



N-acetylcysteine therapy reduces major adverse cardiovascular events in patients with type 2 diabetes mellitus

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ABSTRACT

Background: Effective preventive strategies for major adverse cardiovascular events (MACE) in T2DM patients are limited. Recent studies have explored the cardiovascular benefits of N-Acetylcysteine (NAC), an antioxidant with endothelial protective properties. This study investigates the long-term effects of NAC on MACE risk in T2DM patients, focusing on its potential as an adjunctive therapy.

Methods: This population-based cohort study used data from Taiwan's National Health Insurance Research Database (NHIRD) and included 46,718 T2DM patients diagnosed between 2008 and 2018, with follow-up until December 31, 2021. Propensity score matching (PSM) ensured balanced comparisons between NAC users and non-users. Cox regression and time-dependent Cox hazards models assessed MACE risk, adjusting for multiple covariates.

Results: In the matched cohort of 23,359 NAC users and 23,359 non-users, NAC users had a significantly lower incidence of MACE (41.74 % vs. 46.87 %, $P < .0001$). Adjusted Hazard Ratios (aHRs) indicated a consistent protective effect of NAC against overall MACE (aHR: 0.84; 95 % CI: 0.81–0.86, $P < .0001$). Higher cumulative defined daily doses (cDDD) of NAC correlated with reduced MACE risk, with the highest quartile (Q4) showing an aHR of 0.61 (95 % CI: 0.58–0.64, $P < .0001$).

Conclusion: This study underscores the significant reduction in MACE risk among T2DM patients with long-term NAC therapy. Notably, the findings emphasize NAC's dose-dependent effectiveness in diminishing MACE

Abbreviations: MACE, Major Adverse Cardiovascular Events; NAC, N-Acetylcysteine; T2DM, Type 2 Diabetes Mellitus; PSM, Propensity Score Matching; DDD, Defined Daily Dose; cDDD, Cumulative Defined Daily Dose; HR, Hazard Ratio; aHR, Adjusted Hazard Ratio; CI, Confidence Interval; NHIRD, National Health Insurance Research Database; NHI, National Health Insurance; Q, Quartile; aDCSI, Adapted Diabetes Complications Severity Index; ICD, International Classification of Diseases; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; ICD-10-CM, International Classification of Diseases, Tenth Revision, Clinical Modification; ATC, Anatomical Therapeutic Chemical; NO, Nitric Oxide; ROS, Reactive Oxygen Species; NF- κ B, Nuclear Factor Kappa B; HbA1c, Hemoglobin A1c.

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incidence, indicating its potential as a valuable adjunctive therapy for managing cardiovascular risk in T2DM patients.

1. Introduction

Type 2 diabetes mellitus (T2DM) is a significant global health challenge, with its prevalence steadily increasing over the past few decades [1]. According to the International Diabetes Federation, approximately 463 million adults worldwide were living with diabetes as of 2019, and this number is projected to rise to 700 million by 2045 [1]. The incidence of T2DM is particularly high in low- and middle-income countries due to rapid urbanization, lifestyle changes, and an aging population [2]. This rising prevalence poses substantial public health challenges, as T2DM is associated with a range of serious complications that impact both individuals and healthcare systems [3,4].

T2DM is known to cause a variety of complications, including cardiovascular diseases, renal impairment, neuropathy, retinopathy, and increased susceptibility to infections [5]. Among these, cardiovascular complications such as myocardial infarction, stroke, and heart failure are the leading causes of morbidity and mortality in patients with T2DM [6–9]. These complications not only deteriorate the quality of life but also impose a significant economic burden on healthcare systems globally [8]. Although glycemic control was historically viewed as the cornerstone in preventing major adverse cardiovascular events (MACE) in T2DM [10–12], current strategies emphasize aggressive risk factor modification and a multidisciplinary approach, which have demonstrated efficacy in reducing cardiovascular events in this population. Additional therapies such as statins have been shown to reduce MACE incidence by 24–30 % through their lipid-lowering and anti-inflammatory effects [13]. Despite statin therapy, the residual cardiovascular risk remains; thus, further options are being explored [14,15]. This underscores the ongoing interest in identifying novel or repurposed therapeutic agents to further mitigate ASCVD risk in T2DM patients. Emerging evidence highlights the importance of addressing oxidative stress and inflammation—key contributors to cardiovascular disease in T2DM—as part of a comprehensive preventive strategy. Recent studies have explored the potential cardiovascular benefits of N-Acetylcysteine (NAC), an antioxidant known for its endothelial protective properties [7,16–21]. However, the comprehensive effects of NAC on various types of MACE in T2DM patients have not been fully elucidated.

Given the increasing prevalence of T2DM and the substantial cardiovascular risk associated with the disease [6–9], [6–9] there is a pressing need for effective preventive therapies beyond traditional glucose-lowering agents [10–12]. NAC has shown promise in reducing oxidative stress and inflammation, key factors in the pathogenesis of cardiovascular diseases [7,16–21]. This study aims to investigate the long-term effects of NAC on MACE risk in T2DM patients, focusing on its potential to serve as an adjunctive therapy in cardiovascular risk management. By analyzing data from a large, population-based cohort, this research seeks to provide empirical evidence of NAC's efficacy in reducing cardiovascular events, thereby addressing a critical gap in current diabetes care strategies.

