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REVIEW

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NAD^+ enhancers as therapeutic agents in the cardiorenal axis

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Abstract

Cardiorenal diseases represent a complex interplay between heart failure and renal dysfunction, being clinically classified as cardiorenal syndromes (CRS). Recently, the contributions of altered nicotinamide adenine dinucleotide (NAD^+) metabolism, through deficient NAD^+ synthesis and/or elevated consumption, have proved to be decisive in the onset and progress of cardiorenal disease. NAD^+ is a pivotal coenzyme in cellular metabolism, being significant in various signaling pathways, such as energy metabolism, DNA damage repair, gene expression, and stress response. Convincing evidence suggests that strategies designed to boost cellular NAD^+ levels are a promising therapeutic option to address cardiovascular and renal disorders. Here, we review and discuss the implications of NAD^+ metabolism in cardiorenal diseases, focusing on the propitious NAD^+ boosting therapeutic strategies, based on the use of NAD^+ precursors, poly(ADP-ribose) polymerase inhibitors, sirtuin activators, and other alternative approaches, such as CD38 blockade, nicotinamide phosphoribosyltransferase activation and combined interventions.

Keywords Cardiorenal syndrome, NAD^+ metabolism, Niacin, Nicotinamide, Niacinamide, Nicotinamide riboside, Nicotinamide mononucleotide, Poly(ADP-ribose) polymerases, Sirtuins, CD38, NRH, NMNH, Trigonelline, Ischemia/reperfusion, AKI, Animal models, Clinical trial

Introduction

The intricate relationship between the heart and the kidneys, known as the Cardiorenal Axis, has gained significant attention in recent years. As patients increasingly survive acute and chronic heart and kidney diseases, understanding the interplay between these vital organs becomes crucial [1, 2].

One illustrative example of the cardiorenal axis' role in coordinating cardiac and renal function is the renin-angiotensin-aldosterone system (RAAS), which regulates blood pressure and fluid-electrolyte balance [3]. Upon the detection of a decline in arterial blood pressure by baroreceptors in the carotid sinus, there is an increase in the secretion of renin, which facilitates the conversion of angiotensinogen generated in the liver to angiotensin I. This angiotensin I is subsequently transformed into

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angiotensin II by the angiotensin-I-converting enzyme. Finally, angiotensin II exerts its hypertensive action by stimulating sympathetic activity and arteriolar vasoconstriction, but also its electrolyte-preserving function by inducing tubular electrolyte reabsorption in the kidneys [4].

Cardiorenal diseases can be clinically classified into cardiorenal syndromes (CRS), being characterized by concurrent heart and kidney dysfunction, and organized in five CRS subtypes, according to the duration of the disease (acute or chronic) and the organ that originated the disorder (heart or kidneys) [5–8].

CRS have been associated with depletion nicotinamide adenine dinucleotide (NAD^+), a central coenzyme in cellular metabolism, as it shuttles electrons during redox reactions, participates in over 500 enzymatic processes, and is critical in several signaling pathways (energy metabolism, DNA damage repair, gene expression, and stress response) [9, 10]. This diversity of functions is the reason why a decrease in the bioavailability of NAD^+ is a major contributing factor in a number of human pathological conditions related to neurodegenerative disorders, metabolic diseases and age-related complications [11]. NAD^+ depletion is observed in several cardiovascular pathologies, including myocardial ischemia-reperfusion injury (IRI), cardiomyopathy, heart failure (HF), and atherosclerosis, but also in the context of renal disease, especially in acute (AKI) and chronic renal disease (CKD) [12, 13]. The relationship between NAD^+ level depletion and cardiorenal diseases makes NAD^+ a promising therapeutic target, as studies show that administration of NAD^+ precursors, such as nicotinic acid (NA), nicotinamide (NAM), nicotinamide riboside (NR), and nicotinamide mononucleotide (NMN), effectively raises intracellular NAD^+ levels, providing protection from cardiorenal inflammation, oxidative stress, and organ injury, therefore proving beneficial in the treatment of cardiorenal diseases of various natures [12, 14, 15].

Administration of NAD^+ precursors is not the only NAD^+ enhancing strategy known to efficiently increase NAD^+ levels. Other strategies designed to restore NAD^+ levels in human disease are focused on the modulation of enzymes involved in NAD^+ homeostasis, either via amplification of NAD^+ synthesis through the *de novo*, Preiss-Handler or salvage pathways, or blockade of NAD^+ consumption by the three main families of NAD^+-consuming enzymes: sirtuins, poly(ADP-ribose) polymerases (PARPs), and cyclic ADP(cADP)-ribose synthases [16–18]. Some of these NAD^+ boosting therapeutic strategies have already been under research for more than 20 years, as is the case of NR, which was presented in 2004 as a new NAD^+ precursor [19], while others have only been slightly studied due to their recent discovery, as happens with the reduced versions of the precursors NR (NRH) and NMN (NMNH) [20–23].

This review provides the most updated information on the potential therapeutic effects of NAD^+ enhancers in the cardiorenal axis, in both preclinical and clinical settings. In particular, we focus on the role of NAD^+ augmentation strategies based on the use of NAD^+ precursors, PARP inhibitors (PARPi), sirtuin activators, and other alternative strategies, such as cADP-ribose synthase inhibition or nicotinamide phosphoribosyltransferase (NAMPT) activation (Fig. 1).

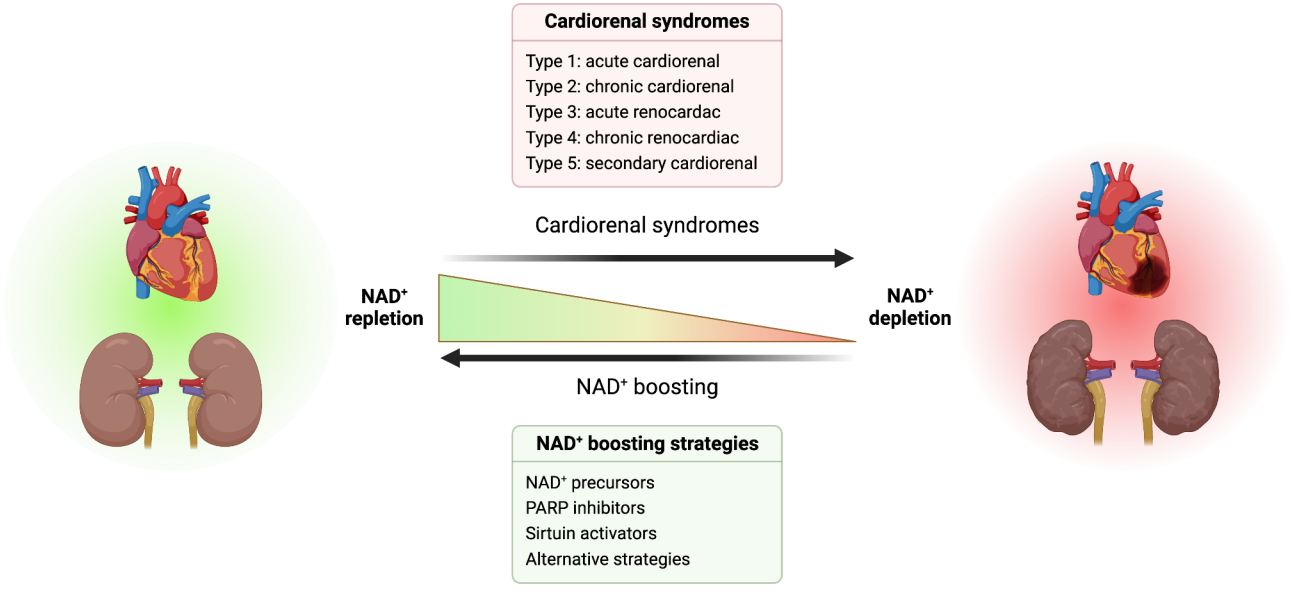

Fig. 1 Pathophysiological NAD^+ depletion by cardiorenal syndromes and recovery through NAD^+ boosting strategies

The cardiorenal syndrome

The heart and kidneys are physiologically interrelated. They are also strongly connected in pathological conditions, in a phenomenon referred to as cardiorenal syndromes (CRS) (Fig. 2) [8]. According to the consensus conference held in 2008 by the Acute Dialysis Quality Initiative, CRS are classified into five subtypes [24].

CRS Type I

In CRS type I, also known as acute cardiorenal, an acute worsening of heart function leads to acute kidney failure. CRS type I commonly occurs in the setting of an acute cardiac disease, such as acute decompensated heart failure (ADHF), after an ischemic (acute coronary syndrome, cardiac surgery complications) or non-ischemic heart disease (valvular disease, pulmonary embolism) [6]. The incidence of CRS type I is high, accounting for around 16% of all hospitalized AKI patients [25]. The presence of ADHF in CRS type I leads to a decreased renal arterial flow, and a consequent reduction in the glomerular filtration rate [26]. However, non-hemodynamic mechanisms have also been proposed as sources of CRS type I, including sympathetic nervous system (SNS) and RAAS activation, chronic inflammation, and an imbalance in the proportion of reactive oxygen species (ROS)/nitric oxide (NO) production [5].

CRS type II

CRS type II, also known as chronic cardiorenal, is caused by chronic abnormalities in heart function that lead to kidney injury or dysfunction. In this case, chronic heart failure (CHF), a pathological condition in which the heart is unable to effectively exert its pumping function, leads to a progressive worsening of the renal function [27]. It

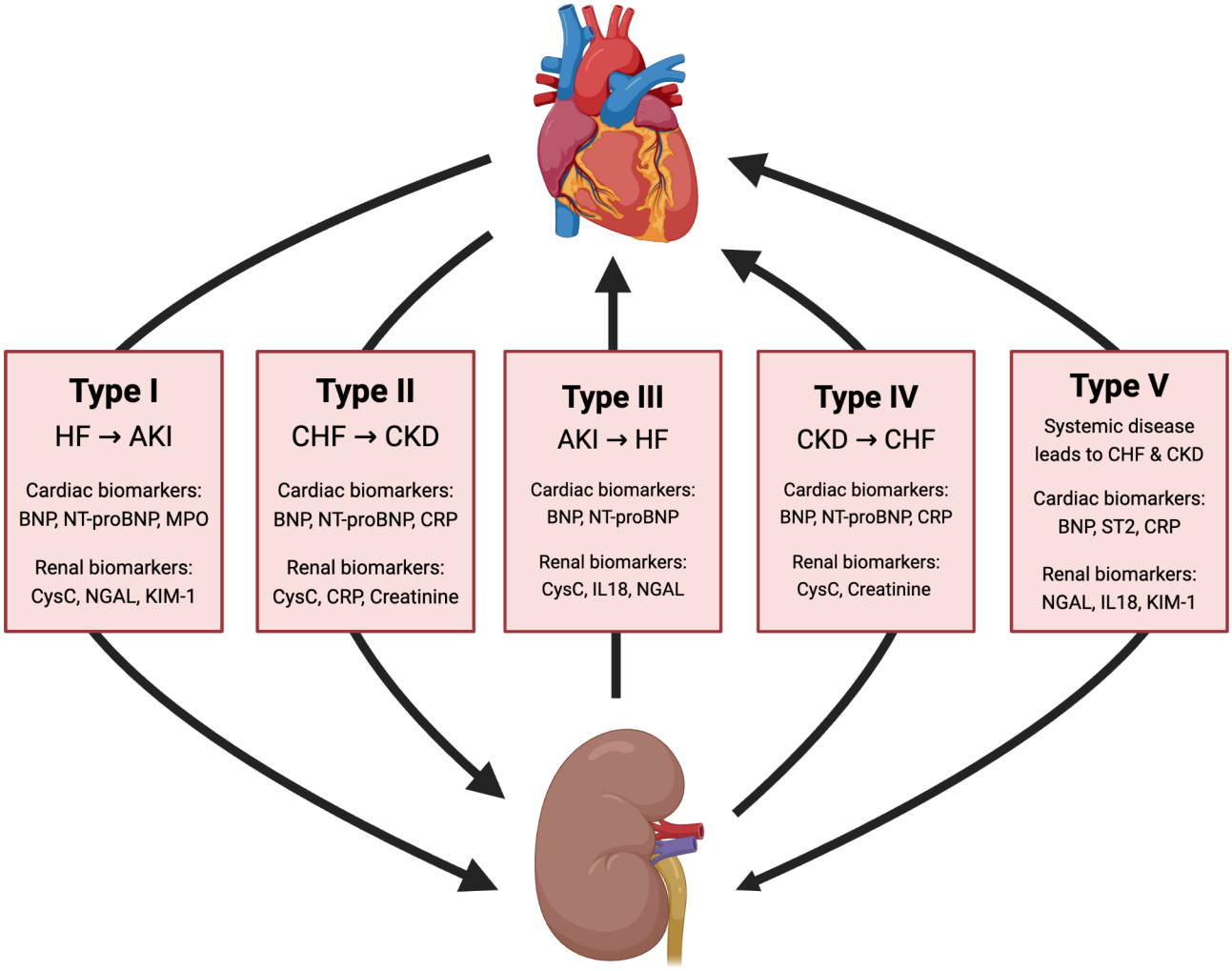

Fig. 2 Classification of cardiorenal syndromes (CRS) and biomarkers with clinical significance. AKI: acute kidney injury; BNP: B-type natriuretic peptide; CHF: chronic heart failure; CKD: chronic kidney disease; CRP: C-reactive protein; CysC: cystatin C; HF: Heart failure; IL-18: interleukin 18; KIM-1: kidney injury molecule 1; MPO: myeloperoxidase; NGAL: neutrophil gelatinase-associated lipocalin; NT-proBNP: N-terminal pro B-type natriuretic peptide; ST2: suppressor of tumorigenicity-2

is estimated that between 20% and 57% of CHF patients present renal failure, which is associated with a poor prognosis and a high risk of re-admission [28]. An example of type II CRS is provided by cyanotic nephropathy, a disease that occurs in patients with congenital heart disease, in which heart disease clearly precedes the onset or progression of CKD [29]. Many pathophysiological mechanisms have been proposed as causes of type II CRS, such as neuro-hormonal activation, renal hypoperfusion and venous congestion, inflammation, atherosclerosis, and oxidative stress [30].

