sheep	Bundgaard et al. 2010 [30]
Chronic heart failure	Heart	Rat	Kong et al. 2010 [31]
Cardiac contractility	Heart	Mice/human (transgenic)	Kohout et al. 2001 [32]
Diabetes	Heart	Rat	Dinçer et al. 2001 [33]
Ventricular tachycardia	Heart	Dog	Zhou et al. 2008 [34]
Pulmonary hypertension	Pulmonary artery	Dog	Tagaya et al. 1999 [35]
Pulmonary hypertension	Lung	Rat	Dumas et al. 1998 [36]
Pulmonary hypertension	Pulmonary artery	Pig	García-Álvarez et al. 2016 [37]
Erectile dysfunction	Corpus cavernosum/ penile artery	Human	Mitidieri et al. 2017 [38]
Cardiac remodelling	Cardiac myocyte	Mice/human (transgenic)	Belge et al. 2014 [39]
Heart failure/ cardiac remodelling	Heart	Mice/knockout mice	Niu et al. 2012 [41]

Many of these direct and indirect mechanisms combine to modulate chronic myocardial remodelling. One important aspect is cardiac myocyte hypertrophy. It has been shown that β3-AR attenuate cardiac myocyte hypertrophy in response to a continuous or repetitive infusion of isoproterenol or angiotensin II and a reduction of hypertrophy in response to different β3-AR agonists. This anti-hypertrophic effect of β3-AR was NO-dependent. β3-AR expression also greatly reduced myocardial interstitial fibrosis due to isoproterenol and angiotensin II infusions.[40] Similar protective effects of β3-AR were reported with preferential β3-AR agonists in mice exposed to trans-aortic constriction, with the subsequent decreased hypertrophy and preserved LV function.[41]

Protective effects of β3-AR agonists at the myocardial level are probably reinforced from indirect effects in peripheral cells/ tissues, i.e. through the coronary vasodilatation via β3-AR-induced endothelial dependent relaxation, as well as the paracrine release of NO and its effects to improve LV relaxation. Moreover, the antioxidant effects of β3-AR signalling may preserve the endothelium of microvasculature from oxidative activation and the ensuing recruitment of monocytes initiating subendothelial inflammation at the core of sustained endothelial dysfunction. Whether this might prevent from chronic development of vascular atherosclerosis or chronic development of diastolic dysfunction initiating HFpEF[42] has yet to be tested in trials with interventions and long follow-up.[40]

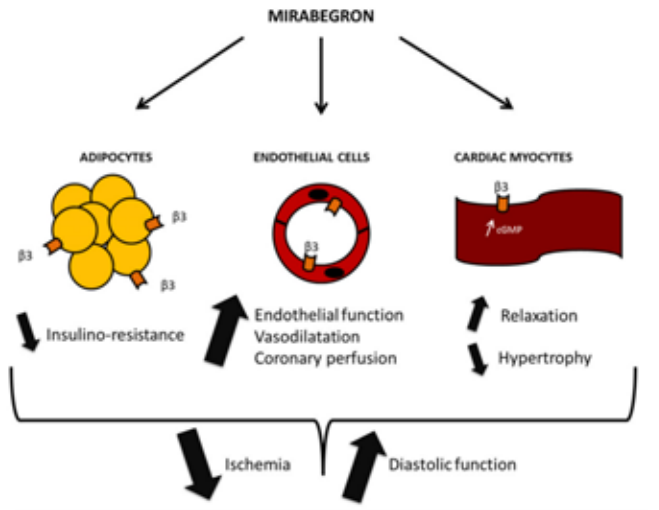

Figure 1. Targets for the therapeutic effect of the β3 adrenergic receptor agonist, mirabegron. (reproduced from reference 46 with permission) As a β3 adrenergic receptor agonist, mirabegron is expected to activate β3 adrenergic receptors in adipocytes (left), resulting in increased adipocyte 'browning', energy expenditure, and peripheral insulin sensitivity; in endothelial cells of the vasculature (centre; including coronary resistance arteries), thereby increasing endothelium-dependent vasodilatation, myocardial perfusion, and paracrine nitric oxide-mediated signalling; and in cardiac myocytes (right), resulting in antioxidant and cyclic guanosine monophosphate-mediated protective effects against remodelling and improved relaxation. Altogether, these effects are expected to prevent myocardial ischaemia and improve diastolic function.

After all, it has to be kept in mind that the expression pattern of β3-AR is more restricted than that of other subtypes, particularly in humans, which makes an extrapolation of findings from other species to the human clinical condition difficult, but it may also result in a smaller potential for side effects. The role of β3-AR gene polymorphisms has been insufficiently explored and may differ even between primate species.[43]

Recent and ongoing clinical trials

The effect of the β3-AR agonist mirabegron on left ventricular ejection fraction (LVEF) was tested in a first-in-man double-blinded clinical trial: *BEAT-HF*.[44] The aim was to test the hypothesis of protective effects of β3-AR agonists (study drug: mirabegron) on myocardial function in patients with stable HFrEF, in sinus rhythm and already taking conventional beta blockers. The primary endpoint, an increase in LVEF after 6 months, was not reached, nor was the secondary end-point of exercise capacity. The trial recruited patients with echo-derived LVEF less than 40%, but when assessed in-trial with a CT-derived measure many had LVEF greater than 40%. An exploratory analysis of patients with baseline CT-derived LVEF <40% indicated that the β3AR stimulation by mirabegron increased LVEF compared to placebo. No safety signals were seen and there was no significant effect compared to placebo on HR or BP.[44,45]

The *Beta3-LVH* trial (rationale recently published[46]) is currently testing the hypothesis that the β3AR agonist (mirabegron) will ameliorate LV hypertrophy and diastolic function in patients with hypertensive structural heart disease, being at high risk of developing HFpEF. Beta3-LVH is a randomized, placebo-controlled, double-blind, two-armed, multicentre, European, parallel group study. A total of 296 patients will be randomly assigned to receive either mirabegron or placebo over 12 months. Beta3-LVH is the first large-scale clinical trial to evaluate the effects of mirabegron on LVMi and diastolic function in patients with LVH.

Moreover, there are ongoing clinical trials in the fields of pulmonary hypertension, erectile dysfunction and obesity β3AR agonists. The *Beta3 Agonist Treatment in Chronic Pulmonary Hypertension Secondary to Heart Failure* (SPHERE-HF) study will evaluate the efficacy and safety of mirabegron in patients with pulmonary hypertension secondary to HF. The *Mirabegron For Erectile Dysfunction* pilot will evaluate the effect of mirabegron on men with both OAB symptoms and mild to moderate ED. The *Efficacy of Pharmacological Stimulation of BAT and WAT in Lean and Obese Young Adults* (MiraBAT) is conducted to determine whether the pharmacological stimulation of supraclavicular Brown Adipose Tissue (BAT or "Brown Fat") and subcutaneous White Adipose Tissue (WAT) using mirabegron is as effective in increasing oxidative metabolism in BAT and WAT as is the exposure to cold. The *Effects of b3-Adrenergic Receptor Agonists on Brown Adipose Tissue* study will test the hypothesis that human BAT can be activated using mirabegron. The efficacy of mirabegron will be compared with cold exposure, as well as to a placebo.

Conclusions

In conclusion, the pleiotropic protective properties of selective β3-AR agonists make these interesting therapeutic agents, especially in the complex syndrome of HF with all its predisposing cardiometabolic conditions and comorbidities.

Declarations of interest

The authors declare no conflict of interest.

Acknowledgements

The authors state that they abide by the authors' responsibilities and ethical publishing guidelines of the International Cardiovascular Forum Journal.[47]

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Genes, Cells, and miRNAs

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Abstract

Novel methods to treat HF include gene, cell and microRNA delivery. There have been few gene therapy trials in HF. The CUPID I and II trials with AAV1.SERCA2a showed unconvincing results. The STOP-HF trial using direct intra-myocardial injection of a non-integrating plasmid vector carrying stromal cell-derived factor-1 showed no clinical effects and the AC6 gene transfer trial using IC infusion of escalating doses of Ad5.hAC6 was similarly negative. Despite high hopes stem cell trials to date in HF have not shown convincing clinical benefits. More recent clinical trials in this area have investigated the injection of cell stimulating paracrine factors (peptides, small molecules, hormone-like molecules) without actual cell delivery. Micro-RNA's (miRNAs) are small non-coding RNA strands, comprising 19-25 nucleotides, that have a distinct signalling role and a various patterns of expression in ischaemic myocardium, hypertrophy, cardiomyopathies, and overt HF. They act at the post-transcriptional regulation level. Numerous novel miRNAs have been discovered, and their in-depth role has been characterised. miRNAs can serve as therapeutic substances or therapeutic targets in a range of cardiovascular diseases. Clinical trials are likely in the near future.

Keywords: heart failure; gene therapy; cell therapy; micoRNA

Citation: Gara E, Lainscak M. Genes, Cells, and MiRNAs. International Cardiovascular Forum Journal. 2019;18:19-22. DOI: 10.17987/icfj.v18i0.617

Introduction

Cardiac gene therapies

Recently, novel methods have emerged that have widened the opportunities to employ a gene therapeutic approach in the treatment of cardiovascular diseases. To optimally employ such strategies an in-depth knowledge of the transcriptome background of the major cardiovascular diseases will be required. Genetic abnormalities in a wide range of cardiovascular disease are well-known and well-described, but a full description of these are beyond the scope of this chapter (e.g. hypertrophic cardiomyopathy or familial hypercholesterolemia).

The cornerstone of future human applications of gene therapy is an efficient and safe vector for gene delivery. The ideal vector should be highly efficient, preferably non-viral, and non-integrating into the host genome. The first human clinical trials employing gene therapy in the cardiovascular field were performed with an adenoviral vector (AAV). Non-viral vectors, however, generally have demonstrated low-efficacy. Recent methods have targeted plasmid-based techniques.[1] Recently Penny and Hammond have reviewed gene based therapy for heart failure (HF) by searching PubMed and ClinicalTrials.gov (without language restrictions) for clinical trials published between January 1990 and October 2016, using the search terms "gene transfer" (and "gene therapy") and "heart failure" and related terms.[2] They found multiple preclinical and some early clinical investigations, but only 4 randomised clinical trials utilising a gene therapeutic approach for HF. These trials mainly used exogenous transfer of a therapeutic gene product with the aim of improving either vascular or myocyte function in the failing hearts, either with intracoronary delivery of a virus vector or direct endocardial injection of a plasmid.

Although there has been a high degree of scientific interest in the field and attention in particular directed at the CUPID I and II trials which aimed to modify myocardial sarcoplasmic reticulum calcium-ATPase (SERCA) in an effort to improve myocardial contractility via an increase in intracellular calcium concentration in the cardiomyocytes of the failing heart, emerging clinical evidence to date has been inconsistent. The phase 2 CUPID trial in 39 HF patients (24 active, 15 placebo) used escalating doses of intra-coronary adeno-associated virus coding for sarcoplasmic reticulum calcium ATPase codes (AAV1.SERCA2a).[3] It showed nominally significant effects on LVEDV and cardiovascular events, which given its small size could not be considered evidence of benefit, especially when the larger CUPID-2 study (in 243 HFrEF patients) comparing high dose AAV1.SERCA2a to placebo showed no clinical or pathophysiological benefit.[4]

The STOP-HF trial used direct intra-myocardial injection of a non-integrating plasmid vector carrying stromal cell-derived factor-1 in an attempt to enhance the activation of cardiac resident stem cells within the failing myocardium. In a trial of 93 ischaemic HF patients no effect on either symptoms or 6 min corridor walk test distance was demonstrated.[5]

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ISSN: 2410-2636

International Cardiovascular Forum Journal 18 (2019)
DOI: 10.17987/icfj.v18i0.617

The AC6 gene transfer trial used IC infusion of escalating doses of adenovirus-5 encoding adenylyl cyclase 6 (Ad5.hAC6) in 42 HFrEF patients versus placebo in 14.[6] It showed no between group differences in either LVEF or exercise tolerance but a difference at 4 weeks in LV peak –dP/dt, but not in LV peak +dP/dt. Thus whilst the possibility of haemodynamic benefits has been established no consistent trial outcomes have been achieved to date by gene therapy in HF patients.

