The Clinical Efficacy of N-Acetylcysteine in the Treatment of ST Segment Elevation Myocardial Infarction
A Meta-Analysis and Systematic Review

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Summary

The aim of this study was to evaluate the clinical efficacy of N-acetylcysteine (NAC) in the treatment of ST segment elevation myocardial infarction (STEMI).

PubMed, EMBASE, Cochrane Library, and Web of Science were searched systematically from the establishment of the database to June 2020. Two researchers independently completed literature screening and data extraction and conducted a meta-analysis.

Nine articles including 1419 patients were enrolled. Meta-analysis showed that all-cause mortality [RR = 0.56, 95%CI (0.33, 0.93), P = 0.02], occurrence of major adverse cardiovascular events (MACE) [RR = 0.63, 95%CI (0.47, 0.85), P = 0.002], and myocardial enzyme hs-TnT level [SMD = -0.42, 95%CI (-0.71, -0.13), P = 0.005] were significantly lower in patients with STEMI treated with NAC than those in the control group. There was no significant difference between the NAC group and the control group in new congestive heart failure [RR = 0.94, 95%CI (0.48, 1.82), P = 0.84], ejection fraction [MD = 2.00, 95%CI (-0.59, 4.60), P = 0.13], and CK-MB [SMD = -0.18, 95%CI (-0.47, 0.11), P = 0.23]. There was no significant difference in the occurrence of adverse reactions between the NAC group and the control group [RR = 1.04, 95%CI (0.57-1.89), P = 0.90].

NAC can reduce the all-cause mortality and MACE cases of STEMI.

Key words: Acute myocardial infarction, All-cause mortality, Major cardiovascular events

Methods

Inclusion and exclusion criteria of literature: Inclusion criteria: (1) the study type was a randomized, controlled study; (2) the language was limited to English.

Exclusion criteria: (1) a repeated publication; (2) a lack of full text, incomplete information or the inability to extract data; (3) the definition of exposure is different from most other literature; (4) an animal experiment; (5) a review and systematic evaluation.

Retrieval strategy: PubMed, EMBASE, Cochrane Library, Web of Science, and other databases were searched. The retrieval time limit was from the establishment of the database to June 2020. The key words in English are: “Myocardial infarction”, “ST elevation myocardial infarction”, and “N-acetylcysteine”.

Literature screening and data extraction: Literature retrieval, screening, and information extraction were completed by two researchers independently. In case of any doubt or disagreement, a third party’s opinion was consulted. Data extraction included author, year, study type, sample size, all-cause mortality, major adverse cardiovas-
cultural events (MACE) defined as death, reinfarction, or a need for revascularization, new generalized heart failure, ejection fraction, myocardial enzymes (CK-MB, hs-TnT), and adverse reactions.

**Methodological quality evaluation:** The literature quality was evaluated by two researchers independently using the Review Manager 5.3 risk assessment tool; according to the Cochrane risk assessment scale, the included literature was evaluated according to random sequence generation, allocation concealment, the blind method, whether the research results were evaluated by blind method or not, the integrity of the results data, the selection and report of research results, and other biases. In cases of disagreement, a decision was made through consultation with a third party. The meta-analysis was performed according to the preferred reporting items for systematic reviews and meta-analyses statement (PRISMA statement).

**Statistical methods:** Review Manager 5.3 was used to analyze the data. RR (95%CI) was used as the binary variable and MD or SMD (95%CI) was used as the continuous variable. $I^2$ was used to evaluate heterogeneity. If heterogeneity tested $P \geq 0.1$ and $I^2 \leq 50\%$, it indicated that there was homogeneity among the studies and the fixed-effect model was used for consolidation analysis; if $P < 0.1$; $I^2 > 50\%$, it indicated that there was heterogeneity among the studies and sensitivity analysis or subgroup analysis was used to find the source of heterogeneity. If heterogeneity was still significant, the random effect model or the abandonment of the results was combined, and descriptive analysis was used. A funnel plot and Egger’s bias test were used to analyze the publication bias of each index when more than 10 articles were included.

