New Investigational Drugs for the Management of Acute Heart Failure Syndromes

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Abstract: Acute heart failure syndromes (AHFS) enclose a broad spectrum of conditions with different clinical presentations, heart failure history, pathophysiology, prognosis and treatment. AHFS represent a major public health problem because of their high prevalence, high rates of mortality and readmissions and significant healthcare costs, and a therapeutic challenge for the clinicians because management strategies vary markedly. Traditionally used drugs for the treatment of AHFS, including diuretics, vasodilators and positive inotropics, improve clinical signs and symptoms as well as hemodynamics, but present important limitations, as they fail to reduce and may even increase in-hospital and postdischarge mortality, especially in patients with coronary artery disease. Thus, we need new pharmacological agents to not only improve signs and symptoms and cardiac performance, but also improve both short- and long-term outcomes (hospitalizations/survival). In the last decade, significant efforts have been made to identify new therapeutic targets involved in the genesis/progression of AHFS and to develop new therapeutic strategies that may safely improve outcomes. As a result, several new families of drugs have been developed and are currently studied in experimental models and in Phase II and III clinical trials, in an attempt to define their efficacy and safety profiles as well as their precise role in the treatment of AHFS patients. This review firstly analyzes the main clinical applications and limitations of conventional drugs, and then focuses on the mechanisms of action and effects of recently approved drugs and of new investigational agents on signs, symptoms, hemodynamics and outcomes in AHFS patients.

Keywords: Acute heart failure syndromes, adenosine antagonists, cardiac myosin activators, inotropes, ixtaroxime, levosimendan, metabolic modulators, natriuretic peptides, relaxin, vasodilators, vasopressin antagonists.

INTRODUCTION

A*cute heart failure* is defined as a gradual or rapid change in the signs and symptoms of heart failure (HF) that require urgent therapy [1-4]. However, the term *acute heart failure* comprises a heterogeneous group of syndromes (AHFS) with different clinical presentations, HF history, pathophysiology, prognosis and response to specific therapies [1-5]. AHFS represent a major public health problem due to their high prevalence, high rates of in-hospital and postdischarge mortality and readmissions and significant healthcare costs [1-5]. HF is the leading cause of hospitalization in patients older than 65 years and account for more than 1 million hospitalizations per year in both the United States and in Europe [4,6-8]. The rate of hospitalization has tripled over the last 25 years and this trend will continue to increase due to progressive aging of the population and improved survival after myocardial infarction [4,6]. Hospitalization for HF is one of the most important predictors of post-discharge mortality and readmission in patients with chronic HF. In fact, almost 50% of patients hospitalized with AHF will be rehospitalized at least once within 6 months after discharge [7,9]. The prognosis of AHFS is uniformly poor if the underlying problem cannot be rectified. Several registries highlight an in-hospital mortality of approximately 4-5% (but ranges from 2%-22%) and, if surviving, a ~10% risk of dying over the next 60 days. Moreover, the risk of death/ rehospitalization within 2-3 months ranges from 20% to 60%, depending on the population studied [6-11]. Finally, AHFS are the most costly cardiovascular disorder. The direct costs represent between 1-2% of the total health budget and >75% is related to hospitalization for decompensated HF [5,12-14].

Patients with AHFS frequently present comorbidities and cardiovascular risk factors, including coronary artery disease (CAD, in 40-68% of patients), abnormalities in cardiac rhythm (mainly atrial fibrillation in ~30% of patients), arterial hypertension (53-73%), diabetes mellitus (27-40%), renal insufficiency (17-30%), chronic obstructive pulmonary disease (30%), valvular dysfunction or pericardial disease [5,8,15,16]. These comorbidities cause and/or contribute to the pathogenesis of AHFS and, therefore, they should be identified and incorporated into the treatment strategy.

CLASSIFICATION OF AHFS

Systolic blood pressure (SBP) levels at hospital admission identify three groups of patients with different risk for subsequent morbidity and mortality that require appropriately tailored pharmacological treatments [2,5-7,10-12,17-20]: 1) *The hypertensive group*. More than half of hospitalized patients with AHFS have a preserved left ventricular ejection fraction (LVEF), high SBP (> 140 mm Hg) and pulmonary congestion [dyspnea, increased pulmonary capillary wedge pressure (PCWP), pulmonary edema] usually without signs of systemic congestion (i.e. peripheral edema, increase in body weigh). 2). *The normotensive group*. These patients (> 40% of all admissions) present low LVEF and signs and symptoms of both pulmonary and systemic con-

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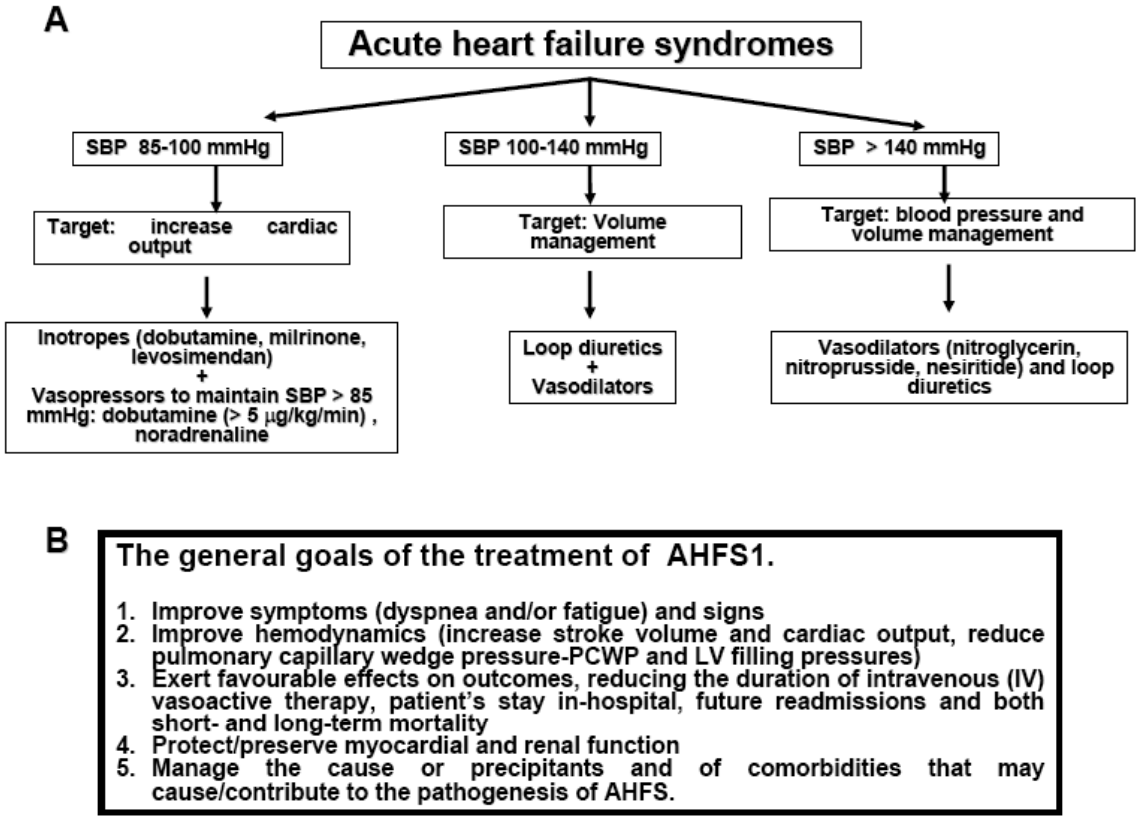

Fig. (1). General treatment of acute heart failure syndromes (AHFS). (**A**) Treatment according to the systolic blood pressure levels at admission. (**B**) The general goals of the treatment of AHFS.

gestion. 3) *The hypotensive group*. A minority (2-8%) of patients present severely impaired LVEF, reduced SBP (≤120 mm Hg) and signs of organ hypoperfusion, (e.g. cold skin, renal dysfunction, or impaired mentation) or cardiogenic shock. Thus, most patients with AHFS primarily present symptoms of pulmonary and/or systemic congestion rather than low LVEF as evidenced by high or normal SBP [17].

GENERAL TREATMENT OF AHFS

Early management of AHFS is critical because the short-term use of drugs may affect long-term morbidity and mortality [1-5]. The treatment approach and the general goals of the treatment are summarized in Fig. (**1**). In patients with AHFS with pulmonary congestion and high or normal SBP treatment is directed to reduce systemic and/or pulmonary congestion and correct the high LV filling pressure using intravenous (IV) vasodilators (e.g. nitroglycerin, nitroprusside, nesiritide) and loop diuretics (furosemide, bumetanide, torasemide). In hypotensive patients early use of positive inotropics (dopamine, dobutamine, milrinone) should be considered when they do not respond to other therapies to relieve congestive symptoms and increase cardiac output. However, loop diuretics, inotropes and vasodilators improve signs and symptoms during hospitalization, but not clinical outcomes (rehospitalizations and/or mortality) (Table **1**). Furthermore, the widespread use of these drugs is based on small, short-term hemodynamic or symptom-focused trials enrolling patients with different clinical presentations (acute *de novo* and acute decompensated chronic HF, preserved or low LVEF and high, normal or low SBP), and associated comorbidities, while their effects on clinical outcomes have been inadequately studied. Concerns about the efficacy and safety of loop diuretics, vasodilators and inotropes have stimulated the development of new drugs for the treatment of AHFS that not only improve symptoms and hemodynamics but that can reduce hospitalizations and mortality without worsening cardiac ischemia and renal function, reducing blood pressure and/or inducing cardiac arrhythmias. In this article we shall review the main clinical applications and limitations of standard therapy and the mechanism of action and effects of new investigational and recently approved drugs on symptoms, hemodynamics and outcomes in AHFS patients. Table **2** shows these new drugs classified according to the SBP levels at hospital admission, Table **1** summarizes their effects on symptoms, hemodynamics and outcomes and Table **3** the major randomized clinical trials that investigated their effects in AHFS, respectively.

DIURETICS

Intravenous administration of loop diuretics is the mainstay therapy in patients with AHFS and clinical evidence of fluid overload, generally manifested by pulmonary and systemic congestion or signs of elevated filling pressures (jugular venous distention, pulsatile hepatomegaly) [1-4]. Loop diuretics inhibit the $Na^+/K^+/Cl^-$ cotransporter (NKCC2)-mediated NaCl reabsorption in the thick ascending loop of Henle increasing the renal excretion of free water, Na^+, K^+, Mg^{2+} and Ca^{2+} [21] and produce a rapid venodilata-

Table 1. Effects of Conventional and New Investigational Drugs on Signs and symptoms, Hemodynamics and Outcomes in Patients with Acute Heart Failure Syndromes

	Reduce Signs and Symptoms	HR	Hypoten-sion	LVFP	CO	Arrhythmia	Renal Function	Neurohu-moral Activation	Effects on Mortal-ity/Hos-Pitalization
Fluid removal									
Diuretics (IV)	Yes	Va	±	↓	0	?	↓	Yes	?
Vasopressin antagonists (O, IV)	Yes	0	No	↓	0	No	0	?	0
Adenosine antagonists (IV)	?↑	0	?	?	?	No	?↑	?	?
Vasodilators									
Nesiritide (BNP) (IV)	Yes	Va	±	↓	No	No	No/↓	?	?↑
Ularitide (urodilatin)	±	0	±	↓	?↑	?	?0	?	?
Relaxin (IV)	Yes	?	Yes	↓	?	No	?0	?	?(↓)
Tezosentan (IV)	0	0	Yes	↓	↑	No	0	?	0
Inotropics (IV) :									
Levosimendan	Yes	↑	±	↓	↑	↑	?	?	?↑
Milrinone	0	↑	±	↓	↑	↑	?	?	?(↑ in CAD)
Cardiac myosin activators	Yes	?	?	?	↑	?	?	?	?
Istaroxime	Yes	↓	No	↓	↑	0	0	No	?

↓ = decrease. ↑ = increase. ± = possible. 0 = no change or neutral ? = unknown.
CAD: coronary artery disease. CO: cardiac output. DD = dose-dependent. HR: heart rate. LVFP = left ventricular filling pressure. O: oral. IV: intravenous. Va: variable.

Table 2. Investigational Pharmacologic Agents for the Treatment of AHFS

A.	**Congestion with normal–high blood pressure**
1.	Vasopressin receptor antagonists:
•	V1A receptor: OPC-21268, Relcovaptan, SR-49059
•	V1G receptor: SSR-149415
•	V2 receptor: Lixivaptan (VPA-985), Mozavaptan (OPC-31260), RWJ-351647, Satavaptan (SR-121463), Tolvaptan (OPC-41061), VP-343
•	V1A/V2 receptors: CL-385004, Conivaptan (YM-087), JTV-605, RWJ-676070
2.	Adenosine A1 receptor antagonists: BG9719 (CVT-124), Tonapofylline (BG9928), FK 838, Rolofillyne (KW-3902 or MK-7418)
3.	Natriuretic peptides: Anaritide (25-amino acid ANP), Carperitide (α-ANP), CD-NP, Nesiritide (hrBNP), Ularitide (proANP 95–126)
4.	Endothelin antagonists: Tezosentan
5.	Nitric Oxide Synthase inhibitors: L-NAME , Tilarginine (L-NMMA)
6.	Relaxin
7.	Drugs that activate directly soluble guanylate cyclase (sGC):
•	sGC stimulators: A-350619, BAY 41-2272, BAY 41-8543, CFM-1571, CY-1, Riociguat
•	sGC activators: Cinaciguat (BAY 58-2667), HMR-1766
8.	Direct renin inhibitors: aliskiren
9.	Aldosterone synthase inhibitors: FAD286, LCI 699, SPP 2475
B.	**Normal-low BP with or without congestion**
1.1.	Novel positive inotropic drugs:
•	Calcium sensitizing agents: ED-57033, EMD-53998, EMD-57033, Levosimendan, MCI-154, Pimobendan, Senazodan
•	Istaroxime (PST-2744)
•	Cardiac myosin activators: Omecamtiv mecarbil (CK-1827452), 116CK-112253, CK-1122534, CK-0689705, CK-1213296
C.	**Other drugs**
1.	Metabolic modulators:
•	Carnitine palmitoyl transferase-1 inhibitors: Etomoxir, Oxfenicine, Perhexiline
•	Long-chain 3-ketoacyl coenzyme A thiolase inhibitors: Trimetazidine
•	Glucagon-like peptide-1 and GLP-1 analogs (AC-2592)
2.	Ranolazine
3.	Ivabradine

Table 3. Major large-Scale Randomized Clinical Trials Comparing the Effects of New Developing Drugs with Placebo or Standard Therapy in Patients with AHFS

