



# Adenosine Receptor Agonists

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## Abstract

Adenosine is a purine nucleoside that binds to adenosine cell surface receptors, which are widely expressed in heart and blood vessel cells as well as in the brain, kidney and adipose tissue. There are 4 subtypes of P1 (adenosine) G protein-coupled receptors (GPCR), named  $A_1$ ,  $A_{2A}$ ,  $A_{2B}$ , and  $A_3$ , which mediate a variety of cardioprotective and regenerative effects. In the heart, these effects are predominantly mediated through  $A_1$  receptors ( $A_1R$ ), which are expressed in atrial and ventricular cardiomyocytes and smooth muscle cells. Pre-clinical studies have reported multiple potential benefits achievable by modulation of adenylyl cyclase with beneficial effects in a variety of pre-clinical models of cardiovascular disease including chronic heart failure (HF).  $A_1R$  blockade (e.g. rolofylline) was however not successful in the PROTECT trial, where 2033 patients with acute HF and renal dysfunction were randomized to rolofylline or placebo, showed no benefit on renal function, symptoms, rehospitalization, or mortality. Following this attention turned to partial adenosine agonists, capadenoson and neladenoson bialanate hydrochloride, which has two phase II studies underway, PANACHE (HFpEF) and PANTHEON (HFREF).

**Keywords:** heart failure; adenosine receptor agonists

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## Introduction

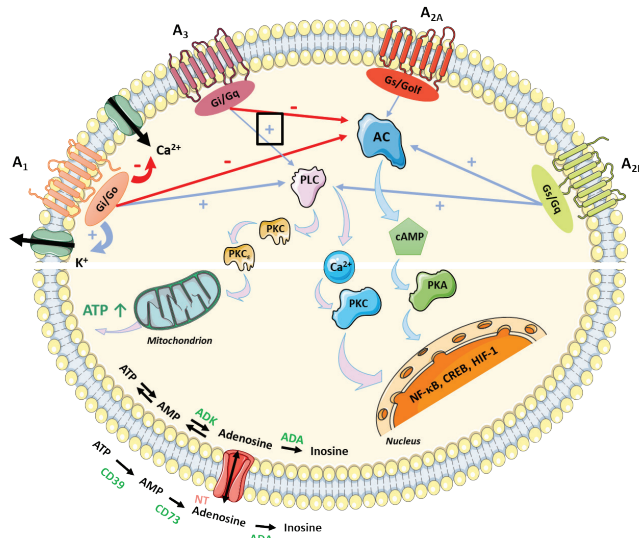
Advances in the management of acute coronary syndrome[1] and improvements in heart failure (HF) treatment have led to significant reductions in both morbidity and mortality.[2-4] Such changes are thought to be responsible for an increase in the prevalence of HF as patients with cardiovascular disorders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

Although several early therapeutic breakthroughs (for example neurohumoral inhibition) have significantly improved mortality and morbidity in patients with HF with reduced ejection fraction (HFREF) from the 1980's to the first decade of the millenium, relatively fewer successes have been reported during the past decade. [6] A purported reason for the failure of recent HFREF treatment trials may be that the addition of yet more haemodynamically active (usually vasodilatory) agents to the standard treatment of care may cause adverse effects such as hypotension or bradyarrhythmias, and thus, incremental improvements may be unattainable with these agents.[7] Data from the ESC Heart Failure Long-Term Registry have demonstrated that desirable

target doses for RAAS-blockers, MRAs, and  $\beta$ -blockers were only achieved in about 30% of patients with chronic HF.[8] These safety concerns have guided the field of research, and there is now a focus on developing novel treatment strategies directly targeting intrinsic myocardial properties, without significantly affecting haemodynamics.[9,10] This shift in focus has led to the development of partial adenosine receptor agonists[11], a group of agents which are thought to be haemodynamically neutral.