### Results

**Basic information of the included literature:** A total of 2139 studies were retrieved from the above database; A total of 2139 studies were retrieved from the above database and 1438 were obtained after the removal of duplicate studies. From among these 1438 studies, 957 reviews and systematic reviews were excluded, leaving 481 studies. A total of 472 of these studies were excluded for various reasons, resulting in the selection of 9 studies for inclusion in the quantitative synthesis (meta-analysis). Finally, a total of 9 RCTs were included, involving 1419 patients. There were no significant differences in the basic information between the two groups. The main characteristics of the included studies are shown in the Table. The medication data of the 2 groups are presented in the Supplemental Table.

**Literature quality evaluation:** Figure 1 summarizes the bias assessment risk of the 9 RCTs. Randomization was mentioned in all studies. However, 8 studies described allocation concealment. All studies described the blinding of patients and personnel and selective reporting. Outcome assessments may be used to improve the therapeutic effectiveness. Seven studies described the binding of outcome data. Only one study described incomplete outcome data. Overall, the quality of the trials selected was high, with a low risk of bias.

**Meta-analysis results**

- **All-cause mortality** A heterogeneity test of 7 studies ($I^2 = 0\% < 50\%; P = 0.44 > 0.1$) was conducted using the fixed effects model, and the pooled effect amount was RR = 0.56; 95%CI (0.33, 0.93); $P = 0.02$. The results showed that NAC significantly reduced the all-cause mortality of myocardial infarction compared to the standard treatment (Figure 2).

- **MACE (major cardiovascular events)** A heterogeneity test of 6 studies ($I^2 = 35\% < 50\%; P = 0.17 > 0.1$) was conducted using the fixed effects model, and the pooled effect amount was RR = 0.63; 95%CI (0.47, 0.85); $P = 0.002$. The results showed that the occurrence of MACE in the NAC group was significantly lower than in the control group (Figure 3).

- **New congestive heart failure** A heterogeneity test of the 3 studies ($I^2 = 31\% < 50\%; P = 0.23 > 0.1$) was conducted using the fixed effects model, and the pooled effect amount was RR = 0.94; 95%CI (0.48,1.82); $P = 0.84$. The results showed that there was no significant difference in the occurrence of new aggressive heart failure between NAC therapy and standard therapy (Figure 4).

- **Ejection fraction** A heterogeneity test of the 3 studies ($I^2 = 0\% < 50\%; P = 0.73 > 0.1$) was conducted using the fixed effects model, and the total effect amount was MD = 2.00; 95%CI (-0.59, 4.60); $P = 0.13$. There was no significant difference in ejection fraction between the NAC and standard therapy (Figure 5).

- **Myocardial enzymes** CK-MB: A heterogeneity test of the

### Table. Basic Information of Included Literature

| Authors       | Year | Research type | Study area | Number of cases | Male/ Female | Age | Control | With or without PCI |
|---------------|------|---------------|------------|----------------|--------------|-----|---------|---------------------|
| Marenzi       | 2006 | RCT          | Italy      | 118            | 62.2 ± 11    | 62.6 ± 12 | PCI     |
| Thiele        | 2010 | RCT          | Germany    | 126            | 68 (57–75)   | 68 (56–76) | PCI     |
| Tanaka        | 2011 | RCT          | Japan      | 38             | 62.8 ± 13    | 60.5 ± 14 | PCI     |
| Talasaz       | 2013 | RCT          | Iran       | 50             | 61 (42–92)   | 61 (40–86) | PCI     |
| Talasaz       | 2014 | RCT          | Iran       | 50             | 61 (42–92)   | 61 (40–86) | PCI     |
| Thayssen      | 2014 | RCT          | Denmark    | 176            | 63.0 (55.0–70.8) | 63.0 (55.0–72.0) | PCI |
| Eshraghi      | 2016 | RCT          | Iran       | 50             | 60.5 ± 14    | 60.1 ± 12.3 | PCI    |
| Pasupathy     | 2017 | RCT          | Australia  | 53             | 64 ± 15      | 64 ± 15    | PCI     |
| Nizari        | 2018 | RCT          | Iran       | 50             | 58.3 ± 11.3  | 58.3 ± 11.3 | PCI     |

NAC indicates N-acetylcysteine; PCI, percutaneous coronary intervention; and RCT, randomized controlled trial.

