

Potential role of *N*-acetylcysteine in cardiovascular disorders

Cardiovascular disorders are a common cause of mortality around the world. The role of antioxidants is controversial in the prevention and treatment of a wide variety of cardiovascular events. *N*-acetylcysteine (NAC) is an antioxidant that is believed to have an adjunctive beneficial effect in different medical conditions. We investigated all of the cardiovascular disorders for which NAC was administered in order to find its possible advantageous impact. We included clinical trials that were conducted in patients with heart failure, myocardial infarction, hypertension, atherosclerosis, ischemic heart disease or those who underwent cardiothoracic surgery. However, to date there is no comprehensive review on the potential impact of NAC in cardiovascular disorders. Therefore, we conducted a systematic literature search in MEDLINE/PubMed. A search strategy using medical subject headings and text keywords such as '*N*-acetylcysteine', 'cardiology', 'cardiac', 'acute care', 'cardiovascular', 'cardiothoracic', 'heart failure', 'myocardial infarction', 'hypertension', 'atherosclerosis' and 'ischemic heart disease' was performed. After a complete literature review, we arranged the data collected on this subject and suggested some aspects for further research.

KEYWORDS: atrial fibrillation ■ cardiovascular disorders ■ ischemic heart disease ■ myocardial infarction ■ *N*-acetylcysteine

N-acetylcysteine (NAC), which has previously been used as a paracetamol antidote, has recently been applied in a variety of indications in clinical practice as an antioxidant, free radical scavenger and mucolytic [1]. The sulphhydryl group in its structure enhances glutathione (GSH) antioxidant capacity, thus empowering NAC to reduce cellular oxidative damage [2,3]. As a GSH precursor, NAC enters cells and is hydrolyzed to cysteine, which can then stimulate GSH synthesis. The low pH in the stomach makes the neutral species of NAC the predominant form after oral intake; therefore, it is readily taken up and is sent to the liver via the portal route, where it is almost entirely converted to cysteine [4]. The liver incorporates the majority of this cysteine into GSH and it is then secreted into the circulation [5]. GSH is composed of three amino acids (glutamate, glycine and cysteine) from which cysteine has the lowest intracellular concentration [6]. GSH is readily oxidized nonenzymatically to glutathione disulfide by electrophilic substances (e.g., free radicals and reactive oxygen/nitrogen species) owing to the presence of the cysteine residue [7]. The glutathione disulfide efflux from cells contributes to a net loss of intracellular GSH. GSH is replenished mainly by *de novo* synthesis; therefore, cysteine availability can limit the rate of GSH synthesis during times of oxidative stress [8]. By the aforementioned

mechanism, NAC could correct or prevent the GSH depletion. In addition, it may scavenge several reactive oxygen species, including hypochlorous acid (HOCl), peroxyxynitrous acid (ONOOH), hydroxyl radical (OH) and hydrogen peroxide (H₂O₂) [9,10]. As it is a potent antioxidant, several significant therapeutic benefits for cardiovascular diseases have been postulated for NAC in clinical trials (TABLE 1), which merit further research.

NAC & cardiothoracic surgery: atrial fibrillation

Atrial fibrillation (AF), is the most common sustained arrhythmia in patients undergoing coronary artery bypass and/or valve surgery, with the incidence ranging from 10 to 65% [11,12]. To date, the renin-angiotensin system [13-15], inflammatory cytokines [13, 16-18] and oxidative stress [19,20] are the main known pathophysiologic pathways in AF. Association between oxidative stress and AF is suggested by current studies [21-23]. As a result of oxidative phenomena, a systemic inflammatory response occurs secondary to ischemia-reperfusion injury during cardiac bypass surgery and formation of reactive oxygen species [23]. Preliminary evidence suggested NAC as a potentially effective agent in preventing postoperative AF [24]. Administration of NAC prior to surgery may prevent postoperative pulmonary atelectasis and

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Table 1. Clinical studies with *N*-acetylcysteine in acute cardiology.