Further animal models and translational studies have aimed to improve the efficiency of gene delivery by methods such as magnetic beads attached to the AAV vector which can drive the homing of therapeutic substances using external magnetic fields[7] or by the use of exogenous cells (e.g. mesenchymal stem cells) as vectors of therapeutic genes in a complex regenerative product. Other gene therapeutic approaches that may offer utility, at least in ischaemic HF, are factors which promote angiogenesis such as VEGF, angiopoietin, and hypoxia-inducible factor alpha-1.

Generally, the studies conducted to date for cardiac gene transfer have shown no major safety signals of concern, in terms of major adverse events related to the gene transfer process. Arrhythmias and mild troponin rises were more commonly seen in those subjects receiving direct endomyocardial injections. Higher doses of gene delivery and more efficient non-viral transfection methods may be needed in larger clinical trials to show clinical benefit in patients with HF.

Stem cells and endogenous cellular responses

Another therapeutic area that has received a lot of scientific interest is that of stem cell therapy for cardiovascular diseases. Despite the high hopes in terms of a possible successful regeneration of the heart, trials to date have not shown convincing clinical benefits. The human heart comprises billions of cells with distinct functions (electro-mechanical conduction, pacemaker function, contraction) and characteristics, such as atrial and ventricular myocytes, Purkinje cells, sinus node cells, cardiofibroblasts, paracrine cells, to name but a few, which are extremely hard to develop in a dish.

The first clinical investigations in this field used cardiac and peripheral myoblasts, which are now not considered sufficiently safe or feasible for larger scale clinical use. Cardiac resident stem cells possess a low capacity for self-renewal, and thus can rarely efficiently regenerate the muscle at the site of a myocardial infarction. Therefore, the majority of clinical studies have been performed with mesenchymal stem cells. A large number of studies have been conducted, and we have learned that: 1) the most efficient delivery route is that of intra-myocardial injection, 2) the homing of the cell into the myocardial tissue remains a limiting factor; 3) tracking the implanted cells is key to establishing the effectiveness of injections; 4) a gold-standard assessment of left ventricular function (such as cardiac magnetic resonance imaging) is warranted in clinical trials; 5) mesenchymal stem cells seem incapable of differentiating to mature cardiomyocytes, rather instead developing only into cardiac precursor cells; 6) the major regenerative potential lies in the paracrine effects of mesenchymal stem cells.[8]

The most recent clinical trials in this area have investigated the injection of cell stimulating paracrine factors (peptides, small molecules, hormone-like molecules) without actual cell delivery. [9] The rationale is that human embryonic stem cells and human induced pluripotent stem cells can differentiate into mature cardiovascular cells from such a pluripotent state if they can be stimulated in-situ. In this context, a number of differentiation protocols exist to develop specific cell types including endothelial cells, cardiomyocytes, and smooth muscle cells. Embryonic stem cell-derived products would need immunosuppressive therapy, in a manner analagous to allogenic heart transplantation. Currently, one clinical trial is running in France, where embryonic stem cell-derived cardiomyocytes are being implanted in the epicardial sheet during coronary-artery-bypass grafting procedures. [10] Human induced pluripotent stem cells are reprogrammed from adult somatic cells, thus there is an option to deliver the patients specific new cardiovascular cells. Initial clinical trials are underway, building on the experience from other indications, such as macular degeneration treatments, pioneered with induced pluripotent stem cells derived epithelial cells. Pluripotent stem cells can give rise to a form of cardiovascular tissue engineering and they can act as a source of cells to repopulate 3D printed biomaterials, which in particular may be attractive for paediatric congenital heart repair procedures.

Beside exogenous cellular therapies, it is well-known that cellular immune responses after major cardiovascular events are activated. These responses include changes in native immune cells which may be modified, boosted or silenced with the therapeutic aim of attenuating cardiovascular inflammation, adverse myocardial remodelling, scarring, and fibrosis.

In the myocardium myocardial resident immune cells exist alongside resident stem cells. These are resident monocytes/macrophages, which are activated and join the circulation in response to stress stimuli and the systemic inflammatory response syndrome (SIRS). In the failing heart, different populations of leukocytes exist, e.g. neutrophils and macrophages. Resident macrophages in the heart usually express CXC-motif-chemokine-ligands, which are reasonable targets in immune-modulation for anti-remodelling and anti-fibrosis treatments in HF. Macrophages after a cardiac event actively secrete a number of substances, which can heavily influence the processes of angiogenesis, remodelling and fibrosis. For instance, secreted proteolytic enzymes (matrix metalloproteinases) influence scarring and myocardial fibrosis. Macrophage-derived VEGF can enhance neo-angiogenesis and can promote the development of collateral vessel networks. Cardiac resident macrophages have an immune memory of residual medullary state, and their secretome pattern is similar. TGF-β becomes highly overexpressed after myocardial events, resulting in excessive fibrous tissue growth, diastolic and systolic dysfunction. Interestingly, the zebra-fish is able to regenerate a sufficient amount of left ventricle after its dissections. In the regenerative process mainly embryo-derived CCR2 negative macrophages play a key important signalling role. For this reason, the regenerative steps of zebrafish heart is a highly attractive process for cardiac researchers. Furthermore, in adult murine heart CCR2 negative embryonic macrophage population is lacking and rather CCR2 blood-derived macrophages are in situ as resident macrophages. Resident macrophages populate around 7-8% of the adult heart, which is a significant number, taken into count those lost after a myocardial infarction. SIRS and inflammatory responses are not only present in failing and

ischaemic hearts but also in heart failure with preserved ejection fraction. Inflammatory responses and enhanced monocyte/macrophage activation has a huge impact on the arterial walls, neo-intima proliferation, and atherosclerosis as well.

Recently, the CANTOS trial,[11] one of the first immune-therapy trials in patients with a history of myocardial infarction and evidence of inflammatory activation, proved that treatment with canakinumab, a neutralising antibody against human IL-1β, was associated with a decrease in the combined end point of nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death, with significance for only one of the three tested doses (the middle dose) versus placebo. However, canakinumab was also associated with a significantly higher incidence of fatal infection compared to placebo. The concept that immune medication can have benefical cardiovascular effects, but the nature of the clinical benefit off-set against its risks have not led to a major uptake of this therapy. The possibility of immune modification for HF remains one of future research effort.

Recent preclinical studies have targeted modification monocyte phenotype from inflammatory to reparative in order to decrease the inflammatory reaction and resultant remodelling. These include immune-modulatory processes, efferocytosis or even gene editing via the CRISPR-cas9 system.

Micro-RNAs

Micro-RNA's (miRNAs) are small non-coding RNA strands, comprising 19-25 nucleotides. They have a distinct signalling role and a various patterns of expression in ischaemic myocardium, hypertrophy, cardiomyopathies, and overt HF. They act at the post-transcriptional regulation level. Numerous novel miRNAs have been discovered, and their in-depth role has been characterised.

miRNAs can serve as therapeutic substances or therapeutic targets in a range of cardiovascular diseases. Furthermore, miRNAs are secreted into body fluid compartments (e.g. pericardial fluid) and into the circulation, thus they may have play a unique biomarker role in cardiovascular diseases. Extracellular miRNAs are usually packed into lipid vesicles. Their circulatory levels change in response to standard HF medication treatment, and in response to the initiation of device therapies.[12] Table 1. shows prominent miRNAs and their role in cardiovascular physiology. Beside cardiac miRNAs, miRNAs of other origins (e.g. liver and other parenchymal tissues) also have an important role in the systemic stress reaction after a cardiovascular event.

Limitations of miRNAs include their expense and the meticulous process of collection and characterisation required for therapeutic use. Identification of miRNAs in blood samples may be time-limited. Furthermore, sex- and age-related variations are not yet fully characterised. A recent large EU funded project the HOMAGE (Heart Omics in Aging) project aimed to identify age-related variations in biomarkers molecules of cardiac diseases. Population-based variation of these expression patterns will help a better understanding of regulatory and biomarker role of miRNAs and may result in further steps towards their modulation and targeted inhibition with therapeutic intent.[13]

Table 1. Role of cardiac miRNAs in different pathophysiological aspects.

	Pro	Anti
Fibrosis	miR133, miR98	miR21, miR29, miR208, miR199b, miR130, miR29, miR24
Angiogenesis	miR126, miR24,	miR92, miR503, miR519, miR34
Apoptosis	miR21, miR1, miR15, miR320	miR15, miR199, miR30
Atherosclerosis, lipid metabolism	miR145, miR33	miR21, miR126
Hypertrophy	miR212, miR208, miR22	miR132, miR133a miR1, miR378

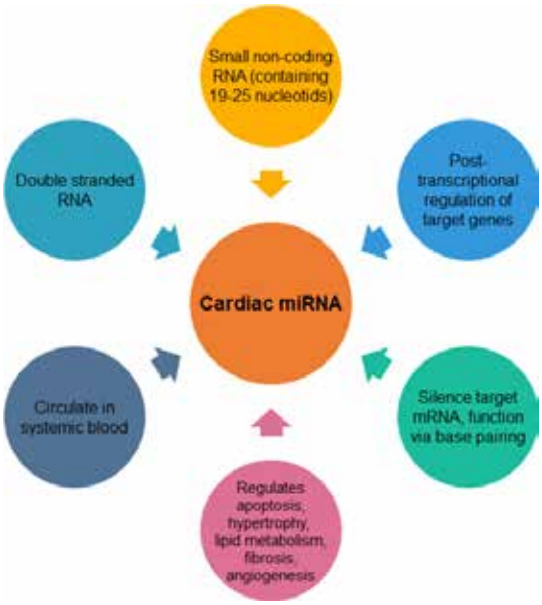

Figure 1. Cardiac miRNAs

Ongoing or recently completed clinical trials have mainly characterised the biomarker role of miRNAs in specific clinical conditions. The MIRRACLE trial investigated the predictive role of the set of circulating miRNAs in non-invasive diagnosis of allograft rejection in a heart transplantation population and validates a predictive role in comparison with endomyocardial biopsies and histology results. Other trials are investigating potential biomarker roles of plasma circulating miRNAs in coronary artery disease or coronary arterial calcification as they have in observational studies in other conditions (e.g. stroke, renal failure).

For therapeutic purposes miRNAs are promising targets. Recently, preclinical translational trials (small and large animals) have showed promising results in ischaemic heart disease, HF and in the arena of cardioprotection. The first-in-human anti-miR trial has just been launched and investigates a safety profile, tolerability and pharmacokinetics of ascending single dose of anti-miR (investigational medicinal product: S95010) in healthy

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DOI: 10.17987/icfj.v18i0.617

male volunteers (NCT03494712).

Future aspects of miRNAs as biomarker or/and therapeutic targets warrant detailed clinical trials to characterise miRNA expression patterns and responses to evidence-based cardiovascular therapies. Furthermore, automated and high-throughput techniques will be essential for reliable processing of miRNAs in clinical practice.[14]

Declarations of interest

The authors declare no conflict of interest.