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| Marenzi       | 2006 | RCT          | Italy      | 118            | 62.2 ± 11    | 62.6 ± 12 | PCI     |
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| Pasupathy     | 2017 | RCT          | Australia  | 53             | 64 ± 15      | 64 ± 15    | PCI     |
| Nizari        | 2018 | RCT          | Iran       | 50             | 58.3 ± 11.3  | 58.3 ± 11.3 | PCI     |
Figure 1. Evaluation of literature quality.

Figure 2. Forest map of all-cause mortality in patients with myocardial infarction treated with NAC versus standard therapy.

Figure 3. Forest map of the incidence of MACE in patients with myocardial infarction compared with NAC versus standard treatment.
two studies \( (I^2 = 0\% < 50\%; \ P = 0.91 > 0.1) \) was conducted using the fixed effects model, and the aggregate effect amount was SMD = -0.18; 95%CI (-0.47, 0.11); \( P = 0.23 \). The results showed that there was no significant difference in CK-MB level between NAC and standard therapy (Figure 6).

hs-TnT: A heterogeneity test of the two studies \( (I^2 = 0\% < 50\%; \ P = 0.78 > 0.1) \) was conducted using the fixed effects model, and the sum effect amount was SMD = -0.42; 95%CI (-0.71, -0.13); \( P = 0.005 \). The results showed that the level of hs-TnT in the NAC group was significantly lower than in the control group (Figure 7).

Adverse reactions: A heterogeneity test of the 3 studies \( (I^2 = 0\% < 50\%; \ P = 0.49 > 0.1) \) was conducted using the fixed effects model, and the pooled effect amount was RR = 1.04; 95%CI (0.57, 1.89); \( P = 0.90 \). There was no significant difference in the occurrence of adverse reactions between NAC and standard therapy (Supplemental Figure).

Sensitivity analysis: A sensitivity analysis was conducted on the sequential deletion of literature for each index, and none influenced the results significantly, indicating that the results of the study are relatively stable.

Discussion

STEMI is a serious disease, which can cause pain, fever, nausea, and other symptoms as well as heart failure and shock. In order to restore myocardial blood supply as soon as possible and prevent infarction enlargement and thrombosis, antiplatelet therapy, anticoagulation, and myocardial reperfusion (percutaneous coronary intervention (PCI) and thrombolysis) are commonly used in clinical treatment. PCI is a treatment method that uses transcar-

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**Table 1:**

| Study or Subgroup | NAC | Control | Mean Difference | Std. Mean Difference | N. Fixed, 95% CI | Year |
|-------------------|-----|---------|-----------------|----------------------|-----------------|------|
| Thiele 2010       | 52.1| 11.6    | -50.6           | -109                 | 65.6%           | 2010 |
| Talasaz 2013      | 4.0 | 5.5     | 5.0             | -6.6                 | 46.3%           | 2013 |
| Nozari 2018       | 180.2| 129.69 | -50.5           | -200                 | -0.20           | 2018 |
| Total (95% CI)    | 100 | 88      | -18             | -0.42                | 100.00%         |      |

**Table 2:**

| Study or Subgroup | NAC | Control | Mean Difference | Std. Mean Difference | N. Fixed, 95% CI | Year |
|-------------------|-----|---------|-----------------|----------------------|-----------------|------|
| Thiele 2010       | 52.1| 11.6    | -50.6           | -109                 | 65.6%           | 2010 |
| Talasaz 2013      | 4.0 | 5.5     | 5.0             | -6.6                 | 46.3%           | 2013 |
| Nozari 2018       | 180.2| 129.69 | -50.5           | -200                 | -0.20           | 2018 |
| Total (95% CI)    | 100 | 88      | -18             | -0.42                | 100.00%         |      |

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**Figure 4:** Forest map of the comparison between NAC treatment and standard treatment in the incidence of new congestive heart failure of myocardial infarction patients.