CRS type III

CRS type III, also known as acute renocardiac, occurs when AKI contributes to the development of acute cardiac injury, by directly or indirectly producing an acute cardiac event. Many acute renal diseases can be associated with this type of syndrome, such as ischemic AKI, nephrotoxic injury, sepsis-associated AKI, etc [31]. Although the association between AKI and cardiac disease is clear [32–34], further prospective studies are needed to understand the incidence of CRS type III, as AKI can affect the heart through direct or indirect mechanisms. Direct mechanisms strongly rely on inflammation since, during IRI, inflammation and apoptosis are induced, leading to tissue damage and organ dysfunction. Therefore, cardiac myocyte apoptosis and inflammatory neutrophil infiltration can be considered two of the most important contributors to the pathophysiology of heart failure during AKI [35]. On the other hand, AKI can cause significant physiological derangement, including oliguria, electrolyte imbalance, acidemia and accumulation of uremic toxins, which may result in lung, brain, and liver dysfunction [36, 37]. These indirect effects can also affect the heart, as well as activate the SNS and the RAAS, causing cardiomyocyte apoptosis [38].

CRS type IV

In CRS type IV, also known as chronic renocardiac, CKD contributes to chronic heart injury, disease and/or dysfunction. Patients with CKD stage 1–3 present 25–100 times higher risk for cardiovascular events than for other renal events [39], heart failure being the most common cardiac manifestation in CKD patients, with a prevalence of almost 28% [40]. It has been demonstrated that inflammation enhances cardiovascular risk and mortality in hemodialysis patients, which furthers the progression of renal parenchyma fibrosis and glomerular sclerosis, declining renal function [41]. These situations in CKD patients can cause endothelial dysfunction, arterial stiffness, and smooth muscle cell proliferation, which may result in CRS type IV [42].

CRS type V

CRS type V, also known as secondary cardiorenal, occurs when cardiac and renal injury are simultaneously present, instead of one preceding the other. In this case, the underlying cause for CRS type V onset is a systemic disease, in which the heart and kidneys are involved secondarily. Therefore, pathophysiology in CRS type V depends on the underlying disease [7]. Type V CRS can be caused by many systemic pathophysiological conditions, such as sepsis, connective tissue disorders, and drug abuse in the case of acute CRS type V, and diabetes, hypertension, and tuberculosis in chronic CRS type V [43].

CRS biomarkers

In cardiorenal syndromes, biomarkers play a crucial role in diagnosis, risk prediction and prognosis in patients. Some biomarkers reflect on hemodynamic changes, others determine organ damage and/or dysfunction, and others may reflect oxidative stress-induced cell damage [2]. CRS biomarkers can be heart- or kidney-specific. During HF, cardiomyocytes increase their release of natriuretic peptides (NPs), including B-type natriuretic peptide (BNP) and N-terminal pro B-type natriuretic peptide (NT-proBNP), aiming to maintain cardiac homeostasis. This makes NP strong biomarkers of acute heart injury, leading to their use in the context of many types of CRS [44]. Other cardiac biomarkers, such as myeloperoxidase (MPO) [45], the suppressor of tumorigenicity-2 (ST2) [46], and C-reactive protein (CRP) [47] are linked to inflammation, which is paramount for the onset of acute and chronic heart failure [48].

Some cardiac biomarkers can also be used as renal biomarkers for CRS, such as neutrophil gelatinase-associated lipocalin (NGAL) and kidney injury molecule 1 (KIM-1) [49], although several kidney-specific biomarkers have been determined. One of the most important elements for studying renal function is the estimated glomerular filtration rate (eGFR) [50], as injured kidneys would have it decreased. Serum creatinine (sCr) [51], cystatin C (CysC), and blood urea nitrogen (BUN) are directly related to the eGFR and can also be used as renal biomarkers [52]. Neutrophil gelatinase-associated lipocalin (NGAL) and interleukin 18 (IL-18) could be considered as inflammation-dependent renal biomarkers, the latter found increased after IRI [53, 54].

NAD+ metabolism

NAD+ biosynthesis

NAD^+ homeostasis is achieved by a fine balance between its biosynthesis and consumption (Fig. 3). NAD^+ can be generated through three pathways, namely, *de novo*, Preiss-Handler, and salvage pathways, being synthesized from tryptophan, NA, and NAM, NMN(H) and NR(H), respectively [55].

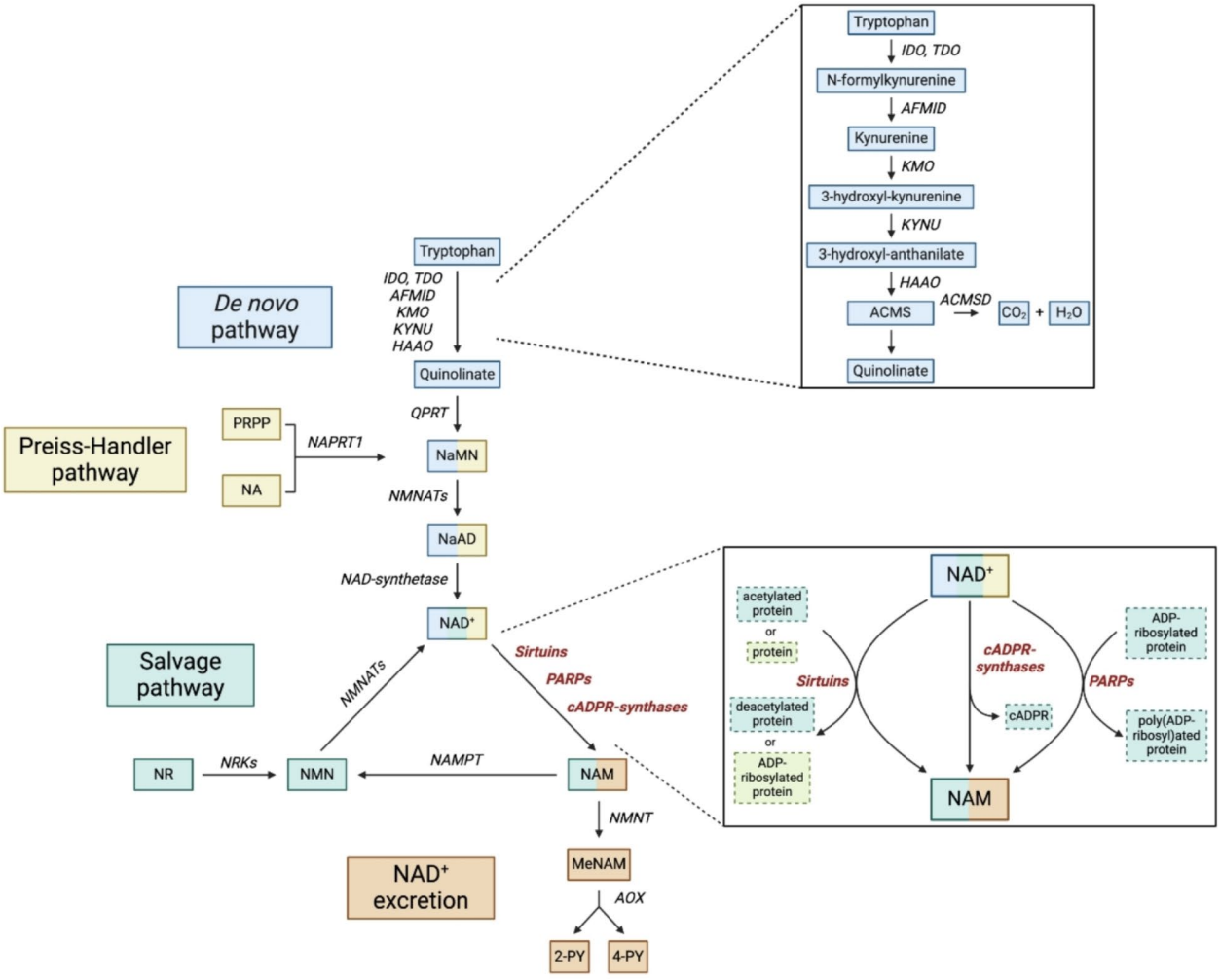

Fig. 3 NAD^+ biosynthesis and consumption. 2-PY: N-methyl-2-pyridone-5-carboxamide; 4-PY: N-methyl-4-pyridone-3-carboxamide; ACMS: α-amino-β-carboxymuconate-ε-semialdehyde; ACMSD: α-amino-β-carboxymuconate-ε-semialdehyde decarboxylase; AFMID: arylformamidase; AOX: aldehyde oxidase; HAAO: 3-hydroxyanthranilic acid oxygenase; IDO: indoleamine 2,3-dioxygenase; KMO: kynurenine 3-monooxygenase; KYNU: kynureninase; MeNAM: methyl nicotinamide; NA: nicotinic acid; NaAD: nicotinic acid adenine dinucleotide; NAM: nicotinamide; NaMN: nicotinic acid mononucleotide; NAMPT: nicotinamide phosphoribosyltransferase; NAPRT1: nicotinic acid phosphoribosyltransferase 1; NMN: nicotinamide mononucleotide; NMNATs: nicotinamide mononucleotide adenylyltransferases; NMNT: nicotinamide N-methyltransferase; PARPs: poly(ADP-ribose) polymerases; PRPP: phosphoribosyl pyrophosphate; QPRT: quinolinate phosphoribosyltransferase; TDO: tryptophan 2,3-dioxygenase

Via *de novo* synthesis, the essential amino acid L-tryptophan suffers a first and rate-limiting oxidation reaction to N-formyl-L-kynurenine by either the tryptophan 2,3-dioxygenase (TDO) or the indoleamine 2,3-dioxygenase (IDO). Although both enzymes catalyze the same reaction, TDO is primarily found in the liver, whereas IDO is widely distributed in various other tissues. Subsequently, N-formyl-L-kynurenine goes through four different consecutive enzymatic reactions to form the intermediate α-amino-β-carboxymuconate-ε-semialdehyde (ACMS). These reactions include (1) hydrolysis by an arylformamidase (AFMID), (2) hydroxylation by the kynurenine 3-monooxygenase (KMO), (3) hydrolysis by the kynureninase (KYNU), and (4) deoxygenation by the 3-hydroxyanthranilic acid oxygenase (HAAO). The ACMS intermediate is highly unstable and can be completely oxidized to CO_2 and water by the α-amino-β-carboxymuconate-ε-semialdehyde decarboxylase (ACMSD), or spontaneously cyclized to quinolinate. Subsequently, quinolinate goes through enzymatic phosphoribosylation to form nicotinic acid mononucleotide (NaMN) by the quinolinate phosphoribosyltransferase (QPRT), this reaction being considered as the second rate-limiting step in this route. NaMN is then converted to nicotinic acid adenine dinucleotide (NaAD) by the nicotinamide mononucleotide adenylyltransferases (NMNATs). Finally, NaAD is converted into NAD^+ by a

glutamine-dependent ligation reaction catalyzed by the NAD^+ synthetase [11, 16, 56].