Acknowledgements

The authors state that they abide by the authors' responsibilities and ethical publishing guidelines of the International Cardiovascular Forum Journal.[15]

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Anticoagulants and Antithrombotics

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Abstract

Hospitalized and stable HF patients are both at increased risk of thrombo-embolic events, making the possibility of protection via the use of anticoagulants and/or antithrombotics attractive. The 2016 ESC guidelines on HF, do not recommend aspirin or anti-coagulation in HF patients in SR, or any antiplatelet drugs in patients with HF without concomitant CAD. NOACs have a favourable safety profile and simplicity of use. This has led to interest in their use in HF. Secondary analyses showed that patients with HF with high cardiovascular risk and/or CAD may benefit from NOACs. However, these benefits in HF patients in SR were not confirmed in the large COMMANDER HF trial where rivaroxaban 2.5 mg twice daily did not reduce the primary endpoint (death from any cause, MI, stroke), nor achieve its primary safety outcome. In patients with HF in AF guidelines recommend an oral anticoagulant to prevent thrombo-embolism for all patients with paroxysmal or persistent/permanent AF and CHA2DS2 VASc ≥2, and for patients with HF and non-valvular AF, eligible for anticoagulation based on a CHA2DS2-VASc score, NOACs rather than warfarin should be considered.

Keywords: heart failure; anticoagulant; anti-thrombotic

Citation: Domienik-Karlowicz J, Lopatin Y. Anticoagulants and Antithrombotics. International Cardiovascular Forum Journal. 2019;18:23-26. DOI: 10.17987/icfj.v18i0.619

Introduction

A substantial number of studies have provided evidence of the link between thrombosis and heart failure (HF). It is important to understand that thrombosis can be both a cause and a consequence of HF. HF itself promotes a state of hypercoagulability, and HF, its complications and progression may result from the consequences of a pre-existing pro-thrombotic state. Many HF patients routinely receive anticoagulant or antithrombotic therapy due to the presence of specific indications for their use, such as atrial fibrillation (AF) or coronary artery disease (CAD). However, the potential clinical benefit of using these agents in the management of HF itself remains a subject of active discussions.

Potential pathophysiological mechanisms leading to thrombosis in heart failure

HF interferes with 3 elements included in the Virchow triad, leading to:

- hypercoagulability, due to increased plasma viscosity, platelet activation, impairment of the protein C pathway and thrombin formation, adenosine-mediated thrombosis;
- haemodynamic changes (stasis) due to low cardiac output, cardiac chamber dilatation, aneurysms of the left ventricle (LV), impaired myocardial contractility;
- endothelial injury/dysfunction related to oxidative stress, a pro-inflammatory state, deficient NO production and many others.

Epidemiology of thrombotic events in patients with heart failure

Pulmonary embolism, peripheral embolism, stroke.

Data from observational studies and secondary analyses of randomized clinical trials indicate a higher risk of thrombotic events in patients with HF than in general population.[1] It was found that in hospitalized HF patients the relative risk for pulmonary embolism and venous thromboembolism (VTE) was 2.15 and 1.21, respectively.[2] Interestingly, the NT-proBNP level may be more useful than the NYHA class as an indicator for identifying patients at a high short-term risk of VTE, whereas elevated D-dimer may be suggestive of high mid-term risk.[3] In patients with HFrEF and in sinus rhythm (SOLVD study), the annual incidence of stroke, pulmonary and peripheral embolism was 2.4 % in women and 1.8 % in men. Moreover, a 53 % increased risk of VTE was observed for every 10 % of reduction in LVEF. [4] Tang et al. in their meta-analysis of 71 studies investigating the risk of VTE in patients hospitalized due to HF found that the overall median symptomatic VTE rate was 2.48 %.[5] However, for patients who did not receive thromboprophylaxis the VTE rate was already 3.73% compared to 1.47% for those who did.

In the Framingham Study based on 5,184 participants over 24 years, the adjusted risk ratio for stroke was 5.4 in men and 6.2 in women (with no adjustment for a presence of AF).[6] Moreover, in a 2007 meta-analysis, 18 in every 1,000 persons with HF

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ISSN: 2410-2636

International Cardiovascular Forum Journal 18 (2019)
DOI: 10.17987/icfj.v18i0.619

experienced a stroke during the first year after the diagnosis of HF, with a maximum stroke rate of 47.4 for every 1000 patients observed after 5-years of follow-up.[7] In the Rotterdam Study, based on 7,546 patients with no history of stroke, the risk of ischaemic stroke increased almost 6-fold during the first month after the diagnosis of HF, but decreased to 3.5 fold for 1-6 months post-onset, and was not significantly elevated from 6 months onwards.[8]

LV thrombi. Epidemiological data on the risk of thromboembolism in patients with LV thrombi and HF are unavailable. Contemporary data estimate the prevalence of LV thrombus at about 15% in patients with ST-segment elevation myocardial infarction and 25% in patients with anterior myocardial infarction.[8]

Clinical models estimating the thromboembolic risk in patients with heart failure

Data from the CORONA and GISSI-HF trials were re-analyzed in order to estimate the actual incidence of, and risk factors for, stroke in patients with HF without AF.[10] Two clinical models for stroke risk in patients, with HF and without AF, were developed. The first model included the following clinical variables: NYHA class, age, insulin-dependent type 2 diabetes mellitus, and the history of previous stroke and body mass index. The second model included plasma NT pro-BNP, type 2 diabetes mellitus, and the history of previous stroke. Interestingly, patients with HF without AF in the upper tercile of the risk score had a rate of stroke that approximated to the rate of risk in HF patients with AF. Both models will require further validation, before they can be recommended for a broader clinical use.

In another study, the predictive accuracy of the CHA2DS2-VASc score was validated in a population of patients with HF (42,987 patients from Danish registries not receiving anticoagulation).[11] The absolute risk of thromboembolism was high independently of the presence of AF, beginning from the CHA2DS2-VASc score exceeding 4. Importantly, the risk was greater with an increasing CHA2DS2-VASc score, but the predictive accuracy was only modest. The clinical utility of the CHA2DS2-VASc score in patients with HF without AF remains to be determined.

Data on safety and efficacy of antithrombotic/ anticoagulants therapy in patients with heart failure

Patients with heart failure in sinus rhythm.

According to the 2016 ESC guidelines on HF [12], in patients with HF who are in sinus rhythm, there is no evidence that oral anticoagulants decrease mortality and morbidity in comparison to placebo or aspirin. Moreover, no benefit has been observed when using antiplatelet drugs in patients with HF without concomitant CAD. WARCEF investigators [13] demonstrated no significant overall difference between warfarin and aspirin in preventing the primary outcome defined as a time to first event in a composite endpoint of ischemic stroke, intracerebral hemorrhage, or death from any cause. Along with that, warfarin therapy was associated with a significant reduction in the risk of stroke compared to aspirin without a significant difference in the risk of intracranial and intracerebral hemorrhages. However, the rate of major hemorrhage was significantly higher with warfarin compared to aspirin, largely due to a more frequent occurrence of major gastrointestinal bleeding.

The advent of NOACs, agents with a favorable safety profile and simplicity of use, has led to further attempts to use them in HF patients. There were some suggestions from secondary analyses that patients with HF with high cardiovascular risk and/or coronary artery disease may benefit from the addition of NOAC therapy. A subgroup analysis from the ATLAS ACS 2-TIMI 51 trial (patients with a recent ACS on dual antiplatelet therapy) showed that rivaroxaban 2.5 mg daily compared with placebo reduced the primary outcome of cardiovascular death, myocardial infarction or stroke, and all-cause death in patients having HF at the time of their ACS.[14] Also a sub-analysis of patients with HF enrolled in the COMPASS trial (patients with a history of stable atherosclerotic disease) suggested some benefits from rivaroxaban treatment (2.5 mg twice daily) in addition to aspirin (100 mg daily).[14]

Both above-mentioned studies noted that the beneficial effects of rivaroxaban were accompanied by an increased rate of bleeding.[14, 15] However, the expectation of additional benefits of including rivaroxaban to standard care in patients HF who are in sinus rhythm has not been confirmed in the COMMANDER HF trial.[16] This double-blind, randomized controlled trial was designed to assess the effectiveness and safety of rivaroxaban in reducing thrombin generation, and as a consequence, mortality, myocardial infarction, or stroke in patients with worsening chronic HF, reduced LVEF, CAD, and no AF. It was shown that rivaroxaban treatment at a dose of 2.5 mg twice daily was not associated with a significantly lower risk of the primary endpoint (death from any cause, myocardial infarction, stroke), nor the primary safety outcome (fatal bleeding or bleeding into a critical space with a potential for causing permanent disability). Moreover, rivaroxaban did not affect the rate of rehospitalization for worsening HF. Thus, the results of the COMMANDER HF trial [16] did not confirm the contribution of atherothrombotic coronary events to the progression of HFrEF of ischaemic aetiology.

Patients with heart failure and atrial fibrillation.

The 2016 ESC guidelines on HF emphasize that patients with HF and AF should generally be anticoagulated, therefore an evaluation of the balance of benefit and the risk of bleeding (using CHA2DS2-VASc and HAS-BLED scores) is indicated. [12] A substantial proportion of patients with HF and AF is characterized by both benefit and risk scores ≥3, indicating that careful consideration should be given before prescribing an oral anticoagulant and that regular patient's control is subsequently needed.

The 2016 ESC guidelines on HF make the following recommendations for the prevention of thromboembolism in patients with HF and concurrent AF [12]:

1. For the estimation of the risk of thromboembolism and the risk of bleeding associated with oral anticoagulation, the CHA_2DS_2-VASc and HAD-BLED scores are recommended tools (IB)
2. An oral anticoagulant is recommended to prevent thromboembolism for all patients with paroxysmal or persistent/permanent AF and CHA_2DS_2-VASc ≥2 without contraindications, and irrespective of whether a rate or rhythm management strategy is used (including after successful cardioversion) (IA)
3. NOAC treatment is contraindicated in patients with mechanical valves, or at least moderate mitral stenosis (IIIB)

Table 1. The hazard ratio (HR) and 95% confidence interval of the efficacy and safety outcomes of NOACs compared with warfarin in AF patients with or without HF

Clinical Trial	RE-LY [17]		ROCKET-AF [18]	ARISTOTLE [19]	ENGAGE AF-TIMI 46 [20]
NOAC	Dabigatran		Rivaroxaban	Apixaban	Edoxaban
	110 mg	150 mg			
AF patients with HF, n	1641	1640	4530	3235	8145
Stroke/systemic embolism	0.99 (0.69–1.42)	0.75 (0.51–1.10)	0.91 (0.74–1.13)	0.55 (0.34–0.91)† 0.98 (0.65–1.49)‡	0.88 (0.69–1.12)⁺ 0.83 (0.55–1.25)⁺⁺
Major bleeding	0.83 (0.64–1.09)	0.79 (0.60–1.03)	N/A	0.81 (0.58–1.14)† 0.62 (0.44–0.88)‡	0.79 (0.65–0.96)⁺ 0.79 (0.54–1.17)⁺⁺
Intracranial haemorrhage	0.34 (0.14–0.80)	0.39 (0.17–0.89)	0.63 (0.40–1.02)	0.25 (0.08–0.73)† 0.20 (0.07–0.58)‡	0.45 (0.28–0.73)⁺ 0.35 (0.14–0.88)⁺⁺
AF patients without HF, n	4374	4436	2551	5885	5926
Stroke/systemic embolism	0.86 (0.67–1.09)	0.61 (0.47–0.79)	0.84 (0.65–1.09)	0.74 (0.57–0.96)	0.87 (0.69–1.11)
Major bleeding	0.79 (0.67–0.94)	0.99 (0.84–1.16)	N/A	0.77 (0.62–0.94)	0.82 (0.68–0.99)
Intracranial haemorrhage	0.28 (0.17–0.47)	0.42 (0.27–0.64)	1.05 (0.93–1.18)	0.47 (0.30–0.73)	0.51 (0.33–0.80)