Acronyms [References]	Patients (n)	Study Design	Treatment/ Comparator	Primary Endpoint	Outcomes
ACTIV in CHF [39, 40]	319 Worsening HF	R, DB, PC, PG, DE	Tolvaptan: 30, 60 or 90 mg/day for up to 2 months Placebo	In-hospital body weight at 24 h and reduction of worsening of HF (death, rehospitalization, or unscheduled visits)	Tolvaptan reduced body weight. There were no differences in worsening HF
ASCEND-HF*	~~7000~~ AHFS	R, DB, PA, PC	Nesiritide: 0.01 μg/kg/min IV (± 2 mg/kg bolus) for 24 to 168 h Placebo	Composite of self-assessed dyspnea at 6 and 24h and HF rehospitalisation and all-cause mortality after 30 days	Currently recruiting patients
BNP-CARDS [82]	75 AHFS and renal dysfunction	R, DB, PC	Nesiritide: 2 μg/kg bolus + 0.01 μg/kg/min for 48 h Placebo	Rise in peak serum creatinine by ≥20% and change in serum creatinine during the first 7 days or discharge	Nesiritide had no impact on renal function
CASINO [148]	299 AHFS, NYHA class IV	R, DB, DD, PC, PG	Levosimendan: 16 μg bolus + 0.2 μg/kg/min for 24 h Dobutamine: placebo bolus + 5-10 μg/kg/min for 24 h Placebo.	Death and rehospitalization due to HF deterioration	Levosimendan improved 6-month survival
COMPASS [73]	1,832 ADHF, dyspnea at rest	P,O	Carperitide: 0.025–0.05 μg/kg/min for 5.2 ± 4.8 days Placebo	Assess the usefulness of carperitide as a first-line drug in patients with AHFS.	Carperitide improved the degree of dyspnea as assessed using the modified Borg scale.
DOSE-AHF*	300 ADHF	R, C, DB, DD using a 2 x 2 factorial design	High intensification (2.5 x oral dose) IV furosemide by either Q12 h bolus or continuous infusion Low intensification (1 x oral dose) IV furosemide by either Q12 h bolus or continuous infusion	Change in serum creatinine and patient global well being assessment from randomization to 72 h	Currently recruiting patients
EVEREST [41,42]	4,133 Worsening HF, NYHA class III-IV	R, DB, PC, Event-driven	Tolvaptan: 30 mg QD or placebo for a minimum of 60 days	Short-term: changes in global clinical status and body weight at day 7 or the day of discharge. Long-term trial: time to all-cause mortality (superiority and noninferiority) and cardiovascular death or HF hospital stay (superiority)	Short-term: tolvaptan improved many, though not all, HF signs and symptoms Long-term: tolvaptan had no effect on long-term mortality or HF-related morbidity
FUSION I [80]	210 AHFS, renal disfunction	Pilot, R, OL, AC, PA	Standard care (SC) SC + nesiritide, 0.005 or 0.01 μg/kg/min for 2 weeks	Safety and tolerability of different nesiritide doses administered as serial outpatient infusions	There was no evidence of worsening renal function
FUSION II [81,82]	911 AHFS, NYHA class III-IV or class III with a CrCl <60 mL/min	R, DB, PA	Nesiritide: 2 μg/kg + 0.01 μg/kg/min for 4 to 6 h, once or twice weekly for 12 weeks Placebo	Composite of all-cause mortality or cardiovascular or cardiorenal hospitalization at 12 weeks	There were no statistically significant differences between groups
HORIZON-HF [159,160]	120 AHF, NYHA II-III	R, PC, DB, PA, DE	Istaroxime: 0.5, 1 and 1.5 μg/kg/min for 6 h Placebo	Changes in PCWP after 6 h of continuous infusion	Ixtaroxime improved PCWP and possibly diastolic function

Table 3. contd…

Acronyms [References]	Patients (n)	Study Design	Treatment/ Comparator	Primary Endpoint	Outcomes
LIDO [146]	203 AHFS/LO	R, DB, DD, PA	Levosimendan: 24 µg/kg bolus + 0.1 µg/kg/min for 24 h Dobutamine: 5 µg/kg/min for 24 h The infusion rate was doubled if the response was inadequate at 2h	Hemodynamic improvement: ≥30% increase in CO and ≥25% decrease in PCWP and LV filling pressures at the end of the 24-h infusion	Levosimendan improved hemodynamics and reduced mortality at 180 days as compared to dobutamine
LINCS [96]	30 ACS and refractory CS	R, PC	Supportive care (SC) alone SC in addition to L-NAME (1 mg/kg + 1 mg/kg/h for 5 h	All cause mortality at 30 days	L-NAME reduced 30-day mortality
OPTIME-CHF [65,133]	949 DHF, LVEF 23%	R, P, DB, PC	Milrinone: 0.5 µg/kg/min for 48 to 72 h Placebo	Cumulative days of hospitalization for cardiovascular cause within 60 days following randomization	Milrinone-treated patients with ischemic etiology had worse outcomes
PRECEDENT [78]	255 ADHF	R, OL, AC, PA	Nesiritide: 0.015 or 0.03 µg/kg/min Dobutamine: ≥5 µg/kg/min	Average heart rate, premature ventricular beats and repetitive beats	Nesiritide did not increase heart rate and produced fewer ventricular arrhythmias than dobutamine
Pre-RELAX-AHF [112]	234 AHF	R, DB, PC, PA, DE	Relaxin: 10-250 µg/kg/day for 48 h Placebo	Assess whether IV relaxin should be pursued in larger studies, identify an optimum dose	Relaxin was associated with favourable relief of dyspnoea and other clinical outcomes
PROTECT-1 [58]	301 AHFS	Pilot	Rolofylline: 10, 20 or 30 mg/day over 4 h for 3 days Placebo	HF signs and symptoms; renal function. Secondary endpoints: morbidity/mortality, renal outcomes	Rolofylline improved dyspnea, decreased worsening of HF and improved renal function
PROTECT-2[a]	2,033 AHFS	R, DB, PC, PA	Rolofylline: 30 mg IV QD Placebo		No difference in primary and secondary endpoints
REVIVE I [150,151]	100 ADHF, dyspnea at rest	R, DB, PC, PA	Levosimendan: 6-12 µg/kg for 50 min + 0.1-0.2 µg/kg/h for 23 h Placebo	Composite of clinical signs and symptoms of HF over 5 days expressed as: improved, worsened (required IV treatment during the study) or unchanged	Levosimendan produced an early improvement more frequent than with placebo.
REVIVE II [152]	600 ADHF, dyspnea at rest	R, M, DB, PC, PA			Levosimendan improved primary endpoints and length of stay. Neutral effects on mortality at 90 days
RITZ-1 [104]	669 ADHF	M, R, DB, PC	Tezosentan: 25 mg/h IV for 1 h, titrated to 50 mg/h for 24-72 h Placebo	Change in dyspnea from baseline at 24 h	No difference in all endpoints. Tezosentan associated with excess of hypotension and renal failure
RITZ-2 [102]	215 ADHF	R, DB, PC	Tezosentan: 50 mg or 100 mg/h IV Placebo	Change in hemodynamic variables, dyspnea score, and safety variables	Both doses produced similar increase in cardiac index and decreases in PCWP
RITZ-4 [103]	193 ADHF after recent AMI	R, DB, PC	Tezosentan: 25 mg/h IV + 50 mg/h for ≤ 48 h Placebo	Composite of death, worsening HF, recurrent ischemia, and recurrent or new MI within the first 72 h	No difference in all endpoints
RITZ-5 [105]	84 Pulmonary edema	R, DB, PC, PA	Tezosentan: 50 or 100 mg/h IV for ≤ 24 h Placebo	Change from baseline to 60 min in arterial oxygen saturation as measured by pulse oxymetry.	No difference in all endpoints. Higher dose had worse effects
RUSSLAND [147]	504 Post-MI HF	R, DB, PC	Levosimendan: 6, 12 or 24 µg/kg + 0.1, 0.2 or 0.4 µg/kg/min over 6 h Placebo	Hypotension or myocardial ischemia at 6 h	No differences among groups. Levosimendan reduced mortality at 14 and at 180 days

Table 3. contd…

Acronyms [References]	Patients (n)	Study Design	Treatment/ Comparator	Primary Endpoint	Outcomes
SIRIUS 1 [83]	24 ADHF, NYHA class III-IV	R, DB, DE	Ularitide: 7.5, 15 or 30 ng/kg/min IV for 24 h Placebo	Hemodynamic improvement at 6 and 24 h and 6 h after end of dosing (30 h)	Urodilatin decreased PCWP, right atrial pressure, and dyspnea
SIRIUS 2 [84]	221 ADHF, dyspnea at rest, NYHA class III-IV	R, DB, PC	Ularitide: 7.5, 15 or 30 ng/kg/min IV for 24 h Placebo	Changes in PCWP and in the patient's self-assessed dyspnea at 6 h	Ularitide significantly lowered cardiac filling pressures and improved dyspnea
SHOCK-2 [97]	79 AMI and CS	R, PC, DE	Tilarginine: 0.15 to 1.5 mg/kg IV + 0.15 to 1.5 mg/kg/h for 5 h Placebo	Change in mean arterial pressure at 2 h	There was no differences among groups
SURVIVE [149]	1327 ADHF/LO	R, DB, PG	Levosimendan: 12 μg/kg bolus + 0.1 μg/kg/min for 50 min for 24 h Dobutamine: 5 μg/kg/min for 24 h	All-cause mortality at 5, 15, 30 and 180 days	No differences on clinical outcome or all-cause mortality at 180 days. Greater reduction of BNP with levosimendan.
TRIDENT-1*	900 ADHF and renal insufficiency	R, DB, PC, PA	Tonapofylline vs placebo	Safety and tolerability of IV tonapofylline when added to standard therapy	Currently recruiting
TRIUMPH [98]	398 AMI and CS	MC, R, DB, PC	Tilarginine: 1 mg/kg bolus + 1 mg/kg//h for 5 h Placebo	All cause mortality at 30 days post randomization.	No differences in all endpoint
URGENT [86]	3000 ADHF	R, DB, PC	Ularitide (dose to be defined). Placebo	Change in dyspnea at 6 h and morbidity and mortality.	Currently recruiting patients
VERITAS 1 and 2 [107]	1435 ADHF, dyspnea at rest	M, R, DB, PC, PA	Tezosentan: 5 mg/h IV + 1 mg/h for 24-72 h Placebo.	Changes in dyspnea over 24 h and death or worsening HF at 7 days	No improvement in co-primary endpoints
VMAC [79]	489 AHFS, dyspnea at rest	M, R, DB	Nesiritide: 2 μg/kg bolus + 0.01-0.03 μg/kg/min for 3 h Nitroglycerin: as needed for 3 h Placebo	Change in PCWP and dyspnea at 3 h after initiation of the study	Nesiritide improved hemodynamic function and self-reported symptoms more effectively than IV nitroglycerin or placebo

AC: active control. ACS: acute coronary syndromes. AMI: acute myocardial infarction. d: days. BNP: B-type natriuretic peptide. CHF: chronic heart failure. CS: cardiogenic shock. DB: double-blind. DD: double-dummy. DE: dose-escalation. ADHF: acute decompensated heart failure. h: hours. HTA: arterial hypertension. IV: intravenously. MI: myocardial infarction. NYHA: New York Heart Association functional classification of HF. OL: open-label. P: prospective. PA: Parallel- assignment. PC: placebo-controlled. PCWP: pulmonary capillary wedge pressure. PG: parallel-group. R: randomized. SB: single-blind. QD: once daily. s.c.; subcutaneous. * www.clinicaltrials.gov.

tion that reduce LV wall tension and myocardial oxygen demands (MVO_2) before initiation of diuresis [22]. They increase urine output, reduce congestion, volume overload and LV filling pressures and rapidly relieve signs and symptoms of HF and improve exercise capacity. These effects explain why in the ADHERE registry loop diuretics were administered to 87% of hospitalized HF patients [14,23]. However, high doses of IV loop diuretics may produce diuretic resistance (an independent predictor of HF death), adverse effects [hypotension, hypovolemia, electrolyte abnormalities (hypokalemia, hyponatremia), worsening of renal function and neurohumoral activation], longer hospitalizations and higher in-hospital mortality rates as compared with non-treated patients [25,28-34]. Moreover, in the ADHERE registry nearly 22% of patients with AHFS and signs and symptoms of fluid overload had minimal weight loss during their hospital stay despite diuretic therapy and 25% of them were readmitted at 60 days postdischarge [23-29]. But despite loop diuretics are the first intervention in AHFS, their use (optimal dosing and duration of treatment) and their effects on disease progression and survival remain unknown, mainly because of ethical difficulties in enrolling patients with symptoms who would benefit from these agents [24,25]. The ongoing DOSE-AHF trial compares high and low doses of furosemide administered over different periods

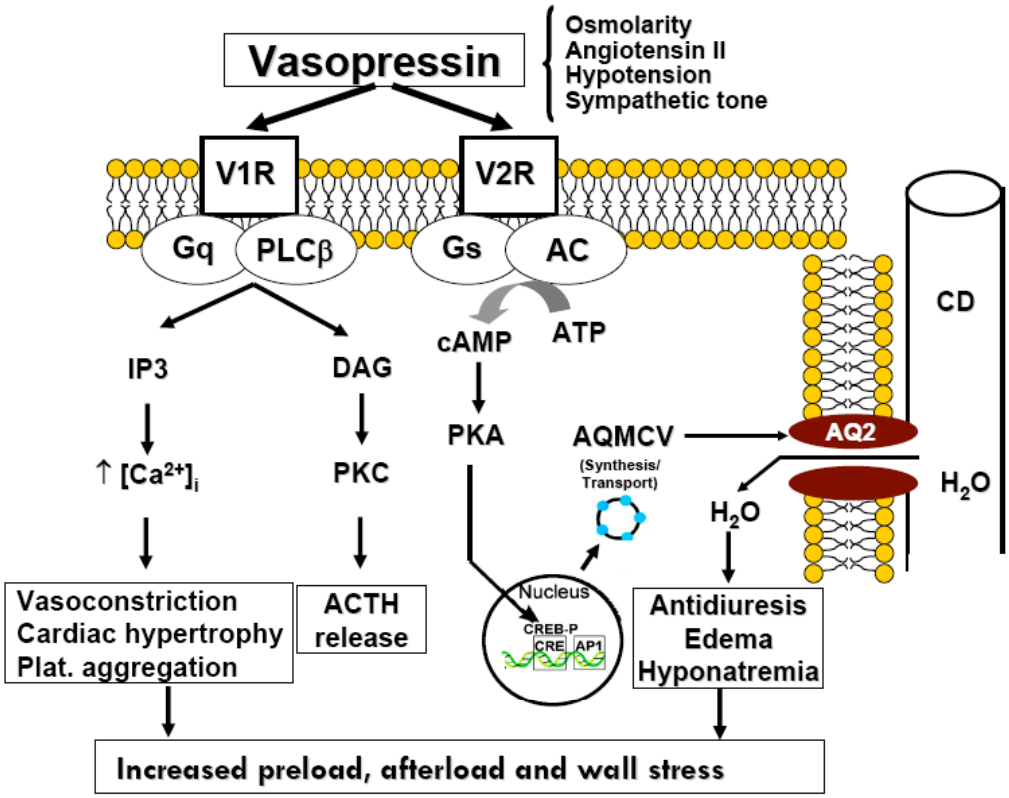

Fig. (2). Effects produced by vasopressin via V1 and V2 receptor activation. AC: adenylyl cyclase, ACTH: adrenocorticotrophic hormone. AP-1: activator protein 1, a transcription factor. AQMCV: aquaporin water channel–containing vesicles. $[Ca^{2+}]_i$: intracellular Calcium concentration. cAMP: cyclic adenosine monophosphate. CD: collecting duct, CREB: cAMP response element binding, a transcription factor. DAG: diacylglycerol. IP3: inositol 1,4,5-triphosphate. G: protein G. PKA: protein kinase A. PLCβ: membrane-bound phospholipase. V1R/V2R: Vasopressin V1 and V2 receptors.

of time to determine the safest and most effective combination (ClinicalTrials.gov: NCT00577135).