2. Patients and methods

2.1. Study population

This study utilized data sourced from Taiwan's National Health Insurance Research Database (NHIRD), a robust repository containing comprehensive information spanning disease diagnoses, procedural details, medication prescriptions, demographics, and beneficiary enrollment profiles [22–25]. To safeguard patient confidentiality, the database employs encrypted identifiers. Furthermore, its seamless

integration with Taiwan's Death Registry ensures meticulous determination of vital status and causes of death, bolstering the study's integrity and credibility. Ethical approval for the study protocols was obtained from the Institutional Review Board of Tzu-Chi Medical Foundation (IRB109-015-B).

Our study focused solely on individuals aged 20 years or older diagnosed with T2DM between 2008 and 2018, with follow-up extending until December 31, 2021. The diagnosis of T2DM in this study was based on either one hospitalization or at least two outpatient visits within one year, coded with ICD-9-CM 250.xx (excluding 250.1x) or ICD-10-CM E11. In Taiwan, the assignment of these diagnostic codes follows American Diabetes Association (ADA) criteria, confirmed by two tests. The accuracy of T2DM diagnoses in the NHIRD has been validated in previous Taiwanese studies [26,27]. The severity of diabetes was further assessed using the adapted Diabetes Complications Severity Index (aDCSI), a validated measure within the NHIRD [26].

To ensure the accuracy of our data, we meticulously excluded patients with missing age-related information from the analysis. NAC use was defined as consistent administration, with an annual average dose exceeding 28 cumulative defined daily doses (cDDD), indicating regular, long-term usage. The index date was set as 1 year following the initial documented use of NAC therapy, surpassing the threshold of 28 cDDDs annually. We rigorously excluded patients with pre-existing MACE before the index date from the analysis. The case group consisted solely of T2DM patients who received a minimum of 28 cDDDs of NAC annually, while the control group comprised individuals who did not receive NAC therapy but were prescribed at least one type of non-NAC antimetabolic agents throughout the entire follow-up period.

2.2. Study covariates and propensity score matching

In our study, participants with T2DM were stratified into distinct age categories at the index date: 20–49, 50–59, 60–69, and ≥ 70 years. We employed propensity score matching (PSM) using a 1:1 nearest neighbor matching method to mitigate potential confounding factors and achieve balance between NAC users and nonusers. Covariates encompassed various factors such as age, sex, income levels, urbanization, types of antidiabetic medications, adapted diabetes complications severity index (aDCSI), and coexisting comorbidities including hypertension, dyslipidemia, peripheral vascular disease, atrial fibrillation, chronic obstructive pulmonary disease, smoking, bronchitis, and cystic fibrosis, as well as medication use and duration of diabetes mellitus up to the index date, detailed in Table 1. Matching of NAC users and nonusers relied on variables collected at this index date, excluding MACE occurrences within 1 year after NAC use to prevent attribution to unrelated risk factors. Baseline matching was conducted prior to analysis to ensure data comparability. Diabetes duration was defined as the time from the initial diagnosis of T2DM to the index date. This variable was included as a covariate in the PSM process to ensure balanced comparison groups and to account for disease severity across both NAC users and non-users. Comorbidities were identified through diagnostic codes recorded in patient records or through at least two outpatient visits within a one-year period preceding the index date. Continuous variables were reported using appropriate measures such as mean $\pm$ standard deviation or median (first quartile and third quartile).

To address multicollinearity and accommodate multiple comparisons, several measures were undertaken. Covariate interdependencies were assessed through variance inflation factor (VIF) analysis, with a VIF threshold of 10 applied to identify and exclude highly correlated variables, thereby minimizing multicollinearity [28]. Additionally, the Bonferroni correction was applied with an adjusted alpha level of $p <$

Table 1

Characteristics of type 2 diabetes mellitus patients receiving long-term N-acetylcysteine and non-N-acetylcysteine use, and incidence of sequential major adverse cardiovascular events (Post-matching).