Study type and patients	Intervention	Outcome	Ref.
<i>In patients undergoing cardiac surgery</i>			
Prospective, randomized, placebo-controlled study (n = 115 patients)	NAC was iv. infused for 1 h before operation at a dose of 50 mg/kg followed by 50 mg/kg/day for 48 h after the operation	NAC was an independent predictor of postoperative AF in multivariable logistic regression analysis (OR: 0.20; 95% CI: 0.04–0.91; p = 0.038)	[27]
Randomized, double-blind, placebo-controlled clinical trial (n = 100 patients)	600 mg orally the day before and morning of operation, a bolus of 10 mg/kg iv. NAC before skin incision followed by perfusion at 12.5 mg/kg/h over 24 h	NAC does not lead to improvements in clinical results and biochemical markers over 4 days	[28]
Case-controlled, randomized clinical trial (n = 20 patients)	iv. NAC 50 mg/kg infused over 30 min at the start of anesthesia induction	NAC limited ischemia reperfusion injury (by a decrease in TNF- α and CK-MB) during operation	[29]
Case-controlled, randomized clinical trial (n = 40 patients)	iv. NAC 50 mg/kg for 3 days	NAC reduced 6 and 24 h postsurgery oxidoinflammatory markers (IL-6, AAGP and CRP)	[38]
Case-controlled, randomized clinical trial (n = 30 patients)	Cardioplegia enriched with NAC 50 mg/kg	NAC minimizes myocardial injury (Tn I and MDA) in the early hours after and during surgery	[39]
Prospective case-controlled, randomized study (n = 35 patients)	Cardioplegia enriched with NAC 0.04 mol/l	NAC increased tissue capacity against oxidative stress and decreased inflammatory response	[40]
Prospective case-controlled, randomized study (n = 30 patients)	Cardioplegia enriched with NAC 4 mmol/l at induction and 2 mmol/l at maintenance	NAC reduced myocardial oxidative stress biomarkers (MDA and neutrophil percentage)	[41]
Blinded placebo-controlled, parallel group, randomized trial (n = 177 patients with pre-existing moderate renal insufficiency)	NAC 100 mg/kg bolus, then 20 mg/kg/h for 4 h after operation	Higher chest-tube blood loss and blood product transfusion in NAC group	[42]
Case-controlled study (n = 10 patients)	NAC 100 mg/kg	NAC potentiates the vasodilator effect of NTG (MAP and PCWP decreased)	[47]
Case-controlled study (n = 18 patients)	NAC 100 mg/kg	NAC increased coronary sinus blood flow when combined with NTG 25 mcg	[48]
<i>In patients with ischemic heart disease</i>			
Double-blind, placebo-controlled trial (n = 46 patients with unstable angina)	NAC 5 g every 6 h	Lower acute MI in NTG combined with NAC, possible risk of hypotension in case of rapid iv. NAC infusion	[49]
Double-blind, randomized, crossover study (n = 10 patients with stable angina)	NAC 2 g iv. in 15 min followed by 5 mg/kg/h for 30 h combined with iv. ISDN 5 mg/h	Time to onset of angina, time to 1-mm ST segment depression and total amount of ST segment depression improved in NAC group. NAC affects and partially prevents the development of tolerance to antianginal effects of ISDN	[64]
Double-blind, randomized, crossover study (n = 7 patients with stable angina)	NAC 600 mg four times daily combined with ISDN 40 mg four times daily	NAC increased the anti-ischemic effects of ISDN by prolonging the time to ST depression and decreasing total ST depression	[64]
<i>In patients with acute myocardial infarction</i>			
Case-controlled, randomized clinical trial (n = 30 patients)	15 g NAC infused over 24 h combined with SK	NAC reduced oxidative stress (MDA) and improved left ventricle function	[69]
Case-controlled, randomized study (n = 16 patients)	NAC infused 20 mg/min iv. for first hour and 10 mg/h in subsequent 23 h (cumulative dose 15 g/24 h)	Combined use of NAC and SK significantly reduced the concentration of plasma lipid peroxidase	[70]
<i>In hypertensive patients</i>			
Randomized, crossover study, (n = 18 smoker hypertensive patients on ACE-I therapy)	NAC 600 mg four times daily	Significant decrease in systolic and diastolic 24 h and daytime blood pressure was achieved with the combination	[76]
AAGP: α 1-acid glycoprotein; ACE-I: Angiotensin-converting enzyme inhibitor; AF: Atrial fibrillation; CRP: C-reactive protein; ISDN: Isosorbide dinitrate; iv.: Intravenous; MAP: Mean arterial pressure; MDA: Malondialdehyde; MI: Myocardial infarction; NAC: N-acetylcysteine; NTG: Nitroglycerin; OR: Odds ratio; PCWP: Pulmonary capillary wedge pressure; SK: Streptokinase; Tn I: Troponin-I.			