Even though NAD^+ can be synthetized by the amino acid L-tryptophan, the main source of intracellular NAD^+ comes from alternative synthesis routes, such as the Preiss-Handler or the salvage pathways, which allow the production of NAD^+ from different metabolic precursors. The Preiss-Handler pathway relies on the enzyme nicotinate phosphoribosyltransferase domain-containing protein 1 (NAPRT1), which catalyzes the transfer of a phosphoribosyl group from a molecule of phosphoribosyl pyrophosphate (PRPP) to nicotinic acid (NA), forming the intermediate NaMN and consuming one ATP molecule in the process. NaMN can then be incorporated into the *de novo* synthesis pathway and continue to the formation of NAD^+ [57, 58].

Alternatively, in the salvage pathway, nicotinamide (NAM), nicotinamide mononucleotide (NMN) or nicotinamide riboside (NR) are converted into NAD^+ in a series of specific reactions. On one hand, NAM can be ribosylated to NMN by the nicotinamide phosphoribosyltransferase (NAMPT) enzyme. On the other hand, NR can be phosphorylated into NMN by nicotinamide riboside kinases (NRKs). Both reactions converge in the intermediate NMN, which can be finally condensed with AMP to form NAD^+ by the NMNATs, which are shared enzymes with the *de novo* synthesis pathway [10, 59, 60].

NAD+-consuming enzymes

Besides its role as a coenzyme, NAD^+ has been found to act as an indispensable substrate for certain enzymatic reactions. In these reactions, NAD^+ loses its ADP-ribose (ADPR) moiety. Four mammalian NAD^+-consuming enzymes have been found: sirtuins, PARPs, cADPR synthases, and sterile alpha Toll/interleukin receptor (TIR)-motif-containing protein 1 (SARM1) [61–64]. However, given that the implication of SARM1 in the cardiorenal axis is still unclear, this review will only focus on the remaining three NAD^+-consuming protein families.

Sirtuins

Sirtuins are class III NAD^+-dependent histone deacetylases that consume one molecule of NAD^+ for each deacetylation reaction [65]. To date, seven sirtuins have been found in mammals, namely SIRT1-7. Mammalian sirtuins are ubiquitously expressed and share a conserved catalytic NAD^+-binding core domain, but can catalyze various enzymatic reactions: deacetylation, ADP-ribose transfer, desuccinylation, demalonylation, and deglutarylation [66–68].

Sirtuins 1, 2, 3, 5 and 7 present deacetylase activity [69–73], while sirtuin 4 acts as an ADP-ribosyl-transferase [74], and sirtuin 6 can catalyze both reactions [75]. Additionally, SIRT5 is also able to act as a desuccinylase, demalonylase and deglutarylase [76]. Even when they share enzymatic activities within the protein family, due to their different subcellular locations they act on different substrates, therefore being involved in distinct cellular functions. While SIRT6 and SIRT7 are nuclear proteins [77], SIRT3, SIRT4 and SIRT5 are mitochondrial sirtuins [78], with SIRT1 being able to shift between the cytoplasm and the nucleus due to different stimuli, such as oxidative stress and DNA damage [79, 80]. Finally, SIRT2 is primarily located in the cytoplasm, although it can migrate to the nucleus during mitosis [81].

Sirtuins have been found to be involved in many human cellular processes, such as inflammation, metabolism, oxidative stress, and cell death [82–90]. Their implication in such a wide diversity of biochemical processes is reflected in their relationship with a plethora of human pathologies, such as cancer, and cardiovascular, respiratory, and neurodegenerative diseases, among others [91–98].

PARPs

PARPs are a family of proteins, 17 in humans, with widespread functions that are vital for cellular maintenance. These multidomain enzymes share the same catalytic domain between them, as well as presenting structural homology with other ADP-ribosyl transferases [99]. PARPs bind NAD^+ and cleave it into NAM, transferring its ADP-ribose group to other proteins (PARylation) or to themselves (auto-PARylation) [100].

PARP1 is the most important PARP protein in its family, comprising over 85% of the stimulated and basal PARP activity, leaving the contribution of other PARPs negligible [101]. PARPs' crucial function for cellular homeostasis relies on their capacity to detect DNA damage and bind to it via its DNA-binding domain. PARPs then transfer poly(ADP-ribose) groups to acceptor proteins and recruit other repair proteins, such as X-ray repair cross-complementing protein 1 (XRCC1) or Ku70, to the damaged DNA sites [102, 103]. In cases of extreme DNA damage, for example due to ischemic injury, PARP1 hyperactivation leads to NAD^+ and ATP depletion, resulting in cell death by necrosis or apoptosis [104–106]. PARPs also present alternative roles, as they are also involved in the regulation of the expression of various proteins implicated in inflammation, such as interleukin 1β (*IL-1β*), tumor necrosis factor α (*TNF-α*), and monocyte chemotactic protein 1 (*MCP-1*) [107, 108].

cADPR synthases

cADP-ribose synthases, also known as lymphocyte antigens CD38 and its homologue CD157, are cell surface ectoenzymes involved in NAD^+ metabolism [109–112]. These enzymes use NAD^+ as a substrate to generate cADPR, a cellular second messenger for calcium

signaling [113]. The main protein in this family, CD38, acts as a cADP-ribose hydrolase, catalyzing the hydrolysis of NAD^+ into cADPR and nicotinic acid adenine dinucleotide phosphate (NaADP) [114].

The stoichiometry of cADP-ribose synthases requires around 100 molecules of NAD^+ per cADPR generated [115], making these enzymes major regulators of NAD^+ levels [116]. This is one of the reasons why cADP-ribose synthase inhibitors, such as the CD38 inhibitor 78c, have been proposed as treatment for conditions which naturally cause NAD^+-level decrease [117, 118]. Treatment with CD38 inhibitors has demonstrated to decrease inflammation [119, 120], as cADPR stimulates calcium release into the cytoplasm which, along with the reactive oxygen species generated by the cADP-ribose synthase, triggers the formation of the NLRP3 inflammasome [121, 122].

NAD+ in the cardiorenal axis

NAD+ in the heart

NAD^+ plays an essential role in nutrient metabolism, as it acts as a shuttle for the transfer of electrons and protons in a wide array of enzymatic reactions, such as the one catalyzed by the glyceraldehyde-3-phosphate dehydrogenase during glycolysis, the isocitrate dehydrogenase, α-ketoglutarate dehydrogenase, and malate dehydrogenase in the TCA cycle, and acting as the first electron donor in the electron transport chain [123, 124]. Given that the heart is one of the most metabolically active organs, and cardiomyocytes are principally powered by aerobic metabolism, NAD^+ is crucial for heart function [125, 126]. Cardiovascular disease can cause the depletion of the cellular reserves of NAD^+, as it occurs in different conditions such as during acute stress generated by myocardial infarction [127]. When cardiomyocytes are faced with an ischemic injury, their mitochondrial function is impaired, leading to the inhibition of oxidative phosphorylation and mitochondrial ATP production, as well as causing a decline in NAD^+ levels [128]. This situation is not limited to myocardial infarction, as NAD^+ depletion can also be observed in dilated cardiomyopathy (DCM), transverse aortic constriction (TAC), and heart failure [129, 130]. Additionally, in both DCM and TAC preclinical and human models, a decrease in the expression of *NAMPT* has been observed, pointing towards deficient NAD^+ synthesis through the salvage pathway [130]. Deficient NAD^+ salvage is not the only mechanism by which NAD^+ biosynthesis is impaired in cardiac disease, as loss-of-function mutations in *KYNU* and *HAAO* genes, codifying for *de novo* pathway enzymes, have been found in patients with congenital cardiac malformations [131].

In addition to deficient NAD^+ synthesis, heart disease also features hyperactivation of NAD^+ consumers, especially the cADP-ribose synthase CD38, and the PARP protein family, which aggravates NAD^+ depletion [132–137].

Apart from its implication on heart disease, NAD^+ metabolism is also involved in cardioprotection, as the activity of the sirtuin protein family, which is largely dependent on NAD^+ intracellular levels, is beneficial in the context of cardiovascular diseases. In fact, sirtuin pharmacological activation has been shown to promote protective effects in several cardiovascular diseases, such as hypertension, fibrosis, hypertrophy, and arrhythmias [138–141]. In summary, NAD^+ deficiency, by its insufficient synthesis or excessive consumption, is strongly related to heart pathophysiology [142].

NAD+ in the kidneys

NAD^+ also plays an important part in kidney homeostasis [12]. The kidney is one of the organs with the highest level of cellular NAD^+, so cellular control of NAD^+ synthesis and consumption is crucial for renal bioenergetic and metabolic homeostasis. In addition, the mammalian renal cortex strongly depends on fatty acid oxidation to produce the ATP that is necessary for solute transport. Given that NAD^+ deficiency in AKI results in impaired fatty acid oxidation, its depletion reduces ATP production and impairs kidney function [15].

In AKI, NAD^+ depletion has been reported [143]. Accelerated NAD^+ consumption has been proposed as a reason for this reduction in cellular NAD^+ levels, as exacerbated PARP activity has been identified in several acute kidney pathologies [144, 145]. Additionally, defective *de novo* NAD^+ synthesis has also demonstrated to be a contributing factor in the decrease of renal NAD^+ levels, especially in the context of renal IRI, which causes a reduction in the expression of *de novo* NAD^+ biosynthetic enzymes and the accumulation of certain intermediates, such as quinolinate [146, 147]. In fact, QPRT, the enzyme that catalyzes the conversion of quinolinate into NaMN, has been found to be impaired in the context of human AKI, suggesting its implication in AKI-related NAD^+ depletion [148]. Loss-of-function mutations in the *HAAO* and *KYNU* genes have also been found in patients suffering from congenital renal defects, further supporting the hypothesis that defective *de novo* NAD^+ biosynthesis could be a main driver of NAD^+ depletion [131]. AKI has also been linked to decreased SIRT1 activity, impairing its protective effects in blood pressure, heart function, kidney fibrogenesis, cyst generation, and renal aging [141, 149–151].

In the context of CKD, nicotinamide N-methyltransferase (NNMT), an enzyme that is responsible for NAD^+ excretion as methyl pyridone, has been found to be frequently hyperactivated [152, 153]. This hyperactivation has been linked to increased apoptosis, inflammation,

fibrosis, oxidative stress, and autophagy dysfunction in other tissues [154–157]. Additionally, in a similar fashion to what occurs in AKI, *de novo* NAD^+ biosynthesis is altered in CKD, as lower baseline levels of tryptophan and higher levels of downstream metabolites, such as quinolinate, were associated with the development of CKD in several large cohorts, including the Framingham Heart Study [158], the Cooperative Health Research in the Augsburg Region Study [159], and the Atherosclerosis Risk in Communities Study [160]. Therefore, low NAD^+ levels, caused by reduced synthesis or increased consumption and excretion, are strongly related to kidney disease [12].

Therapeutic strategies targeting NAD+ metabolism to combat cardiorenal disease

As NAD^+ deficiency has proven to be a determining factor in cardiorenal diseases, NAD^+ repletion strategies, aimed at increasing intracellular NAD^+ levels, have risen as therapeutical options for the treatment of a number of cardiovascular and renal disorders. NAD^+ enhancing can be achieved by supplementation with NAD^+ precursors, inhibition of NAD^+ consumption, especially through PARP inhibition, but also through sirtuin activation and other alternative strategies.

NAD+ precursors

Nicotinic acid

Nicotinic acid (NA), a vitamer of vitamin B_3, is an essential nutrient for humans that needs to be incorporated from food sources such as meat, fish, grains, and vegetables [161]. The importance of maintaining proper NA levels has been clearly stablished, as its deficiency is known to cause pellagra, a disease characterized by diarrhea, sun-sensitive dermatitis, inflammation of the mouth and tongue, delirium, dementia and, if untreated, death [162].

Given that NAD^+ deficiency has been described in cardiorenal disease, NA administration can be used as a strategy to increase intracellular NAD^+ levels through the Preiss-Handler pathway [163]. NA has robustly demonstrated beneficial effects in experimental models of cardiovascular diseases (Table 1), especially those of vascular origin, such as atherosclerosis. NA has proven to slow down disease progression in mouse models lacking the low-density lipoprotein (LDL) receptor (LDL-R) by reducing atherosclerotic lesion size. Furthermore, NA has proved to mediate in the inflammatory nature of atherosclerosis by reducing the expression of the immune inflammation marker *Mcp-1* in cultured macrophages [164]. The effect of NA in oxidative stress and inflammation has also been studied in cultured human aortic endothelial cells. NAD^+ administration in this model inhibits vascular oxidative stress by reducing angiotensin II-induced ROS production, LDL oxidation and expression of the inflammatory biomarker *TNF-α* [165]. This effect has also been demonstrated in a rabbit model for acute vascular inflammation and endothelial dysfunction. In this case, NA reduces endothelial expression of the vascular cell adhesion molecule 1 (*Vcam-1*), intercellular adhesion molecule 1 (*Icam-1*) and *Mcp-1*. In vivo, NA also inhibits intima-media neutrophil recruitment and protects against TNF-α-induced vascular inflammation [166].