	Never-NAC users		NAC users		ASMD
	N = 23,359		N = 23,359		
	N	%	N	%	
Age (mean ± SD)	57.63 ± 14.93		57.89 ± 15.26		
Age, median (IQR; Q1, Q3), years-old	58.00 (47.00,69.00)		58.00 (47.00,69.00)		
Age group, years					0.0110
18–49	6894	29.51 %	6999	29.96 %	
50–59	5396	23.10 %	5359	22.94 %	
60–69	5341	22.86 %	5263	22.53 %	
≥70	5728	24.52 %	5738	24.56 %	
Sex					0.0119
Female	10,546	45.15 %	10,409	44.56 %	
Male	12,813	54.85 %	12,950	55.44 %	
Income levels (NTD)					0.0120
Low incomd/Financial dependent	7355	31.49 %	7405	31.70 %	
<20000	10,403	44.54 %	10,408	44.56 %	
2001–30000	2820	12.07 %	2732	11.70 %	
30001–45000	1869	8.00 %	1900	8.13 %	
>45000	912	3.90 %	914	3.91 %	
Urbanization					0.0047
Rural	7276	31.15 %	7327	31.37 %	
Urban	16,083	68.85 %	16,032	68.63 %	
Combined Types of Antidiabetic Medications					0.0210
0	15,090	64.60 %	14,893	63.76 %	
1	2977	12.74 %	2970	12.71 %	
2	2002	8.57 %	2075	8.88 %	
3	1633	6.99 %	1698	7.27 %	
≥4	1657	7.09 %	1723	7.38 %	
Antidiabetic Medications					
Insulin	2609	11.17 %	2712	11.61 %	0.0801
Metformin	5502	23.55 %	5322	22.78 %	0.0183
Sulfonylureas	5921	25.35 %	5484	23.48 %	0.0435
Sodium-Glucose Cotransporter 2 inhibitors	962	4.12 %	832	3.56 %	0.0291
Alpha-Glucosidase Inhibitors	1388	5.94 %	1327	5.68 %	0.0111
Thiazolidinediones	1253	5.36 %	1037	4.44 %	0.0426
Dipeptidyl Peptidase-4 inhibitors	711	3.04 %	640	2.74 %	0.0179
Glucagon-Like Peptide-1 agonists	984	4.21 %	1183	5.06 %	0.0404
Adapted Diabetes Complications Severity Index (mean ± SD)	2.37 ± 2.07		2.34 ± 2.04		
Median (IQR; Q1, Q3)	2.00 (1.00,4.00)		2.00 (1.00,4.00)		
Adapted Diabetes Complications Severity Index					0.0030
0	5085	21.77 %	5144	22.02 %	
1	4143	17.74 %	4077	17.45 %	
2	4970	21.28 %	4946	21.17 %	
≥3	9161	39.22 %	9192	39.35 %	
Coexisting Comorbidities					
Hypertension	8648	37.02 %	8511	36.44 %	0.0120
Dyslipidemia	5918	25.33 %	5791	24.79 %	0.0125
Peripheral Vascular Disease	369	1.58 %	414	1.77 %	0.0148
Atrial fibrillation	155	0.66 %	232	0.99 %	0.0365
COPD	8428	36.08 %	8002	34.26 %	0.0381
Smoking	4361	18.67 %	4579	19.60 %	0.0236
Bronchitis	7727	33.08 %	7865	33.67 %	0.0783
Cystic fibrosis	0	0.00 %	0	0.00 %	0.0000
Mediations use					
Statins	2153	9.22 %	2176	9.32 %	0.0034
Antiplatelet Agents	1494	6.40 %	1581	6.77 %	0.0149
ACE Inhibitors/ARBs	3470	14.86 %	3512	15.03 %	0.0048
Beta-Blockers	2594	11.10 %	2553	10.93 %	0.0090
N-acetylcysteine					
cDDD, Mean (SD)	3.10 ± 6.05		130.97 ± 274.31		
cDDD, Median (IQR)	0.00 (0.00,3.60)		57.60 (37.81,113.20)		
cDDD					
Never use	23,359	100.00 %	0	0.00 %	
Q1: Median (IQR): 65,000 mg (59,000, 70,000)	0	0.00 %	5852	25.05 %	
Q2: Median (IQR): 92,000 mg (83,000, 102,000)	0	0.00 %	5943	25.44 %	
Q3: Median (IQR): 154,000 mg (133,000, 184,000)	0	0.00 %	5717	24.47 %	
Q4: Median (IQR): 428000 mg (293000, 771000)	0	0.00 %	5847	25.03 %	
Daily density, DDD; Mean (SD)	0.23 ± 0.45		1.48 ± 8.38		
Daily Density, DDD; Median (IQR)	0.00 (0.00,0.20)		0.90 (0.55,1.20)		
Daily Density, DDD					
Never use	23,359	100.00 %	0	0.00 %	
<1	0	0.00 %	12,769	54.66 %	
>1	0	0.00 %	10,590	45.34 %	

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0.05 divided by the number of comparisons to control the familywise error rate across multiple statistical tests [29]. This adjustment maintained a stringent significance threshold, enhancing the robustness of our results.

2.3. Outcome variables

In this study, MACE served as the primary endpoints. MACE were defined and identified using specific ICD-10 codes and corresponding ICD-9-CM codes. Acute myocardial infarction was identified by ICD-10 codes I21 and I22, corresponding to ICD-9-CM code 410. Acute coronary syndrome and ischemic heart disease were identified by ICD-10 codes I21-I24, corresponding to ICD-9-CM codes 410–414. Cerebrovascular accidents were identified by ICD-10 codes I63, I65, and I66, corresponding to ICD-9-CM codes 430–437. Heart failure was identified by ICD-10 codes I11.0, I50, and I97.1, corresponding to ICD-9-CM code 428. Cardiovascular death was defined as death related to cardiovascular causes and identified by ICD-10 codes I20-I25, I50, I60-I69, I46.1, and I46.9, corresponding to ICD-9-CM codes 410–414 and 430–438, as documented in the last hospital admission or emergency department record. These definitions were based on established criteria referenced from the literature [30,31].

To ensure that our cohort represented a primary prevention population, only patients without a history of MACE at baseline were included. Baseline characteristics in Table 1 reflect chronic conditions and comorbidities common in patients with T2DM; however, these conditions are distinct from the acute cardiovascular events classified as MACE. Importantly, none of the ICD codes for MACE overlap with those used to define the baseline comorbidities, allowing us to exclude individuals with prior MACE events and maintain a primary prevention cohort. MACE cases were categorized into subgroups, including acute myocardial infarction, acute coronary syndrome, ischemic heart disease, cerebrovascular accidents, heart failure, and cardiac death.

2.4. NAC exposure

In our investigation, NAC prescriptions were meticulously coded using the Anatomical Therapeutic Chemical (ATC) classification system, allowing precise retrieval of pharmaceutical claims data from the NHIRD. The defined daily dose (DDD) of NAC, as established by the World Health Organization, is set at 600 mg. To evaluate the intensity of NAC usage, we calculated each patient's cumulative NAC dose by dividing the total prescribed NAC dose by the number of prescription days. This approach enabled differentiation between various levels of NAC exposure, classified as average daily doses below or above 1 DDD. NAC was typically administered orally in divided doses throughout the day, reflecting real-world prescription patterns.