In an attempt to obtain more effective diuresis, preserve renal function and exert favourable effects on outcomes as compared to loop diuretics, two new groups of drugs are under investigation, the vasopressin receptor antagonists and the adenosine A1 receptor antagonists.

1. VASOPRESSIN RECEPTOR ANTAGONISTS

Arginine vasopressin (AVP) is a nonapeptide released from the neurohypophysis in response to increases in plasma osmolarity, hypovolemia, hypotension and angiotensin II that plays a key role in the control of body water content (Fig. **2**) [30,31]. AVP stimulates three typical G-protein-coupled receptors. V1A and V1B receptors are linked to the inositol 1,4,5-triphosphate and 1,2-diacylglycerol signaling pathway. Stimulation of V1A receptors increases intracellular Ca^{2+} concentrations ($[Ca^{2+}]_i$) and cardiac contractility and produces vasoconstriction, platelet aggregation, and vascular and myocardial hypertrophy and remodeling [30,31]. Stimulation of V1B receptors in the anterior pituitary increases adrenocorticotropin release. V2 receptors, expressed on the basolateral membrane of the renal collecting ducts, mediate the antidiuretic effects of AVP. They are coupled to the adenylyl cyclase-cyclic adenosine 3′,5′-monophosphate (cAMP)-protein kinase A (PKA) pathway. PKA increases the synthesis and shuttling of aquaporin 2 water channel-containing vesicles (AQMCV) from cytoplasmic vesicles to the luminal surface of the renal collecting ducts (and inhibites the endocytosis of the vesicles), where they are inserted into the apical cell membrane [30]. As a result, AVP increases free water reabsorption from the filtrate, decreases serum osmolarity and increases LV end-diastolic volume and pressure. In patients with AHFS the increase in AVP plasma levels adversely affect LV function by increasing peripheral vascular resistances and systemic and pulmonary congestion, and contributes to the development of hyponatremia (serum Na^+ concentration <135 mmol/L) [30,31]. Hyponatremia is present in ≈25% of patients with AHFS and is an independent predictor of post-discharge mortality and HF hospitalization [32].

The clinical development of V1A receptor antagonists was halted because some of them act as partial agonists producing vasoconstriction and hemodynamic deterioration [30,31]. V2 receptor antagonists are termed *aquaretics*, because they produce a prominent solute-free water and a modest Na^+ excretion; unlike loop diuretics, they do not activate the renin-angiotensin-aldosterone system (RAAS) or compromise renal function [33,34]. Thus, they may represent a therapeutic approach to elevate serum Na^+ concentrations in patients with AHFS and hyponatremia without compromising renal function [30-34]. Only V2 (lixivaptan, mozavaptan and tolvaptan) or dual V1A/V2 receptor antagonists (coni-

vaptan) have been studied in AHFS. Conivaptan, lixivaptan, mozavaptan and tolvaptan, have been approved for the treatment of hyponatremia due to inappropriate AVP secretion, HF and cirrhosis with ascites.

1.1. Tolvaptan

In patients with chronic HF and fluid overload, tolvaptan (30-60 mg od) reduces PCWP, improves dyspnea, increases urine output to a similar degree to furosemide, decreases urine ~~osmorality~~, body weight and peripheral edema and normalizes serum Na^+ in patients with hyponatremia, without changes in heart rate, blood pressure, serum K^+, or renal function [30,31,35-38]. Tolvaptan presents an oral availability of 40% and reaches peak plasma concentrations (C_{max}) within 2 h [42]. It binds (99%) to plasma proteins, is extensively metabolized (renal excretion is <1%) and presents a half-life of 6-9 h [36]. The most common side effects are thirst, dry mouth, hypernatremia and polyuria [30,31].

In the ACTIV in CHF study, tolvaptan increased urine output, reduced body weight, edema and furosemide use during hospitalization, and normalized serum Na^+ in hyponatremic patients, but no differences were observed in rehospitalization rates over the 60-day follow-up period as compared to placebo [39]. A post-hoc subgroup analysis of this trial suggested that 60-day mortality was lower in tolvaptan-treated patients with renal dysfunction (blood urea nitrogen (BUN) >29 mg/dL) or severe systemic congestion, suggesting a potential advantage of the drug over loop diuretics [40]. However, this study was not sufficiently powered nor designed to assess mortality. The EVEREST program evaluated the short- and long-term effects of tolvaptan (30 mg/day) added within 48 h of admission to standard therapy in patients hospitalized for worsening HF and signs of volume expansion. In the short-term, oral tolvaptan, added to standard therapy, improved global clinical status, decreased body weight and loop diuretic use and produced modest improvements in dyspnea and edema, and a greater correction in serum Na^+ as compared with placebo [41]. In the long-term trial, tolvaptan improved some signs and symptoms (dyspnea, body weight and edema) but no significant differences between the tolvaptan-treated and control groups with respect to all-cause mortality or a composite of cardiovascular death or HF hospitalization were observed after a median follow-up of 9.9 months [42]. Moreover, there were no significant differences between treatment groups for more than a dozen prespecified subgroups defined by sex, geography, dyspnea, LVEF, NYHA functional class, measures of renal function, and use of standard HF medications. Tolvaptan increased thirst, dry mouth and serum Na^+ levels, but frequencies of major adverse events (renal failure and hypotension) were similar to those found in the placebo group.

1.2. Conivaptan

In a dose-ranging pilot study in 170 patients hospitalized for worsening HF on standard therapy, IV conivaptan (20 mg bolus followed by 2 successive 24-h infusions of 40, 80, or 120 mg/day) increases urine volume and decreases body weight, but no significant changes in respiratory symptoms or body weight are found [43]. Conivaptan is well tolerated, the most common adverse events being infusion-site reactions.

1.3. Lixivaptan

In diuretic-requiring patients with NYHA class II-III, oral lixivaptan (30-400 mg/day) increases urine volume, solute-free water excretion and serum Na^+ without producing neurohormonal activation or renal dysfunction [44]. The most frequent adverse events are diarrhea, headache, dizziness, orthostatic tachycardia and dry mouth.

In summary, vasopressin receptor antagonists added to standard therapy increase diuresis without worsening renal function, decrease pulmonary and systemic congestion and normalize the natremia in hyponatremic patients with AHFS, but they do reduce HF-related morbidity and mortality. Long-term studies are needed to define their efficacy and safety, in addition to or instead of the current diuretic therapy, in the early management of patients with AHFS, signs of congestion and hyponatremia and in those resistant to conventional loop diuretics.

2. ADENOSINE A1-RECEPTOR ANTAGONISTS

Renal function is one of the most important determinants of survival in patients with HF. Worsening of renal function (defined as a rise in serum creatinine >0.3 mg/dL) occurs in 20-30% of AHFS patients and is associated with Na^+ and water retention, longer hospitalizations, higher in-hospital mortality and post-discharge rates of death and readmission [45-47]. Renal worsening may result from hemodynamic abnormalities [low cardiac output leading to reduced renal blood flow and glomerular filtration rate (GFR)], high venous pressure, neurohumoral activation and structural renal dysfunction due to diabetes, hypertension and arteriosclerosis, and may be aggravated by high-dose loop diuretics [6,29,45].

Adenosine binds to four G protein-coupled receptors. Stimulation of A1 and A3 receptors induces, *via* $G_{i/o}$ proteins, inhibition of adenylyl cyclase and of N-, P-, and Q-type Ca^{2+} channels and activation of several types of K^+-channels and phospholipase Cβ; stimulation of A2a and A2b receptors leads to adenylyl cyclase activation *via* G_s proteins and to the phosphoinositide metabolism *via* G_q [48]. Activation of A1 (and possibly A3) cardiac receptors contributes to ischemic preconditioning and protects the heart against infarction, arrhythmias or postischemic contractile dysfunction. Stimulation of A1 receptors also activates an inwardly rectifying K^+ current (I_{KAdo}) present in the atria and in the sinoatrial and atrioventricular (AV) nodes; as a result, adenosine shortens the atrial action potential, hyperpolarizes the membrane potential and slows heart rate and AV conduction. Stimulation of A2a receptors produces coronary vasodilation and increases cardiac contractility.

Adenosine plays an important role in the regulation of renal function [49,50]. Increased concentrations of Na^+ and Cl^- at the macula densa stimulate local generation of adenosine. Stimulation of renal adenosine A1 receptors located in the preglomerular afferent arteriole and proximal tubule contributes to the tubuloglomerular feedback, a macula densa mechanism that adjusts afferent arteriole resistance and GFR

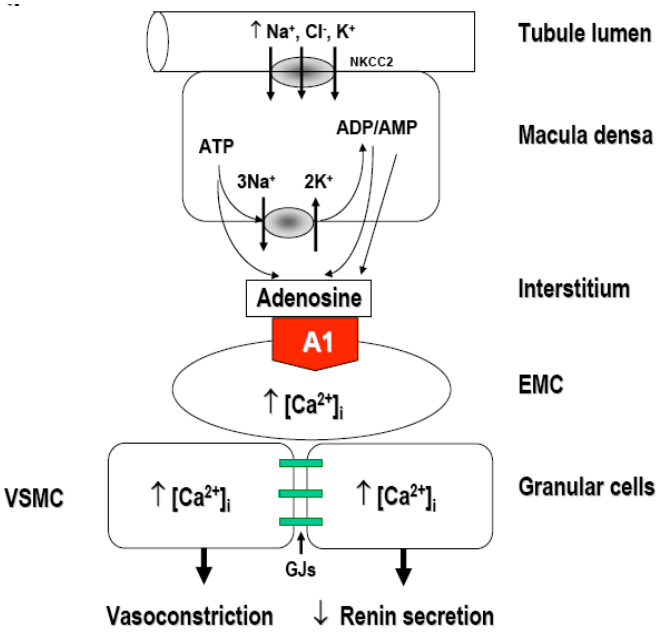

Fig. (3). Proposed mechanism of action of adenosine in the regulation of the tubuloglomerular feedback. ATP/ADP/AMP: adenosine triphosphate/adenosine diphosphate/adenosine monophosphate. EMC: extraglomerular mesangial cells. GJs: gap-junctions. VSMC: vascular smooth muscle cells**.** Modified from Vallon [59].

in response to changes in the salt concentration of early distal tubular fluid. It has been proposed that Na^+-K^+-$2Cl^-$ co-transport-dependent hydrolysis of ATP in macula densa cells (or in the tubular cells in close proximity to the juxtaglomerular apparatus) increases the synthesis of AMP, which can be dephosphorylated in the cell to adenosine by the cytosolic 5'-nucleotidase and/or may leave the cell, being converted by plasma membrane-bound endo-5'-nucleotidases into adenosine (Fig. **3**). In the interstitium adenosine activates A1 receptors at the surface of extraglomerular mesangial cells and increases cytosolic Ca^{2+} concentrations. The coupling between extraglomerular mesangial cells, granular cells containing renin, and smooth muscle cells of the afferent arteriole allows the propagation of the Ca^{2+} signal, resulting in afferent arteriolar vasoconstriction and inhibition of renin secretion [49]. As a consequence, activation of A1 receptors reduces renal blood flow and GFR and increases Na^+ reabsorption in the proximal tubule and the collecting duct, so that the distal delivery of filtrate is reduced, decreasing the natriuretic response to loop/distal diuretics [49,50]. Stimulation of renal A2 receptors produces a dilatation of postglomerular arterioles increasing blood flow in the renal medulla.

Plasma adenosine levels are increased in AHFS, which may contribute to a decrease in renal blood flow and GFR and the progressive renal dysfunction. In contrast, A1-receptor antagonists (A1RA) inhibit afferent arteriolar vasoconstriction and Na^+ reabsorption in the proximal tubule and the collecting duct, increasing renal blood flow, GFR, urinary flow and diuretic responsiveness [49,50]. Thus, A1RA might preserve renal function while simultaneously promoting natriuresis in patients with AHFS.

2.1. BG9719

A randomized, double-blind, ascending-dose, crossover study evaluates 3 doses of BG9719, an orally active A1RA, designed to yield serum concentrations of 0.1, 0.75, or 2.5 μg/mL in 63 patients with congestive HF [51]. Patients receive placebo or 1 of 3 doses of BG9719 on 1 day and the same medication plus furosemide on a separate day. BG9719 increases GFR, urine output and Na^+ excretion with little kaliuresis, improves dyspnea and edemas and decreases body weight, without changes in morbidity and mortality for worsening of HF [58]. Furosemide alone decreases GFR, but when BG9719 is added to furosemide, urine volume and Na^+ excretion additionally increases without deterioration in GFR.

2.2. Tonapofylline (BG9928)

In patients with HF and systolic dysfunction on standard therapy, tonapofylline (3, 15, 75, or 225 mg/day) dose-dependently increases Na^+ excretion (primary end point) with little kaliuresis, improves dyspnea and edemas and at doses ≥15 mg decreases body weight, without changes in creatinine clearance (CrCl), morbidity and mortality for worsening of HF [52]. The TRIDENT-1 trial (NCT00709865) analyzes the efficacy and safety of tonapofylline added to standard therapy in patients with acute HF and impaired renal function (GFR ≥20 and ≤70 mL/min/1.73 m^2).

2.3. SLV320

This pyrrolo-pyrimidine derivative is an A1RA and a phosphodiesterase (PDE) 4 inhibitor [53]. In 111 patients with chronic HF requiring treatment with diuretics the IV administration of SLV320 (5, 10, or 15 mg) improves renal-function measures [urine volume, and Na^+ and K^+ excretion and cystatin C plasma levels (a marker of renal function)], but does not modify PCWP (the primary end point), systemic vascular resistances and cardiac output [54], while furosemide, that exerts a more prominent natriuretic effect, exerts a negative effect on renal function. SLV320 is well tolerated and no serious adverse events are observed. A Phase II trial evaluates the effects of SLV320 in patients with AHFS and renal dysfunction **(**NCT00744341).