In the context of renal disease, NA has proven to enhance renal function in vivo, also presenting positive effects on cardiac function (Table 1). NA dietary supplementation in a nephrectomized rat model of CKD was effective in attenuating the expression of the inflammation and oxidative stress-related markers cyclooxygenase 1 (*Cox-1*), *Mcp-1*, plasminogen activator inhibitor type 1 (*Pai-1*), nuclear factor κB (*Nf-κB*), and transforming growth factor β (*Tgf-β*), as well as in ameliorating hypertension, with a reduction of both systolic (SBP) and diastolic blood pressures (DBP) [167]. The protective effect of NA in cardiorenal disease has been reinforced by other study that used the same nephrectomized rat model. NA administration through drinking water was able to improve lipid metabolism, and reduce hypertension (SBP and DBP) and proteinuria [168].

In IRI models, such as bilateral-occlusion induced injury, NA also presents renoprotective effects. In fact, NA administration via oral gavage (OG) produced a reduction in the expression of the cardiac disease marker troponin T (*TrT*), as well as improved renal function through reduction in sCr and BUN [169].

Given that NA can be considered as the first described antidyslipidemic drug, its effects in human cardiovascular health have already been thoroughly studied (Table 2). In this sense, NA supplementation shows beneficial effects in the lipid profile, generally reducing triglyceride content and increasing high-density lipoprotein (HDL) levels, but it fails to improve cardiovascular clinical outcomes [170–174]. On the other hand, other studies proved that NA supplementation reduces ischemia-related heart damage [175] and slows the progression of atherosclerosis [176–179]. In line with these results, The Coronary Drug Project demonstrated that, in patients with verified evidence of one or more myocardial infarctions, NA treatment significantly reduced the incidence of definite nonfatal myocardial infarction. In a 15-year follow-up of this project, a reduction of 6.2% in absolute mortality was seen in treated patients [180]. The latter effect was confirmed by the Stockholm Ischaemic Heart Disease Secondary Prevention Study, in which a reduction of 7.8% in absolute mortality was observed among NA-treated myocardial infarction patients [175].

Table 1 Preclinical evidence of the use of NAD^+ precursors in cardiovascular and renal disease

Precursor	Model	Dose & Administration	Outcomes	Ref
NA	Atherosclerosis *Ldlr*$^{-/-}$ and *Gpr109a*$^{-/-}$ C57BL/6 mice	0.3% NA in chow for 10 weeks	↓ Disease progression ↓ Atherosclerotic lesion size ↓ *Mcp-1* expression	[164]
	Human aortic endothelial cells	0.25–1 mM NA for 24 h	↓ ROS production, LDL oxidation and inflammation marker expression	[165]
	New Zealand white rabbit model of vascular inflammation and endothelial dysfunction by nonocclusive periarterial carotid collar	0.6%/1.2% NA in chow for 14 days	↓ Expression of *Vcam-1*, *Icam-1* and *Mcp-1* ↓ Neutrophil infiltration ↓ TNF-α-induced inflammation	[166]
	Nephrectomized Sprague-Dawley rat model of CKD	50 mg/kg/day in water for 12 weeks	↓ Expression of *Cox-1*, *Mcp-1*, *Pai-1*, *NF-κB* and *Tgf-β* ↓ SBP and DBP	[167]
	Nephrectomized Sprague-Dawley rat model of CKD	50 mg/kg/day in water for 12 weeks	Improved lipid metabolism ↓ Hypertension and proteinuria	[168]
	IRI Sprague-Dawley rat model by bilateral occlusion of renal pedicles	100 mg/kg/day by OG for 10 days	↓ Expression of troponin T ↓ SCr and BUN	[169]
NAM	ApoE-deficient C57BL/6 mice	0.25%/1% NAM in water for 4 days	↑ Plasma and aortic concentrations of IL-10 ↓ *Tnf- α* expression	[187]
	ApoE/Ldlr$^{-/-}$ C57BL/6 mice	100 mg/kg/day MeNAM in water for 8 weeks	↓ Macrophage infiltration	[188]
	DOX-induced cardiotoxicity in Sprague-Dawley rats	600 mg/kg/day NAM by OG for 28 days	↓ Expression of *Nf-κB* and *Il-6*	[189]
	C57BL/6 mouse model of cardiac arrest by i.v. administration of KCl	Single dose of 100 mg/kg NAM i.v.	↑ Survival ↓ Blood NAMPT levels	[190]
	C57BL/6 mouse model of hypertension induced by L-NAME	500 mg/kg/day NAM in water for 2 months	Improved kidney function ↓ Urinary albumin/creatinine ratio ↓ Renal inflammation	[193]
	Glycerol injection rhabdomyolysis-induced AKI C57BL/6 mouse model	400 mg/kg/day NAM i.p. for 4 days	↓ Kidney injury ↓ Inflammatory response	[194]
	C57BL/6 mouse model of renal fibrosis by UUO	200/400/800 mg/kg/day NAM i.p. for 14 days	↓ Tubule atrophy ↓ Apoptosis ↓ Renal inflammation	[195]
NR	DOX-induced cardiotoxicity in C57BL/6 mice	Single dose of 100/300/500 mg/kg NR i.p.	↓ Cardiac injury and myocardial dysfunction	[203]
	Genetic cardiomyopathy *Lmna*$^{H222P/H222P}$ mice	400 mg/kg NR in chow for 9 weeks	Improved cardiac function ↑ Survival	[204]
	HFpEF C57BL/6J mouse model induced by HFD and L-NAME	400 mg/kg/day NR in chow for 8 weeks	Improved cardiac function Reversal of the HFpEF phenotype	[206]
	TAC-induced cardiac hypertrophy C57BL/6J mice	400 mg/kg/day NR by OG for 8 weeks	↓ Expression of *Tnf-α* and *Il-1β* ↓ NLRP3 activation ↓ Oxidative stress ↑ SIRT3 activation	[208]
	SRF^{HKO} DCM mice	450 mg/kg/day NR in chow for 45 days	↓ Heart failure	[130]
	AKI induced by bilateral IRI in Wistar rats	500 mg/kg/day NR by OG for 2 weeks	↑ SIRT1 activity ↑ Autophagy No benefit in renal tubular damage and profibrotic gene expression	[143]
	Genetic diabetes 2 model of db/db C57BL/6 mice	500 mg/kg/day in chow for 20 weeks	↓ Albuminuria and *Kim-1* expression ↓ Inflammation ↑ Mitochondrial function	[209]

Table 1 (continued)

Precursor	Model	Dose & Administration	Outcomes	Ref
NMN	Heart failure *Ndufs4*-KO mice induced by TAC	500 mg/kg NMN once every 3 days i.p. for 33 days	↓ Development of heart failure	[219]
	Heart failure Klf4-deficient mice induced by TAC	Single dose of 500 mg/kg/day NMN i.p.	↓ Cardiac injury ↑ Mitochondrial fatty acid oxidation ↓ Cell death	[220]
	DOX-induced cardiotoxicity in C57BL/6 mice	180 mg/kg/day NMN i.p. for 10 (acute) or 65 (chronic) days	↑ Survival ↓ Bodyweight loss, cardiotoxicity, and loss of physical function	[221]
	DOX-induced cardiotoxicity in Sprague-Dawley rats	500 mg/kg NMN i.p. every 3 days for 12 weeks	↓ Cardiac dysfunction and injury ↓ NLRP3 inflammasome ↓ Oxidative stress	[222]
	Isoproterenol-induced cardiac fibrosis and hypertrophy C57BL/6 mice	500 mg/kg NMN i.p. for 12 days	↓ Cardiac dysfunction, fibrosis, and hypertrophy	[225]
	Wistar rat model of LADCA-IRI	100 mg/kg/day NMN every other day i.p. for 28 days	↑ Mitochondrial function ↓ Infarct size ↓ ROS levels ↑ Mitochondrial activity	[226]
	C57BL/6 mouse model of LADCA-IRI	Single dose of 500 mg/kg NMN i.p.	↓ Infarct area	[227]
	Friedreich's ataxia FXN-KO mouse model	500 mg/kg NMN i.p. twice weekly for 4–5 weeks	↑ Cardiac function ↑ SIRT3 activation	[228]
	Hypoxic HK-2 cells C57BL/6 mouse IRI model by clamp of the left renal pedicle	500 mg/kg NMN i.p. twice	↓ Tubular cell DNA damage ↓ Cellular senescence ↓ Inflammation ↓ Fibrosis	[229]
	Cisplatin-induced AKI mice	500 mg/kg NMN i.p. twice	↓ BUN and sCr	[230]
	Adriamycin-induced AKI C57BL/6 mice	500 mg/kg NMN i.p. for 14 days	↑ Body and renal weight ↓ SCr ↓ Albumin-creatinine ratio ↓ Histological changes	[231]
NMNH	C57BL/6 N mice IM-PTEC model for hypoxia-reoxygenation	250 mg/kg NMNH i.p. in the in vivo model and 500 μM NMNH in the in vitro model	↑ In vivo NAD^+ levels ↓ In vitro expression of *Kim-1* and *Tfam*	[21]
NRH	Cisplatin-induced AKI C57BL/6NTac mouse model	250 mg/kg NRH i.p. for 72 h	↑ NAD^+ levels ↓ BUN ↑ Urine urea ↓ Expression of fibronectin, *Bip*, *Bax* and *Tgf-β1*	[23]
Trigonelline	IM-PTECs	1 mM trigonelline	↑ NAD^+ levels in kidney cells	[235]

ApoE: apolipoprotein E; AKI: acute kidney injury; Bax: bcl-2-like protein 4; Bip: binding immunoglobulin protein; BUN: blood urea nitrogen; Cox-1: cyclooxygenase 1; CKD: chronic kidney disease; DBP: diastolic blood pressure; DCM: dilated cardiomyopathy; DOX: doxorubicin; HFD: high-fat diet; HFpEF: heat failure with preserved ejection fraction; Icam-1: intercellular adhesion molecule 1; IL-6: interleukin 6; IL-10: interleukin 10; IM-PTECs: immortalized proximal tubular epithelial cells; IRI: ischemia-reperfusion injury; i.p.: intraperitoneally; i.v.: intravenously; Kim-1: kidney injury molecule 1; LADCA-IRI: left anterior descending coronary artery IRI; LDL: low-density lipoprotein; Ldlr: low-density lipoprotein receptor; L-NAME: L-arginine methyl ester; Mcp-1: monocyte chemotactic protein 1; NAMPT: nicotinamide phosphoribosyltransferase; OG: oral gavage; Pai-1: plasminogen activator inhibitor type 1; ROS: reactive oxygen species; SBP: systolic blood pressure; SCr: serum creatinine; TAC: transverse aortic constriction; Tfam: mitochondrial transcription factor A; Tgf-β: transforming growth factor β; TNF-α: tumor necrosis factor α; UUO: unilateral urethral obstruction; Vcam-1: vascular cell adhesion molecule 1.

More recent studies have aimed to elucidate the effect of NA in cardiovascular health. One of these studies is the HDL-Atherosclerosis Treatment Study, which proved that NA administration in combination with simvastatin, a cholesterol-lowering agent, significantly reduces coronary stenosis when compared to placebo. In the same study, combined simvastatin-NA treatment also reduced the incidence of several clinical endpoints: death from coronary causes, nonfatal myocardial infarction, confirmed stroke or revascularization for worsening ischemia [181].