Adherence was inferred based on consistent prescription refills, with patients categorized as adherent if they maintained an annual cumulative dose exceeding 28 cDDD's each year. The quartiles were defined as

follows: Q1 (lowest exposure), Q2, Q3, and Q4 (highest exposure), with the specific cDDD ranges for each quartile based on the distribution of NAC doses in our cohort. All statistical models were adjusted for the covariates mentioned above, ensuring a comprehensive evaluation of NAC's impact on major adverse cardiovascular events.

2.5. Statistical analysis

To address potential confounding factors, our Cox regression models were adjusted for various covariates, including age, sex, income levels, urbanization, types of antidiabetic medications, diabetes complications severity index (aDCSI), coexisting comorbidities, medication use, and duration of T2DM up to the index date [32]. Additionally, to compare MACE incidence between NAC users and non-users, we utilized a time-dependent Cox hazards model, also adjusted for the mentioned covariates. NAC use data were updated quarterly to capture its dynamic nature, allowing for a precise characterization of NAC status as a time-dependent variable. Follow-up periods were classified as "unexposed" if NAC was not used for at least 3 consecutive months, accounting for intermittent patterns in NAC use and reducing potential exposure misclassification. Event-free person-years prior to the first NAC prescription were also categorized as unexposed periods, ensuring consistency in the exposure assessment. Competing risk analysis was performed to consider mortality risk [33].

Cumulative incidences of MACE were assessed using the Kaplan-Meier method, with differences between NAC users and non-users evaluated using a stratified log-rank test (sFig. 1). Similarly, MACE incidence according to different cDDD levels was estimated using the Kaplan-Meier method, with differences assessed using a stratified log-rank test (sFig. 2). All statistical analyses were conducted using SAS software (version 9.4; SAS Institute, Cary, NC, USA), ensuring rigorous and robust data analysis.

3. Results

After PSM, the study included 46,718 individuals diagnosed with T2DM in Taiwan between 2008 and 2018. Both NAC users and nonusers had similar average ages at T2DM diagnosis, 57.89 years and 57.63 years, respectively, indicating a well-balanced age distribution between the groups. An exhaustive evaluation confirmed uniform distribution of all covariates between NAC users and nonusers, highlighting the effectiveness of our adjustment process in achieving covariate equivalence (as outlined in Table 1), with all absolute standardized mean differences below 0.1 [34].

3.1. Crude risk of MACE in matched T2DM patients

Table 2 presents the crude risk of MACE incidence in PSM patients with T2DM receiving long-term NAC therapy versus those who did not receive NAC. Among the matched cohort, comprising 23,359 NAC users

Table 1 (continued)

	Never-NAC users		NAC users		ASMD
	N = 23,359		N = 23,359		
	N	%	N	%	
Duration of diabetes mellitus up to the index date, years					
Mean (SD) follow-up	0.31 ± 0.07		0.35 ± 0.04		0.5306
Median (IQR) follow-up	0.00 (0.00,0.02)		0.00 (0.00,0.02)		0.8940
Follow-up time, years					
Mean (SD) follow-up	5.87 ± 4.30		6.05 ± 4.67		<0.0001
Median (IQR) follow-up	4.79 (2.35,8.47)		4.99 (2.10,9.11)		0.8831

Abbreviations: NAC: N-Acetylcysteine; ASMD: Absolute Standardized Mean Difference; N: Number; SD: Standard Deviation; IQR: Interquartile Range; Q: Quartile; NTD: New Taiwan Dollar; COPD: Chronic Obstructive Pulmonary Disease; and ACE Inhibitors/ARBs: Angiotensin-Converting Enzyme Inhibitors/Angiotensin Receptor Blockers.

Table 2

Crude risk of major adverse cardiovascular events incidence in propensity score matched patients with type 2 diabetes mellitus receiving long-term N-acetylcysteine and non-N-acetylcysteine therapy.

Events	Never NAC users N = 23,359		NAC users N = 23,359		P Value
	N	%	N	%	
Overall Major Adverse Cardiovascular Events	10,948	46.87 %	9750	41.74 %	<0.0001
Acute myocardial infarction	803	3.44 %	707	3.03 %	0.012
Acute Coronary Syndrome/ Ischemic Heart Disease	7786	33.33 %	6459	27.65 %	<0.0001
Cerebrovascular accidents	5700	24.40 %	5081	21.75 %	<0.0001
Heart Failure	3387	14.50 %	3144	13.46 %	0.0454
Cardiac death	1702	7.29 %	1559	6.67 %	0.0094

Abbreviations: NAC: N-Acetylcysteine; N: Number.

and 23,359 non-NAC users, the overall incidence of MACE was significantly lower in NAC users compared to non-NAC users (41.74 % vs. 46.87 %, $P < .0001$). Specifically, the incidence of acute myocardial infarction was 3.03 % in NAC users and 3.44 % in non-NAC users, with a significant difference ($P = 0.012$). The incidence of Acute Coronary Syndrome/Ischemic Heart Disease (ACS/IHD) was also significantly lower in NAC users compared to non-NAC users (27.65 % vs. 33.33 %, $P < .0001$). Similarly, cerebrovascular accidents were less frequent among NAC users (21.75 %) compared to non-NAC users (24.40 %), with a significant difference ($P < .0001$). Heart failure incidence was slightly lower in NAC users (13.46 %) than in non-NAC users (14.50 %), reaching statistical significance ($P = 0.0454$). Furthermore, cardiac death was significantly less common in NAC users (6.67 %) compared to non-NAC users (7.29 %), with a P value of 0.0094. Overall, these results indicate that long-term NAC therapy is associated with a reduced risk of various major adverse cardiovascular events in patients with Type 2 Diabetes Mellitus.