consequently can improve systemic oxygenation in patients undergoing cardiac surgery [25]. The significant role of oxidative stress in the pathogenesis and progression of postoperative AF has been demonstrated [22]. Conversely, the potential benefits of perioperative NAC on the prevention of complications after cardiothoracic surgery has been evaluated in a meta-analysis [26]. The findings showed that the use of NAC significantly decreased the risk of developing postoperative AF by 36%. In another prospective randomized, placebo-controlled pilot study of 115 patients undergoing coronary artery bypass surgery and/or valve surgery, NAC intravenous infusion for 1 h before the procedure at a dose of 50 mg/kg followed by infusion for 48 h after operation at a dose of 50 mg/kg/d decreased the incidence of AF [27], in this study NAC acted as an antioxidant. However, NAC was unable to show any beneficial effect on outcome over 4 days of follow-up of patients undergoing cardiac surgery as an anti-inflammatory agent [28].

Following sulfhydryl group donation and acting as an antioxidant, NAC can decrease ischemia-reperfusion injury and potentiate the vasodilator effects of nitroglycerin (NTG) and angiotensin-converting enzyme inhibitors [29]. As hypertension and ischemia are the risk factors for postoperative AF [30], beneficial effects of NAC might partly be explained by its anti-ischaemic and vasodilator actions. Although NAC can suppress plasma and tissue angiotensin-converting enzyme activity [31,32] its role in reducing the blood pressure (BP) in different studies was not consistent. In experimental studies NAC reduced BP in rats by enhancing nitric oxide (NO)-dependent vasodilation [33–35]. However, in a study which evaluated the effects of NAC on systolic and diastolic BP in patients with chronic kidney disease, no changes in these parameters were observed [36]. This finding was in contrast with another study on hypertensive patients with Type 2 diabetes [37], which found that NAC and L-arginine administration for 6 months reduced systolic, diastolic and mean BP. The failure of the former study, in which NAC was ineffective in reducing BP, could be attributed to the relatively short treatment period, during which positive endothelial effects may not have had time to fully develop [36].

According to our existing data, NAC administration during cardiovascular surgery for the prevention of AF seems reasonable. However, its effective dose and duration of administration should be evaluated in future studies.

NAC & cardiothoracic surgery: reperfusion damage during cardiopulmonary bypass surgery

The effectiveness of relatively high doses of NAC as an antioxidant in cardiopulmonary bypass (CPB) patients has been evaluated by several studies [28,38–40]. No improvement in patients' mortality and morbidity, such as myocardial infarction, bleeding, transfusion requirements, intubation time, length of hospital stay or biochemical markers, such as troponin T, CK-MB, creatinine, hemoglobin and platelets, were reported with high doses of NAC [28]. However, in a case-controlled, randomized study of 40 patients undergoing surgery, NAC administered intravenously at a dose of 50 mg/kg for 3 days decreased pump-induced oxidative and inflammatory response and increased tissue capacity against oxidative stress during CPB [38,40]. Supplementation of cardioplegia solution with high doses of NAC as a precursor of GSH, reduced myocardial injury during and after cardiac surgery as assessed by decreasing the levels of troponin-I and malondialdehyde levels [39]. Köksal *et al.* evaluated the efficacy of low dose NAC against myocardial ischemia-reperfusion damage in coronary artery bypass surgery [41]. NAC had not shown beneficial effects on hemodynamic parameters and CK-MB levels. However, malondialdehyde and neutrophil percentage were significantly lower with NAC. The authors concluded that low-dose NAC, a powerful antioxidant, as an adjunct to cardioplegic solutions, can significantly reduce myocardial oxidative stress in coronary bypass surgery with cardiopulmonary bypass, but may not restore the myocardial injury [41].