Legend:
N/A, not available
†HR and 95% CI for patients with left ventricular systolic dysfunction.
‡HR and 95% CI for patients with heart failure and preserved ejection fraction.
⁺ HR and 95% CI for patients with heart failure NYHA I-II
⁺⁺ HR and 95% CI for patients with heart failure NYHA III-IV

4. Combination of an oral anticoagulant and an antiplatelet agent is not recommended in patients with chronic (>12 months after an acute event) coronary or other arterial disease, because of a high-risk of serious bleeding. Single therapy with an oral anticoagulant is preferred after 12 months (IIIC)
5. For patients with HF and non-valvular AF, eligible for anticoagulation based on a CHA_2DS_2-VASc score, NOACs rather than warfarin should be considered for anticoagulation as NOACs are associated with a lower risk of stroke, intracranial hemorrhage and mortality, which outweigh the increased risk of gastrointestinal haemorrhage (IIaB)

Data on efficacy and safety of NOACs (dabigatran, rivaroxaban, apixaban and edoxaban) compared with warfin in additional analyses in patients with AF with HF versus without HF are summarized in table 1. Based on the results of the meta-analysis [21], which included patients with AF and HF (13,384 patients treated with NOACs and 13390 patients treated with warfarin), single-/high-dose NOAC regimens have a significantly better efficacy and safety profile compared with warfarin. Low-dose regimens had similar efficacy and safety levels to those of warfarin. Currently, head-to-head comparisons between NOACs in patients with AF and HF are not available.

Patients with LV.

According to the ESC guidelines for the management of acute MI in patients presenting with ST-segment elevation, when LV thrombus is recognized, anticoagulation should be administered for up to 6 months guided by repeated imaging.[22] The standard care for patients with LV thrombus is anticoagulation with warfarin, this practice is based on studies performed in the thrombolytic era in post MI patients. The results of the use of NOACs in patients with LV thrombus were combined in a meta-summary of 36 clinical cases, where HF was one of the most common comorbidities [23]. LV thrombus resolution with NOACs was noted in most patients with median duration of treatment to resolution equal to 1 month. There were minimal bleeding and no embolic events reported. Further clinical trials will provide more robust data regarding the efficacy and safety of NOACs in patients with LV thrombus.

Conclusions

To this date, there still is no conclusive evidence that HF itself should be an indication for anticoagulant/antithrombotic therapy. Recommendations for anticoagulant therapy in AF are similar in patients, with and without HF. The efficacy and safety of NOACs are similar, regardless of concomitant HF.

Declarations of interest

The authors declare no conflict of interest.

Acknowledgements

The authors state that they abide by the authors' responsibilities and ethical publishing guidelines of the International Cardiovascular Forum Journal.[24]

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Potassium Binders

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Abstract

Hyperkalaemia is common in treated HF, especially if on RAAS inhibitor drugs and in the presence of impaired renal function. The signs and/or symptoms of hyperkalaemia include weakness, fatigue, and/or paralysis, nausea and constipation and bradyarrhythmias. ECG changes include peaked T waves, prolonged PR interval, wide QRS complex duration, the loss of P waves, and finally a sine-wave pattern. Emergency severe hyperkalaemia treatment to counteract its negative impacts includes using insulin infusion with glucose, beta-agonists (e.g. salbutamol) or 8.4% sodium bicarbonate and augmenting potassium removal from the body using cation exchange resins, loop diuretics or dialysis. Two newer agents have been approved for the treatment of hyperkalaemia ZS-9 and patiromer and these two agents are promising agents in the management of hyperkalaemia in the setting of HF, with the need for trials to prove their role in this setting, and whether they can safely allow RAASi drugs to be used at their recommended doses without the risk of hyperkalaemia.

Keywords: heart failure; potassium; hyperkalaemia; patiromer; ZS-9

Citation: Tycinska A and Jankowska, EA. Potassium Binders. International Cardiovascular Forum Journal. 2019;18:27-30. DOI: 10.17987/icfj.v18i0.621

Introduction

Hyperkalaemia is a very common condition in cardiovascular patients. It can result from increased potassium intake, impaired distribution between the intracellular and extracellular spaces, and/or reduced renal excretion. Hyperkalaemia is particularly prevalent in patients older than 65 years with advanced chronic kidney disease (CKD), diabetes, and/or chronic heart failure. Hyperkalaemia has been classified into mild (K+ of 5.0–5.5 mEq/L), moderate (K+ of 5.5–6.0 mEq/L) and severe (K > 6.0 mEq/L), which allows a better stratification of the risk for patients.[1]

The American Heart Association (AHA) defines hyperkalaemia, when serum potassium values exceed 5.0 mEq/L, and the European Society of Cardiology (ESC) guidelines warn for caution over these values.[2,3] The optimal serum potassium value for patients with cardiovascular disease is considered to be betwen 4 and 5 mEq/L.

Epidemiology of hyperkalaemia

Hyperkalaemia is rarely detected in a general population. Among patients hospitalized for any cause, the incidence of hyperkalaemia ranges between 1-10%.[4] In a general population of patients (including about 10% of them with chronic kidney disease [CKD]), the prevalence of hyperkalaemia is estimated to be about 3% of all emergency room visits and of hospital admissions.[5,6,7]

In the contemporary era, the prevalence of hyperkalemia as well as the rate of hospitalizations due to hyperkalaemia is increasing, which is strongly related with the more widespread use of the renin-angiotensin-aldosterone system (RAAS) blockers.[8] In patients with heart failure (HF), the prevalence of hyperkalaemia depends on the severity of HF, the age of a patient, the presence of concomitant diseases (mainly: CKD and diabetes mellitus [DM]), as well as the use of other drugs, in particular RAAS blockers. The prevalence of hyperkalaemia in patients with HF increases to 5% with a concomitant dual RAAS blocker therapy, and rises to up to 10% in patients with accompanying CKD.[9,10]

While initiating or titrating the dose of drugs blocking the RAAS in patients with HF, it is crucial to assess the risk of hyperkalaemia, as many of these patients already have impaired potassium excretion, placing them at an increased risk, in particular the elderly and those with renal impairment or diabetes.[6,11,12] As the RAAS blockers are life-saving drugs in patients with HF, the inability of their clinical use or optimal up-titration the dose due to hyperkalaemia is a serious therapeutic barrier. Concerning the tolerability of medications used for the treatment of HF patients and the potential increased risk of hyperkalaemia, it is worthwhile to notice that the results of the PARADIGM-HF trial revealed in sacubitril/valsartan group the lower risk of hyperkalaemia as compared with the enalapril group.[13]

Clinical entities favouring the development of hyperkalaemia in heart failure

The pathophysiology of hyperkalaemia in patients with HF

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International Cardiovascular Forum Journal 18 (2019)
DOI: 10.17987/icfj.v18i0.621

Table 1. Clinical entities increasing the risk of hyperkalaemia in patients with heart failure

Clinical entities	Mechanisms leading to hyperkalaemia
CKD	impaired elimination - lower potassium clearance
	tubulointerstitial dysfunction - lower tubular potassium secretion
	metabolic acidosis - potassium shift from the intracellular to the extracellular space
Diabetes type 2	insulin deficiency and hypertonicity - diminished ability to shift potassium to the intracellular space
	hyporeninemic hypoaldosteronism - decreased tubular potassium secretion
RAAS blockers	decreased aldosterone in HF ; decreased absorption of sodium in the distal tubules; decreased potassium excretion (Na+/K+ pump)
Other medications used for HF treatment	beta-2 receptor blockers - reduced renin production and hampered potassium redistribution to the intracellular space
	heparin - reduced aldosterone production
	digitalis glycosides - Na-K-ATPase inhibition

CKD - chronic kidney disease; HF - heart failure; RAAS - renin-angiotensin-aldosterone system. (Kovesdy CP. Updates in hyperkalemia: Outcomes and therapeutic strategies. Rev Endocr Metab Disord. 2017 March ; 18(1): 41–47.).

is complex. The key factors favouring the occurrence of hyperkalaemia are shown in Table 1.

There is no direct relationship between the occurrence and severity of clinical symptoms and the severity of hyperkalaemia. Indeed, most patients with hyperkalaemia are asymptomatic. Hyperkalaemia is usually discovered through the blood screening, and when diagnosed, additional investigations such as electrocardiograms are performed to determine the severity of its clinical consequences.

The signs or/and symptoms of hyperkalaemia result from the interference of potassium with neuromuscular systems including skeletal muscle (weakness, fatigue, and paralysis as results of the decrease of muscle strength), visceral smooth muscle (nausea and constipation) and finally myocardial muscle (additional contractions and bradyarrhythmias).[14] In the ECG, hyperkalaemia mainly affects the depolarization period, which translates into the following changes observed along with increasing serum potassium levels: peaked T waves, prolonged PR interval, wide QRS complex duration, the loss of P waves, and finally a sine-wave pattern - a prognostically bad forerunner of impending ventricular fibrillation and asystole.[14]

Treatment of hyperkalaemia in emergency conditions

The main goal of acute or severe hyperkalaemia treatment is to counteract its negative impact on muscles (myocardial, skeletal and smooth muscles) by transferring potassium cations from the extracellular volume to the cells and/or removing them from the body, thus normalizing the serum potassium level without causing hypokalaemia. The intensification of intracellular potassium shift can be achieved by using insulin infusion with glucose, beta-agonists (e.g. salbutamol) or 8.4% sodium bicarbonate. The augmented potassium removal from the body can be obtained using cation exchange resins, loop diuretics or dialysis.