3.2. MACE risk in matched T2DM patients by NAC dosage

Patients receiving NAC showed a significantly reduced risk of MACE compared to those who never used NAC, with aHRs of 0.84 (95 % CI: 0.81–0.86, $P < .0001$), and 0.78 (95 % CI: 0.76–0.81, $P < .0001$) after competing risks analysis (Table 3). The Kaplan-Meier plots in sFig. 1 illustrate the cumulative incidence of MACE among T2DM patients treated with NAC compared to those who did not receive NAC. The

Table 3

Major adverse cardiovascular events risk among matched type 2 diabetes mellitus patients receiving N-acetylcysteine at various daily intensity and cumulative doses.

	Major Adverse Cardiovascular Events risk					
	Crude HR(95%CI)	P-value	aHR ^a (95%CI)	P-value	aHR ^b (95%CI)	P-value
NAC (ref. Never-NAC use)	1.00	–	1.00	–	1.00	–
NAC use	0.87 (0.85, 0.89)	<0.0001	0.84 (0.81, 0.86)	<0.0001	0.78 (0.76, 0.81)	<0.0001
cDDD of NAC (ref. Never-NAC use)	1.00	–	1.00	–	1.00	–
Q1	0.95 (0.91, 1.01)	0.0713	0.98 (0.91, 1.07)	0.2621	0.96 (0.92, 1.01)	0.0833
Q2	0.88 (0.85, 0.92)	<0.0001	0.90 (0.86, 0.94)	<0.0001	0.84 (0.8, 0.88)	<0.0001
Q3	0.88 (0.84, 0.92)	<0.0001	0.86 (0.82, 0.9)	<0.0001	0.79 (0.75, 0.82)	<0.0001
Q4	0.77 (0.73, 0.8)	<0.0001	0.64 (0.61, 0.67)	<0.0001	0.61 (0.58, 0.64)	<0.0001
P for trend		<0.0001		<0.0001		<0.0001
Daily Density, DDD of NAC (ref. Never-NAC use)	1.00	–	1.00	–	1.00	–
<1	0.93 (0.9, 0.96)	<0.0001	0.87 (0.81, 0.89)	<0.0001	0.81 (0.76, 0.84)	<0.0001
≥1	0.80 (0.77, 0.83)	<0.0001	0.82 (0.80, 0.87)	<0.0001	0.77 (0.76, 0.82)	<0.0001
P for trend		<0.0001		<0.0001		<0.0001

ABBREVIATIONS: NAC: N-acetylcysteine; ref.: Reference; HR: Hazard ratio; aHR: Adjusted hazard ratio; CI: Confidence interval; Q: Quartile; DDD: Defined daily dose; cDDD: Cumulative defined daily doses.

^a The time-varying Cox model, which treats NAC use as a dynamic variable, was adjusted to account for several factors. These include age, sex, income levels, urbanization, types of antidiabetic medications, diabetes complications severity index (aDCSI), coexisting comorbidities, medication use, and duration of T2DM up to the index date.

^b The Fine and Gray method was adapted to estimate the hazard of HCC considering competing risks from death.

results demonstrate a significantly lower cumulative incidence of MACE in the NAC-treated group compared to the non-NAC group. The log-rank test for the Kaplan-Meier curves indicates a statistically significant difference ($P < 0.0001$), suggesting that NAC treatment is associated with a reduced risk of cardiovascular events in T2DM patients.

When stratified by cDDD of NAC, patients in the highest quartile (Q4) exhibited the lowest risk of MACE, with an aHR of 0.61 (95 % CI: 0.58–0.64, $P < .0001$). This dose-dependent trend was consistent across all quartiles, with significant reductions in MACE risk observed in Q2 (aHR: 0.84, 95 % CI: 0.80–0.88, $P < .0001$) and Q3 (aHR: 0.79, 95 % CI: 0.75–0.82, $P < .0001$). sFig. 2 presents the Kaplan-Meier curves for the cumulative incidence of MACE among T2DM patients treated with NAC, stratified by cDDD categories. The data indicate a dose-dependent relationship, with higher cDDD categories of NAC correlating with a progressively lower incidence of MACE. The stratified log-rank test reveals significant differences across the cDDD categories ($P < 0.0001$), supporting the dose-dependent protective effect of NAC against cardiovascular events in T2DM patients. sFig. 3 shows the correlation between cDDDs of NAC and HRs for MACE in T2DM patients. The analysis demonstrates a clear inverse relationship, where increasing cDDDs of NAC are associated with progressively lower HRs for MACE.

For daily NAC dose intensity, patients receiving less than 1 DDD had an aHR of 0.81 (95 % CI: 0.76–0.84, $P < .0001$). Those with a daily dose of 1 DDD or more exhibited further risk reduction, with an aHR of 0.77 (95 % CI: 0.76–0.82, $P < .0001$). Trend analysis confirmed a significant dose-response relationship for both cumulative and daily doses of NAC, with P values for trend consistently <0.0001 across all models. These findings indicate that higher NAC exposure, both cumulatively and daily, is associated with a progressively lower risk of MACE in matched T2DM patients.

Fig. 1 illustrates the cumulative incidence of MACE among NAC users and non-users, showing a significantly lower risk in the NAC cohort. The dose-dependent effect of NAC on MACE incidence is further highlighted, with higher cumulative daily doses of NAC associated with progressively reduced risk over time.