In conclusion, administration of NAC in patients undergoing cardiovascular surgery could reduce the oxidative stress in the myocardium. Further research is needed for assessment of this reduction on patients' long-term morbidity and mortality in clinical practice.

NAC & complications of cardiovascular interventions

It was reported that high doses of NAC can increase bleeding duration and blood transfusion requirement following cardiac surgery in patients with pre-existing moderate renal insufficiency. Administration of NAC (100 mg/kg as bolus followed by infusion at rate of 20 mg/kg/h until 4 h after cardiopulmonary bypass) significantly increased 24-h chest tube drainage and red blood cell transfusion requirement [42]. This

phenomenon, along with NAC nephroprotective effect, should be kept in mind in the perioperative risk–benefit evaluation [43].

Administration of NAC plus hydration had a contradictory effect on prevention of contrast media agent-induced acute kidney injury in high-risk patients following cardiovascular interventions [44,45].

At present, in most centers, NAC is used as a prophylactic agent for acute kidney injury following contrast media and cardiovascular interventions [46].

NAC & ischemic heart disease

Nitrate tolerance is a well-known problem in the treatment of patients with ischemic heart disease. Concomitant administration of intravenous NTG and NAC, as a GSH precursor, in patients with ischemic heart disease could augment NTG-related systemic [47] and coronary [48] hemodynamic effects [49]. In one study, during the long-term treatment (4 months of follow-up) of patients with unstable angina, the combination of NTG and NAC, associated with conventional medical therapy, decreased the occurrence of death, myocardial infarction or refractory angina requiring revascularization [50]. However, at the dosage used in that study (three tablets of NAC 600 mg/day), the incidence of side effects (mainly intolerable headache) was higher in the combination group [50]. In addition, NAC delayed the tolerance to hemodynamic effects of NTG during prolonged intravenous administration [51,52]. NTG needs to be converted to NO in order to activate guanylate cyclase and subsequent smooth muscle relaxation. When the rate of this bioconversion decreased, tolerance to NTG effects may take place [53]. By acting as a cofactor in nitrate ester reductase [54] or through increasing the formation of S-nitrosothiols, NAC can accelerate NTG bioconversion [55–57]. In addition, formation of S-nitroso-NAC may increase the antiplatelet activity of NTG [58]. This effect is important in patients with acute coronary syndrome in prevention of thrombosis [59] and coronary vasospasm [60]. It has also been proposed that NAC can prevent cardiomyocytes from injury and dysfunction during periods of ischemia [61,62] and reperfusion [63].

Concomitant administration of NAC, as a GSH precursor, with other nitrates except NTG, such as isosorbide dinitrate, can prevent the development of antianginal tolerance [64]. In ten stable angina pectoris patients treated with intravenous isosorbide dinitrate 5 mg/h combined with NAC 2 g intravenously over 15 min followed by 5 mg/kg/h

or matching placebo for 30 h in a double-blind, randomized, crossover study with a washout interval of 8 days, time to onset of angina, time to 1-mm ST segment depression and total amount of ST segment depression improved in the NAC group [64]. With respect to the gastrointestinal side effects of NAC in long-term administration, lower oral doses were recommended for nitrate tolerance prevention in the management of chronic stable angina [65]. However, low oral doses of NAC in combination with ISDN, had less beneficial effect on ST segment depression in comparison with the higher intravenous doses [66].

It was concluded that NAC can prevent and even reverse the nitrate tolerance in treatment of ischemic heart diseases [64].