2.4. Rolofylline

In patients hospitalised with HF, fluid overload, impaired renal function [CrCl of 20-80 ml/min] and diuretic resistance, IV infusion of rolofylline (2.5-50 mg/day) dose-dependently increases urine output, renal blood flow and GFR, decreases serum creatinine and reduces the dose of loop diuretics as compared with placebo [55,56]. Interestingly, the increase in GFR persists much longer than predicted by the half-life of rolofylline and its metabolites (12-14 h) [56].

The PROTECT trials evaluated the effects of rolofylline in addition to IV loop diuretics in patients hospitalised for HF within 24 h with signs of fluid overload, impaired renal function (GFR 20-80 ml/min) and high BNP or NT-proBNP plasma levels (>500 pg/mL or >2000 pg/ml, respectively). Because A1RA may lower seizure threshold, patients at risk

were pretreated with lorazepam as seizure prophylaxis [57]. In the PROTECT-1 pilot study, compared with placebo, rolofylline increased diuresis and improved dyspnea while preserving renal function. Interestingly, treatment with 30 mg, the dose selected for the pivotal trials, was associated with a trend toward reduced 60-day mortality or readmission for cardiovascular or renal causes [58]. Adverse events were similar across treatment groups and no seizures were reported. The PROTECT-2 trial, however, showed no differences in primary (effect on HF signs and symptoms and renal function) and secondary efficacy endpoints (composite of death, cardiovascular or renal hospitalization) between the rolofylline and placebo group [http://www.theheart.org/article/998299.do]. There was a trend toward a lower incidence of adverse cardiac events with rolofylline, but a higher rate of neurological events, specifically seizures (0.8% vs 0%) and strokes (1.2% vs 0.5%).

Conclusions. In short-term studies, A1RA and loop diuretics inhibit Na^+ reabsorption in different nephron segments, and their combination could potentially enhance diuresis and prevent the worsening of renal function. However, A1RA may increase renin release and lower seizure threshold [57]. Moreover, stimulation of cardiac A1 receptors may exert a cardioprotective effect as they inhibit neurohumoral activation and myocardial hypertrophy and remodelling and is critical for ischemic pre-conditioning [59]. Therefore, it is possible that A1RA should require high renal specificity [67]. In conclusion, further trials are required to confirm the beneficial effects of short-duration trials and to establish the suitable dose range and the long-term cardiac and renal safety in patients with AHFS.

VASODILATORS

High LV filling pressure (resulting in cardiopulmonary congestion) with normal or high SBP is the main cause for HF hospitalization [2,6,8,11,12]. Increased LV filling pressure produces: 1) an increase in ventricular wall tension and MVO_2; 2) a reduction in myocardial perfusion (due to a decrease in the coronary perfusion pressure and the compression of intramural coronary vessels decreasing subendocardial blood flow), increasing the risk of ischemia in patients with or without CAD; and 3) neurohumoral activation [2]. In this context, IV vasodilators and loop diuretics (which produce a venodilator effect), can rapidly improve congestive symptoms and hemodynamics in AHFS patients with normal or high SBP [1-4,50]. Venous vasodilation relieves pulmonary congestion and decreases PCWP, LV filling pressures, wall stress and MVO_2, while arteriolar vasodilatation reduces peripheral vascular resistances, increases cardiac output, improves peripheral hypoperfusion and reduces LV filling pressures and MVO_2.

In patients with AHFS and CAD, coronary perfusion is diminished due to increased LV filling pressures (which increases MVO_2 and decreases subendocardial blood flow) and autoregulation becomes exhausted, so that coronary blood flow becomes totally dependent on systemic pressure [2,61,62]. Under these conditions, even when short-term infusions (<48 h) of vasoactive drugs (nitroprusside, nesiritide, dobutamine, dopamine, milrinone, and enoximone) can temporarily improve symptoms and hemodynamics, they may also increase myocardial ischemia by increasing cardiac contractility and/or heart rate while simultaneously decreasing blood pressure and coronary perfusion, thus leading to myocardial injury. This explains why these drugs increase in-hospital and post-discharge mortality in patients with CAD who develop drug-related hypotension [60,63-65]. Moreover, hypotension induced by vasodilators may also result in renal hypoperfusion and possible dysfunction [63-66].

1. ATRIAL NATRIURETIC PEPTIDES (ANPs)

ANPs are endogenous hormones released implicated in the regulation of blood pressure and fluid homeostasis [67,68]. Three main endogenous natriuretic peptides have been identified: atrial (ANP, 28-amino acids), brain (BNP, 32-amino acids) and C-type (CNP, 22-amino acids). Urodilatin is the main natriuretic peptide in the urine, but is not detected in plasma. It originates from the same common precursor as ANP, but presents an extension of 4 amino-acids in the N-terminus [ANP-(95-126)] [69]. All four peptides contain a 17-amino-acid core ring and a cysteine bridge. ANP and BNP are produced by myocardial cells in response to myocardial stretch and increased intracardiac volume/pressure and activate three different natriuretic peptide receptors (NPRs) (Fig. **4**). NPR-A and NPR-B contain a domain with guanylyl cyclase (GC) activity that catalyzes the synthesis of cyclic guanosine 3´-5´-monophosphate (cGMP), which mediates most known effects of natriuretic peptides, whereas NPR-C is not coupled with this enzyme. ANP and BNP bind to NPR-A, activate GC activity and increase the levels of cGMP producing venous and arterial vasodilatation, diuresis and natriuresis, inhibition of the RAAS, sympathetic tone and release of vasopressin and endothelin-1, and antifibrotic, anti-hypertrophic and lusitropic effects [68]. Thus, the release of ANP and BNP is a compensatory mechanism of the neurohumoral activation in patients with HF [67,68]. CNP released by shear stress from endothelial cells binds to NPR-B, increases cGMP levels in the vessels and produces venodilation, inhibits cell growth and proliferation, prevents cardiac remodeling after myocardial infarction and decreases aldosterone release. Thus, CNP presents limited renal actions and minimal effects on blood pressure. A third receptor (NPR-C) clears natriuretic peptides from the circulation through receptor-mediated internalization and degradation. Urodilatin is synthesized in the distal and collecting ducts, and following luminal secretion, stimulates NPR-A, inhibiting the reabsorption of Na^+, Cl^- and water [69].

Analogs of human ANP (anaritide and carperitide) and BNP (nesiritide) synthesized by genetic recombination have been investigated as potential therapies for the treatment of AHFS and other diseases. Nesiritide is approved in the United States and carperitide in Japan, for the treatment of AHFS in patients with dyspnea at rest or with minimal activity.

1.1. Carperitide

In patients with HF, the IV infusion of ANP (40 pmol/kg/min) produces diuresis and natriuresis, increases the GFR and decreases renin and aldosterone plasma levels,

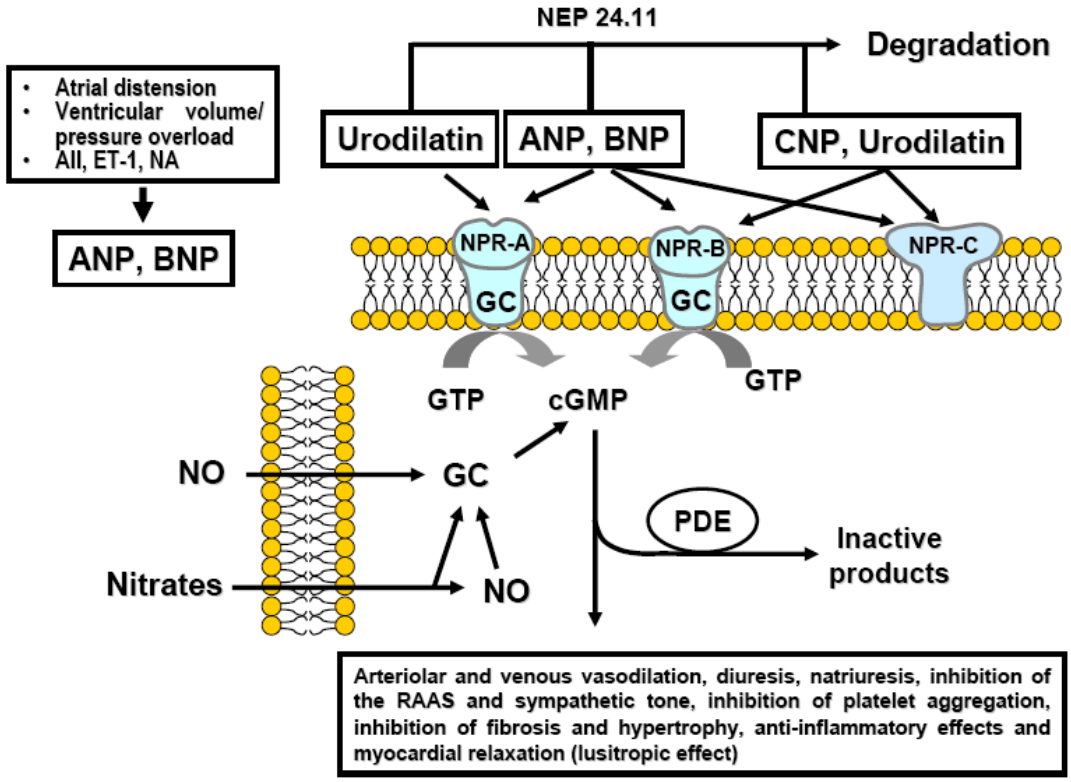

Fig. (4). Signal transduction pathways of atrial natriuretic peptides (ANPs), nitric oxide (NO) and nitrates. AII: angiotensin II. ANP: atrial natriuretic peptide. BNP: natriuretic peptide type-B. CNP: natriuretic peptide type-C. cGMP: cyclic guanosine monophosphate. ET-1: endothelin 1. GC: guanylyl ~~cylase~~ guanylate cyclase. GTP: guanosine 5´-triphosphate. NA: noradrenaline. NEP 24.11: neutral endopeptidase. NO: nitric oxide. PDE: phosphodiesterase. NPR: atrial natriuretic peptide receptors. RAAS: renin-angiotensin-aldosterone system.

blood pressure and PWCP [70]. In a 6-year prospective open-label registry including 3,777 patients with AHFS, IV carperitide (0.085 μg/kg/min for 65 h) improves symptoms in 82% of the patients, the benefit being greater in those with decompensated chronic HF [71]. In a randomized controlled trial, patients with AHFS were treated during the acute phase with carperitide (0.01–0.05 μg/kg/min for 72 h) or placebo plus standard therapy [72]. During an 18-month follow-up, a significant reduction of death and rehospitalization occurs in the carperitide as compared with the control group (11.5% vs 34.8%), suggesting that carperitide improves the long-term prognosis of these patients. Finally, in the COMPASS study, carperitide achieves recovery from the acute phase to the chronic phase in 83% of the patients and improves the degree of dyspnea [73]. The incidence of adverse drug reactions is low, the most frequent being hypotension (3.5%). An ongoing trial analyzes the effects of carperitide on short- and long-term prognosis in patients with cardiac and renal failure (NCT00613964).

1.2. Nesiritide (hrBNP)

BNP is released from the ventricles in response to increased pressure/volume, so that its plasma levels are increased in patients with HF and are used as an aid to diagnosis [67,68,74]. In patients with AHFS, IV infusion of nesiritide (0.015-0.6 μg/kg/min for 4-24 h) produces natriuresis, improves HF signs, symptoms (dyspnea and fatigue) and hemodynamics (decreases systemic and pulmonary vascular resistances, increases cardiac output) and inhibits neurohumoral activation (decreases plasma norepinephrine and aldosterone levels) [75-78]. Nesiritide reaches steady-state plasma levels in 90-120 min and presents a volume of distribution (Vd) of 0.19 L/kg and a mean terminal elimination half-life of 18 min [68,74]. The most common adverse effects are hypotension, headache, and nausea.

The PRECEDENT trial compared nesiritide and dobutamine in patients with AHFS with a previous history of ventricular tachycardia [78]. Both drugs similarly improve signs and symptoms of HF, but dobutamine produces proarrhythmic effects, whereas nesiritide has a neutral effect on ventricular ectopy, suggesting that it may be safer than dobutamine. The VMAC trial compared the efficacy and safety of nesiritide, nitroglycerin, or placebo in patients with AHFS [79]. Drugs and placebo were given for 3 h, followed by nesiritide or nitroglycerin for 24 h. At 3 and 24 hours, nesiritide reduced PCWP more than either nitroglycerin or placebo, but both drugs produced a similar improvement of dyspnea and global clinical status as compared to placebo. Moreover, no significant differences in 30-day rehospitalization or 6-month mortality were observed. Hypotension was more common and prolonged with nesiritide (2.2 h vs 0.7 h), while headache was more frequent with nitroglycerin (8% vs 20%). However, the meta-analyses of 5 randomized studies suggested that nesiritide significantly increased the risk of worsening renal function compared with control therapy and 30-day mortality in comparison with standard diuretic and vasodilator therapies [64]. Whether worsening renal function reflects hemodynamic effect or renal injury is unknown.

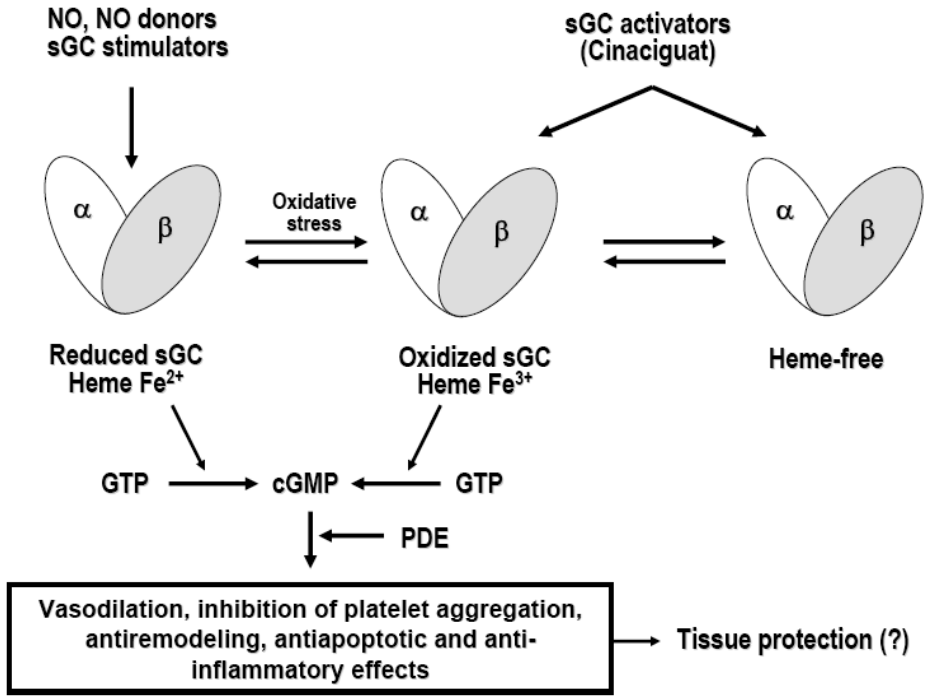

Fig. (5). The NO-sGC-cGMP signalling pathway and the mechanism of action of sGC activators and stimulators. sGC stimulators stimulate the enzyme directly and enhance sensitivity of the reduced enzyme to low levels of bioavailable NO, while sGC activators activate the NO-unresponsive, heme-oxidized or heme-free enzyme. cGMP: cyclic guanosine monophosphate. GTP: guanosine 5'–triphosphate. NO: nitric oxide. PDE: phosphodiesterase. sGC: soluble guanylyl cyclase.