3.3. Types of MACE risk reduction in T2DM patients with NAC treatment

For acute myocardial infarction, NAC use was associated with a significantly reduced risk, with a crude HR of 0.93 (95 % CI: 0.84–0.97, $P = 0.0463$), an aHR of 0.96 (95 % CI: 0.87–0.97, $P = 0.0467$), and an aHR considering competing risks of 0.87 (95 % CI: 0.79–0.97, $P = 0.009$) (Table 4). In the case of Acute Coronary Syndrome/Ischemic Heart Disease, NAC use showed a significant risk reduction with a crude HR of

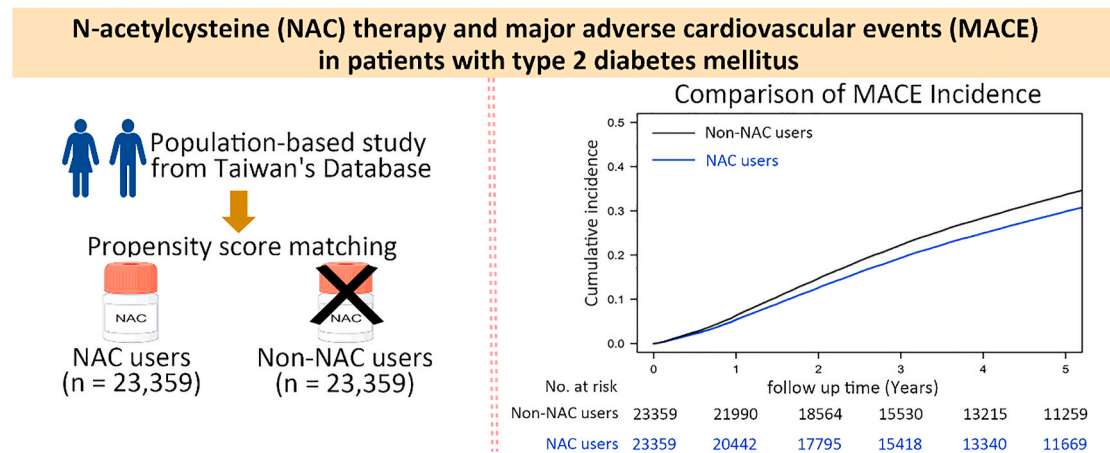


Fig. 1. Incidence of Major Adverse Cardiovascular Events in Type 2 Diabetes Mellitus patients receiving N-acetylcysteine therapy compared to non-NAC users. Long-term NAC therapy is associated with a significantly reduced MACE risk, demonstrating a dose-dependent effect across quartiles of cumulative daily dose.

Table 4

Risk of various types of major adverse cardiovascular events in matched type 2 diabetes mellitus patients with or without N-acetylcysteine treatment.

	Major Adverse Cardiovascular Events risk								
	Crude HR(95%CI)		P-value	aHR ^a (95%CI)		P-value	aHR ^b (95%CI)		P-value
Acute myocardial infarction									
NAC (ref. Never-NAC use)	1.00	—	—	1.00	—	—	1.00	—	—
NAC use	0.93	(0.84, 0.97)	0.0463	0.96	(0.87, 0.97)	0.0467	0.87	(0.79, 0.97)	0.009
Acute Coronary Syndrome/Ischemic Heart Disease									
NAC (ref. Never-NAC use)	1.00	—	—	1.00	—	—	1.00	—	—
NAC use	0.82	(0.8, 0.85)	<0.0001	0.81	(0.78, 0.83)	<0.0001	0.76	(0.73, 0.79)	<0.0001
Cerebrovascular accidents									
NAC (ref. Never-NAC use)	1.00	—	—	1.00	—	—	1.00	—	—
NAC use	0.92	(0.89, 0.95)	<0.0001	0.93	(0.89, 0.96)	0.0001	0.86	(0.83, 0.89)	<0.0001
Heart Failure									
NAC (ref. Never-NAC use)	1.00	—	—	1.00	—	—	1.00	—	—
NAC use	0.97	(0.92, 0.99)	0.0443	0.96	(0.93, 0.99)	0.0484	0.93	(0.88, 0.98)	0.0378
Cardiac death									
NAC (ref. Never-NAC use)	1.00	—	—	1.00	—	—	1.00	—	—
NAC use	0.95	(0.91, 0.98)	0.0409	0.92	(0.89, 0.96)	<0.0001	0.90	(0.83, 0.97)	0.0152

ABBREVIATIONS: NAC: N-acetylcysteine; ref.: Reference; HR: Hazard ratio; aHR: Adjusted hazard ratio; CI: Confidence interval.

^a The time-varying Cox model, which treats NAC use as a dynamic variable, was adjusted to account for several factors. These include age, sex, income levels, urbanization, types of antidiabetic medications, diabetes complications severity index (aDCSI), coexisting comorbidities, medication use, and duration of T2DM up to the index date.

^b The Fine and Gray method was adapted to estimate the hazard of HCC considering competing risks from death.