Approach to reduce the risk of hyperkalaemia when using the RAAS blockers

In order to prevent or reduce the risk of hyperkalaemia in patients treated with RAAS blockers, it is necessary to implement some clinical efforts, including a regular assessment of renal function and the use of adequate diuretic doses, screening and correction of potential metabolic acidosis, discontinuation of other medications impairing renal potassium excretion (including nonsteroidal anti-inflammatory drugs), the initiation of RAAS blockers with low doses along with a careful monitoring of serum potassium and creatinine.[14]

Potassium binding agents

Current strategies for pharmaceutical treatment of hyperkalaemia resulting from CKD or drug-induced hyperkalaemia tend to use cation exchange resins. The first and the oldest substances (used for over 60 years) of this type is sodium polystyrene sulphonate (SPS).[15] When using this agent in emergency situations, it should be remembered that its onset of action is seen after several hours following oral administration.[16] The evidence supporting the clinical use of this drug is based on one study involving 32 patients with azotemia, showing a significant decrease of serum potassium level of 0.9 mEq/L within 24 hours.[17] Due to the lack of alternative methods, SPS has become the main and most widely used therapeutic agent for hyperkalaemia. It is an organic cation exchange resin, which exchanges potassium for sodium in the gastrointestinal (GI) tract. The drug has important life threatening adverse side effects, including: colon injury and transmural necrosis [18] and hypernatremia.[19]

In recent years, two newer agents have been approved for the treatment of hyperkalaemia. The first one, sodium zirconium cyclosilicate (ZS-9), is an inorganic, non-absorbing, microporous compound, acting as a selective sodium-potassium cationite, which catches potassium ions in the GI tract. It is believed that micropores present in the molecule resemble physiological potassium channels, due to which the agent neither captures nor binds calcium or magnesium ions (as it occurs in the case of aforementioned polystyrene sulphonates). ZS-9 is not absorbed in the GI tract, because of its insoluble properties. Thus, the agent is thought to be safe.[20]

ZS-9 was studied in 94 outpatients with HF treated with RAAS blockers (the HARMONIZE trial).[20,21] At first, all patients enrolled into the study received an open-label ZS-9 (three times per day for 48h), which reduced serum potassium to normal levels within 48 hours in the majority of subjects.[20] Then the drug was assessed in the subgroup of normokalaemic patients, where 3 doses (5, 10 and 15 g once daily) were similarly effective in lowering and maintaining potassium levels, despite the continuation of RAAS blockers.[20,21] Side effects, including peripheral oedema and mild hypokalaemia (potassium level 3.0 to <3.5 mEq/L) were observed only when higher doses of the agent were used and were very rare (oedema occurred in one, two, and five patients in the 5 g, 10 g, and 15 g dose groups, respectively, and one patient in the placebo arm, and mild hypokalaemia

Table 2. Current treatments for hyperkalaemia

	Mechanism of action	Adverse effects
SPS/CPS	Removal Onset: 60-180 mins Duration: 240-360 K reduction: 0.5-1.0 per 1 g resin	Nausea, constipation, diarrhea, paralytic ileus, cecal perforation, hypercalcemia, hypernatremia
Hemodialysis	Removal Onset: <10 mins Duration: <60-180 K reduction : 1.2-1.5/h	Hypokalaemia, arrhythmias
Loop diuretic (furosemide)	Removal Onset: Immediate 15 mins Duration: 120-180	Ototoxicity, hypokalaemia, nephrotoxicity
Insulin + dextrose	Translocation Onset: <15-30 mins Duration: 240-360 K reduction: 0.5-1.5 mEq/L (dose dependent)	Hypoglycaemia, hyperosmolarity, volume overload
Beta-adrenergic agonists	Translocation Onset: 3-5 mins onset Duration: 1-4 h K reduction: 1.6-1.7/2 h (salbutamol)	Tremor, tachycardia
Sodium bicarbonate (Only in patients with metabolic acidosis – bicarbonate <22mEq/L)	Translocation (doubt effect) Correction of acidosis Onset: 30-60 mins (onset). Duration: 2-6 h	Hypernatremia, volume overload, tetany, hypertension
Calcium gluconate	Translocation Stabilise myocardium, protect cardiomycytes Onset: 1-3 mins Duration: 30-60 mins K reduction: 0.5-1.5 mEq/L	Hypercalcemia, tissue necrosis

CPS= calcium polystyrene sulfonate; SPS= sodium polystyrene sulfonate

occurred in one patient in the 10 g dose group and three patients in the 15 g dose group).[21] A currently ongoing trial with ZS-9 is recruiting patients with HF and high serum potassium (>5.0 mEq/L) to initiate and intensify the RAAS blockers (PRIORITIZE HF, ClinicalTrials.gov Identifier: NCT03532009).

The next drug is calcium patiromer - a safe, oral non-absorbable potassium-binding agent, approved by the FDA. It is a non-resorbable polymer with the ability to exchange cations in the GI lumen which, as a counter ion, contains a calcium-sorbitol complex.[8,22] Patiromer is a high-performance polymer with the main part of its action occurring in the distal part of the colon, where potassium concentration is the highest. Because of its low viscosity, the agent easily mixes with water or food, and a small amount of sorbitol per dose does not cause osmotic diarrhoea.[8,22] The late onset of patiromer action, about 7 hours after administration, classifies the agent as a drug for the treatment of chronic hyperkalaemia. In comparison to resins, calcium patiromer can be administered 1-2 times per day, and its side effects are much less pronounced.[22] The agent is of a particular importance for patients treated with RAAS blockers, allowing to add/optimize dosage of these drugs and reducing the risk of hyperkalaemia.

The PEARL-HF study included patients with HF (mean LVEF 40±12%) treated with spironolactone, randomized to either patiromer (originally named RLY5016) or placebo. After 28 days of therapy, in an active group hyperkalaemia (K+>5.5 mEq/L) was present in 7% as compared to 25% in a placebo arm ($p<0.05$). At the end of the treatment period, RLY5016 had significantly lowered serum potassium levels relative to placebo, with a difference between groups of -0.45 mEq/L ($p<0.001$).[23] Consequently, more patients receiving RLY5016 were able to receive the 50 mg dose of spironolactone without hyperkalaemia as compared to a placebo arm (91% vs 74%, $p=0.019$). The results regarding the effective up-titration of spironolactone and hyperkalaemia prevention were similar in patients with HF with versus without concomitant kidney dysfunction (GFR <60mL/min./1.73m3).[23] The drug was relatively well tolerated as the occurrence of mild side effects (bloating, diarrhoea, vomiting) was approximately 20%.[24] However, more RLY5016-treated patients had hypokalaemia (<3.5 mEq/L) than placebo patients (6 versus 0%, respectively), and significantly more RLY5016-treated patients had serum potassium <4.0 mEq/L than patients receiving placebo (47 vs. 10%, respectively, $p<0.001$). In addition, more patients in the RLY5016 group were able to have their spironolactone dose up-titrated as compared with patients in the placebo group (91 vs.74%, $p<0.05$).

In the OPAL-HK study, among patients with CKD taking RAAS inhibitors (RAASi), the most frequently reported side effects of patiromer (in up to 11% of patients) were those related to the GI tract, such as constipation, bloating, and nausea.[25] In the AMETHYST-DN study, among patients with HF, diabetes, CKD, and hyperkalemia treated with ACE-I/ARBs, patiromer was well tolerated and effective in terms of decreasing potassium level.[26]

When patiromer binds potassium, it usually releases calcium. Calcium ions may be absorbed by the intestine, then excreted to the urine, bound to other anions or rebound to patiromer. The moderate increase of calcium urine excretion together with reduced magnesium urine secretion may increase the risk of calcium-containing kidney stones. On the other hand, calcium released from patiromer in the small bowel may act as a phosphate binder, which could be useful for patients with CKD requiring phosphate-binding agents.

Due to its mechanism of action, patiromer may interacts with numerous drugs, reducing their the bioavailability. Therefore, the FDA has recommended to administer patiromer 6 hours prior to or after the administration of other drugs.[8]

Adverse effects of calcium patiromer are not serious or potentially life-threatening and mainly concern GI disorders such as constipation, diarrhoea (occurring in 5% and 3% of patients, respectively). Particular attention should be paid to hypokalaemia (serum potassium <3.5 mEq/L), which was seen, but was relatively rare, namely 3% of patients in the OPAK-HK trial and 6% outpatients in the AMETHYST-DN trial.[26]

Currently ongoing trials are recruiting patients with kidney

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DOI: 10.17987/icfj.v18i0.621

dysfunction, including those with end stage kidney disease (Use of Patiromer to Transition Chronic Kidney Disease Patients With Hyperkalemia to a Plant-rich Diet, ClinicalTrials.gov Identifier: NCT03183778 and The Effects of Patiromer on Serum Potassium Level and Gut Microbiome of ESRD Patients With Hyperkalemia, ClinicalTrials.gov Identifier: NCT03326583, respectively).

Conclusions

Hyperkalaemia is common in patients with HF, particularly in elderly and in subjects with comorbidities (CKD and DM). Hyperkalaemia may limit the introduction/up-titration of life-saving drugs blocking the RAAS. Recently, new drugs (zirconium cyclosilicate and patiromer) have been approved to treat hyperkalaemia. They are safe and effective in lowering potassium level in HF patients. Clinical studies of patiromer and ZS-9 have demonstrated a dose-dependent potassium-lowering effect for both agents. They may be helpful in optimising RAASi therapies in patients with hyperkalaemia. However, their benefits on long-term outcomes should be further evaluated in larger and longer randomised clinical trials concentrating on clinical outcome events. Also, drug-drug interactions have been demonstrated with patiromer but not yet investigated with ZS-9. Although there are some concerns about hypomagnesaemia and positive calcium balance from patiromer, and sodium overload from ZS-9, both agents have been shown to be well tolerated. Upcoming clinical trials should aim to investigate whether these new treatments for hyperkalaemia could plausibly improve clinical outcomes in specific patient groups that are prone to arrhythmias (e.g. patients with pre-existing cardiovascular disease, or patients with advanced CKD. Despite these gaps of knowledge, in light of their pharmacological properties and available evidence collected so far, patiromer and ZS-9 are promising agents in the management of hyperkalaemia in cardiovascular patients. The treatment and prevention of significant hyperkalaemia has received increasing attention in recent times.[27]

Declarations of interest

The authors declare no conflict of interest.

Acknowledgements

The authors state that they abide by the authors' responsibilities and ethical publishing guidelines of the International Cardiovascular Forum Journal.[28]

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Hypoglycaemic Agents in Patients with Heart Failure

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Abstract

Impaired glucose metabolism and diabetes are both very common in HF, and associated with worse functional status and prognosis. More lenient rather than strict glycaemic control is advised in patients with HF. In patients with diabetes and HF glycaemic control should be implemented gradually and moderately, giving preference to those drugs that have been shown to be safe and effective. SGLT2 inhibitors improve CV outcomes and reduce the risk of hospitalisations for heart failure, and are as a result the preferred glucose-lowering agents in T2DM patients at risk for, or with, established HF. Metformin is considered safe in HF with diabetes and is a preferred agent for glycaemic control in this setting. Sulfonylurea treatment seems to be associated with a higher risk of HF hospitalisation and is not indicated in patients with heart failure. GLP-1 receptor agonists have been proven to reduce macrovascular end points in patients with type II diabetes, however, they seem at most ineffective in patients with HF with reduced ejection fraction, and are not therefore the preferred agents in this patient population. DPP-4 inhibitors (gliptins) have only a limited effect on glucose control and no benefit on cardiovascular events and therefore do have compelling arguments for use in HF patients with type 2 diabetes.

Keywords: heart failure; diabetes mellitus; therapy; SGLT2 inhibitors

Citation: Rosano GMC Seferović P. Hypoglycaemic Agents in Patients with Heart Failure. International Cardiovascular Forum Journal. 2019;18:31-35. DOI: 10.17987/icfj.v18i0.623

Introduction

Impaired glucose metabolism and diabetes are very common in heart failure (HF), and diabetes is associated with poorer functional status and worse prognosis in patients with HF. Glucose control improves microvascular, and to a certain extent also macrovascular complications in diabetic patients. However, whether strict glycaemic control adds benefits greater than its risks compared to more lenient glycaemic control in improving the risk of cardiovascular (CV) events in patients with HF is uncertain. Amongst untreated diabetic patients with HF a higher Hemoglobin A1c (HbA1c) is associated with a greater risk of future CV events. However, this is not the case once treatment for diabetes has been implemented. Furthermore, observational data suggest that aggressive glucose control is associated with an increased risk of events in diabetic patients with heart failure. In patients with diabetes and HF glycaemic control should be implemented gradually and moderately, giving preference to those drugs that have been shown to be safe and effective.[1]

It is well known that in diabetic patients with HF, insulin and glucose-lowering agents that cause sodium retention increase the risk of worsening HF and hospitalisation.