Because of this possibility of risk function, the FUSION trials studied the safety of nesiritide in patients with advanced HF and renal insufficiency (GFR < 60 ml/min/1.73m^2). In the FUSION I trial, serial infusions of nesiritide were well tolerated, with no evidence of worsening renal function [80]. In patients with advanced HF and more than two HF hospitalizations within the past year the FUSION II trial found that nesiritide did not modify all-cause mortality/hospitalization for cardiovascular or renal causes, all cause mortality or cardiovascular hospitalization [81]. Moreover, in patients with renal insuficiency rises in serum creatinine > 0.5 mg/dL occurred more often in the placebo group, suggesting that nesiritide did not worsen renal function. In the BNP-CARDS trial nesiritide had no impact on renal function or 30-day death/hospital readmission in patients with ADHF and renal dysfunction [82]. Despite all this evidence, further information on long-term efficacy and safety of the nesiritide in patients with ADHF is needed. Both aspects are analyzed in the ASCEND-HF (NCT 00475852) trial, which randomizes 7,000 patients with AHFS to placebo or nesiritide within 48 h of hospitalization for a minimum of 24 h up to a maximum of 7 days, in addition to standard care. Primary endpoints are rehospitalization due to HF and all-cause mortality from randomization through 30 days and self-assessed dyspnea at 6 or 24 h. Other clinical endpoints include number of days alive and outside the hospital at day 30, all-cause mortality through 180 days, HF rehospitalization and renal dysfunction.

1.3. Ularitide

In patients hospitalized for decompensated HF, the SIRIUS trials found that IV ularitide improves dyspnea and hemodynamics (reduces PCWP and increases cardiac output) and decreases SBP and N-terminal pro-BNP levels without changes in heart rate, GFR or serum creatinine [83-85]. The reduction in PCWP and peripheral resistances persists for up to 90 min, while ANP produces a transient decrease of both parameters. Mortality at day 30 tends to be lower in favour of ularitide [84]. The most common adverse effects are sweating, dizziness and hypotension requiring termination of infusion; complete resolution of hypotension was approximately 0.5-1 h in most cases. Thus, ularitide may be a therapeutic alternative in patients with AHFS with renal dysfunction, although further studies in larger numbers of patients are required to confirm these benefits. The ongoing URGENT trial analyzes the effects of ularitide on patients with dyspnea secondary to AHFS [86].

2. SOLUBLE GUANYLATE CYCLASE (SGC) ACTIVATORS

The activation of the NO-sGC-cGMP pathway plays a central role in regulating many physiological processes, including vascular tone, cellular growth and contractility, inflammation, platelet aggregation, neurotransmission, neuronal plasticity and learning (Fig. **5**) [87]. Under physiological conditions sGC exists as reduced NO-sensitive sGC and a pool of oxidized and heme-free NO-insensitive sGC. In HF, several mechanisms can decrease NO-mediated cGMP production: 1) reduced bioavailability of NO attributable to impaired production and/or excessive degradation via the chemical interactions with $^{\bullet}O_2^-$; 2) oxidation of the sGC heme moiety to its NO-insensitive ferric state, and 3) irreversible loss of the enzymatic capacity by downregulation of sGC protein levels [88].

Therapeutic strategies to increase the NO-sGC–cGMP pathway include: 1) nitrovasodilators which stimulate the reduced sGC form containing the heme moiety with a ferrous iron (Fe^{2+}) after bioconversion to NO. However, their efficacy is limited by the development of tolerance after sustained administration and the inability to activate NO-insensitive sGC. 2) PDE inhibitors prevent the breakdown of cGMP to GMP. 3) Drugs that can activate sGC independently of NO release [89]. The *sGC stimulators* stimulate the sGC directly and enhance the sensitivity of the reduced sGC to low levels of bioavailable NO, but do not affect the oxidized sGC. Conversely, *sGC activators* directly activate sGC in its NO-insensitive, oxidized (or heme-free) state, induces cGMP generation, vasodilation, antiplatelet activity, potent antihypertensive effects and a hemodynamic profile comparable to that of organic nitrates [90]. In addition, they present several advantages over nitrates, as they do not need to be bioactivated and do not promote oxidative stress and reflex neurohumoral vasoconstriction leading to tolerance [89].

2.1. Cinaciguat (BAY-58-2667)

This is a potent NO-independent sGC activator [half maximal effective concentration (EC_{50}) and receptor affinity (K_d) 6.4 and 1.2 nM, respectively] [90]. In healthy volunteers, IV infusion of cinaciguat (50-250 μg/h for up to 4 h) decreases blood pressure and increases heart rate and plasma levels of cGMP [91]. Pharmacokinetics shows low interindividual variability [91]. Cinaciguat reaches C_{max} values within 30 minutes, declining rapidly once infusion is stopped (dominant half-life, 0.2-0.3 h). Renal clearance accounts for less than 1% of the total body clearance

A Phase II uncontrolled trial investigated the effect of IV cinaciguat using initial dose-finding studies (50, 100, 200 and 400 μg/h) and then evaluated cinaciguat in 60 patients with AHFS using the optimised starting dose of 100 μg/h, which could be titrated after 2, 4 and 6 h to doses between 50 and 400 μg/h depending on hemodynamic response [92]. Cinaciguat reduced PCWP, right atrial pressure, systemic and pulmonary vascular resistance and increased cardiac index. The proportion of patients responding with a reduction of PCWP ≥4 mmHg vs baseline was 53% after 2 h and 90% after 6 h; the improvement of dyspnea increased during and after 6 h of infusion. The most frequently reported adverse event was hypotension. These preliminary results should be confirmed in randomized, placebo-controlled clinical trials to understand the role of this new therapeutic strategy for AHFS. A phase II study with infusion periods of 24 to 48 h is currently enrolling patients.

3. NITRIC OXIDE SYNTHASE INHIBITORS

Cardiogenic shock (CS) is the leading cause of death among hospitalized patients with acute myocardial infarction despite successful coronary revascularization and inotropic support [93,94]. It has been hypothetized that myocardial infarction can cause a systemic inflammatory response syndrome that increases the levels of inflammatory mediators (ie, bacterial lipopolysaccharide, tumor necrosis factor-α, and interleukin-1) and the expression of inducible nitric oxide synthase (iNOS). This increase leads to high levels of NO and cytotoxic NO-derived species (peroxynitrite), which might cause inappropriate systemic vasodilatation, coronary hypoperfusion, and cardiodepression [94]. This led to the use of nonselective NOS inhibitors (tilarginine, L-NAME) in an attempt to produce vasoconstriction, increase mean blood pressure and coronary perfusion pressure and reduce the cardiodepressant effects of NO.

In a pilot (not placebo-controlled) trial in patients with CS, tilarginine (1 mg/kg bolus followed by 1 mg/kg/h for 5 h) added to conventional therapy increases mean arterial blood pressure, urine flow and cardiac output [95]. In the LINCS study, L-NAME increases blood pressure at 24 h and urine output and decreases 30-days mortality (27% vs 67% in the control group) in patients with CS refractory to supportive care [96]. Both studies suggest that NOS inhibitors might be beneficial in patients with refractory CS. In the SHOCK-2 trial, however, tilarginine increases mean arterial pressure (primary end point) at 15 minutes, but not at 2 h, compared with placebo, but it has no effect on survival, even when the study was not powered to assess the effects on mortality [97]. Moreover, the TRIUMPH trial demonstrates that tilarginine does not improve 30-day or 6-month mortality, shock resolution or duration of CS (primary endpoints) and that similar percentages of patients have HF in the tilarginine and placebo groups [98]. These findings confirm once more that even when small clinical trials prove encouraging, randomized, double-blind, placebo-controlled studies are mandatory for evaluating the efficacy and safety of new investigational drugs.

4. ENDOTHELIN ANTAGONISTS

Endothelin-1 (ET-1) is a 21-amino acid potent vasoconstrictor peptide with inotropic and mitogenic properties which exerts its effects through activation of two distinct G-protein coupled ET_A and ET_B receptors [99]. High ET-1 levels at admission for AHFS correlate with the severity of hemodynamics and are an independent predictor of mortality [100,101]. These findings were the rationale for using ET-1 receptor antagonists in AHFS. The effect of the non-selective ET_A and ET_B receptor antagonist tezosentan on AHFS was studied in the RITZ and VERITAS trials (Table **2**) [99,102-107]. The RITZ trials found no differences in terms of dyspnea and time to worsening HF or death between tezosentan and placebo, but tezosentan was associated with an excess of symptomatic hypotension, dizziness and renal failure. The VERITAS trials were discontinued because of the low probability of achieving a beneficial effect. Thus, the future of endothelin antagonists in the management of AHFS is uncertain.

5. RELAXIN

This hormone belonging to the insulin superfamily of peptides modulates cardiovascular responses (increases plasma volumen, cardiac output and heart rate and decreases peripheral vascular resistances) to pregnancy [108]. Relaxin binds to two G-protein-coupled relaxin family receptors (RXFP1 and RXFP2) (Fig. **6**) and produces vasodilation [via increased cAMP levels, upregulation of endothelial NOS (NOS3) and stimulation of endothelial endothelin type B receptors], increases cardiac contractility and cardiac output, renal blood flow and GFR, inhibits platelet aggregation and

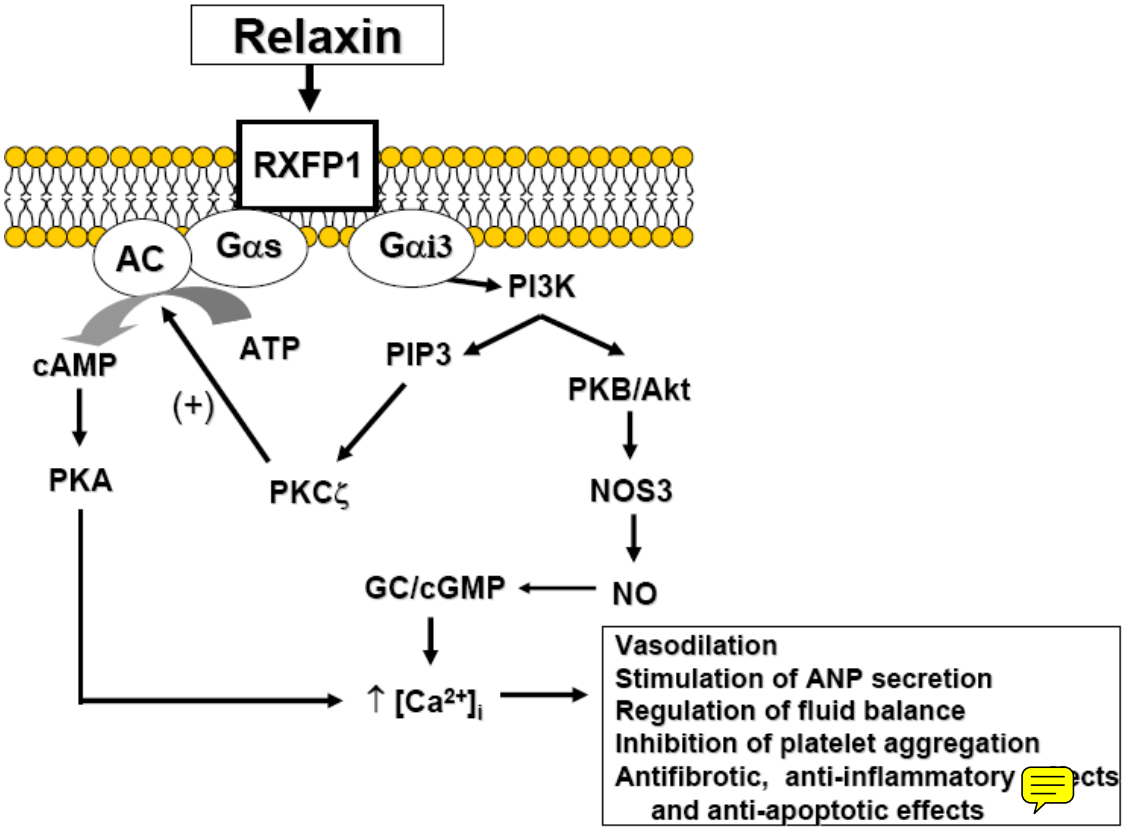

Fig. (6). Signalling pathways activated by relaxin following the stimulation of RXFP1 receptors. Activation of RXFP1 receptors increased cAMP accumulation via $G\alpha_s$ and recruits $G\alpha_{i3}$ which activates the protein $G\beta\gamma$-phosphoinositide 3-kinase (PI3K)-protein kinase c zeta (PKCζ) pathway to further increase cAMP. AC: adenylyl cyclase. ATP: adenosine 5'-triphosphate. cGMP: 3',5'-cyclic guanosine monophosphate. Gα: protein G. GC: guanylyl cyclase. NO: nitric oxide. NOS3: endothelial nitric oxide synthase. PI3P: phosphatidylinositol 3-phosphate. PKA: protein kinase A. PKB: protein kinase B.

exerts antifibrotic, anti-inflammatory (down-regulates pro-inflammatory cytokines linked to outcome in HF, i.e., TNF-α, TGF-β) and anti-apoptotic effects [108,109]. Relaxin plasma levels and cardiac expression of relaxin genes (RLN1 *and* RLN2) increases in patients with HF, and thus, it has been hypothetized that relaxin might have beneficial effects in patients with AHFS and normal or high SBP [110].

In an open-label trial in 16 patients with stable HF, IV recombinant human relaxin (10 to 960 μg/kg/day) improved hemodynamics (reduced PCWP and peripheral vascular resistances and increased cardiac output) and reduced serum creatinine and NT-proBNP levels, without inducing hypotension [111]. The Pre-RELAX trial compared relaxin and placebo in patients with AHFS and normal-to-increased SBP [112]. Intravenous infusion of relaxin for 48 h rapidly (within 6 h) improved dyspnea and other signs of HF and reduced the length of stay (10.2 vs 12 days in the placebo group) and cardiovascular deaths or readmissions due to heart or renal failure at day 60 (2.6% vs 17.2% in the placebo group). These effects were most pronounced in the group receiving relaxin 30 μg/kg/day. However, the number of serious adverse events was similar between groups. Despite the small sample size and the absence of a single primary endpoint limited the findings of this trial, these data support the further development of relaxin as a novel therapeutic approach for patients with AHFS and normal or increased SBP. In fact, the dose of 30 μg/kg/day was selected for further assessment of relaxin in a Phase III study (RELAX-AHF-1).