Although the effect of NA in human health and disease has been mainly studied in the context of cardiovascular disease, its impact on renal disorders has also been

Table 2 Completed clinical trials

Precursor	Conditions	Dose	Outcomes	Reference / Clinical Trial ID
NA	CAD	1000 mg/day NA orally for 12 months	↓ LDL-C ↑ HDL-C ↑ ApoA levels	[170]
	CAD	2 g/day NA orally for 24 weeks	↓ LDL-C, triglycerides, ApoB levels, and lipid/lipoprotein ratios ↑ ApoA levels and HDL-C ↓ High-sensitivity CRP levels	[171] NCT00271817
	CAD	1.5–3 g/day NA orally for 2.5 years	↓ Total cholesterol, LDL-C, triglycerides, and ApoB levels ↑ HDL-C	[172]
	Coronary heart disease, cerebrovascular or carotid disease, or peripheral arterial disease	1.5–2 g/day orally NA for 3 years	↑ HDL-C ↓ LDL-C and triglycerides	[173] NCT00120289
	Myocardial infarction, cerebrovascular disease, peripheral arterial disease, or diabetes mellitus with CAD	2 g/day NA orally for 3–6 weeks	↑ HDL-C ↓ LDL-C	[174] NCT00461630
	Myocardial infarction	3 g/day NA orally for 5 years	↓ Total cholesterol and triglycerides ↓ Total mortality and ischemic heart disease mortality	[175]
	Ischemic heart disease	500–750 mg/day NA orally for 3 years	↓ Total cholesterol ↑ HDL-C ↑ Number of stable plaques in the carotid area	[176]
	CAD	1000 mg/day NA orally for 1 year	↑ HDL-C ↓ Carotid intima-media thickness increase	[177]
	CAD or carotid/peripheral atherosclerosis	2 g/day NA orally for 1 year	↑ HDL-C ↓ LDL-C ↓ Carotid wall area	[178] NCT00232531
	CAD	Increasing doses from 250 mg to 4 g NA orally for 2.5 years	↓ LDL-C ↑ HDL-C ↑ Frequency of disease regression ↓ Incidence of cardiovascular events	[179]
	Myocardial infarction	3 g/day NA orally for 6 years	↓ All-cause mortality	[180]
	CAD	2 g/day NA orally for 3 years	↓ Proximal percent stenosis ↓ Incidence of death from coronary causes, confirmed myocardial infarction or stroke, or revascularization for worsening ischemic symptoms	[181]
	CKD	500 mg/day NA orally for 6 months	↑ HDL-C ↓ Triglycerides ↓ Phosphorous level ↑ eGFR	[182]
NAM	Autosomal dominant polycystic kidney disease	3 g/day NAM orally for 1 year	Safety and tolerability of NAM treatment	[197] NCT02140814 NCT02558595
	Hemodialysis	1500 mg/day NAM orally for 8 weeks	↓ Calcium-phosphorous product ↑ HDL-C	[198] NCT00316472
	Peritoneal dialysis	1500 mg/day NAM orally for 8 weeks	↓ Plasma phosphorous	[199] NCT00508885
NR	Heart failure	Up to 2 g/day NR orally for 12 weeks	Safety and tolerability of NR treatment ↑ Whole blood NAD^+ levels	[210] NCT03423342

ApoA: apolipoprotein A; ApoB: apolipoprotein B; CAD: coronary artery disease; CRP: C-reactive protein; eGFR: estimated glomerular filtration rate; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol.

slightly examined. The only clinical trial in which NA was used to treat a renal disease showed that NA treatment in CKD patients produced a reduction in phosphorous levels and an increase in the eGFR, accompanied by beneficial cardiovascular outcomes such as increased HDL and decreased triglyceride levels (Table 2) [182].

Alternatively to its potential as an NAD^+ enhancer, NA is able to activate the GPR109A G protein-coupled receptor, which is present in adipocytes and immune cells [183]. In mouse adipocytes, activation of this receptor reduces cAMP levels, decreasing the activity of hormone-sensitive lipase and reducing hydrolysis of triglycerides to free fatty acids [184]. Activation of the GPR109A receptor by NA has, therefore, antilipolytic effects, decreasing free fatty acid and triglyceride plasma levels [164, 185].

Even though the efficacy of NA as a NAD^+ boosting agent is unquestionable, it is necessary to remark that some of its beneficial effects in the cardiorenal axis, especially those related to its anti-dyslipidemic function, may be due to its ability to activate the GPR109A receptor.

Nicotinamide

Nicotinamide (NAM), also known as niacinamide, is the aminated form of the vitamin B_3 vitamer NA that can be incorporated into the NAD^+ pool through the salvage pathway [16]. In terms of side effects, NAM presents an advantage over NA, as due to its slightly different formula, NAM does not produce skin flushing, which is considered a main adverse effect of the administration of NA in doses that exceed nutritional needs [186].

In preclinical studies, NAM has demonstrated several beneficial effects on atherosclerosis-related cardiovascular inflammation (Table 1). In fact, NAM administration through drinking water in a model of atherosclerotic apolipoprotein E (ApoE)-deficient mice helped to increase plasma concentrations of the anti-inflammatory cytokine interleukin 10 (IL-10), an increase which was also present in the aorta, accompanied by a reduction in the abundance of inflammatory TNF-α [187]. These anti-inflammatory effects can also be triggered through administration of 1-methylnicotinamide (MeNAM), the methylated form of NAM, whose dietary administration has been shown to reduce macrophage infiltration in atherosclerotic *ApoE/Ldlr*$^{-/-}$ mice [188]. The anti-inflammatory effects of NAM have also been studied in experimental models of various cardiovascular diseases, such as the doxorubicin (DOX)-induced cardiotoxicity rat model, where NAM administration via OG reduced the expression of the inflammation markers *NF-κB* and interleukin 6 (*IL-6*) [189]. In addition, in a rodent model of cardiac arrest induced by potassium chloride, NAM significantly increased survival and reduced NAMPT concentration in blood [190], which may lead to decreased inflammation, as elevated blood NAMPT levels have been related with inflammatory disorders [191]. However, recent findings showed that NAMPT levels are related to the circadian regulation of locomotor activity and energy expenditure, reflecting that the reduction in NAMPT concentration in blood might derive from its circadian variations rather than from NAM treatment and inflammation [192].

The potential benefits of NAM administration have also been assessed in the context of renal health (Table 1). In a mouse model of L-arginine-methyl-ester (L-NAME)-induced hypertension, NAM improved kidney function, seen as a reduction of the urinary albumin/creatinine ratio, and suppressed renal inflammation by inhibiting TNF-α signaling [193]. In mouse models of glycerol rhabdomyolysis-induced AKI and renal interstitial fibrosis through unilateral urethral obstruction (UUO), NAM intraperitoneal (i.p.) administration alleviated kidney injury and limited the inflammatory response through the blockade of the TNF-α and IL-1β inflammatory pathways [194, 195].

The high similarity between NAM and NA could explain why NAM has not been a main subject of research in human cardiovascular health, with the only exception being an ongoing clinical trial in patients that underwent on-pump cardiac surgery (Table 3) [196]. In contrast, NAM supplementation has been more thoroughly studied in the context of human renal disease. One of the clinical trials confirmed NAM safety and tolerability in autosomal dominant polycystic kidney disease patients, but failed to detect any beneficial effect [197]. In contrast, other clinical trials conducted in dialysis patients found that NAM supplementation was effective in reducing serum phosphorus levels and increased HDL levels (Table 2) [198, 199]. The potential beneficial effects of NAM supplementation in renal health is currently being studied in other clinical trials, measuring vitamin A, NAM levels [200], and early graft function [201] in kidney transplant, and in-hospital mortality, need for new renal transplant, and persistent renal dysfunction in AKI patients (Table 3) [202].

Nicotinamide riboside

Nicotinamide Riboside is the ribosylated form of nicotinamide, which can be introduced into the NAD^+ biosynthesis pathways through its conversion to NMN by NRKs [19].

In the cardiovascular setting, NR has proven to exert protective effects in several preclinical models for human pathologies (Table 1). In a mouse model of DOX-induced cardiomyopathy, NR elevated NAD^+ levels, reduced cardiac injury and necrosis, as well as myocardial dysfunction. These effects were recapitulated in cultured cardiomyocytes, where NR reduced oxidative stress by reducing ROS formation via SIRT1 activation [203].

Table 3 Ongoing clinical trials

Precursor	Conditions	Dose	Primary outcomes	Phase	Reference / Clinical Trial ID
NAM	On-pump cardiac surgery	3 g/day NAM orally for 3 days	Change in troponin T levels	Phase 2	[196] NCT04750616
	Kidney transplant	1 g/day NAM orally for 6 months	Change in blood vitamin A and NAM levels	Phase 1	[200] NCT05702398
	Kidney transplant	1 g NAM orally in 3 doses	Efficacy on early graft function assessed by CRR2	Phase 1	[201] NCT05513807
	Septic shock-induced AKI	1 g/day NAM orally for 3 days	Reduction in in-hospital mortality, need for a new kidney transplant, or persistent kidney dysfunction	Phase 3	[202] NCT04589546
NR	Heart failure with preserved ejection fraction	900 mg/day NR orally for 6 weeks	Submaximal exercise endurance	Phase 2	[211] NCT04913805
	Stage-1 systolic hypertension	1 g/day NR orally for 3 months	Systolic blood pressure	Phase 2	[212] NCT03821623
	Cancer-related cardiac dysfunction	1 g/day NR orally for as long as the patient receives treatment	Prevention in left ventricular systolic function	Phase 2	[213] NCT05732051
	Heart failure	Escalating dose up to 2 g/day NR orally for 2 weeks	Comparison of whole blood NAD^+ levels	Phase 1	[214] NCT04528004
	Acute kidney injury	2 g/day NR orally for 8 weeks orally	eGFR levels	Phase 2	[215] NCT04342975
	Chronic kidney injury	1 g/day NR orally for 3 months	Carotid-femoral pulse wave velocity	Phase 2	[216] NCT04040959
NMN	Hypertension	800 mg/day NMN orally for 2 months	Flow mediated dilation Brachial-ankle pulse wave velocity	Phase 2	[232] NCT04903210
	Diabetic kidney disease	2 g/day NMN orally for 6 months	Change in urinary albumin to creatinine excretion ratio	Phase 2	[233] NCT05759468

AKI: acute kidney injury; eGFR: estimated glomerular filtration rate.

In another mouse model of genetic cardiomyopathy caused by laminin A/C mutation, NR rescued cardiac NAD^+ levels and improved survival and cardiac function, measured by echocardiography [204]. NR administration has also proven beneficial in heart failure with preserved ejection fraction (HFpEF), which accounts for approximately 50% of all heart failures [205]. NR dietary supplementation in a high-fat diet (HFD) and L-NAME-induced HFpEF murine model rescued NAD^+ levels, improved cardiac function and reversed the HFpEF phenotype [206]. Cardiac hypertrophy, a common feature to many cardiovascular diseases [207], may also be potentially treated with NR, as OG administration with this precursor in a murine model of myocardial TAC-induced hypertrophy triggered SIRT3 activation through the regulatory SIRT3/MnSOD axis. The activation of this axis by NR led to reduced IL-1β and TNF-α levels and inhibition of the NLRP3 inflammasome, as well as ameliorated oxidative stress through a reduction in malondialdehyde (MDA) levels, resulting in alleviated cardiac hypertrophy and dysfunction [208].

In the context of dilated cardiomyopathy (DCM), NR dietary supplementation attenuates the development of HF, by stabilizing myocardial NAD^+ levels in a mouse model of DCM induced by inactivation of the serum response factor (SRF^{HKO} model) [130].

NR supplementation has also been modestly studied in the context of renal disease (Table 1). In a rat model of AKI induced by bilateral IRI, NR pretreatment rescued NAD^+ levels, which enhanced SIRT1 activity and increased autophagy through increased expression of Microtubule-associated protein 1 A/1B-light chain 3 B (*LC3B*) and *p62*. However, NR OG administration failed to ameliorate renal tubular damage and expression of the profibrotic genes *Tgf-β1*, inhibin subunit beta-A and Periostin [143].

In kidney inflammation, NR dietary supplementation has also demonstrated protective abilities. Treatment with NR in a type-2 diabetes genetic mouse model prevented several manifestations of kidney dysfunction. In fact, NR reduced albuminuria and *Kim-1* expression, decreased expression of the inflammation genes *Il-6*, *Mcp-1* and *TNF-α*, and augmented mitochondrial biogenesis [209].

Although NR safety and tolerability has already been stablished, its efficacy as a therapeutic agent for cardiorenal diseases remains to be studied (Table 2) [210]. Current ongoing clinical trials aim to determine the effect of NR supplementation in several cardiovascular ailments, measuring exercise endurance in HFpEF patients [211], systolic blood pressure in hypertension patients [212], left ventricular ejection fraction in the context

of cancer-related cardiac dysfunction [213], and whole blood NAD^+ levels in heart failure patients (Table 3) [214]. The same applies to kidney disease, with clinical trials focused on NR supplementation in the context of AKI to determine eGFR levels [215], and in CKD patients in order to study carotid-femoral pulse wave velocity (Table 3) [216], but only one of them is already completed. The completed randomized crossover clinical trial conduced in CKD patients showed that NR supplementation, accompanied by Coenzyme Q10, improved markers of mitochondrial metabolism and lipid profiles (Table 2) [217].