NAC & cardiac remodeling

N-acetylcysteine prevented left ventricular (LV) remodeling and dysfunction, interstitial fibrosis, pulmonary congestion and right ventricular hypertrophy and improved survival in animal studies [67]. It has been shown that NAC may also reduce reperfusion ischemia, injury [29], arrhythmias and extension of infarction [68]. Thrombolytic agents in post-acute myocardial infarction may cause reperfusion injury with manifestation of myocardial stunning, arrhythmias, myocardial damage and extension of the infarct size. NAC in combination with streptokinase significantly decreased oxidative stress and improved ventricular function in patients with myocardial infarction [69]. Concomitant administration of NAC and reperfusion therapy in myocardial infarction significantly decreased oxidative stress following a decline in plasma hydroperoxide concentration [70]. Additional infarct size reduction and preservation of LV function have been reported following infusion of NAC during thrombolysis. Antioxidant properties and increase in endogenous NO production [71] by NAC in patients with acute myocardial infarction may prevent the occurrence of future cardiac events [72]. Following a reduction in proinflammatory cytokines, NAC exerts its beneficial anti-inflammatory actions [73,74], such as diminish the renin–angiotensin system activity [75]. The NAC protective effect on NO degradation can reduce acute myocardial infarction episodes [49,76]. In a crossover study in 18 hypertensive patients who were smokers, which examined angiotensin-converting enzyme inhibitor, the combination administration of NAC (600 mg four times daily) and angiotensin-converting enzyme inhibitors resulted in a significant decrease in systolic and diastolic 24 h BP and daytime BP [76].

Following myocardial infarction, a variety of changes in size, shape and function may take place in the LV in response to ischemia [77]. These changes may manifest as LV wall thinning, dilation, infarct extension, inflammation and necrotic myocyte resorption, fibroblast accumulation and scar development, endothelial cell activation and neovascularization [78]. Several pathophysiologic pathways contribute to LV remodeling, one of which is oxidative stress [79]. NAC was effective in preventing cardiac remodeling in animal models of myocardial infarction [80] and ventricular hypertrophy in mice with aortic constriction [81]. Matrix metalloproteinases (MMPs), a family of structurally similar zinc-dependent proteinases, are other important mediators that contribute significantly to LV remodeling [82]. The level of MMPs was increased by TNF- α , a proinflammatory cytokine [83,84]. This cytokine can also stimulate fibrosis [83,84] and has a role in heart failure progression [85]. The adverse effects of TNF- α on the cardiovascular system are related to the cell's GSH storage status. By increasing GSH content in cardiac tissue, NAC protects myocytes against TNF- α -induced oxidative stress and negative inotropic effect [80,86]. Another important mediator that has a central role in remodeling is TGF- β 1; NAC was reported to inhibit TGF- β 1-stimulated collagen [87], fibronectin and VEGF production [88, 89] and also binding of TGF- β 1 to its receptor [90,91].

These findings show the impact of NAC on different pathophysiologic pathways involved in cardiac remodeling that promote NAC administration in addition to other routine medications in myocardial infarcted patients.

Atherosclerosis

Matrix metalloproteinases released by activated cardiomyocytes macrophages can cause rupture of atherosclerotic plaque in unstable vascular syndromes [92–97]. NAC decreased gelatinolytic activity and MMP-9 expression by macrophages in animal model of atherosclerosis. These effects may be related to NAC's capacity to scavenge reactive oxygen species [98] or a direct interaction with gelatinase [99]. Therefore, NAC therapy may be useful in inhibition of the matrix degradation and improvement of the vascular stability in both early and late stages of atherosclerosis. In another study it was demonstrated that although NAC does not have any effect on basal vasomotor tone, its administration could improve endothelium-dependent responses in patients with and

without endothelial dysfunction or atherosclerosis [100]. Increasing the bioavailability of NO by forming S-nitroso-*N*-acetylcysteine and a S-nitrosocysteine [58] and NAC antioxidant properties [101] could be potential mechanisms underlying the improvement in endothelial function with this low-molecular-weight thiol. The support for the latter mechanism is NAC inability in potentiating endothelium-dependent vasodilation in normal volunteers in whom oxidative stress is low [102]. All of these findings could support the administration of NAC in patients with atherosclerosis.