6. DIRECT RENIN INHIBITORS (DRIS)

Renin catalyzes the first rate-limiting step of the RAAS, and cleaves angiotensinogen to angiotensin I (AI), the main route to angiotensin II (AII) formation [113,114]. DRIs block the formation of AI and AII without affecting kinin metabolism, and in contrast with angiotensin-converting enzyme inhibitors (ACEIs) and AII-receptor blockers (ARBs), they inhibit plasma renin activity. Very recently, a (pro)renin receptor for prorenin and renin has been identified [115]. Its stimulation not only facilitates angiotensinogen generation but also leads to the activation of signal transduction pathways different from angiotensin II receptor signals [116] (Fig. **7**).

Aliskiren is an orally effective, nonpeptide, low molecular weight DRI [114]. It presents a low oral bioavailability (2.5%) and reaches C_{max} levels within 3-6 h and and steady-state plasma concentrations after 5-8 days. It presents a Vd of 135 L, is excreted almost completely by fecal route (only 0.6% in the urine) and presents a long half-life (24-40 h) [113,114]. The ALOFT trial analyzed the effect of aliskiren in hypertensive patients with congestive HF (NYHA class III-IV) treated with beta-blockers, ACEIs/ARBs, and aldos-

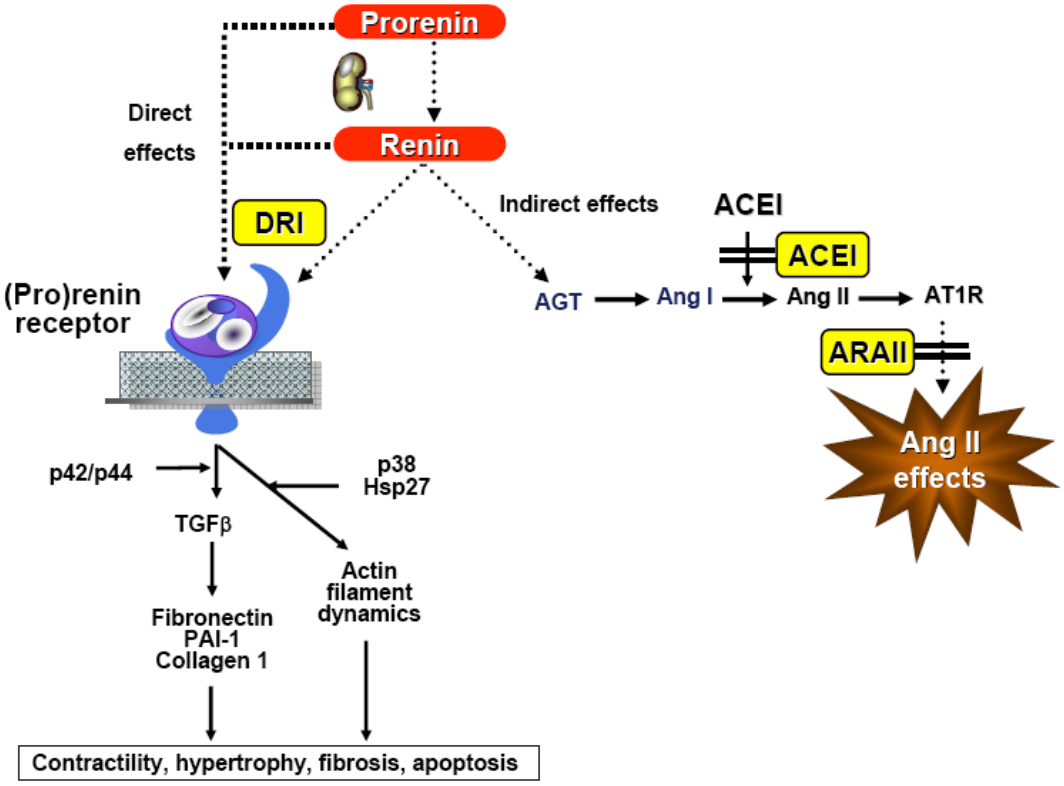

Fig. (7). Signal transduction pathways activated by prorenin and renin following the activation of the (pro)renin receptor. ACE: angiotensin converting enzyme. ACEI: ACE inhibitors.AGT: angiotensinogen. AngI/II: angiotensin I and II. ARBs: angiotensin II AT1 receptor blockers. DRI: direct renin inhibitor. Hsp27: heat shock protein 27. PAI-1: plasminogen-activator inhibitor-1. p38/42/44: mitogen-activated protein kinases (MAPK). TGFβ: transforming growth factor beta.

terone antagonists [117]. After 12-weeks, aliskiren reduced LV filling pressures, plasma renin activity, levels of NT-proBNP and urinary aldosterone levels. Rates of renal dysfunction, symptomatic hypotension, and hyperkalemia were about the same in both groups. The ASTRONAUT trial will evaluate whether early initiation of aliskiren therapy delays cardiovascular death and HF re-hospitalization within 6 months, post-hospitalization for an acute decompensated HF.

7. ALDOSTERONE SYNTHASE INHIBITORS

Aldosterone has an important role in the pathophysiology of HF [118]. It produces Na^+ and water retention, hypokalemia, sympathetic activation, parasympathetic inhibition, myocardial and vascular fibrosis, baroreceptor dysfunction, and vascular damage and impairs arterial compliance [118,119]. Moreover, there is a relationship between plasma aldosterone concentrations and mortality in patients with HF [118] and clinical trials have shown that administration of mineralocorticoid receptor (MR) antagonists (spironolactone, eplerenone) on top of standard therapy reduces the risk of both morbidity and mortality in patients with severe HF [120] and in patients after myocardial infarction [121]. Angiotensin converting enzyme inhibitors (ACEIs), angiotensin II AT1 receptor blockers (ARBs) and MR antagonists transiently reduce aldosterone plasma levels in patients with HF; however, aldosterone levels can be elevated in the long term (aldosterone scape). Moreover, the non-MR-mediated (non-genomic) actions of aldosterone are 'insensitive' to MR antagonists [122]. A novel therapeutic strategy for the treatment of HF with potential to overcome the drawbacks of MR antagonists is the blockade of aldosterone production by inhibiting the aldosterone synthase (CYP11B2), the key enzyme involved in the biogenesis of aldosterone, which is widely expressed in the cardiovascular system and is stimulated by angiotensin II [123]. Aldosterone production by the failing heart has been suggested on the basis of catheter-obtained aldosterone concentrations across the heart [124], and the finding that CYP11B2 mRNA levels are elevated by 4- to 6-fold in patients with hypertrophic cardiomyopathy [125].

Aldosterone production inhibition by FAD286 protects against angiotensin II–induced organ damage [126]. In rats with congestive HF, long-term administration of the aldosterone synthase inhibitor FAD286 reduces LV end-diastolic pressure, LV relaxation constant and LV dilation, hypertrophy and collagen accumulation, improving cardiac systolic and diastolic functions [127]. These effects are more marked than those induced by spironolactone, probably because only FAD286 improves endothelial function and normalizes the HF-induced enhancement in myocardial production of reactive oxygen species as well as HF-induced reduction in LV AT_2 receptors/ACE-2 expression. Whether these more marked effects of aldosterone synthase inhibitors will result in a further reduction in morbidity and mortality in HF patients should be defined in future clinical trials.

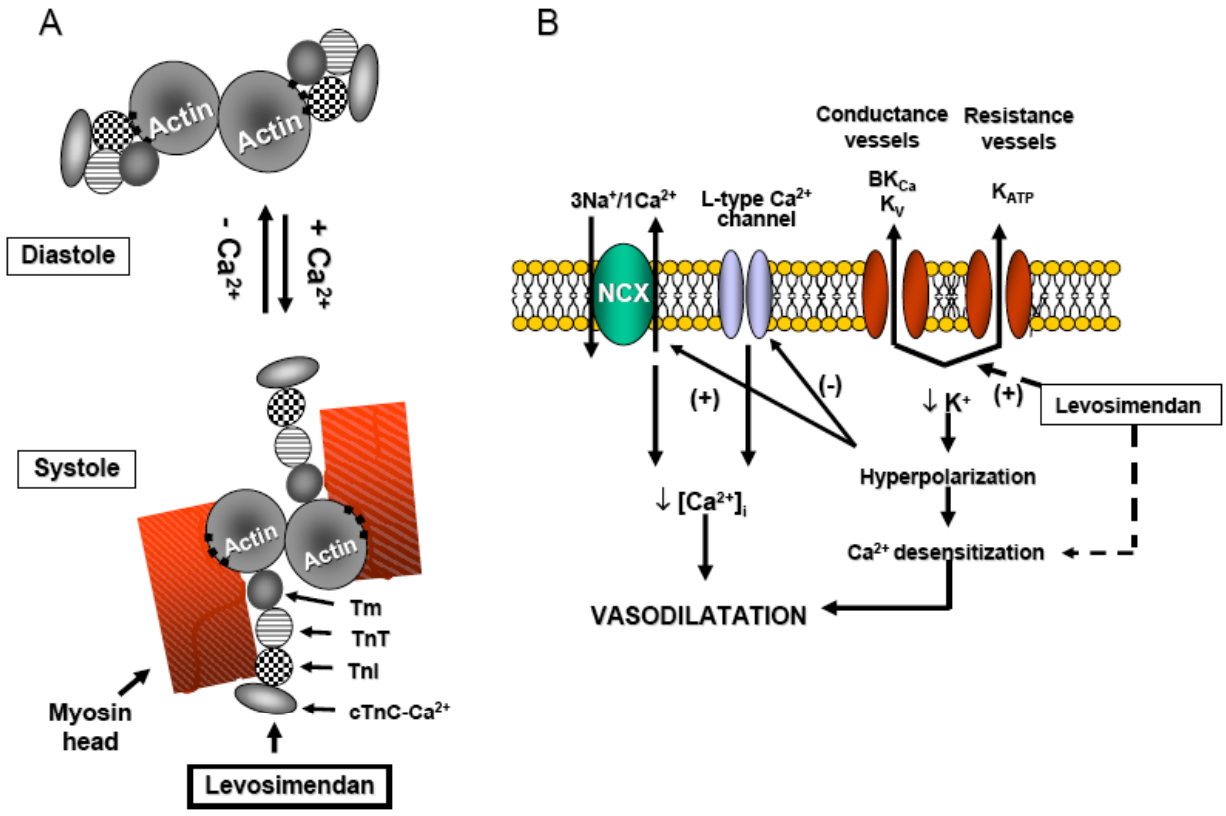

Fig. (8). Mechanism of action of levosimendan. **A**) Inotropic effect of levosimendan. The panel shows the major contractile proteins: actin, tropomyosin (Tm), and the troponin (Tn) complex, formed by TnT, TnC, and TnI. During the diastole, TnI binds tightly to actin and keeps Tm in a position where it inhibits the interaction between actin and myosin. During the systole the $[Ca^{2+}]_i$ rises, Ca^{2+} binds to the N-terminus of TnC and induces a conformational change in the Tn complex, so that TnI and Tm move away from the myosin binding sites on the actin (dashed line) allowing cross-bridge formation to take place. Levosimendan binds to TnC and stabilizes the conformation of the Ca^{2+}-TnC complex. **B**) Vasodilator effect of levosimendan. Levosimendan activates both mitochondrial and sarcolemmal ATP-dependent K^+ (K_{ATP}) channels in resistance vessels and Ca^{2+}-activated (K_{Ca}) and voltage-dependent K^+ channels (K_V) in conductance vessels. K^+ channels opening leads to membrane hyperpolarization and lowers $[Ca^{2+}]_i$ by decreasing the open probability of L-type Ca^{2+} channels and promoting the forward mode of Na^+-Ca^{2+} exchanger (NCX). Levosimendan also decreases Ca^{2+} sensitivity of contractile proteins. (+): activation. (-): inhibition. Taken from Tamargo *et al.* [137].

POSITIVE INOTROPIC AGENTS

Conventional inotropic agents [e.g., sympathomimetics (dopamine, dobutamine) and phosphodiesterase 3 (PDE3) inhibitors (milrinone)] increase the cellular levels of cAMP and activate cAMP-dependent protein kinase A (PKA) [1,3,4]. Sympathomimetics increases cAMP production via direct activation of β1-adrenergic receptors and PDE3 inhibitors by blocking the enzyme that breaks down cAMP. Intravenous ~~inotropic~~ ^ are indicated to improve signs, symptoms and hemodynamics (increase cardiac output, reduce PCWP and LV filling pressures) in patients with reduced LVEF and peripheral hypoperfusion (SBP < 100 mm Hg, cold skin, decreased renal function, impaired mentation) with or without congestion or pulmonary edema despite the use of diuretics and vasodilators at optimal doses [4]. They can also be used to stabilize patients at risk of progressive hemodynamic collapse or as a "bridge" until other life-saving therapy (coronary revascularization, mechanical circulatory support, ventricular assist devices, or cardiac transplantation) can be undertaken [1-4,128]. In end-stage patients for whom other therapies are not appropriate, inotropics may be considered as a palliative option of end-of-life care. In the ADHERE registry ~10% of the patients were treated in-hospital with inotropic agents and, in general, they have higher blood urea nitrogen levels, lower SBP, and lower LVEF [12].

Advantages and Disadvantages of Inotropic Agents

Although short-term treatment with conventional inotropic drugs may relieve signs and symptoms and improve hemodynamics in patients with AHFS, their benefits are counteracted by serious adverse effects, including: increase in heart rate, contractility and MVO_2, neurohumoral activation, proarrhythmia, intracellular Ca^{2+} overload (which increases wall tension and induces arrhythmias and myocyte cell death) and hypotension (especially at high doses) which reduces coronary perfusion [106,129,130]. The underlying etiology of AHFS has important implications not only for the long-term outcome. Viable and not contracting (hybernating) myocardium is present in up to 60% of the patients with AHFS and chronic ischemia [131] and they present a worse prognosis than patients with nonischemic etiology. In the presence of a hibernating myocardium the increase in cardiac contractility without a previous restoration of coronary blood flow can result in a supply and demand mismatch (increased MVO_2 and decreased coronary perfusion) that increases the

underlying myocardial ischemia and the incidence of ventricular arrhythmias and promotes/accelerates the progression of HF [65,66,128,130-134]. In the OPTIME-CHF trial, milrinone worsens outcomes (hospitalization for cardiovascular causes within 60 days and the composite of death or rehospitalization) in patients with CAD, particularly in those who develop hypotension [65,133]; in contrast, outcomes tend to improve in nonischemic patients. Furthermore, two meta-analysis found that IV conventional inotropic agents that increase cardiac cAMP levels increase in-hospital and post-discharge mortality in patients with AHFS, particularly in those with CAD, as compared to placebo [135,136]. Thus, in AHFS, IV inotropes are indicated only in hypotensive patients with impaired end-organ perfusion and when needed, they should be withdrawn as soon as adequate organ perfusion is restored and/or congestion reduced [1-5,8,11,64,128].