In the past decade a new wave of glucose lowering agents has become available for the management of diabetes and much new data on their long-term safety has become more recently available. For some of these drugs conflicting results have been reported, for some others the safety profile in HF has not been adequately characterized whilst for others a significant benefit in preventing HF has been suggested.

Metformin

The glucose lowering mechanism of metformin is predominantly due to a decrease in hepatic glucose production. Therefore, these drugs do not directly affect insulin sensitivity. Metformin is at the present the only available biguanide and it has been developed in an era when it was supposed that glucose lowering per se would be safe and have beneficial effects on CV outcome, so that only evidence of hypoglycaemic efficacy was deemed

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ISSN: 2410-2636

International Cardiovascular Forum Journal 18 (2019)
DOI: 10.17987/icfj.v18i0.623

necessary if standard safety signals had been excluded. Therefore, there are no large randomised trials available on the CV safety and efficacy of metformin. The only randomised trial with metformin in patients with new onset of diabetes was the UK Prospective Diabetes Study (UKPDS) 34.[2] The study found a significant reduction in CV outcomes with metformin compared to sulfonylureas and insulin in obese diabetic patients. Cohort studies [3] reported a superiority on HF outcomes of metformin over sulfonylureas or glitazones. Subsequently, meta-analyses reported a superiority of metformin over other glucose lowering drugs in reducing cardiovascular events and heart failure in an unselected population of diabetic patients.

Heart failure had long been considered a contraindication for the use of metformin because of concerns regarding an increased risk of precipitating lactic acidosis. However, cohort studies assessed the effect of metformin in patients with HF treated with metformin and did not find a significant risk. A meta-analysis of most of the available studies included 34,000 diabetic patients with heart failure.[4] Metformin was found to reduce by 20% the relative risk of worsening heart failure and death compared to other glucose lowering drugs. Two studies that have investigated the effect of metformin in patients with heart failure found a non-significant trend towards a beneficial effect of metformin.[5,6]

Kidney dysfunction is a relative contraindication for metformin as it reduces the renal elimination of the drug. However, Aguilar et al. found that in patients with HF and diabetes there was no interaction between kidney function and outcomes. Instead they found a clear trend for beneficial effects of metformin especially in patients with a glomerular filtration rate <60.[5]

As mentioned above for the reason that metformin has been developed more than 30 years ago proper randomised studies on its safety and efficacy in patients with, or at high risk to develop, HF are lacking. It is fair to conclude, however, that with the large number of patients included in retrospective cohort studies, no evidence of safety concerns in those patients at risk for HF has been seen.

Sulfonylureas in HF

Like biguanides, the cardiovascular safety of sulfonylureas has never been prospectively tested. Available cohort studies with this class of drugs are heterogeneous and have shown neutral or increased CV event rates in diabetic patients. The situation with sulfonylureas is more complicated than for metformin, since several sulfonylureas have become commercially available.

There are no specific studies investigating patients with HF and diabetes. Therefore, the knowledge on the effect of this class of drugs is deduced from unselected cohorts of diabetic patients who developed heart failure.

A recent propensity score matched analysis of 130,000 patients found an inferiority of sulfonylureas in direct comparison to metformin users with respect to HF hospitalization rates.[7] In this unselected cohort of diabetic patients, the hospitalisations for heart failure were significantly increased by sulfonylurea treatment. In another analysis in more than 300,000 diabetic patients [8] a similar risk of heart failure was found for sulfonylureas and acarbose compared to an increased risk with glinide treatment. Prevalent HF in this study was rare and even cardiac co-morbidity was less than 20%. A third cohort study [9] including nearly 500,000 patients reported an increased risk for HF hospitalisations with sulfonylureas and insulin compared to non-users, and a decreased risk for glitazones, gliptins and metformin.

Therefore, in unselected diabetic cohorts sulfonylurea treatment seems to be associated with a higher risk of HF hospitalisation compared to metformin, gliptins or glitazones and a similar risk compared to insulin or acarbose. Due to the complete lack of data in diabetic patients with HF, and considering the signals of an increased risk for HF, sulfonylureas are not indicated in patients with heart failure.

DPP-4 inhibitors

The DPP-4 inhibitors (gliptins) stimulate insulin secretion by increasing plasma levels of incretins.[10] Three large scale randomized clinical trials have been performed to assess the CV safety of DPP-4 inhibitors to date. These studies were designed to demonstrate non-inferiority of these molecules against placebo and recruited diabetic patients at increased CV risk. All DPP-4 inhibitors outcome trials met the primary composite endpoint of non-inferiority versus placebo (combinations of CV death, non-fatal MI, non-fatal stroke etc.). It is important to remind ourselves, however, of the purpose of a non-inferiority end-point. If we are comparing a new treatment with established therapy we may be comfortable knowing we can exclude the fact that the new drug is significantly worse than established treatment within a pre-set limit, if for example it had other advantages, in tolerability or price for example. If the comparator in a non-inferiority trial is placebo, however, all we can say with a positive trial is that the new drug is no worse than placebo (or nothing!). This would only be acceptable to guide clinical use if some other worthwhile benefit had been shown, and if that is merely a reduction in glucose levels with no outcome benefits, this may not be convincing enough to adopt the new drug into clinical practice. The primary end-points of these three trials therefore merely show that these drugs have a small glucose lowering effect and are not worse than placebo in reducing CV events. Indeed they were not shown to be significantly better either. In the three trials although major cardiac events were not different to placebo, the incident hospitalization rates for HF differed. The Saxagliptin Assessment of Vascular Outcomes Recorded in patients with diabetes mellitus - Thrombolysis In Myocardial Infarction 53 (SAVOR-TIMI 53) [11] studied 16,492 patients with type 2 diabetes with or at risk for CV events for a median of 2.1 years. The primary end point (the composite of CV death, MI, or ischemic stroke) did not differ (1.00; 95% CI, 0.89 to 1.12; P=0.99 for superiority; P<0.001 for non-inferiority), however, a statistically significant 27% increase in hospitalisation for HF was observed in the patients randomised to saxagliptin as compared to placebo (3.5% vs 2.8%; p=0.007). The alogliptin in Examination of Cardiovascular Outcomes vs Standard of Care in Patients with Type 2 Diabetes and Acute Coronary Syndrome (EXAMINE) trial assessed 5,380 patients with type 2 diabetes and either an AMI or unstable angina requiring hospitalization within the previous 15 to 90 with non-inferiority primary end point of the composite of CV death, nonfatal MI, or nonfatal stroke.[12] The primary (HR, 0.96; P<0.001 for non-inferiority) showed neither risk nor benefit on the background of a mean difference of –0.36 percentage

points in glycated Hb. (P<0.001). However there was a non-significant increased risk of hospitalisations for HF with alogliptin (HR 1.19; 95% CI 0.90-1.58) in the same direction as that seen with saxagliptin. The Trial Evaluating Cardiovascular Outcome with Sitagliptin (TECOS) [13] randomised 14,671 type 2 diabetics aged at least 50 and with established CV disease for a median follow-up of 3.0 years, leading to a small average difference in glycated hemoglobin levels of –0.29 percentage points. The primary outcome (the composite of CV mortality, nonfatal MI, nonfatal stroke, or hospitalization for unstable angina) did not differ (HR, 0.98) and in this case the rate of hospitalization for heart failure also did not differ between the two groups (HR, 1.00; 95% CI, 0.83 to 1.20; P=0.98).

Meta-analyses of the 3 randomised controlled studies consistently reported an increased risk of HF hospitalisations with DPP4is as a group, even thought he three individual trials differed in this regard. The US FDA released a drug safety communication about the potential increase in the risk of HF with saxagliptin and alogliptin but not with sitagliptin.[14-15] Such heterogeneous results raised concerns of increased HF hospitalization risk for DPP-4 inhibitors as a whole as stated in 2016 ESC HF guidelines.[1] The Cardiovascular and Renal Microvascular Outcome Study with Linagliptin in patients with type 2 diabetes (CARMELINA) [16] was significant for non-inferiority against placebo on MACE but also showed no benefit in any other CV end-point including hospitalisations for heart failure. The Cardiovascular Outcome Study of Linaglitpin versus Glimepiride in Patients with Type 2 Diabetes (CAROLINA) [17] will help address the differences in CV risk of the two drugs. However, this is a class of drug with only a limited effect on glucose control and no difference to placebo with regard to cardiovascular events does not appear to have compelling arguments for use in HF patients with type 2 diabetes. Given the high cost of these medications it is difficult to justify their clinical use in this regard.

SGLT-2 inhibitors in HF

SGLT-2 inhibitors are glucose lowering drugs that block the SGLT-2 receptors in the proximal tubule of the kidney, thus leading to increased urinary glucose excretion along with sodium.[18-19] Three SGLT-2 inhibitors - canagliflozin, dapagliflozin, and empagliflozin - have been approved for the treatment of T2DM by regulatory agencies in Europe and United States. Recently three landmark trials reported that SGLT-2 inhibitors demonstrated remarkable improvements in CV outcomes especially hospitalisation for HF in patients with T2DM, beyond lipid lowering.

The Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients Removing Excess Glucose (EMPA-REG OUTCOME) [20] randomised 7,020 patients with T2DM and established CV disease to receive 10 mg or 25 mg of empagliflozin or placebo once daily. After a median observation time of 3.1 years, empagliflozin (pooled 10 mg and 25 mg doses) showed a significant 14% relative risk reduction (RRR) in the primary composite endpoint of CV death, nonfatal myocardial infarction or nonfatal stroke. Moreover empagliflozin significantly reduced death from CV causes, death from any cause and hospitalisation for HF by 38%, 32% and 35% respectively. Empagliflozin was also associated with slower progression of renal disease than was placebo.[21] Post-hoc analysis of the EMPA-REG OUTCOME trial demonstrated that empagliflozin reduced HF hospitalisation and CV death consistently in patients with, and without baseline HF.[22] The Canagliflozin Cardiovascular Assessment Study (CANVAS) Program, integrated data from two trials involving a total of 10,142 participants with T2DM and high CV risk.[23] Participants were randomised to canagliflozin or placebo and after a mean follow-up of 188.2 weeks canagliflozin showed a significant 14% RRR in the primary composite endpoint of CV death, nonfatal myocardial infarction, or nonfatal stroke. Canagliflozin significantly reduced the risk of hospitalisation for HF and a renal composite outcome by 33% and 40% respectively. The study reported however a disturbing increase in amputations in patients receiving canagliflozin.

More recently the Dapagliflozin Effect on CardiovascuLAR Events study (DECLARE) evaluated 17,160 patients, of which 10,186 without atherosclerotic cardiovascular disease for a median of 4.2 years.[24] In the primary outcome analysis, dapagliflozin met the prespecified criterion for noninferiority to placebo. In the two primary efficacy analyses, dapagliflozin did not reduce significantly MACE (8.8% vs 9.4%; hazard ratio, 0.93; 95% CI, 0.84 to 1.03; P=0.17) but did show a 17% lower rate of cardiovascular death or hospitalization for heart failure (4.9% vs. 5.8%; hazard ratio, 0.83; 95% CI, 0.73 to 0.95; P=0.005). The rate of hospitalization for heart failure was reduced by 27% (HR 0.73; 95% CI, 0.61 to 0.88). Renal events were reduced by 14% by dapagliflozin (HR, 0.76; 95% CI, 0.67 to 0.87). Therefore, the study demonstrated a significantly lower rate of cardiovascular death or hospitalization for heart failure in a population with a baseline risk lower than that of patients included in EMPA-REG and CANVAS.