0.82 (95 % CI: 0.80–0.85, $P < .0001$), an aHR of 0.81 (95 % CI: 0.78–0.83, $P < .0001$), and an aHR considering competing risks of 0.76 (95 % CI: 0.73–0.79, $P < .0001$). For cerebrovascular accidents, the risk was also significantly lower in NAC users, with a crude HR of 0.92 (95 % CI: 0.89–0.95, $P < .0001$), an aHR of 0.93 (95 % CI: 0.89–0.96, $P = 0.0001$), and an aHR considering competing risks of 0.86 (95 % CI: 0.83–0.89, $P < .0001$). Regarding heart failure, NAC use was associated with a reduced risk, with a crude HR of 0.97 (95 % CI: 0.92–0.99, $P = 0.0443$), an aHR of 0.96 (95 % CI: 0.93–0.99, $P = 0.0484$), and an aHR considering competing risks of 0.93 (95 % CI: 0.88–0.98, $P = 0.0378$). Finally, for cardiac death, NAC use was linked to a lower risk, with a crude HR of 0.95 (95 % CI: 0.91–0.98, $P = 0.0409$), an aHR of 0.92 (95 % CI: 0.89–0.96, $P < .0001$), and an aHR considering competing risks of 0.90 (95 % CI: 0.83–0.97, $P = 0.0152$). These findings indicate that NAC treatment is associated with a significantly reduced risk of various MACE types in T2DM patients, even after adjusting for multiple covariates and considering competing risks from death.

4. Discussion

This study is the first to demonstrate the dose-dependent efficacy of NAC in reducing MACE in patients with T2DM. Utilizing a robust dataset

from Taiwan's National Health Insurance Research Database, our findings reveal that long-term NAC therapy is associated with a significantly lower risk of MACE, including acute myocardial infarction, acute coronary syndrome/ischemic heart disease, cerebrovascular accidents, heart failure, and cardiac death. Specifically, the overall incidence of MACE was significantly lower in NAC users (41.74 %) compared to non-NAC users (46.87 %) ($P < .0001$) (Table 2). The incidence rates of acute myocardial infarction, acute coronary syndrome/ischemic heart disease, cerebrovascular accidents, heart failure, and cardiac death were also significantly reduced in NAC users ($P < .05$ for all comparisons) (Table 2, Table 3, Table 4). The results underscore the novel discovery of NAC's protective cardiovascular effects, particularly in a dose-dependent manner, as higher cDDD of NAC were correlated with progressively lower risks of MACE (sFig. 1, sFig. 2, sFig. 3).

Cardiovascular complications represent a severe and significant health burden for patients with T2DM, contributing substantially to morbidity and mortality. Globally, individuals with T2DM are 2–4 times more likely to develop cardiovascular diseases compared to those without diabetes [6,7]. In Taiwan, cardiovascular diseases account for a significant proportion of mortality among diabetic patients, with approximately 35 % of all deaths attributed to these complications [7]. The economic impact is equally profound, with diabetes-related

cardiovascular complications costing healthcare systems billions of dollars annually. For instance, in the United States alone, the annual direct medical costs associated with cardiovascular diseases in diabetes patients exceed \$37 billion [8]. The high prevalence of these complications not only deteriorates patient quality of life but also imposes a heavy financial burden on healthcare systems globally [4]. Cardiovascular diseases remain a leading cause of death among individuals with diabetes [7]. Despite advances in glucose-lowering therapies, effective preventive strategies for MACE are limited. Our study is the first to confirm the dose-dependent effects of NAC in reducing the risk of various MACE types (Table 3 and sFig. 1), providing valuable insights into its potential role in comprehensive cardiovascular risk management for diabetic patients.

The cardioprotective effects of NAC can be attributed to several fundamental mechanisms that collectively contribute to the reduction of MACE in patients with T2DM. NAC enhances endothelial function by increasing the bioavailability of nitric oxide (NO), improving vascular reactivity and endothelial health [7,16,17]. Its potent antioxidant properties reduce oxidative stress by scavenging reactive oxygen species (ROS) and replenishing intracellular glutathione, which is crucial in preventing endothelial dysfunction and atherosclerosis [7,18,19]. Furthermore, NAC has significant anti-inflammatory effects by inhibiting nuclear factor kappa B (NF- κ B), thereby reducing the production of pro-inflammatory cytokines and mitigating chronic inflammation associated with atherosclerosis [20,21]. These combined actions lead to the stabilization of atherosclerotic plaques, reducing the likelihood of plaque rupture and subsequent thrombotic events such as myocardial infarction and stroke [7,16–21]. Additionally, NAC exhibits antithrombotic effects by modulating platelet function and inhibiting thromboxane synthesis [8,35], which further decreases the risk of thrombotic events. Clinically, these mechanisms translate into a significantly lower incidence of various MACE types in NAC users, including acute myocardial infarction, acute coronary syndrome/ischemic heart disease, cerebrovascular accidents, heart failure, and cardiac death (Table 2). This underscores NAC's potential as a valuable adjunctive therapy in cardiovascular risk management for diabetic patients.

Previous studies have predominantly focused on the benefits of glucose-lowering medications in T2DM management [10–12] with limited attention to the direct cardiovascular protective effects of adjunct therapies like NAC. For instance, studies have shown that traditional glucose-lowering agents such as metformin, sulfonylureas, and insulin significantly reduce HbA1c levels and improve glycemic control, which can indirectly reduce cardiovascular risk. However, the direct impact of these agents on cardiovascular outcomes varies [10,11] with some studies indicating potential cardiovascular benefits and others showing neutral effects [12]. However, these studies often do not directly address the cardiovascular outcomes associated with these therapies beyond glucose control [10–12]. Definitive evidence that cardiovascular disease in T2DM can be reversed or prevented through improved glycemic control remains incomplete [10–12]. This conclusion awaits large, long-term clinical trials using modern treatment strategies, including drug combinations designed to maximize HbA1c reduction while minimizing hypoglycemia and weight gain [10]. Current research indicates the need for such trials to ascertain the full potential of glycemic control in mitigating cardiovascular risks in T2DM patients. Research on antioxidants, including NAC, has indicated potential cardiovascular benefits, primarily through mechanisms such as reducing oxidative stress and inflammation [7,16–21]. Our study is novel in that it comprehensively demonstrates the dose-dependent effects of NAC on MACE reduction in a large-scale, real-world population. Utilizing a cohort of 46,718 T2DM patients from Taiwan's NHIRD, our findings provide empirical evidence that long-term NAC therapy significantly lowers the incidence of MACE, including acute myocardial infarction, acute coronary syndrome/ischemic heart disease, cerebrovascular accidents, heart failure, and cardiac death (Table 2, Table 3, Table 4). These results align with and extend the existing literature by