Concerns about the efficacy and safety of conventional inotropics have stimulated the development of new agents with a cAMP-independent mechanism of action, that improve cardiac output and relieve symptoms without increasing $[Ca^{2+}]_i$, MVO_2 and mortality rates.

1. LEVOSIMENDAN

Levosimendan has a dual mechanism of action. In the heart, it binds to the N-terminal domain of troponin (TnC) (Fig. **8**), stabilizes the Ca^{2+}-TnC complex and increases the binding affinity of TnC for intracellular Ca^{2+}. Hence, levosimendan accelerates the cross-bridge association rate and decelerates the dissociation rate, improving contractility without increasing Ca^{2+} transients or MVO_2 [137-140]. Binding of levosimendan to TnC is Ca^{2+}-dependent$_i$, increasing at higher $[Ca^{2+}]_i$, but decreasing when the $[Ca^{2+}]_i$ is low [138]. This may explain why it does not modify or even improves diastolic relaxation in patients with acute myocardial ischemia and after coronary angioplasty [139-141].

In vascular smooth muscle cells, levosimendan activates both mitochondrial and sarcolemmal ATP-dependent K^+ (K_{ATP}) channels in resistance vessels and Ca^{2+}-activated (K_{Ca}) and voltage-dependent K^+ channels (Kv) in large conductance vessels [139,142] (Fig. **8**). This leads to membrane hyperpolarization and lowers $[Ca^{2+}]_i$ by decreasing the open probability of L-type Ca^{2+} channels and promoting the forward mode of Na^+-Ca^{2+} exchanger. Both mechanisms decrease $[Ca^{2+}]_i$ and peripheral vascular resistances, reduce MVO_2 and increase coronary blood supply to the ischemic myocardium [137,139,140]. Membrane hyperpolarization can also indirectly decrease Ca^{2+} sensitivity of contractile proteins, while opening of K_{ATP} channels protects the myocardium against ischemia/reperfusion [142].

In vitro, high concentrations of levosimendan inhibit PDE3 activity, but whether this effect plays a role at therapeutic concentrations is uncertain [128,139].

In patients with AHFS levosimendan exhibits a linear pharmacokinetics and reaches steady-state within 5 h of a constant IV infusion. It binds to plasma proteins (95-98%), has an elimination half-life of ~ 1 h and a Vd of 20 L [139,143]. Levosimendan is excreted into the small intestine and reduced by intestinal bacteria to an amino phenolpyridazinone metabolite (OR-1855), which by acetylation leads to an active N-acetylated conjugate (OR-1896) [139,143]. OR-1896 reaches C_{max} 2 days after stopping a 24-h infusion, binds to plasma proteins (40%) and presents a half-life of 70-80 h, which explains why the effects of levosimendan persist for 1 week following a 24-h IV infusion [143].

Clinical Studies

In patients with AHFS, levosimendan improves HF signs, symptoms and hemodynamics (increases cardiac output and reduces PCWP, systemic and pulmonary vascular resistances) and its effects persist in patients treated with β-blockers [128,139,140]. Moreover, it improves LV diastolic dysfunction [128,140] and reduces BNP and ET-1 plasma concentrations, proinflammatory cytokines (interleukin-6) and soluble apoptosis mediators (soluble Fas and Fas ligand) [128,143-145].

Six trials studied the long-term effects of levosimendan in patients with AHFS (Table **2**). The LIDO study compared the effects of levosimendan and dobutamine [146]. At the end of the 24-h infusion, hemodynamic improvement was observed in more patients treated with levosimendan (28% vs 15%, P = 0.02). In a post-hoc analysis, levosimendan reduced both 31-and 180-day mortality and prolonged the median number of days alive out of hospital at 180 days as compared to dobutamine. Headaches and migraines were more frequent with levosimendan and cardiac adverse effects (rhythm disorders and myocardial ischemia) with dobutamine. The RUSSLAN trial evaluated the safety and efficacy of a 6-h infusion of levosimendan or placebo in patients with HF complicating acute myocardial infarction [147]. Levosimendan did not induce hypotension or ischemia and reduced the risk of worsening HF and death during both the 6 h infusion and over 24 h. Mortality was significantly lower with levosimendan compared with placebo at 14 and 180-day retrospective follow-up. Finally, the CASINO trial compared levosimendan, dobutamine and placebo in patients hospitalized with HF. The study terminated prematurely when 227 patients were enrolled, after an interim analysis revealed a clear mortality benefit at 6 months of levosimendan over both placebo and dobutamine (15.3% vs 39.6% and 24.7%, respectively) [148].

Three trials, however, found that despite the fact that levosimendan improved symptoms and hemodynamics, it produced a greater incidence of adverse events, and similar mortality rates to dobutamine and placebo. The SURVIVE found no differences in all-cause mortality at 30 and 180 days (26% vs 28%), number of days alive and out of the hospital and patient global assessment at 180 days between levosimendan and dobutamine [149]. However, patients treated with levosimendan were more likely to experience atrial fibrillation, hypokalemia, and headache and less likely to show worsening of HF compared with dobutamine. Interestingly, in patients receiving beta-blockers, mortality was significantly lower for levosimendan than dobutamine at day 5. The REVIVE I and II trials analyzed the effects of levosimendan or placebo, in addition to standard care, on patient status [150-152]. In both trials during the 5 days of the study, levosimendan significantly improved a composite of clinical symptoms, decreased creatinine and BNP plasma levels and shortened the stay in the intensive care unit as

compared to placebo, but these effects were not accompanied by a reduction in mortality [151,152]. However, the levosimendan group presented a higher incidence of headache, hypotension, ventricular tachycardia and atrial fibrillation, and a trend toward increased all-cause mortality at 90 days.

The most common side effects in these trials are headache, dizziness, nausea and hypotension [139,140,146-152]. Levosimendan does not present serious interactions with other drugs commonly prescribed to HF patients, including ACEIs, ARBs, diuretics, β-blockers and digoxin.

Future developments. In Europe, levosimendan is indicated in patients with AHFS secondary to cardiac systolic dysfunction without severe hypotension [4]. However, because of the contradictory results of randomized clinical trials, it is neccessary to define the safest dosing and timing of infusion, the subset of patients who may benefit more from the drug and its possible arrhythmogenic risk in AHFS patients compared with conventional inotropics.

2. ISTAROXIME

This agent exhibits a novel dual mechanism of action. It inhibits Na^+-K^+ ATPase activity at the sarcolemma, increasing $[Ca^{2+}]_i$ during the systole and cardiac contractility, and stimulates the sarcoplasmic reticulum (SR) Ca^{2+}-ATPase isoform 2a (SERCA2a) activity, leading to rapid sequestration of cytosolic Ca^{2+} into the SR during diastole and myocardial relaxation [153-155]. In dogs with chronic ischemic HF, IV istaroxime (0.5-5 μg/kg for 1 h) increases LV ejection fraction, decreases LV end-systolic/diastolic volumes and improves myocardial relaxation, without increasing heart rate and MVO_2 or producing proarrhythmic or changes in intracardiac conduction velocity or PR and QT intervals of the electrocardiogram [154-157].

Clinical trials. Patients with chronic stable HF and LV dysfunction received 4 sequentially increasing infusions of istaroxime (0.005-5 μg/kg/min for 6 h). At doses ≥ 1 μg/kg/min. istaroxime lowered PCWP (the primary end point) and increased cardiac contractility and cardiac output, but no changes in circulating neurohormones, renal function or MVO_2 were observed [155-158]. The HORIZON-HF trial compared istaroxime and placebo in patients with AHFS and low LVEF [159,160]. Intravenous infusion of istaroxime for 6-h decreased PCWP (the primary end point), right atrial pressure, LV end-diastolic volume, heart rate and diastolic stiffness, while increased SBP. There were no changes in neurohormones, blood urea nitrogen, creatinine, or troponin I, but serum Na^+ decreased in all groups. Istaroxime plasma levels increased rapidly, reached steady state levels after 4-5 h and presented a short half-life (< 1 h) and a large Vd (2 L/kg). Istaroxime was converted into 3 less active metabolites and was not excreted by the kidney. Adverse effects (nausea, vomiting and injection site pain) dissipated within minutes after the infusion ended. Despite these encouraging results, this was a short-term dose-ranging study performed in patients with no evidence of hypotension or end-organ dysfunction, the decrease in PCWP was modest, and cardiac index and stroke work index were improved only with the highest dose tested. Thus, the future of istaroxime will depend on its effects on clinical outcomes in hypotensive patients with AHFS and end-organ dysfunction [159]. A Phase II placebo-controlled trial assesses the safety and efficacy of istaroxime in patients hospitalized for AHFS not requiring inotropic therapy (NCT00838253).

3. CARDIAC MYOSIN ACTIVATORS

According to the crossbridge theory for muscle contraction, movement of actin among the myosin filaments is accomplished by the repetitive attachment and detachment of myosin heads (myosin cross-bridges) to and from actin filaments [137,161,162]. During the process ATP is hydrolyzed. Molecular events begin during the diastole (Fig. **9**), when a molecule of ATP binds with high affinity to the myosin head which rapidly detaches the myosin heads from actin producing muscle relaxation. Myosin ATPase rapidly hydrolyses myosin-bound ATP to adenosine diphosphate (ADP) and organic phosphate (Pi), and the myosin-ADP-Pi complex increases the affinity for actin. During this step the energy of the ATP is tranferred to the myosin head, causing a shape change, so that the myosin head is cocked and placed in line with its binding site on the actin filament. When the $[Ca^{2+}]_i$ increases and the binding site on the actin filament becomes available, the myosin head weakly binds to the active site on actin and a cross-bridge is formed causing the release of Pi. This release is associated with a strong binding of myosin to actin, and the energy of ATP produces a conformational change of the myosin cross-bridge, so that the myosin head flexes, pulling the actin filaments 10-nm towards the center of the sarcommere. Finally, ADP dissociates from the myosin head, which causes the dissociation of the myosin head from the actin filament, and myosin returns to its original configuration and prepares the cycle to repeat.

Cardiac myosin activators are a novel class of inotropic drugs that directly activate cardiac myosin ATPase and accelerate the rate of actin-dependent Pi release (step 4). This mechanism results not in an increase in the velocity of cardiac contraction, but instead, in a lengthening of the systolic ejection time, which increases cardiac contractility without altering cAMP levels, $[Ca^{2+}]_i$, SR Ca^{2+} content or Na^+/Ca^{2+} exchange [137,161,162]. Omecamtiv mecarbil (formerly CK-1827452) is a selective cardiac myosin activator without PDE inhibitor activity. In rat isolated cardiac myocytes and in animal models, including infarcted rats and tachypacing- and pacing-plus-infarction-induced HF in dogs, omecamtiv mecarbil increases fractional shortening and LV function (stroke volume and cardiac output) by lengthening LV systolic ejection time and decreases LV end-diastolic pressure without affecting the velocity of cardiac contraction, MVO_2, arterial blood presure, coronary blood flow or diastolic function [137,161-165].

Clinical trials. A Phase II double-blind, randomized, placebo-controlled trial studies 5 cohorts of patients with stable HF under standard therapy receiving IV infusions of escalating doses of omecamtiv mecarbil [166,167]. The duration of infusion ranges between 2 h (cohorts 1 and 2), 24 h (cohorts 3 and 4) and 72 h (cohort 5). Omecamtiv mecarbil significantly prolongs systolic LV ejection time and fractional shortening at plasma concentrations >100 ng/mL, stroke volume at concentrations > 200 ng/mL and cardiac output at > 300 ng/mL. At plasma levels >400 ng/mL, increases in

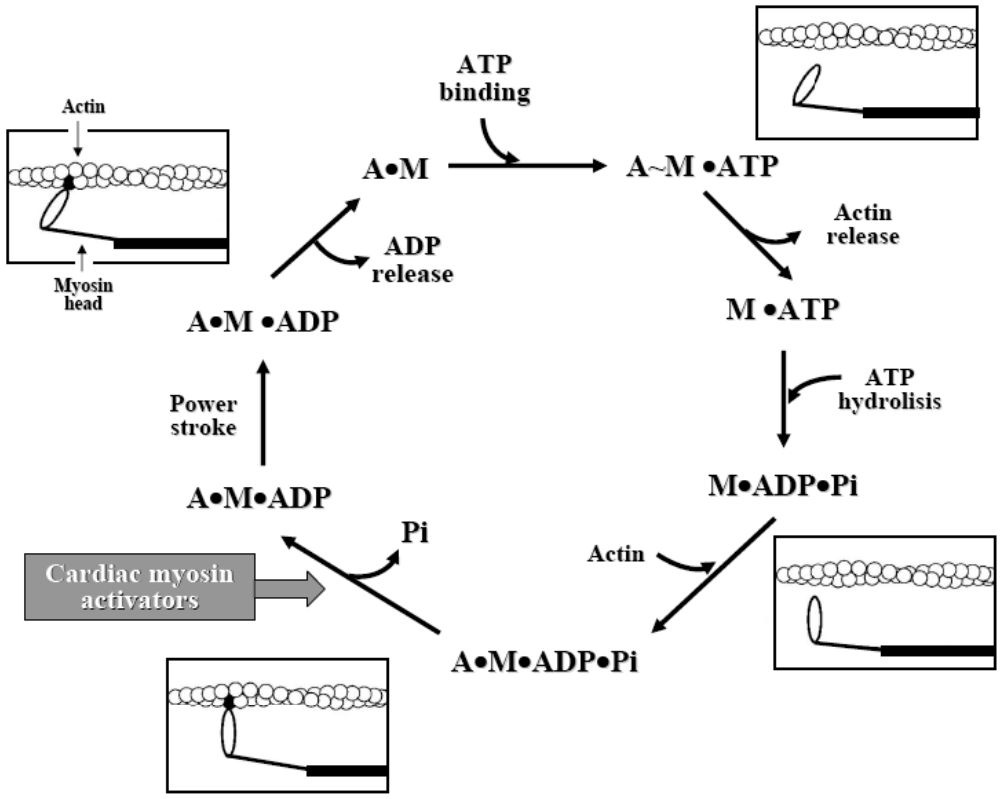

Fig. (9). The myosin cross-bridge cycle including the mechanism of action of cardiac myosin activators. See text for discussion. A: actin. ADP: adenosine diphosphate. ATP adenosine-5'-triphosphate. M: myosin. Pi: inorganic. Taken from Tamargo *et al*. [137].

stroke volume and cardiac output appears due to a decline in heart rate. There is a linear dose-response correlation for increases in systolic ejection time, stroke volume, fractional shortening and ejection fraction and for decreases in LV end systolic volume. Omecamtiv mecarbil reaches peak plasma concentrations withing 1-3 h and presents a half-life of 18 h [168]. Side effects (postural dizziness, headache, chest tightness, palpitations and light-headedness) dissipate promptly after discontinuation of the infusion.