Heart failure

Heart failure is another cardiovascular disorder in which oxidative stress is involved in the pathogenesis. An increase in glutathione peroxidase prevents LV remodeling and failure after myocardial infarction [103,104]. In a prospective, randomized, placebo-controlled trial including 134 hemodialysis patients (64 patients were on NAC and 70 patients received placebo), treatment with NAC 600 mg per day was demonstrated to reduce heart failure symptoms and other cardiovascular events [105].

A decrease in serum TNF- α was not achieved by its antagonists (e.g., etanercept or infliximab) [85,106]; however, administration of NAC normalized serum TNF- α and improved heart failure in rats with cardiac injury [86]. Therefore, NAC may be considered as a potential inexpensive, safe adjunctive therapy for the management of heart failure. Further studies are needed for clarification of NAC effects in heart failure.

Conclusion & future perspective

N-acetylcysteine is a safe and nontoxic antioxidant with generally mild adverse effects (e.g., nausea, vomiting, flushing, rash, pruritis, bronchospasm, chest pain, hypotension and dizziness) when used in high doses (e.g., as an acetaminophen antidote) [107,108] that is hypothesized to have several positive effects in prevention of cardiovascular disorders. Its beneficial positions have been confirmed to some extent in previous studies. Due to the frequency of the morbidity and mortality associated with the aforementioned cardiovascular disorders, reducing the burden of these problems by means of an adjunct safe medication would be of high value. However, there are some controversies about NAC and cardiovascular disorders, such as different doses of NAC, time of its initiation with respect to the event and length of therapy, that must be clarified in future studies.

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Executive summary**Introduction**

- N-acetylcysteine (NAC) is a potent antioxidant for which clinical trials postulate several significant therapeutic benefits for cardiovascular diseases.

NAC & cardiothoracic surgery: atrial fibrillation

- Atrial fibrillation (AF) is the most common sustained arrhythmia in patients undergoing coronary artery bypass and/or valve surgery.
- Renin-angiotensin system, inflammatory cytokines and oxidative stress are the main known pathophysiologic pathways in AF.
- A meta-analysis showed that the use of NAC significantly decreased the risk of developing postoperative AF, while it was unable to show any positive effect on the outcome of patients.
- NAC can decrease ischemia-reperfusion injury and potentiate the vasodilator effects of nitroglycerin and angiotensin-converting enzyme inhibitors.

NAC & cardiothoracic surgery: reperfusion damage during cardiopulmonary bypass surgery

- Supplementation of cardioplegia solution with high doses of NAC reduced myocardial injury during cardiac surgery.
- Low-dose NAC, as an adjunct to cardioplegic solutions, can significantly reduce myocardial oxidative stress in cardiopulmonary bypass surgery but may not restore the myocardial injury.

NAC & complications of cardiovascular interventions

- High-doses of NAC can increase bleeding duration and blood transfusion requirement following cardiac surgery.
- NAC plus hydration had a contradictory effect on the prevention of contrast media agent-induced acute kidney injury following cardiovascular interventions.
- Reduction of postcardiothoracic surgery complications (e.g., stroke, myocardial infarction and mortality) was observed following NAC administration in a meta-analysis.

NAC & ischemic heart disease

- Concomitant administration of intravenous nitroglycerin and NAC could increase nitroglycerin-related systemic and coronary hemodynamic effects.
- NAC can prevent and even reverse nitrate tolerance in the treatment of ischemic heart diseases.

NAC & cardiac remodeling

- NAC in combination with streptokinase significantly decreased oxidative stress, improved ventricular function and reduced acute myocardial infarction episodes.
- NAC protects myocytes against TNF- α -induced oxidative stress and negative inotropic effect.
- NAC inhibits TGF- β 1-stimulated collagen, fibronectin and VEGF production and also binding of TGF- β 1 to its receptor.
- NAC effects on different pathophysiologic pathways involved in cardiac remodeling promote its administration in myocardial infarcted patients.

Atherosclerosis

- NAC therapy may be useful in inhibiting the extracellular matrix degradation and improving vascular stability in both early and late stages of atherosclerosis.

Heart failure

- Treatment with NAC in hemodialysis patients was shown to reduce heart failure symptoms and other cardiovascular events. Its administration can also normalize serum TNF- α .

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