highlighting NAC's potential as a complementary therapeutic strategy in managing cardiovascular risk in T2DM patients.

This study possesses several strengths and limitations that merit consideration. Among its strengths, the use of a large, population-based cohort from Taiwan's NHIRD enhances the generalizability of the findings by providing a robust and representative sample size of 46,718 T2DM patients. The comprehensive nature of the NHIRD data allows for detailed patient information and thorough investigation of the long-term effects of NAC on MACE. The application of PSM, time-varying Cox models, and adjustment for multiple covariates ensures the robustness of the results by minimizing potential confounding factors. However, the observational nature of the study inherently subjects it to unmeasured confounding despite these adjustments. For instance, the absence of data on lifestyle factors, such as diet and physical activity, as well as laboratory measures like lipid levels—key determinants of cardiovascular health—limits our ability to fully account for all potential confounders. The observational design of this study inherently limits its ability to establish causality, and the results should be considered hypothesis-generating. Further validation through rigorously designed randomized controlled trials (RCTs) is essential to confirm the safety, efficacy, and long-term outcomes of the intervention [36–40]. The study also could not accurately assess patients' adherence to NAC therapy, leading to potential variations in the observed effects. Nevertheless, if compliance with NAC use was poor in the NAC user group, the conclusion of reduced MACE risk would be underestimated rather than invalidated. Additionally, potential misclassification of outcomes due to coding errors or variations in clinical practice remains a limitation. Despite these challenges, the study provides valuable real-world evidence. Future RCTs are necessary to validate these findings, establish causality, and further elucidate the mechanisms by which NAC may reduce cardiovascular risk in T2DM patients. These future studies could provide more definitive insights and potentially support the integration of NAC into comprehensive cardiovascular risk management strategies for diabetic patients.

5. Conclusions

Our study provides compelling evidence for the dose-dependent cardiovascular protective effects of NAC in T2DM patients. These findings underscore the importance of considering NAC as a valuable adjunctive therapy in reducing the burden of MACE, thereby improving clinical outcomes and enhancing the quality of life for diabetic patients. While our findings are promising, they should be interpreted with caution. Large-scale RCTs are needed to validate these observations and fully assess the intervention's potential to reduce cardiovascular disease risk in the diabetes population.

CRedit authorship contribution statement

Mingyang Sun: Conceptualization, and, Design, Collection and Assembly of Data, Manuscript Writing, Final Approval of Manuscript. **Zhongyuan Lu:** Conceptualization, and, Design, Formal analysis, and, Interpretation, Manuscript Writing, Final Approval of Manuscript. **Wan-Ming Chen:** Conceptualization, and, Design, Formal analysis, and, Interpretation, Manuscript Writing, Final Approval of Manuscript. **Shuang Lv:** Collection and Assembly of Data, Formal analysis, and, Interpretation, Final Approval of Manuscript. **Ningning Fu:** Collection and Assembly of Data, Final Approval of Manuscript. **Yitian Yang:** Collection and Assembly of Data, Formal analysis, and, Interpretation, Final Approval of Manuscript. **Yangyang Wang:** Collection and Assembly of Data, Final Approval of Manuscript. **Mengrong Miao:** Collection and Assembly of Data, Final Approval of Manuscript. **Szu-Yuan Wu:** Conceptualization, and, Design, Collection and Assembly of Data, Formal analysis, and, Interpretation, Administrative Support, Manuscript Writing, Final Approval of Manuscript. **Jiaqiang Zhang:** Manuscript Writing, Final Approval of Manuscript.

For software

Project name: Not applicable.
 Project homepage: Not applicable.
 Archived version: Not applicable.
 Operating system(s): Not applicable.
 Programming language: Not applicable.
 Other requirements: Not applicable.
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 Any restrictions to use by nonacademicians: Not applicable.

Ethics approval and consent

The study protocols were reviewed and approved by the Institutional Review Board of Tzu-Chi Medical Foundation (IRB109-015-B).

Consent for publication

Not applicable.

Availability of data and material

The datasets supporting the study conclusions are included within this manuscript and its supplementary files.

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Competing interests

The authors have no potential conflicts of interest to declare.

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The datasets supporting the study conclusions are included in the manuscript. We utilized data from the National Health Insurance Research Database and the Taiwan Cancer Registry database. Due to the Personal Information Protection Act executed by Taiwan's government starting in 2012, access to the data underlying these findings is restricted and cannot be made available in the manuscript, supplemental files, or public repositories. Data requests can be submitted via a formal proposal to the ethics review committee of the relevant governmental department in Taiwan. Further information regarding data access can be found at the following links: [NHIRD Data Subsets](#) and [NHIRD Contact Information](#).

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.atherosclerosis.2025.119117>.

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