**Figure 5:** Forest map of NAC versus standard treatment for ejection fraction in patients with myocardial infarction.

**Figure 6:** Forest map of NAC versus standard treatment on CK-MB in patients with myocardial infarction.

**Figure 7:** Forest map of NAC versus standard treatment in patients with myocardial infarction on hs-TnT.
cardiac catheter technology to clear the stenosis or even occlusion of the coronary artery lumen, thereby improving the blood perfusion of the myocardium, and is currently applied for patients with acute coronary syndrome or chronic stable angina that is refractory to optimal medical therapy. However, possible complications during PCI still exist, including coronary perforation, abrupt vessel closure (AVC), stent deformation (and loss), wire fracture (and loss), device embolization, and rotational atherectomy burr entrapment. It has been confirmed that STEMI can cause oxidative stress and reperfusion injury. In the first few minutes of reperfusion, free radicals can be produced in various ways. Oxidative stress can easily lead to cardiomyocyte necrosis and spread from endocardium to epicardium. After PCI, because the coronary artery is less obstructed, blood flow recovers faster and these adverse reactions are more obvious. Recent experiments have shown that the use of free radical scavengers before reperfusion in patients with acute myocardial infarction can significantly reduce the infarct area. NAC is an effective antioxidant, which can directly scavenge hydroxyl free radicals, which can reduce the oxidative damage of target tissues and allow for sufficient oxygen consumption. Nozari et al. found that injecting a high dose of NAC before PCI significantly reduced the hs-TnT level and improved coronary perfusion caused by thrombolysis in myocardial infarction (TIMI) flow after PCI. Pasupathy et al. demonstrated that the infarct size decreased in patients with acute STEMI after PCI when a large dose of NAC was injected intravenously.

An in vitro study showed that NAC inhibits platelet aggregation in obese patients. Another in vitro study found that NAC increased the bioavailability, thus playing an anti-aggregation effect. One possible explanation of the antiplatelet effect is that NAC may increase the glutathione and antioxidant capacity of the platelets. Horowitz et al. pointed out that NAC can cooperate with nitroglycerin in vasodilation. Packer et al. reported that NAC can enhance the anti-aggregation effect of nitroglycerin in ischemic patients. Inflammation, fibrosis, and other pathological phenomena may be involved in the structural changes that take place after myocardial infarction (MI). TGF-β is one of the main markers and can lead to the accumulation of an extracellular matrix by reducing the production of collagenase and promoting the production of atherosclerosis by increasing the synthesis of collagen. Talasaz and coauthors found that in patients who received NAC, the serum levels of matrix metalloproteinase (MMP)-9 and MMP-2 after 72 hours were significantly lower than those in the placebo group. The increase in TGF-β level suggests that NAC can prevent cardiac remodeling after acute myocardial infarction. After STEMI, matrix metalloproteinases (MMPs) play a role in structural changes associated with remodeling. Talasaz et al. also found that NAC may help reduce levels of MMP-2 and MMP-9.

A total of 9 RCTs were included in this meta-analysis and all subjects had STEMI. After the analysis, it was found that all-cause mortality and MACE occurrence in the NAC group were significantly lower than in the placebo group. There were no significant differences in heart failure, ejection fraction, or CK-MB, which may be due to a lack of data. However, after the use of NAC, hs-TnT decreased significantly, and the occurrence of adverse reactions did not increase compared to the control group. Therefore, NAC has a certain myocardial protective effect on STEMI patients, which is worthy of clinical promotion.

The study has the following limitations: (1) The data of some indicators is limited, and the sample is small; (2) The included studies were helpful to evaluate the short-term effects of NAC, but its long-term impact on STEMI patients is not clear; (3) Most of the studies did not use MRI or echocardiography and lack some evaluation indicators.

In conclusion, the use of NAC on STEMI patients can reduce all-cause mortality, cases of MACE, myocardial infarction size, and hs-TnT level. Future studies should focus on the mechanism of the benign effects of NAC on STEMI patients, the interaction between NAC and other STEMI drugs, and the long-term effects of NAC on the heart. Due to limited clinical data on patients with STEMI that were treated with NAC, the above conclusions need to be further verified.

Disclosure

Conflicts of interest: None.

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Supplemental Files
Supplemental Table
Supplemental Figure
Please see supplemental files; https://doi.org/10.1536/ihj.20-519