Because of the novelty of the mechanism of action and the absence of clinical trials in patients with AHFS, specific studies in AHFS patients are required to confirm the efficacy and safety of omecamtiv mecarbil. Three ongoing Phase II, randomized, placebo controlled trials analyze the pharmacokinetics, efficacy and safety of omecamtiv mecarbil in patients with stable heart failure (NCT00624442, NCT00748579) and with ischemic cardiomyopathy (NCT00682565).

OTHER DRUGS

1. Metabolic Modulators

In the healthy human heart, free fatty acids (FFA) are the preferred metabolic substrate, accounting for 60–90% of the energy generated, while glucose and lactate represent much of the remaining substrate [169-171]. However, FFA oxydation requires approximately 10–15% more oxygen for a given quantity of ATP synthesis than do carbohydrates. In patients with HF, plasma levels of FFA increase due to catecholamine-induced lipolysis and upregulation of genes associated with FFA use via peroxisome proliferator–activated receptor-α activation [171]. High FFA levels increase MVO_2, inhibit pyruvate dehydrogenase activity and glucose oxidation, increase lactate and intracellular acidosis, impair Ca^{2+} handling and LV contractility and disrupt cellular function leading to myocyte apoptosis. All these changes impair LV performance and increase the risk of arrhythmias and postinfarction angina [172].

Metabolic modulators are drugs that shift myocardial substrate utilization from FFA to carbohydrates to optimize metabolic efficiency, reverse cellular abnormalities and improve LV function in patients with HF [169,171]**.** They were initially developed as antianginal agents for patients who were not candidates for revascularization [173]. Fatty oxidation inhibition can be accomplished by: a) inhibition of carnitine palmitoyl transferase I (CPT-I), an enzyme critical for mitochondrial uptake of FFA, with etomoxir, perhexiline and oxfenicine, and b) inhibition of FFA oxidation with trimetazidine, a long-chain 3-ketoacyl coenzyme A thiolase inhibitor with additional effects. Perhexiline, trimetazidine and etomoxir improve symptoms, exercise tolerance, and LVEF in small trials performed in patients with chronic HF and CAD [171,174], but they have not been studied in patients with AHFS.

Another therapeutic approach is to improve glucose uptake and oxidation. The glucagon-like peptide-1 [GLP-1] is a natural incretin that increases insulin secretion and decreases glucagon secretion from the pancreas in a glucose-dependent manner [175]. GLP-1 has a half life of < 2 minutes, due to

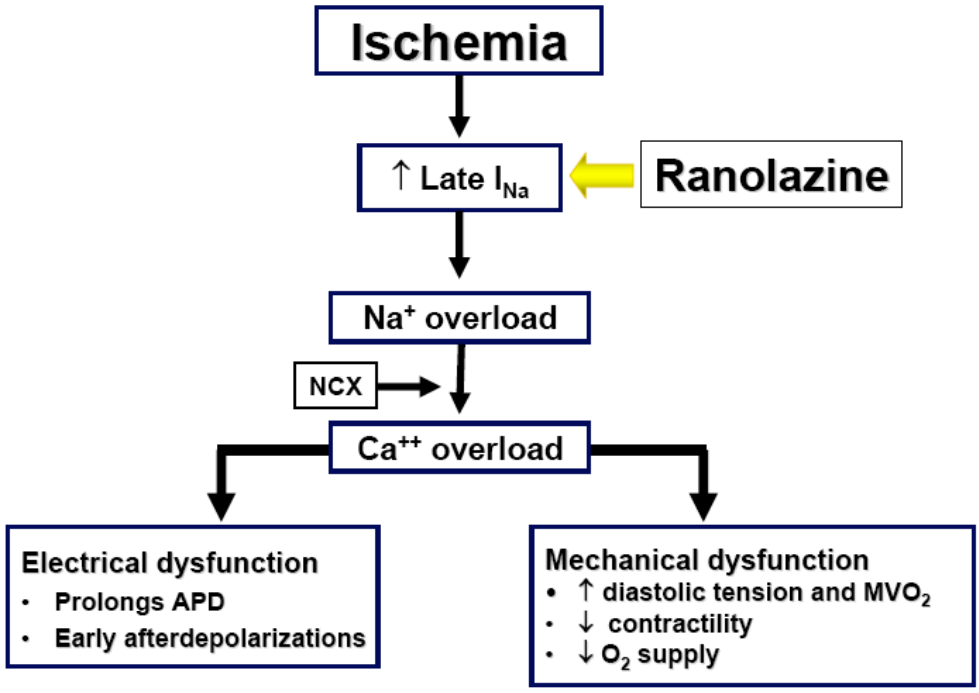

Fig. (10). Mechanism of action of ranolazine. In the presence of HF there is a pathological increase of the late I_{Na} that leads to an increase in the intracellular Na^+ concentration ($[Na^+]_i$) which leads to the activation of the reverse mode of the Na^+/Ca^{2+} exchanger (NCX), with the subsequent influx of Ca^{2+}. The increase in intracellular Na^+ and Ca^{2+} produces: a) e*lectrical instability*, characterized by a prolongation of the cardiac action potential duration (APD) and the appearance of early afterdepolarizations, and b) *mechanical dysfunction* characterized by impaired LV diastolic relaxation and increased LV end-diastolic pressure (myocardial stiffness) and myocardial O_2 demans (MVO_2) and decreases subendocardial O_2 supply.

rapid degradation by the enzyme dipeptidyl peptidase-4. In patients with acute myocardial infarction, NYHA class II-III and LV ejection fraction <40%, the IV infusion of GLP-1 added to background therapy improves LVEF and functional capacity in diabetic and non-diabetic patients [176-178]. GLP-1 is well tolerated with minimal episodes of hypoglycaemia and gastrointestinal side effects (nausea). Thus, GLP-1 might represent a new altenative in patients with AHFS and type 2 diabetes. A Phase 2, randomized, placebo-controlled trial (NCT00099580) analyzes the effects of the subcutaneous infusion of AC-2592 (2.5 pmol/kg/min for 5 weeks), a GLP-1 analog, in 12 patients with advanced chronic HF (NYHA class III-IV) despite standard therapy. AC-2592 significantly improved LVEF, maximum myocardial ventilation oxygen consumption, 6-minute walk distance and quality of life score. The most common adverse event reported was mild to moderate nausea.

2. RANOLAZINE

Ranolazine is a novel antianginal drug which inhibits the late inward Na^+ current (late I_{Na}) with minimal effect on peak sodium current during the upstroke of the cardiac action potential [179,180]. The late I_{Na} increases in certain pathological conditions such as myocardial ischemia and HF [179,180]. This increase of the late I_{Na} results in increased intracellular levels of Na^+ that activate the reverse mode Na^+-Ca^{2+} exchange leading to an increase in Ca^{2+} entry into the myocytes and in $[Ca^{2+}]_i$. This Ca^{2+} overload is associated with mechanical (impaired LV relaxation and increased end-diastolic pressure during the diastole) and electrical (cardiac arrhythmias associated with prolongation of the cardiac action potential) dysfunction.

Ranolazine inhibits the abnormal late I_{Na}, prevents the intracellular Na^+ and Ca^{2+} overload and improves myocardial relaxation reducing LV end-diastolic pressure and MVO_2 (Fig. **10**) Thus, even when ranolazine has no effect on cardiac contractility, it improves diastolic relaxation, reduces LV diastolic stiffness and LV end-diastolic pressure and increases LVEF, stroke volume and cardiac output and decreases LV end-diastolic pressure in canine and human failing hearts [179-182]. Moreover, the improvement of diastolic relaxation is expected to exert cardioprotective actions by increasing O_2 supply and decreasing MVO_2 in the ischemic myocardium [180]. Interestingly, these effects occur in the absence of changes in heart rate, blood pressure, coronary blood flow or MVO_2 consumption. Early studies found that IV administration of an immediate-release formulation of ranolazine improves the peak filling rate in patients with HF and in patients with ischemic cardiomyopathy produces a downward shift of the pressure-volume relationship during diastole accompanied by a reduction in mean diastolic wall stress and an increase in end-diastolic volume [183,184]. In patients with prior myocardial infarction (LVEF ≤35%), IV ranolazine (200 or 500 μg/kg) significantly improves diastolic function in non-infarcted ischemic segments [185]. Ranolazine is well tolerated. The most common side effects are dizziness, nausea, asthenia and constipation. These results suggest that ranolazine improves LV diastolic distensibility in patients with ischemic HF. Finally,

IV ranolazine improves diastolic relaxation in patients with long QT syndrome variant 3 associated with sustained late I_{Na} current (LQT3-deltaKPQ) [186]. However, ranolazine has not been studied in patients with AHFS.

3. IVABRADINE

In patients with HF, high heart rates are directly related to the risk of cardiac decompensation and overall mortality [187,188]. In fact, several therapeutic approaches reducing heart rate exert a favourable effect on prognosis, while agents that increase heart rate tend to increase mortality [188]. Thus, a long-term reduction in heart rate may be a useful therapeutic target in patients with HF, probably because this intervention is expected to reduce MVO_2 and increases the time available for LV diastolic filling and diastolic coronary perfusion [187].

Ivabradine is a specific and selective inhibitor of the pacemaker current (I_f), a hyperpolarization-activated, mixed Na^+/K^+ inward current that underlies the diastolic depolarization phase in sinoatrial node myocytes [189]. Ivabradine reduces heart rate without affecting SBP or cardiac contractility. In a rat model of post myocardial infarction HF, ivabradine does not modify myocardial contractility but decreases heart rate and LV end-systolic diameter and increases stroke volume [190-192]. In addition, ivabradine decreases noradrenaline plasma levels and LV collagen density and increases LV capillary density without modifying LV weight and blunts mRNA, and protein expressions of ACE and angiotensin II type 1 receptor. These findings suggest that ivabradine improved LV function and structure. In patients with regional/global systolic dysfunction, IV ivabradine reduces heart rate without affecting LV function [193] and in patients with advanced HF (mean LVEF 21%) treated with beta-blockers ivabradine increases stroke volume and LV systolic work and preserves cardiac output. In these studies, ivabradine was well tolerated, the most common side effects being transient visual disturbances [194]. All these data suggested that ivabradine may represent a new approach in HF associated with LV dilation, such as ischemic and dilated cardiomyopathy. However, in the BEAUTIFUL trial, enrolling in patients with CAD and LV dysfunction (LVEF <40%), ivabradine did not affect the admission to hospital for new-onset or worsening HF [195]. Thus, further studies are needed to determine the precise potential benefit of optimal heart rate control in HF patients. The ongoing SHIFT trial analyzes the effects of ivabradine on morbidity/mortality in 6,000 patients with impaired LV function and moderate-to-severe HF.

CONCLUSIONS

AHFS represent a major challenge for clinicians because of their high prevalence and associated morbidity and mortality, and a huge burden for the healthcare system and society. Conventionally used drugs (diuretics, vasodilators and inotropes) improve signs and symptoms and hemodynamics, but they do not reduce, or may even increase, in-hospital and postdischarge mortality. Thus, we have an unmet need for new agents that safely improve both short- and long-term outcomes in these patients. During the last decade several putative targets involved in the initiation and/or progression of AHFS have been identified and new families of drugs are currently being evaluated, both in experimental models, which helps us to better understand the pathophysiology, and in randomized clinical trials in patients with AHFS. However, the results of clinical trials have been disappointing in terms of efficacy and safety, so that up to now, none of the new drugs have demonstrated a consistent benefit on in-hospital and/or postdischarge survival or in readmissions compared to placebo or conventional therapies. Moreover, the only two approved drugs for the treatment of AHFS have had serious safety concerns [62,149-152].

There are several reasons for these dissapointing results [2]. 1) The main problem is the limited understanding of the pathophysiological mechanisms that really contribute to the genesis/maintenance of the different AHFS, which hinders the rational development of new more effective and safer drugs. The identification of epiphenomena as a therapeutic target can explain why some new drugs cannot improve patients´ outcomes. 2) The positive results observed in animal models are rapidly translated to small short-term hemodynamic or symptom-focused designs performed primarily to meet regulatory requirements, while the most important questions, including mechanistic hypotheses and the effect of interventions on rehospitalizations/mortality, have been inadequately studied. Because improving postdischarge outcomes is the most important goal in AHFS, the effects of emerging drugs should be evaluated in large-scale, randomized, controlled trials with outcome-driven to fully define their efficacy and safety and to understand the impact of new impact of new therapeutic strategies on long-term outcomes. 3) The marked variation in the design of clinical trials, which included heterogeneous populations, different surrogated end points, dosages and duration of the treatment, and delay between admission and treatment. These differences may hinder the comparison of the results obtained from different clinical studies. In the near future, we expect that a better understanding of the pathophysiology of AHFS would allow us to identify possible therapeutic targets that can reduce the morbidity, mortality and economic burden of AFHS.

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ABBREVIATIONS

A1RA	=	A1-receptor antagonists
ACE	=	angiotensin converting enzyme
ACEI	=	ACE inhibitors
AHFS	=	acute heart failure syndromes
ANP	=	atrial natriuretic peptides
ARB	=	angiotensin II AT1 receptor ~~blocker~~
ATP	=	adenosine-5'- triphosphate
AVP	=	arginine vasopressin
BNP	=	atriuretic peptide type-B
CAD	=	coronary artery disease

cAMP	=	cyclic adenosine 3′,5′-monophosphate
cGMP	=	cyclic guanosine 3´-5´-monophosphate
CrCl	=	creatinine clearance
CS	=	cardiogenic shock
DAG	=	diacylglycerol
GFR	=	glomerular filtration rate
HF	=	heart failure
IP3	=	inositol 1,4,5-triphosphate
IV	=	intravenous
LV	=	left ventricular
LVEF	=	left ventricular ejection fraction
MVO_2	=	myocardial oxygen demands
NO	=	nitric oxide
NPR	=	natriuretic peptide receptor
PCWP	=	pulmonary capillary wedge pressure
PDE	=	phosphodiesterase
PKA	=	protein kinase A
RAAS	=	renin-angiotensin-aldosterone system
RXPF	=	relaxin family receptor
SBP	=	systolic blood pressure
SERCA2a	=	Ca^{2+}-ATPase isoform 2a
sGC	=	soluble guanylyl cyclase
SR	=	sarcoplasmic reticulum

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