The effect on HF hospitalisation was not among elements of composite primary endpoint in the EMPA-REG OUTCOME and CANVAS trials but it was in DECLARE where it was specifically adjudicated. Importantly these three trials showed early, marked and sustained benefit with STGL2i in terms of HF hospitalisation. This class of drugs seems to have, beyond glucose lowering, several important haemodynamic, neurohumoral, renal, metabolic and vascular favourable effects which might have contributed to positive outcomes. The increased risk of amputation, bone fractures and volume depletion with canagliflozin is a concern that relates only to this compound.

The positive findings of these trials suggest a class effect of SGLT-2 inhibitors [38] at least for HF and renal related outcomes. This is supported by the findings of CVD-REAL study which assessed real-life data of 309,056 patients with T2DM across 6 countries.[25]. Compared with other T2DM agents, SGLT-2 inhibitors were associated with 39% RRR of HF hospitalisation and 51% RRR of death from any cause. The reduction in CV MACE end-points seen with two agents may not be a class effect as it was not seen with Dapagliflozin. As this class of agent improves CV outcome and reduces the risk of hospitalisations for heart failure, SGLT-2 inhibitors should be the preferred glucose-lowering agents in T2DM patients at risk for, or with, established HF.

Glucagon-like peptide 1 (GLP-1) receptor agonists and the risk of HF

Glucagon-like peptide 1 (GLP-1) has a number of physiological effects. The main effect is stimulating glucose-dependent insulin

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DOI: 10.17987/icfj.v18i0.623

release from the pancreatic islets but it also inhibits inappropriate post-prandial glucagon release and reduces food consumption.[26] The GLP-1 receptor agonists have been tested in large outcomes trials in patients with type II diabetes mellitus. The ELIXA trial which enrolled 6,068 patients within 180 days of an acute coronary syndrome, showed that the GLP-1 receptor agonist lixisenatide did not increase the risk of hospitalisation for HF (HR 0.96, 95%CI 0.75-1.23, p=0.75).[27], but it also failed to reduce the primary endpoint of the trial (a composite of CV death, myocardial infarction, stroke or hospitalisation for unstable angina), so it was a neutral trial.

In contrast, the LEADER trial that included 9,340 diabetic patients showed that liraglutide reduce the primary composite endpoint of CV death, myocardial infarction or stroke by 13%.[28] The study failed to show a significant reduction in the risk of hospitalisation for HF (HR=0.87, 95%CI 0.73-1.05, p=0.14). Similarly, in SUSTAIN-6, a shorter trial of 2.1 years including 3,297 diabetic patients, the rate of HF hospitalisation was not reduced by the once weekly GLP-1 receptor agonist semaglutide (HR=1.11, 95%I 0.77-2.78, p=0.57) (29), despite a significant reduction in the primary end-point (composite of CV death, nonfatal MI, or nonfatal stroke) (HR, 0.74; 95% CI, 0.58 to 0.95, p<0.02 for superiority), despite it being formally a non-inferiority trial.

In the LIVE trial 241 patients with heart failure and an ejection fraction of ≤45% (30% had type II diabetes mellitus) were randomised to liraglutide or placebo for 24 weeks.[30] No change in left ventricular ejection fraction between the two groups was detected, heart rate increased in the liraglutide group. Serious adverse cardiac events were statistically significantly higher in the liraglutide group casting some clouds over the safety of these drugs in patients at increased risk, or with diagnosed heart failure. Therefore, GLP-1 receptor agonists have been proven to reduce macrovascular end points in patients with type II diabetes, however, they seem at most ineffective in patients with HF with reduced ejection fraction, and are not therefore the preferred agents in this patient population.

Insulin and the risk of heart failure

Insulin increases sympathetic activity and Na retention. Therefore, it is theoretically detrimental for patients with heart failure. The anti-natriuretic effect of insulin is evident even in physiological concentrations[31], and the sodium-retaining effect of insulin on the kidney is not affected by insulin resistance existing in other tissues.[32] Fluid retention caused by insulin may contribute to weight gain, and may lead to worsening of HF. Insulin may also cause hypoglycemia which has been associated with poor CV outcomes, including HF. The CHARM trial suggested higher risk of HF and worse outcomes in heart failure patients on insulin compared to those using oral glucose-lowering agents.[33] The UKPDS trial [34] did not find any significant difference in the incidence of HF between patients receiving insulin or sulphonylureas. The ORIGIN trial [35] in 12,537 patients with different levels of altered glucose metabolism and CV risk factors randomized to basal insulin glargine or control, showed no differences in cardiovascular outcomes, including HF hospitalization, but was comparing insulin glargine with other anti-diabetic medication, some of which have subsequently been shown to increase the risk of HF. The DEVOTE trial [36] found that the ultralong-acting insulin degludec was non-inferior to glargine with respect to the incidence of major cardiovascular events. Nevertheless, hospitalization for HF was not included in the primary composite outcome and was also not a secondary end-point in this trial. Although current data suggest mostly neutral effects of insulin therapy on HF outcomes, future clinical trials are needed to address the therapeutic benefits of these agents. Insulin should be, however, avoided as much as possible in patients with heart failure because of the risk of precipitating HF hospitalization, and the lack of clear evidence of benefit in terms of major CV outcomes in HF patients.

Conclusions

Glucose lowering agents may increase the risk of cardiovascular events especially when a tight glycaemic control strategy is pursued. After the withdrawal of Rosiglitazone, a thiazolidinedione, from the European market because of an increased risk of CV events including heart failure, the negative effect of glucose lowering agents in patients with HF or at increased risk of HF has become more evident.

Therefore, glucose lowering treatment should be carefully evaluated and gradually implemented in diabetic patients with HF and in patients at increased risk of developing heart failure. In the management of diabetic patients with HF preference should be given to drugs that have been shown to be safe and effective. Metformin can be safely used in diabetic patients with HF but caution should be exerted in patients with impaired renal function. Sulphonylureas may increase the risk of worsening HF, possibly related to hypoglycaemia and, therefore, should be avoided

Metiglinides and insulin may induce water retention and should be used with caution in patients with HF. Alpha glucosidase-inhibitors are devoid of any effect on insulin, water and Na retention, and are safe to use in patients with HF. Thiazolidinediones are increase the risk of HF worsening and hospitalisations from HF and they are contraindicated in patients with HF. DPP-4 inhibitors have a small effect on glucose control especially given their high cost. As there remain are doubts concerning their safety in HF, they should not be routinely used in patients with heart failure. GLP-1 receptor agonists seem to be safe to use in patients with HF. There is ample evidence to support the use of SGLT-2 as a class as the drugs of choice for the treatment of diabetes mellitus in patients with heart failure.

Declarations of interest

The authors declare no conflict of interest.

Acknowledgements

The authors state that they abide by the authors' responsibilities and ethical publishing guidelines of the International Cardiovascular Forum Journal.[37]

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International Cardiovascular Forum Journal 18 (2019)
DOI: 10.17987/icfj.v18i0.625

Iron Therapy

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Abstract

Iron deficiency (ID) is one of the most common co-morbidities in patients with heart failure (HF). It has its highest prevalence in elderly subjects, women, decompensated subjects, and patients with numerous co-morbidities. ID is associated with worse symptoms, poorer quality of life, reduced exercise capacity, and a high morbidity and mortality. Both ID and the anaemia it can lead to can be harmful in HF. Repletion of iron stores has been shown to be effective in HF and detection and treatment of ID are now recommended in major HF guidelines. This paper summarises iron therapy for ID in HF patients.

Keywords: heart failure; iron; iron deficiency; anaemia; iron supplementation therapy

Citation: Jankowska E, Drozd M, Tkaczyszyn M, Ponikowski P. Iron Therapy. International Cardiovascular Forum Journal. 2019;18:36-40. DOI: 10.17987/icfj.v18i0.625

Introduction

Iron deficiency (ID) belongs to the most common co-morbidities in patients with heart failure (HF), with the highest prevalence in elderly subjects, women, decompensated subjects, patients with numerous co-morbidities, including those with diabetes and chronic kidney disease (CKD).[1-3] ID has several unfavourable consequences for patients with HF, including augmented HF symptoms, poor quality of life, reduced exercise capacity, high morbidity and mortality.[1-3] ID itself needs to be differentiated from ID-related anaemia (IDA). Although untreated and long-lasting ID can lead to anaemia, ID itself has several clinical negative consequences in HF. Luckily, there are safe and effective therapeutic options, which thorough the repletion of ID (regardless of concomitant anaemia), bring clinical benefits for patients with HF.[4-6]

Pathophysiology of iron deficiency in heart failure

Iron plays a crucial role for optimal functioning of both haematopoietic and non-haematopoietic cells, being directly involved mainly in aerobic cellular energy metabolism in mitochondria.[1,7] Therefore, iron is particularly crucial for optimal functioning of tissues with high energy demand, such as myocardium and skeletal muscles.[1] This is in opposition to traditional approach, which has related ID with the development of anaemia, immunodeficiency and coagulopathy.[1,8]

The underlying mechanisms of the origin of ID in patients with HF is unknown. Based on our historical understanding of iron metabolism, the development of ID is associated with reduced iron intake, excessive iron loss and/or abnormal iron distribution to body compartments, where it remains unavailable for cells requiring iron for their metabolic needs. Some evidence suggests that ID can be secondary to inadequate dietary iron intake [9,10] or/and reduced gastrointestinal iron bioavailability (due to intestine wall oedema, use of drugs increasing gastric pH, food reducing iron absorption) in patients with HF.[11,12] ID can result from gastrointestinal iron loss, due to local inflammation or concomitant therapy with antiplatelets or/and anticoagulants. It should be noted that none of these potential pathomechanisms have been proven to promote ID in the course of HF.

Although anticipated, the pathogenesis of ID in the course of HF is different from the pathomechanisms leading to ID in the course of CKD. Patients with CKD develop predominantly functional ID, as a consequence of augmented inflammation and high circulating hepcidin, which traps iron in the mononuclear phagocyte system and makes it unavailable for metabolic needs.[7,13-15] It should be emphasised that – although hypothesised - there is no evidence linking inflammation and ID in patients with HF. Importantly, patients with HF both in chronic [2] and acute settings [3] demonstrate extremely low (but not high) circulating hepcidin, indicating severely depleted iron stores in the body. ID in the course HF is absolute in the vast majority of cases.

Diagnosis of iron deficiency in heart failure

Based on haematological practices, bone-marrow aspiration with the assessment of iron content directly in bone marrow is the ‘gold standard’ method to identify ID.[8,16-19] Due to its invasiveness and limited accessibility in a daily clinical practice (particularly among patients with cardiovascular diseases), the

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ISSN: 2410-2636

approach based on the assessment of circulating iron biomarkers is more convenient for the diagnosis of ID in patients with HF. Circulating ferritin is a reliable surrogate of iron stored in the body (mainly in hepatocytes and reticuloendothelial cells). In general, the lower the serum ferritin, the more depleted are the iron stores in the body. But ferritin is also an acute phase protein, hence its production is increased in case of accompanying inflammation. [8,19,20] Therefore, in a general population, absolute ID is diagnosed when serum ferritin is <30 µg/L or even <12–15 µg/L [8,19,21] However, due to concomitant low-grade inflammation present in the course of HF, higher cut-off values of serum ferritin are valid for the diagnosis of ID in patients with HF.

The second iron biomarker required for the diagnosis of ID is transferrin saturation (Tsat), which indicates a reduced pool of utilized iron. Tsat is the percentage of transferrin which binds iron, and is calculated as a ratio of serum iron and TIBC × 100% (TIBC, total iron binding capacity—by transferrin).[1] It is worthy of note that neither serum iron nor serum transferrin alone are recommended for the diagnosis of ID in patients with HF.