Nicotinamide mononucleotide

Nicotinamide mononucleotide (NMN) is a nucleotide consisting of NAM, ribose, and a phosphate group. Structurally, NMN differs from NR in the presence of the phosphate radical and is only one adenine nucleotide away from NAD^+. Through the salvage pathway, NR is phosphorylated to NMN by the NRKs, which is then adenylated to NAD^+ via NMNATs [218].

NMN administration has shown protective effects in several animal models of cardiovascular diseases (Table 1). For instance, NMN was able to blunt the development of HF after TAC through the prevention of excessive mitochondrial protein acetylation in stress sensitive Nfusf4-KO [219] and Klf4-KO [220] mice. In another murine model of DOX-induced cardiotoxicity, NMN i.p. administration significantly increased NAD^+ levels, improving survival and protecting against bodyweight loss, cardiotoxicity and loss of physical function in an uphill treadmill exhaustion test [221]. In a similar model in rats, NMN alleviated cardiac dysfunction and injury, also blocking the activation of the NLRP3 inflammasome and reducing oxidative stress by reducing MDA levels [222].

In the context of cardiac fibrosis, NMN was able to alleviate cardiac dysfunction, fibrosis and hypertrophy in a mouse model of isoproterenol-induced cardiac disease. NMN administration increased the NAD^+/NADH ratio, as well as *Sirt1* expression, ameliorating oxidative stress. This cardioprotective effect may be dependent on Smad3 deacetylation, as the TGF-ß/Smad signaling pathway plays a causal role in cardiac fibrosis through Smad3 phosphorylation or acetylation, leading to the regulation of the expression of profibrotic genes under TGF-ß control [223, 224]. NMN treatment was able to reduce acetylated Smad3 levels in both isoproterenol-treated mice, as well as in a TGF-ß-induced in vitro model of cardiac fibrosis. Altogether, these results suggest that signaling via NAD^+/SIRT1/Smad3 deacetylation may be responsible for the anti-fibrotic effects of NMN [225].

NMN pretreatment in a rat model of IRI, in this case caused by occlusion of the left anterior descending coronary artery (LADCA), proved to improve myocardial function and decrease infarct size, also decreasing ROS levels and improving mitochondrial activity [226], while another murine model for LADCA-ligation IRI (LADCA-IRI) showed that NMN pretreatment protected the heart from IRI in both ischemia and reperfusion phases, by reducing infarct area [227]. Finally, in a mouse model of Friedreich's ataxia, a rare neurodegenerative disease frequently accompanied by cardiomyopathy, NMN administration was able to restore cardiac function to near-normal levels through SIRT3 activation [228].

In contrast to cardiovascular diseases, the impact of NMN administration in renal health has received much limited attention, with just a few preclinical studies available in the literature (Table 1). In an in vitro hypoxia-reperfusion AKI model in Human Kidney-2 (HK-2) cells, NMN supplementation significantly reduced tubular cell DNA damage and cellular senescence. These results were also confirmed in an IRI mouse model. In this model, generated by clamping of the left renal pedicle, NMN showed anti-inflammatory effects by reducing the expression of senescence and inflammation-associated *Il-6* and *Il-8* [229].

The beneficial effects of NMN administration in chemotherapy-mediated nephrotoxicity has also been studied. In a cisplatin-induced AKI mouse model, NMN i.p. administration proved to reduce sCr and BUN levels, and showed protection from AKI in a SIRT1-dependent manner [230]. These results were corroborated in a subsequent study using an adriamycin-induced AKI murine model. Mice supplemented with NMN maintained body and kidney weight, and showed reduced sCr levels, and urinary albumin-to-creatinine ratio [231].

Although promising, the beneficial effects of NMN administration to fight cardiorenal disease are based on preclinical evidence. At the moment, only two clinical trials are being carried out in the context of cardiorenal disease, one focused on hypertensive patients [232] and another in diabetic kidney disease patients (Table 3) [233].

Next-generation NAD+ precursors

In addition to the classical NAD^+ precursors (NA, NAM, NR, and NMN), in recent years we and others have described a new generation of NAD^+ enhancers with potential applications in cardiorenal disease. Although research with these next-generation NAD^+ precursors is still in its infancy, their administration has already shown promising results (Table 1). One of these enhancers is the reduced form of NMN (NMNH), which has been proposed as a novel NAD^+ precursor, as it has been postulated that, in cells, NMNH is converted into NADH via the same NMNATs that convert NMN into NAD^+ [234]. We previously described that NMNH is able to increase

NAD^+ levels in a number of mouse tissues, including the heart and kidneys, to a higher extent than its oxidized counterpart (Table 1). Not only NMNH increased NAD^+ content, but also protected conditionally immortalized proximal tubular epithelial cells (IM-PTECs) against hypoxia/reoxygenation injury, which was confirmed by a decrease in the expression of the kidney injury biomarker *Kim-1*, and the mitochondrial function biomarker *Tfam* (mitochondrial transcription factor A) [21].

Dihydronicotinamide riboside (NRH) is the reduced form of nicotinamide riboside. NRH has been described to increase cellular NADH levels through its conversion to NMNH by the enzyme adenosine kinase, which is subsequently converted into NADH via NMNATs. In a pioneering study, NRH i.p. administration was shown to increase NAD^+ levels in murine renal cells, as well as to protect the kidneys in cisplatin-induced AKI mice, which was confirmed by a decrease in BUN and an increase in urine urea. NRH administration by i.p. injection was also able to reduce the expression of fibronectin, binding immunoglobulin protein (*Bip*), bcl-2-like protein 4 (*Bax*), and *Tgf-β1*, which are markers of glomerular dysfunction, endoplasmic reticulum stress, apoptosis, and fibrosis, respectively (Table 1) [23].

The newest NAD^+ precursor to be described is trigonelline, a methylated form of NA. In a recently published study, trigonelline has been described, for the first time, as a cellular NAD^+ enhancer. In fact, trigonelline can be incorporated into the NAD^+ pool through the Preiss-Handler pathway, due to its resemblance to NA, being able to increase NAD^+ content in vitro in muscle (C2C12 myoblasts), liver (HepG2 cells), and kidney (IM-PTECs) cells (Table 1) [235]. However, the effect of trigonelline on renal health, and whether it can raise NAD^+ levels in heart tissues, remains to be discovered.

PARP inhibitors

Poly(ADP-ribose) polymerases (PARPs) are major NAD^+ consumers, with PARP1 accounting for the largest amount of PARP activity in cells and being the greatest NAD^+ consumer in the nucleus [236, 237]. In fact, acute activation of PARP1 can lead to the depletion of 50–80% of total cellular NAD^+ [238]. Therefore, their inhibition accounts for a method of boosting the cellular NAD^+ levels, which could ameliorate the NAD^+ depletion that several pathophysiological conditions present with [99, 221]. Given that cardiorenal diseases usually present with both NAD^+ depletion and PARP hyperactivation, PARP inhibitors (PARPi) have arisen as promising therapeutic agents [128, 131, 135–137, 142, 144, 145, 218, 239].

Many of the PARPi that have already been commercialized are used as synthetic lethality agents for the treatment of cancer, specifically breast and ovarian cancer [240, 241]. Examples of commercial anti-cancer PARPi are Olaparib, Niraparib and Rucaparib [242–244]. However, other compounds, such as INO-1001, have been proposed as PARP inhibitors that could be of use in other pathologies [245]. In the cardiovascular setting, INO-1001 intravenous (i.v.) administration in a porcine model of LADCA-IRI led to improved functional recovery, based on several cardiac health parameters, such as increased stroke volume, cardiac index, and mixed venous oxygen saturation (Table 4) [246]. This cardioprotective effect has also been confirmed in murine models, in which INO-1001, administered subcutaneously, helped to reduce mortality and improved cardiac function in a mouse model of DOX-induced heart failure and a LADCA-ligated rat heart failure model [247]. INO-1001 subcutaneous administration has also proven effective in attenuating oxidative stress (reduced MDA levels), inflammation (reduced expression of *Tnf-α*) and fibrosis in the context of diabetic disease [137]. INO-1001 subcutaneous administration in animal models of cardiovascular disease proved to inhibit PARP activity, especially PARP1, also increasing *Sirt1* expression in cardiac tissue, which demonstrates that these outcomes in the cardiovascular setting are a direct effect of PARP inhibition [137, 246].

Another example of the application of PARPi for cardiovascular diseases is 3-aminobenzamide (3-AB) [248]. 3-AB i.v. administration has proven to reduce infarct size after ischemic insult, not only in perfused isolated mouse hearts [249], but also in LADCA-IRI rats [250], and rabbits [251]. The cardioprotective role of 3-AB was also patent in other cardiovascular health parameters, such as left ventricular end-systolic diameter, left ventricular end-diastolic diameter, end-diastolic volume, and left-ventricular ejection fraction in a myocardial infarction rat model [252].

Although an ischemic insult would also be deleterious for the kidneys, the effect of 3-AB on renal health has been timidly assessed (Table 4). 3-AB i.p. administration in rats after renal IRI, achieved by bilateral renal artery clamp, reduced IRI-induced increase in sCr, BUN, and aspartate aminotransferase (AST), as well as decreased the levels of oxidative stress markers, such as MDA and protein carbonyl content, and ameliorated histological alterations, reducing tubular dilation and medullar hemorrhage [253]. In addition, subcutaneous administration of the PARPi 4-hydroxy-quinazoline (4-HQ) in a rat model of kidney transplant rejection was able to reduce oxidative stress (reduction in nitrotyrosine levels) and to suppress the apoptotic response (inhibiting proapoptotic *Bax* and inducing antiapoptotic *Bcl2* expression), attenuating organ rejection [254]. In another study, Olaparib i.p. administration in a mouse model of lipopolysaccharide-induced AKI proved to

Table 4 Preclinical and clinical evidence of the use of PARPi in cardiovascular and renal diseases

Model/Condition	Dose & Administration	Outcomes/Expected outcomes	Ref / Clinical Trial ID
LADCA-IRI Landrace pigs	1 mg/kg INO-1001 i.v. infusion over 20 min (1 ml/min)	↑ Functional recovery during reperfusion	[246]
LADCA ligation-induced heart failure in Wistar rats DOX-induced heart failure in BALB/c mice	3 mg/kg INO-1001 subcutaneously via osmotic pump	↓ Mortality ↑ Cardiac function	[247]
Type 2 diabetes db/db C57BLKS/J mice	5 mg/kg/day INO-1001 subcutaneously via osmotic pump	↓ Inflammation and oxidative stress ↓ Hypertension ↑ *Sirt1* expression	[137]
Isolated SV129 mice heart perfusion	10 mg/kg 3-AB i.v. twice	↓ Infarct size	[249]
LADCA-IRI Wistar rats	10 mg/kg 3-AB i.v. twice	↑ Myocardial infarct size ↓ Plasma creatine phosphokinase activity and myeloperoxidase activity Preservation of myocardial ATP levels	[250]
IRI-LADCA New Zealand white rabbits	10 mg/kg 3-AB intra-arterially twice	↓ Infarct size ↓ Myocardial dysfunction	[251]
LADCA ligation myocardial infarction Wistar rats	30 mg/kg/day 3-AB i.p. for 15 days	Restoration of cardiovascular health parameters ↓ Myocardial injury ↓ Infarct size, increase in left-ventricular mass, and pathological score	[252]
Bilateral renal artery clamp-IRI Sprague-Dawley rats	10 mg/kg 3-AB i.p. twice	↓ SCr, BUN, and AST ↓ Oxidative stress and restoration of antioxidant enzymes levels ↓ Histological alterations	[253]
Renal transplantation model using inbred Fischer rats	40 mg/kg/day 4-HQ subcutaneously for 10 days	↓ Rejection processes ↓ Pro-apoptotic proteins ↑ Anti-apoptotic proteins ↓ Oxidative stress	[254]
Lipopolysaccharide-induced AKI LADCA mice	Single dose of 5 mg/kg Olaparib i.p.	↓ Serum urea, sCr and uric acid Restoration of kidney redox balance	[255]
ST-elevation myocardial infarction	Single dose of 200/400/800 mg INO-1001 i.v.	Non-significant reduction of CRP and IL-6 levels	[256] NCT00271765

3-AB: 3-aminobenzamide; 4-HQ: 4-hydroxy-quinazoline; AST: aspartate aminotransferase; BUN: blood urea nitrogen; CRP: C-reactive protein; DOX: doxorubicin; IL-6: interleukin 6; i.p.: intraperitoneally; i.v.: intravenously; LADCA-IRI: left anterior descending coronary artery ischemia-reperfusion injury; sCr: serum creatinine.

mediate against secondary kidney injury by restoring serum levels of urea, creatinine and uric acid, and downregulating the expression of inflammation markers, such as *Tnf-α* and *Il-1β* [255].