## Adenosine Receptor Signalling

Adenosine is a purine nucleoside that binds to adenosine cell surface receptors, which are widely expressed in heart and blood vessel cells as well as in the brain, kidney and adipose tissue.[12,13] There are 4 subtypes of P1 (adenosine) G protein-coupled receptors (GPCR), named  $A_1$ ,  $A_{2A}$ ,  $A_{2B}$ , and  $A_3$ , which mediate a variety of cardioprotective and regenerative effects. [14,15] In the heart, these effects are predominantly mediated through  $A_1$  receptors ( $A_1R$ )[11], which are expressed in atrial and ventricular cardiomyocytes[16] and smooth muscle cells. [17] Activation of  $A_1R$  reduces the intracellular levels of cyclic adenosine monophosphate (cAMP) by inhibiting adenylyl cyclase[18], modulating protein kinase C, and opening ATP-sensitive potassium channels (Figure 1).[19]



**Figure 13.1. Adenosine metabolism and signaling**

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

Pre-clinical studies have reported that modulation of adenylyl cyclase attenuates sympathetic over-activation and stimulates a release of atrial natriuretic peptide.[20] Furthermore, it has been shown that an adenosine activation of  $A_1$ R improves mitochondrial function[21,22], attenuates cardiac hypertrophy and fibrosis[23], modulates derangements in cardiac metabolic profile[24], and exerts cardioprotective effects by maintaining intracellular calcium homeostasis and preventing ischaemia. Due to this broad spectrum of mechanisms, adenosine  $A_1$ R activation has been shown to exert beneficial effects in a variety of pre-clinical models of cardiovascular disease associated with ischaemia/reperfusion (I/R), arrhythmogenesis, myocardial stunning, ventricular dysfunction, acute myocardial infarction, apoptosis, and chronic heart failure (Table 1).[25-27]

### Concept of Adenosine $A_1$ R Blockade

Several complex effects of adenosine on the kidney, such as sodium reabsorption in the proximal tubules, vasoconstriction of afferent renal arterioles, and enhanced tubuloglomerular feedback in the macula densa have been described, which all lead to fluid overload and decreased glomerular filtration rate. [28,29] Approximately 50% of chronic HF patients and 2/3 of patients with acute HF have renal dysfunction, therefore adenosine-related renal effects are highly undesired and raise major safety concerns.[30] These renal effects raise the question whether adenosine  $A_1$ R blockade may be potentially beneficial in HF and this led to large-scale drug development programs with adenosine  $A_1$ R antagonists (e.g. rolofylline).

**Table 1. Adenosine receptor signaling. Beneficial effects of partial  $A_1$ R agonists in heart failure**

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

Two smaller randomized, controlled clinical trials reported positive effects of rolofylline on renal function in patients with acute and chronic HF.[31,32] However, a subsequent larger phase 3 study did not confirm these findings. In the **PROTECT** trial, 2033 patients with acute HF and renal dysfunction were randomized to receive either rolofylline, an adenosine  $A_1$ R antagonist, or placebo. Treatment with rolofylline showed no benefit on renal function, symptoms, rehospitalization, or mortality during the follow-up of 60 days[33], but increased rates of seizures and stroke were reported in this group. However, no temporal relation to rolofylline infusion and no specific stroke subtype which predicted stroke in the rolofylline group was reported.[34]

### Full vs Partial Adenosine $A_1$ R Agonists

The neutral results of the PROTECT trial indirectly influenced the continued development of adenosine  $A_1$ R agonists. Given the fact that adenosine receptors are expressed on the vast majority of cells, it became obvious that full adenosine agonists activated not only the desired target cells, but also activated cells involved in a variety of diverse physiological processes.[35] Due to the widespread distribution and diverse function of  $A_1$ R, the cardioprotective effects may have been counteracted by various unintended off-target effects, such as atrioventricular block, bradycardia, and negative inotropic and dromotropic effects. [11,12,36] Therefore, partial adenosine  $A_1$ R agonists have been designed to exert cardioprotective and anti-remodelling effects, while maximizing safety by limiting negative side effects. In general, partial agonists are low efficacy ligands that elicit only submaximal effects compared to full agonists.[35] Therefore,

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

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

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

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

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

## Conclusions

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

PANTHEON will provide new evidence for the role of partial adenosine A1R agonists in heart failure therapy.

## Declarations of interest

The authors declare no conflict of interest.

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

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