The 2016 ESC/HFA guidelines on HF management recommend routine screening for ID using serum ferritin and Tsat among all patients with HF, regardless of haemoglobin level, LVEF, renal function, etc.[22] They recommend to use the following definition of ID: serum ferritin <100 µg/L, or ferritin between 100–299 µg/L and Tsat <20%.[22] This definition has been used in CKD [20] and also in major clinical trials in HF with intravenous and oral iron supplementation.[4-6,23]

Other novel iron biomarkers are under investigation in HF, but so far without any clinical implications. Our group has recently proposed a new pathophysiological definition of ID using the combination of low serum hepcidin (indicating depleted iron stores more accurately than ferritin, regardless of concomitant inflammation) and high serum soluble transferrin receptor (sTfR) (indicating intracellular iron depletion).[2,3] TfR is the membrane molecular pathway for iron import into the cell; it is upregulated when intracellular metabolic needs for iron are not met, as the augmented membrane expression of TfR facilitates the iron influx to the cells; the overexpressed TfR is later shed to the circulation and is detected as a soluble form.[24]

Prevalence of iron deficiency in heart failure

ID is a common co-morbidity in patients with HF. When applying the definition of ID recommended by the 2016 ESC/HFA guidelines on HF management [22], the prevalence of ID in a general population of HF patients ranges between 37-74%. [2,3,25-32] ID is present across the whole spectrum of HF, regardless of LVEF.[27,31-33]

The following clinical features increase the risk for ID among patients with HF: female gender, advanced NYHA class, high plasma N-terminal pro-B-type natriuretic peptide (NT-pro-BNP), high serum high-sensitivity C-reactive protein (hsCRP), low haemoglobin level and decompensated status.[26,27,29,33]

Clinical consequences of iron deficiency in heart failure

ID translates into impaired aerobic performance expressed as lower peak oxygen consumption VO2 (peak VO2), higher ventilatory response to exercise (VE-VCO2 slope) in patients with HFrEF and HFpEF [25,30,34], and reduced submaximal exercise capacity reflected by the shorter 6-minute walking test (6MWT) distance in patients with HFrEF and HFpEF.[30] It should be noted that the unfavourable impact of ID on both peak VO2 and VE-VCO2 slope in patients with stable HFrEF has been independent and much stronger than the effect of anaemia on these parameters.[34] ID also worsens health related quality of life (HRQoL) expressed, for example using the Minnesota Living with Heart Failure Questionnaire in patients with HF.[35,36]

Among cohorts including patients within the whole spectrum of HF, ID (regardless of accompanying anaemia) has been shown to be an independent predictor of higher all-cause mortality, an increased risk of heart transplantation, and an increased risk of the composite endpoint of mortality and nonfatal cardiovascular events (HF hospitalization, acute coronary syndrome, severe arrhythmia or stroke).[3,25,26,27,29,37,38,39]

Oral iron supplementation in heart failure

Until now, only one study investigating oral iron supplementation in patients with HF has been executed and published, the IRONOUT-HF study.[23] Patients with symptomatic HFrEF (LVEF ≤40%, NYHA class II-IV) and ID defined as previously (serum ferritin 15-100 µg/L, or serum ferritin 101–299 µg/L with Tsat <20%; with a haemoglobin level 9-15 g/dL for males and 9-13.5 g/dL for females) were randomized to either oral iron polysaccharide (150 mg twice daily) (n=111) or placebo (n=114) for 16 weeks. The primary endpoint, a change in peak VO2, did not differ between the oral iron and placebo groups; in addition there were no differences between treatment groups in changes in 6MWT distance. Oral iron supplementation as compared to placebo treatment resulted in clinically meaningless increases in Tsat (+3%, p=0.003) and serum ferritin (+11 µg/L, p=0.06, borderline).[23] These results do not support the use of oral iron supplementation in patients with HFrEF.

Intravenous iron supplementation in heart failure

It should be emphasised that earlier parenteral iron preparations were administered as an iron oxyhydroxide complex [40,41], which induced a lot of free and toxic iron, translating into oxidative stress and related adverse events, such as: hypotension, nausea, vomiting, abdominal and lower back pain, peripheral oedema and a metallic taste.[42,43] The contemporary parenteral formulas (mainly ferric carboxymaltose, FCM) contain iron in a core surrounded by a carbohydrate shell, which has allowed to eliminate the aforementioned adverse reactions and side effects.[44]

The majority of clinical evidence regarding intravenous iron supplementation in patients with HF comes from 3 clinical trials. [4-6] In the FAIR-HF study [4], the Ganzoni formula [45] was used to calculate the required cumulative FCM dose, based on current body weight, actual and the target haemoglobin level of a supplemented patient. The dosing frequency was 200 mg of FCM weekly until iron repletion was achieved (the correction phase) and then every 4 weeks during the maintenance phase. In the CONFIRM-HF study [5] as well as in the EFFECT-HF study [6], FCM was administered according to a fixed scheme based on the subject's weight and haemoglobin concentration at screening and administered at weeks 0 and 6. Further FCM

International Cardiovascular Forum Journal 18 (2019)
DOI: 10.17987/icfj.v18i0.625

doses could be administered at weeks 12, 24, and 36 if ID was still present, but more than 75% of patients required only 2 doses in total. This new dosage pattern was in alignment with the total iron dosing applied in the FAIR-HF study.[46]

In the FAIR-HF study, 304 ambulatory patients with symptomatic HF with LVEF ≤40% (NYHA II) or ≤45% (NYHA III), with ID (serum ferritin <100 µg/L, or serum ferritin 100–300 µg/L and Tsat <20%) with haemoglobin 9.5–13.5 g/dL were randomized in a 2:1 ratio to either intravenous FCM (dosing already explained above) or intravenous saline. Primary endpoints were self-reported patient global assessment (PGA) at week 24 and NYHA class at week 24, adjusted for baseline NYHA class, both of which improved in the FCM arm as compared to a saline control.[4] The improvement in aforementioned characteristics were seen separately in both anaemic and non-anaemic patients, even though the clinical improvement in non-anaemic patients was not accompanied by an increase in haemoglobin level.[46] The treatment with FCM (as compared with placebo administration) resulted also in an increase of the 6MWT distance and quality of life assessments. The rates of death, adverse events, and serious adverse events were similar in the two study groups.[4]

In the CONFIRM-HF study, ambulatory patients with HF in NYHA class II-III with LVEF ≤45%, BNP >100 pg/mL or NT-proBNP >400 pg/mL, with ID (defined as in the FAIR-HF study) and haemoglobin level <15 g/dL were randomized 1:1 to either FCM or placebo for 52 weeks (doses as described above). Treatment with FCM as compared to placebo increased the 6MWT distance at week 24 (primary endpoint).[5] The treatment effect of FCM was consistent in all clinical subgroups and was seen up to week 52. Throughout the study, an improvement in NYHA class, PGA, QoL, and Fatigue Score in patients treated with FCM was demonstrated with a statistical significance confirmed from week 24 onwards. Treatment with FCM as compared to placebo was associated with a reduction in the risk of HF hospitalizations at week 52 (one of the secondary endpoints). The number of deaths and adverse events were similar in both study groups.[5]

In the EFFECT-HF study, ambulatory patients with HF in NYHA class II-III with LVEF ≤45%, a reproducible peak VO2 of 10 to 20 mL/kg/min, BNP >100 pg/mL or NT-proBNP >400 pg/mL, with ID (defined as in the FAIR-HF study) and haemoglobin level <15 g/dL were randomized 1:1 to either FCM or standard care for 24 weeks (doses as in the CONFIRM-HF study).[6] At 24 weeks, peak VO2 (primary endpoint) decreased in the control group, but was maintained on FCM ($p<0.05$). PGA and NYHA class also improved on FCM as compared to standard of care.[6]

In other smaller studies in patients with HFrEF, the following beneficial effects of intravenous iron therapy were demonstrated: within echocardiography parameters (an increase in LVEF, a reduction in LVSD, LVDD, LVPW, IVS thickness, left ventricular mass index, left ventricular end systolic volume, an improvement in S', E', a decline in E/E', a reduction in peak systolic strain rate) [47-51] and within some biomarkers (a reduction in plasma NT-proBNP and CRP.[48]

Recently 2 meta-analyses (one based on a classical methodological approach [52], the other one using individual patient data [53]) have provided additional evidence regarding the safety and efficacy of intravenous iron supplementation in patients with HF.

The meta-analysis of Jankowska EA et al. included 5 trials in iron deficient patients with HF and LVEF ≤45% (509 patients received intravenous iron therapy - the majority were treated with FCM - compared with 342 controls), with at least a single-blind randomization without a concomitant therapy with erythropoiesis-stimulating agents.[52] This meta-analysis revealed that intravenous iron therapy in iron deficient patients with HF and LVEF ≤45% reduced the risk of the combined endpoint of all-cause death or cardiovascular hospitalization, the risk of the combined endpoint of cardiovascular death or HF hospitalization, and the risk of HF hospitalization, but without an effect on either all-cause or cardiovascular mortality (which may be due to a low number of reported events and a relatively short follow-up).[52]

The meta-analysis of Anker SD et al. utilized the individual patient data extracted from four clinical trials comparing FCM (n=504) with placebo (n=335) in iron deficient patients with systolic HF.[53] As compared with a placebo group, patients receiving FCM had lower rates of recurrent CV hospitalizations and CV mortality, lower rates of recurrent HF hospitalizations and CV mortality, lower rates of recurrent CV hospitalizations and all-cause mortality.[53] Time-to-first-event analyses showed similar findings, with a somewhat attenuated treatment effects.[53]

Clinical implications

All aforementioned evidence led to the formulation of the following recommendations regarding the diagnosis and treatment of ID in patients with HF in 2016 ESC/HFA guidelines on HF management [22]:

"The following diagnostic tests (including ferritin and transferrin saturation) are recommended for initial assessment of a patient with newly diagnosed HF in order to evaluate the patient's suitability for particular therapies, to detect reversible/treatable causes of HF and comorbidities interfering with HF (Class of recommendations I, Level of evidence C)."

"Intravenous FCM should be considered in symptomatic patients with HFrEF and iron deficiency (serum ferritin <100 µg/L, or ferritin between 100-299 µg/L and transferrin saturation <20%) in order to alleviate HF symptoms and improve exercise capacity and quality of life (Class of recommendations IIa, Level of evidence A)".

Future directions

ID is highly prevalent and has numerous unfavourable consequences for patients with HF across the whole spectrum of LVEF, but surprisingly its origin still remains unknown. Although intravenous iron supplementation has been shown to improve exercise capacity, improve quality of life and alleviate HF symptoms in iron deficient patients with HFrEF, there is no definitive data that this therapy would also improve clinical outcomes in this patient population. Also, it has not been demonstrated if intravenous iron supplementation is safe and effective in iron deficient patients with acute HF and patients with HFmrEF/HFpEF. Therefore, a series of trials is ongoing in order to validate the aforementioned concepts (HEART-FID, AFFIRM-AHF, FAIR-HF2, FAIR-HFPEF, PREFER-HF, IRONMAN).

Declarations of interest

The authors declare no conflict of interest.

Acknowledgement

The preparation of the manuscript was supported by the National Science Centre (Poland) grant number 2014/13/B/NZ5/03146.

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Published by Barcaray Publishing (Dubai, Hong Kong, London), C/0 T&F Group, The Maze Tower, Sheikh Zayed Road, PO Box 58531, Dubai, United Arab Emirates