Although the results in preclinical models of cardiorenal disease are promising, only one PARPi, INO-1001, has made it to the clinic in this context. INO-1001 administration in patients with ST-elevation myocardial infarction has demonstrated effective in decreasing inflammation, as confirmed by a reduction of serial CRP and IL-6 levels, although it did not to reach statistical significance [256]. Apart from this study, no other completed or ongoing clinical trials in non-cancer patients exist for PARPi, highlighting the need for clinical research to consolidate the cardio- and renoprotective effects that PARPi have demonstrated in preclinical models.

Sirtuin activators

The sirtuin protein family is involved in a plethora of major cellular processes, including inflammation, oxidative stress, apoptosis, autophagy, metabolism, and cell proliferation [61]. Sirtuin loss of function has been linked to a number of pathologies, including cardiac, such as cardiac hypertrophy and fibrosis developed by loss of SIRT3 function, and renal disorders, as IRI and diabetic kidney disease, which are aggravated by SIRT1 loss of function [257, 258]. At the same time, sirtuin activation has been shown to play protective roles [55] in cardiorenal disorders, such as hypertension [259], atherosclerosis [260], CAD [261], myocardial IRI [262], heart failure [263], cardiac fibrosis [264], kidney fibrosis [265], and AKI [230]. This has spiked the interest in new small-molecule modulators able to increase sirtuin activity [266].

The phenolic antioxidant 3,4′,5-trihydroxystilbene, also known as resveratrol, was the first sirtuin activator to be described. Resveratrol is a natural substance found in grapes, wine, peanuts, soy or berries [267], and acts both as a ROS scavenger [268] and a SIRT1 activator

[88, 269]. Resveratrol is, with no doubt, the most studied sirtuin activator, also in the cardiorenal context.

In a mouse model for LADCA-IRI, resveratrol administration by OG improved cardiac function, increased survival rate, decreased infarct and risk areas, and inhibited NLRP3 inflammasome and apoptosis (Table 5) [270]. Another rodent IRI model, in this case of isolated heart ischemia in Zucker obese rats, showed that resveratrol OG administration improved coronary flow (CF), aortic flow (AF), and left ventricular developed pressure (LVDP), and reduced the incidence of ventricular fibrillation and infarct size [271]. To determine whether the beneficial effects of resveratrol administration are mediated by SIRT1 activation, *Sirt1-KO* DOX-induced cardiomyopathy mice were used. Resveratrol i.p. administration in this model increased *Sirt1* expression, which was linked to a reduction in the inflammatory response via decreased expression of *Tnf-α* and *Il-1*β, and ameliorated oxidative stress by decreasing 4-hydroxynonenal (4-HNE) and 3-nitrotyrosine levels, therefore blocking cardiomyocyte apoptosis [272]. Finally, in a cardiorenal rat model of hypertension induced by nephrectomy in rats, resveratrol OG administration reduced SBP, as well as endothelin-1 (ET-1) and angiotensin II levels, reflecting a protective effect against hypertension [273].

As SIRT1 activation has also been linked to renoprotection [86], resveratrol has been studied as a potential therapeutic agent in the context of kidney disease (Table 5). In a rat model of partial nephrectomy-induced CKD, resveratrol OG administration improved kidney function via BUN and sCr level reduction, ameliorated renal fibrosis, confirmed by collagen-1 and fibronectin reduced expression, and reduced cardiac hypertrophy by decreasing left ventricular (LV) mass and left ventricular end-diastolic diameter (LVEDD) [274]. In another study, sepsis-induced AKI mice administered i.p. with resveratrol showed ameliorated histological alterations, such as reduced histological edema, inflammation, and glomerular enlarging; lowered sCr, BUN, NGAL and KIM-1 levels, and decreased levels of the inflammation markers TNF-α and Il-1β. These physiological and molecular effects were reflected in an overall increase in survival [275].

Piceatannol, another natural phenol present in grapes, passion fruit seed, and blueberries, known to activate SIRT1 [276, 277] has proven to prolong allograft survival, and to reduce histologic damage and mononuclear cell infiltration in a rat model for kidney transplant [278]. This compound is demonstrating a promising therapeutic potential for renal diseases, as it has also proven to attenuate fibrosis, by reducing the expression of the fibrosis-related markers collagen I, fibronectin, α-smooth muscle actin (*α-Sma*) and connective tissue growth factor (*Ctgf*), in a UUO-induced kidney fibrosis murine model [279].

Other phenolic compounds, such as genistein, a natural flavonoid present in legumes, such as fava beans and soybeans [280], have also demonstrated protective effects in the kidney, seen as a reduction in sCr and BUN levels, and reduced apoptosis, in a mouse model of IRI. This effect proved to be mediated by SIRT1 activation, as genistein increased *Sirt1* expression in renal cells and its beneficial effects were abolished when SIRT1 was inhibited by sirtinol, a potent sirtuin inhibitor [281].

Although SIRT1 has attracted most of the attention, the cardioprotective and renoprotective roles of SIRT3 have also been studied. In the cardiac context, administration of spinacetin, a flavonoid glycoside, was able to activate the SIRT3/AMPK/mTOR pathway in a doxorubicin-induced cardiotoxicity rat model. Activation of this axis resulted in increased cardiomyocyte survival, reduced expression of myocardial damage biomarkers (e.g. *lactate dehydrogenase*, *TrT*), inhibited apoptosis and induced autophagy [282]. Similarly, administration of 2-APQC, a synthetic small-molecule activator of SIRT3, attenuated cardiac hypertrophy and prevented the development of interstitial fibrosis in a isoproterenol-induced heart disease rat model [283].

Regarding the relationship between SIRT3 and renal health, reduced levels of SIRT3 have been associated with oxidative stress and mitochondrial damage in cisplatin-induced AKI mice. In this model, administration of either AICAR (5-aminoimidazole-4-carboxamide-1-β-d-ribofuranoside) or ALCAR (acetyl-L-carnitine), restored *Sirt* expression, improving kidney function, as determined via reduced BUN and sCR [284]. In another study, this time using a IRI rat model, AICAR administration also reduced sCR and serum urea levels, attenuating IRI-induced nitrosative stress and monocyte/macrophage infiltration, ameliorating in this way the development of acute tubular necrosis [285].

Evidence of the application of sirtuin activators for cardiorenal disease is essentially preclinical, with just a few ongoing or completed clinical trials. In patients with high risk of cardiovascular disease, resveratrol, in combination with grape extract, reduced the levels of the inflammation markers CRP, TNF-α, and PAI-1, and increased anti-inflammatory IL-10, adiponectin, and soluble intercellular adhesion molecule 1 (sICAM-1) [286]. The same clinical trial also revealed that the combination of resveratrol and grape extract was effective in improving the lipid profile, reducing LDL-C and ApoB levels, as well as decreasing LDL-C oxidation [287]. To this date, further clinical trials to support the beneficial effect of resveratrol supplementation on cardiovascular health are being held, one studying its effects on endothelial function in CAD and diabetes mellitus patients [288], other focused on cardiovascular recovery in overweight and obese individuals [289], another aiming to

Table 5 Preclinical and clinical evidence of the use of sirtuin activators in cardiovascular and renal diseases

Model/Condition	Dose & Administration	Outcomes/Expected outcomes	Ref / Clinical Trial ID
LADCA-IRI C57BL/6 mice	320 mg/kg/day resveratrol by OG for up to 14 days	↑ Cardiac function and survival ↓ Infarct and risk area ↓ NLRP3 inflammasome and apoptosis	[270]
Isolated-IRI Zucker rats	5 mg/kg/day resveratrol by OG for 3 weeks	↑ CF, AF, and LVDP ↓ Ventricular fibrillation and infarct size	[271]
Sirt1-KO DOX-induced cardiomyopathy C57BL/6 mice	10 mg/kg/day resveratrol i.p. for 5 weeks	↑ *Sirt1* expression ↓ *Tnf-α* and *Il-1β* expression ↓ 4-HNE and 3-nitrotyrosine levels ↓ Apoptosis	[272]
Nephrectomy-induced hypertension Sprague Dawley rats	10/50 mg/kg/day resveratrol by OG for 4 weeks	↓ SBP, ET-1, and angiotensin II	[273]
Partial nephrectomy CKD Sprague-Dawley rats	20 mg/kg/day resveratrol by OG for 12 weeks	↓ BUN and sCr levels ↓ Collagen-1 and fibronectin expression ↓ Cardiac hypertrophy	[274]
Sepsis-induced AKI Sprague-Dawley rats	Single dose of 3/10 mg/kg resveratrol i.p.	↓ sCr, BUN, NGAL, KIM-1 levels ↓ TNF-α and IL-1β levels ↑ Survival	[275]
ACI-to-Lewis rat kidney transplant model	30 mg/kg/day piceatannol i.v. for 60 days	↑ Allograft survival ↓ Histological damage ↓ Mononuclear cell infiltration	[278]
UUO-induced renal fibrosis C57BL/6 mice	50 mg/kg/day piceatannol i.p. for 2 weeks	↓ Expression of collagen I, fibronectin, *α-Sma* and *Ctgf*	[279]
BALB/c mouse model of IRI induced by clamping of the renal pedicles	Single dose of 5/10 mg/kg genistein i.v.	↓ sCr and BUN levels ↓ Apoptosis	[281]
Doxorubicin-induced heart disease in Sprague Dawley rats	50/100 mg/kg/day spinacetin for 14 days intragastrically	↓ Cardiomyocyte toxicity ↓ Apoptosis ↑ Autophagy	[282]
Isoproterenol-induced cardiac fibrosis in SD rats	10/20/30 mg/kg/day 2-APQC for 4 weeks intragastrically	↓ Myocardial hypertrophy ↓ Myocardial fibrosis	[283]
Cisplatin-induced AKI C57BL/6J mice	500 mg/kg/day AICAR i.p. for 3 days	↓ sCr and BUN levels ↓ Hyaline casts, tubular cell degeneration and necrosis	[284]
Sprague Dawley rat model of IRI by clamping of the renal pedicles	Single dose of 500 mg/kg AICAR i.v.	↓ sCR and serum urea levels ↓ IRI-induced nitrosative stress ↓ Monocyte/macrophage infiltration ↓ ATN development	[285]
High-risk CVD patients	8/16 mg/day resveratrol orally for 12 months	↓ CRP, TNF-α, PAI-1, IL-10, adiponectin, sICAM-1 levels ↓ LDL-C, ApoB, LDL-C oxidation	[286] [287] NCT01449110
Diabetes and metabolic diseases	2 g/day resveratrol orally for 6 weeks	Change in serum levels of NO Change in heart levels of NOS	[288] NCT03762096
Overweight patients	500 mg/day resveratrol orally for 7 days	Improved autonomic and cardiovascular recovery Improved complete blood count, blood glucose, triglycerides, and total cholesterol	[289] NCT06020313
CAD	1 g/day resveratrol orally for 90 days	Change in SIRT1 and SIRT3 levels and expression Change in *Bcl-2*, *Xiap*, *c-Iap-1*, and survivin expression Change in soluble receptor for advanced glycation end-products levels and expression	[290] NCT05808387
CKD	400 mg/day resveratrol orally for 6 weeks	Change in vascular endothelial function	[291] NCT03597568

4-HNE: 4-hydroxynonenal; α-Sma: α-smooth muscle actin; AF: aortic flow; AKI: acute kidney injury; ApoB: apolipoprotein B; ATN: acute tubular necrosis; Bcl-2: B-cell lymphoma 2; BUN: blood urea nitrogen; CAD: coronary artery disease; CF: coronary flow; CKD: chronic kidney disease; Ctgf: connective tissue growth factor: c-Iap-1: cellular inhibitor of apoptosis 1; ET-1: endothelin 1; Il-1β: interleukin 1 β; IL-10: interleukin 10; i.v.: intravenously; KIM-1: kidney injury molecule 1; LADCA-IRI: left anterior descending coronary artery ischemia-reperfusion injury; LDL-C: low-density lipoprotein cholesterol; LVDP: left ventricular developed pressure; NGAL: neutrophil gelatinase-associated lipocalin; NO: nitric oxide; NOS: nitric oxide synthase; PAI-1: plasminogen activator inhibitor type 1; OG: oral gavage; SBP: systolic blood pressure; sCr: serum creatinine; sICAM-1: soluble intercellular adhesion molecule 1; Tnf-α: tumor necrosis factor α; UUO: unilateral urethral obstruction; Xiap: X-linked inhibitor of apoptosis protein.

determine the effect of resveratrol on *SIRT1* and *SIRT3* expression, inhibition of apoptosis proteins, and inflammation [290], and one of them focused on the effect of resveratrol on the activity of SIRT1 and SIRT3, and inflammation [290]. In contrast, resveratrol administration in the context of renal health is not common, with only one clinical trial being conducted to study whether resveratrol can improve vascular endothelial function in CKD patients [291].

Alternative strategies

The potential of NAD^+ metabolism modulation as a therapeutic avenue for cardiorenal disease has mainly focused on the administration of NAD^+ precursors, the blockade of its major consumers, the PARPs, and the activation of sirtuins. The promising results obtained have sparked the interest in alternative strategies with therapeutic potential.

One of these strategies focuses on CD38, a member of the NAD^+-dependent cADP-ribose synthases. Blocking CD38 activity potentially increases NAD^+ levels, triggering protective effects in cardiorenal disease [57]. In the cardiovascular setting, 78c, a known inhibitor of CD38 [292], has demonstrated cardiac protection in an isolated heart perfusion mouse model, increasing the recovery of the contractile function, the nitric oxide synthase (NOS)-dependent CF, the content of the NOS cofactor tetrahydrobiopterin, and reducing infarct size (Table 6) [293]. Other CD38 inhibitors, such as luteolinidin, the most potent flavonoid CD38 inhibitor, and MK-0159, a synthetic CD38 inhibitor, have also proven to protect the heart during IRI in preclinical models, increasing NOS-dependent CF, and reducing infarct size [294, 295].

Another alternative strategy to raise NAD^+ content involves NAMPT. Given that NAMPT is considered one of the rate-limiting enzymes in the salvage pathway [296], NAMPT activators could be used to enhance cellular NAD^+ levels [297]. In a mouse model of LADCA-IRI, a ferroptosis-associated circular RNA (FEACR) which was found to be expressed in cardiomyocytes during IRI-induced ferroptosis, has proven to interact with NAMPT and enhance its stability, protecting cardiomyocytes from IRI-induced ferroptosis in the process [298]. Another NAMPT activator, 1-(3,6-Dibromo-carbazol-9-yl)-3-phenylamino-propan-2-ol (P7C3), has shown beneficial effects in a genetic mouse model of diabetes, reducing blood glucose levels, and improving cardiac electric (QTc interval, JT interval, ST elevation) and function (ejection fraction, fractional shortening) parameters [299].

Finally, combined interventions that target NAD^+ metabolism at different levels are also being tested. In this context, the combination of sirtuin activators and NAD^+ precursors to treat cardiorenal disease has already been studied. In fact, NR administration in combination with pterostilbene, a resveratrol analog, has proven to activate SIRT1 in AKI patients. This clinical trial was designed to uniquely confirm the safety and tolerability of the treatment, also proving

Table 6 Preclinical and clinical evidence of the use of alternative NAD^+ enhancers in cardiovascular and renal diseases

Model/Condition	Dose & Administration	Outcomes/Expected outcomes	Ref / Clinical Trial ID
Isolated heart perfusion C57BL/6 mice	1–40 nM 78c administered by a Harvard pump	↑ Contractile function and NOS-dependent CF ↓ Infarct size	[293]
Isolated heart perfusion Sprague-Dawley rats	5/15/25/50 µM luteolinidin by osmotic pump	↑ NOS-dependent CF ↑ NOS activity ↑ LVDP, rate-pressure product, left ventricular end diastolic pressure and CF ↓ Infarct size	[294]
LADCA-IRI C75BL76 mice	Single dose of 30 mg/kg MK-0159 by OG	↓ Infarct size	[295]
LADCA-IRI C75BL76 mouse model	FEACR administered by adenovirus vector	↓ Ferroptosis	[298]
Genetic diabetes 2 model of db/db C57BL/6 mice	10 mg/kg P7C3 i.p. for 4 weeks	↓ Blood glucose levels ↓ QTc interval, JT interval, and ST elevation ↑ Ejection fraction, fractional shortening, body weight, LV wall mass ↓ Infarct size	[299]
AKI	2000 mg/day NR and 400 mg/day pterostilbene orally for 2 days	Safety and tolerability ↑ NAD^+ levels	[300] NCT03176628
AKI	2000 mg/day NR and 400 mg/day pterostilbene orally for 8 weeks	Change in eGFR levels Incidence of myocardial infarction	[215] NCT04342975

NOS: nitric oxide synthase; CF: coronary flow; LVDP: left ventricular developed pressure; LADCA-IRI: left anterior descending ischemia reperfusion injury; i.p.: intraperitoneally; LV: left ventricle; AKI: acute kidney injury; eGFR: estimated glomerular filtration rate.

that it increased whole blood NAD^+ levels [300]. The promising results obtained have led to another clinical trial (currently ongoing), in which AKI patients are being treated with this combination in hopes to experience a benefit in their renal (improvement of their AKI through eGFR increase) and cardiac (decrease in the frequency of myocardial infarction) health [215].

Potential side effects of NAD+ enhancement

NAD^+ enhancement offers a promising therapeutic approach for treating cardiorenal diseases, which is reflected in the growing number of studies in which this strategy is used. However, tweaking NAD^+ cellular balance might not come without risks. In this section, we discuss on the potential side effects that targeting NAD^+ metabolism may have.

NAD+ precursors

NAD^+ precursors are generally considered to be safe, as they are present in many food sources in small quantities, such as eggs (NA), meat (NAM), edamame (NMN) or milk (NR) [301, 302]. However, supranutritional dietary intake of NAD^+ precursors may lead to undesirable effects.

The recommended dietary allowance for NA is established at 16–18 mg, according to the National Institutes of Health [303], but consumption of more than 30 mg of NA has been described to cause cutaneous vasodilation that can lead to skin flushing, resulting in sensations of burning, tingling, and itching via activation of the GPR109A receptor [304]. Although administration of NAM can overcome this undesired reaction, as it does not trigger GPR109A activation, NAM accumulation might lead to other undesired effects, such as end-product inhibition of NAD^+-consuming enzymes, including sirtuins, at least in vitro [305]. Moreover [306], increased NAM dietary intake has been reported to induce methyl donor depletion in rats, as NAM can be irreversibly methylated into MeNAM by NMNT [307]. Such depletion of methyl donors has been linked to inhibited growth of rodent pups and increased liver steatosis in adult rodents [308].

The mononucleotide and riboside forms of NAM (NMN and NR) are also generally considered as safe and, as NAM, lack the effects derived from GPR109A activation. Despite their good safety profile, potential side effects resulting from their long-term administration cannot be neglected. In fact, NMN is known to allosterically activate SARM1, an NADase involved in axonal degeneration [309]. Activation of SARM1 by NMN accumulation leads to a sharp increase in NAD^+ consumption, which ultimately elicits axonal degeneration in vitro [310, 311] and in vivo [312].

NR, on the contrary, does not trigger SARM1 activation, and has shown to cause few and mild side effects in healthy adults, such as nausea and leg cramps [313, 314]. However, the reduced stability of NR in blood must be considered [314, 315], as its degradation in plasma leads to the formation of NAM, potentially leading to its accumulation and derived side effects [310]. Moreover, NR administration unavoidably results in NMN accumulation during its path to NAD^+ synthesis via the salvage pathways [316] which might, in the long term, trigger SARM1 activation.

PARP inhibitors

Given that PARP inhibitors have mainly been used for the treatment of different types of cancer, rather than for their potential as NAD^+ enhancers, the majority of adverse effects are reported in relation to the treatment of cancer patients. In this scenario, anemia is one of the most common side effects, occurring in 44% of patients treated with Olaparib [317]. This negative effect may be an on-target adverse effect related to PARP2 inhibition and erythrogenesis, as the deletion of PARP2 has been described to impair the differentiation of erythroid progenitors and to reduce life expectancy in mouse erythrocytes [318].

Other PARP inhibitors are also known to produce side effects. For example, low doses of 3-aminobenzamide (3-AB) stimulate angiogenesis in endothelial cells in vitro [319], something that must be considered when treating cancer patients with 3-AB, as an increased angiogenic potential may promote tumor growth and metastasis [320].

Sirtuin activators

Most sirtuin activators are naturally-occurring molecules whose potential adverse effects, if any, are not described. Nevertheless, some widely used sirtuin activators may have some secondary effects worth mentioning.

Resveratrol, based on its structural similarity to diethylstilbestrol, a synthetic estrogen, may also act as a phytoestrogen, acting as an agonist of estrogen receptors [321]. Additionally, this compound has been reported to reduce cell growth and induce apoptosis in normal cells when administered at high doses, via activation of the mitogen-activated protein kinase (MAPK) in a MEK-1, Src, matrix metalloproteinase, and epidermal growth factor receptor dependent manner [322, 323].

Piceatannol and genistein, both natural polyphenols known to activate SIRT1, can influence many cellular processes as well [277, 281, 324]. For instance, both compounds are known to induce cell cycle arrest and apoptosis [325, 326], effects that might be considered beneficial in the fight against cancer, but that must be accounted

for as probable side effects when using piceatannol and genistein in the treatment of cardiorenal disease.

Future directions

Research on NAD^+ metabolism interventions as tools to combat a wide array of genetic and acquired disorders has rapidly evolved in the last two decades, partly triggered by the outstanding results obtained in preclinical models of disease. In the context of cardiorenal disease, the clearest example is nicotinic acid, which has been used as an anti-dyslipidemic drug for more than 50 years. However, whether the positive effects on cardiorenal health that NA exerts are due to its role as an NAD^+ precursor or its ability to activate the GPR109A receptor remain unclear. Interestingly, the administration of other NAD^+ precursors that do not interact with this receptor, such as NR, NMN and their reduced forms, has also proven to protect against cardiorenal disease, supporting the use of strategies aimed at enhancing NAD^+ levels as novel therapeutic avenues for combating such diseases, at least in animal models.

In fact, while preclinical studies have provided compelling evidence regarding the beneficial effects of NAD^+ repletion strategies in cardiorenal health, the translation of these findings to humans remains a work in progress, as the outcomes of the clinical trials have not met the high expectations derived from animal studies. This lack of translatability may be due to two main reasons: the limited NAD^+ enhancing potential of the classical NAD^+ precursors, and the absence of long-term clinical trials. Administration of classical NAD^+ precursors, such as NMN or NR, usually leads to twofold increases in intracellular NAD^+ levels, at best, which might limit their biological effects. Next-generation NAD^+ enhancers, such as NRH or NMNH, arise as potent alternatives, as they are able to increase NAD^+ levels to a much higher extent than their oxidized counterparts.

Apart from the limitation in their NAD^+-enhancing capacity, the duration of the human trials has been limited to several weeks in most cases, hindering the possibility to evaluate the long-term effects of NAD^+ enhancement in cardiorenal syndromes. For instance, in the case of NR administration in humans, the median duration of NR treatment is 8 weeks, which might not be sufficient to fully elucidate the long-term impact of NR in health [327].

Another interesting point is that almost every effort to target NAD^+ metabolism in the cardiorenal context has been focused on the use of NAD^+ precursors, leaving other strategies, such as PARP inhibition and sirtuin activation in the background. In fact, certain alternative strategies designed to increase NAD^+ levels have also been timidly studied, such as CD38 inhibition or NAMPT activation.

Finally, the potential synergistic effects of the application of different strategies at the same time is largely unexplored. To date, only one clinical trial has aimed to improve cardiorenal health through the administration of NAD^+ precursors (NR) and SIRT1 activators (pterostilbene), demonstrating that this combination is safe, well tolerated, and effective in increasing whole blood NAD^+ levels. The combination of molecules targeting NAD^+ metabolism at different levels might hold the key to unlock the full potential of these therapies.

Overall, this review highlights the significant advances in the field of NAD^+ modulation in the onset, progression, and potential therapy for cardiorenal diseases. Even though there is still a long way to go, the first steps have already been taken, and NAD^+ repletion strategies are here to stay.

Author contributions

Conceptualization: M.M-B., J.R., M.J.R-R., R.Z-P. and R.R-R.Writing—original draft preparation: M.M-B.Writing—review and editing: J.R., M.J.R-B, R.Z-P. and R.R-R.Visualization: M.M-B.Supervision: J.R., M.J.R-B., R.Z-P. and R.R-R. Project administration: R.Z-P. and R.R-R.Funding acquisition: R.Z-P. and R.R-R. All authors have approved the submitted version and have agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Competing interests

The authors declare no competing interests.

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