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Impact of TNF-α inhibitor therapy on cardiovascular outcomes in ankylosing spondylitis: a nationwide population-based study

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Abstract. – OBJECTIVE: This study aimed to evaluate the association between tumor necrosis factor-α inhibitor (TNFi) therapy and cardiovascular (CV) outcomes, as well as all-cause mortality, in patients with ankylosing spondylitis (AS).

PATIENTS AND METHODS: This retrospective cohort study included 24,986 patients newly diagnosed with AS between 2010-2019 without a history of CV diseases, using data from the Korean National Health Insurance Service. CV events were observed through the end of 2021. After exposure density sampling (1:1), we investigated the association among use of TNFi, duration of TNFi use, and risk of the composite CV outcome (ischemic stroke, heart failure, ischemic heart disease, or CV death) and all-cause mortality.

RESULTS: Overall, TNFi users (N = 8,650) and non-users (N = 8,580) had a comparable risk of the composite CV outcome. However, prolonged TNFi use (≥ 1 year) was associated with a significantly lower risk of the composite CV outcome [adjusted hazard ratio (aHR): 0.72, 95% CI: 0.55-0.93, $p = 0.012$] and all-cause mortality (aHR: 0.37, 95% CI: 0.21-0.66, $p < 0.001$) compared to discontinued TNFi use (< 1 year), with adjustments made for age, sex, disease duration, hypertension, diabetes, hyperlipidemia, chronic kidney disease, non-steroidal anti-inflammatory drug (NSAID) use, body mass index (BMI), and smoking status.

CONCLUSIONS: TNFi therapy did not reduce CV events in AS patients. However, long-term TNFi therapy is likely to be beneficial in reducing CV events and all-cause mortality compared to discontinuing TNFi therapy in patients with AS.

Key Words:
TNF-α inhibitor, Cardiovascular, Mortality, Ankylosing spondylitis.

Introduction

Ankylosing spondylitis (AS) is a chronic inflammatory disease that primarily affects the axial skeleton, leading to progressive stiffness and disability[1]. Beyond its characteristic musculoskeletal symptoms, AS is associated with an increased risk of cardiovascular (CV) disease, which is a leading cause of morbidity and mortality in this patient population[2,3]. The heightened CV risk in AS patients is largely attributed to systemic inflammation, which promotes atherogenesis and exacerbates existing CV conditions, as well as a higher prevalence of traditional CV risk factors compared to the general population[2].

Tumor necrosis factor-α inhibitors (TNFi) have revolutionized the treatment of AS, offering significant relief from symptoms and halting disease progression[4-6]. These biological agents target TNF-α, a key cytokine involved in the inflammatory cascade of AS[1,7]. TNFi has been shown to reduce sub-clinical atherosclerosis and alter the lipid profiles in AS patients, suggesting a poten-

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tial benefit in reducing CV risk[2]. Additionally, a recent Mendelian randomization study[8] demonstrated a causal association between TNF-α inhibition and the reduction of risk for multiple CV diseases or decreased metabolic CV risk factors. However, the relationship between TNFi use and CV outcomes in AS patients remains unclear, with limited data available.

Observational studies on TNFi use and CV risk in AS patients have offered mixed results. Some studies[9,10] have suggested that TNFi use is associated with a reduced risk of CV events, while others[11,14] did not find significant effects. Notably, Shi et al[12,14] showed that a high inflammatory burden, such as elevated erythrocyte sedimentation rate (ESR), was a strong predictor of CV events in their recent studies. In particular, they proposed that the observed CV benefits of TNFi in AS patients were likely due to inflammation control rather than the direct effects of medication. Another study[15] reported that TNFi therapy provided CV benefits in patients with rheumatoid arthritis (RA) by reducing the incidence of myocardial infarction (MI) in those who responded to treatment. This suggests that the therapeutic effects of TNFi, while primarily driven by inflammation control, may offer additional protective benefits against CV events, particularly in patients who respond well to treatment. Therefore, while TNFi may offer CV benefits through effective inflammation control, further research is necessary to elucidate the specific and long-term effects of TNFi on CV outcomes in AS patients, particularly considering varying drug responses and usage patterns.

No study to date has analyzed differences in CV outcomes based on drug response or TNFi usage patterns in AS patients. To address this gap, we investigated the impact of TNFi therapy on CV disease risk in a large AS cohort. Our objectives were 1) to determine how TNFi use influences the risk of CV disease in AS patients compared to non-users in a nationwide cohort and 2) to assess the potential benefits of long-term TNFi therapy (≥ 1 year) on CV outcomes and all-cause mortality compared to short-term use (< 1 year). Utilizing data from the Korean National Health Insurance Service claims database (NHID), we conducted a nationwide, population-based, retrospective cohort study to evaluate the associations between TNFi use and CV outcomes, considering both short-term and long-term usage patterns.

Patients and Methods

Study Design and Data Source

This nationwide, population-based, retrospective cohort study used data from the Korean NHID. The NHID encompasses the entire population of Korea due to the government's mandatory National Health Insurance (NHI) system and medical aid program. The database includes comprehensive information like demographics, socioeconomic data, death-related data (date and cause of death), medical treatments, procedures, medical check-up data, disease diagnoses [International Classification of Diseases 10th revision (ICD-10)], and rare intractable diseases (RID) registration information[16]. AS was included in the RID registration program by the NHI in 2009, providing patients with enhanced coverage of their medical costs. Patients must meet the standardized diagnostic criteria established by the NHI to be registered in the RID program[17].

Study Population

Patients with claims data for AS between January 1, 2010, and December 31, 2019, were extracted from the NHID. AS patients were identified using the ICD-10 code M45 along with the RID code V140. The inclusion criteria required a diagnosis of AS confirmed by at least two outpatient visits at least 7 days apart. In the RID program, a diagnosis of AS was established based on the modified New York criteria[18].

To include only incident AS cases, a washout period from 2007 to 2009 was applied. Patients were excluded if they had a prior diagnosis of AS during this period. Additionally, those diagnosed with other rheumatic diseases (rheumatoid arthritis, adult-onset Still's disease, juvenile idiopathic arthritis, systemic lupus erythematosus, idiopathic inflammatory myopathy, systemic sclerosis) or potential AS-mimicking diseases (diffuse idiopathic skeletal hyperostosis, osteitis condensans, Paget's disease), or those younger than 16 years at the time of AS diagnosis were excluded. Additionally, individuals with a history of CV diseases (ischemic heart disease, stroke, and heart failure) before AS diagnosis or those with exposure to TNFi before AS diagnosis were excluded. The patient selection flow is illustrated in Figure 1.

Exposure Measures and Grouping

The primary exposure of interest was the use of TNFi. TNFi users were defined as patients who received at least one prescription for any TNFi

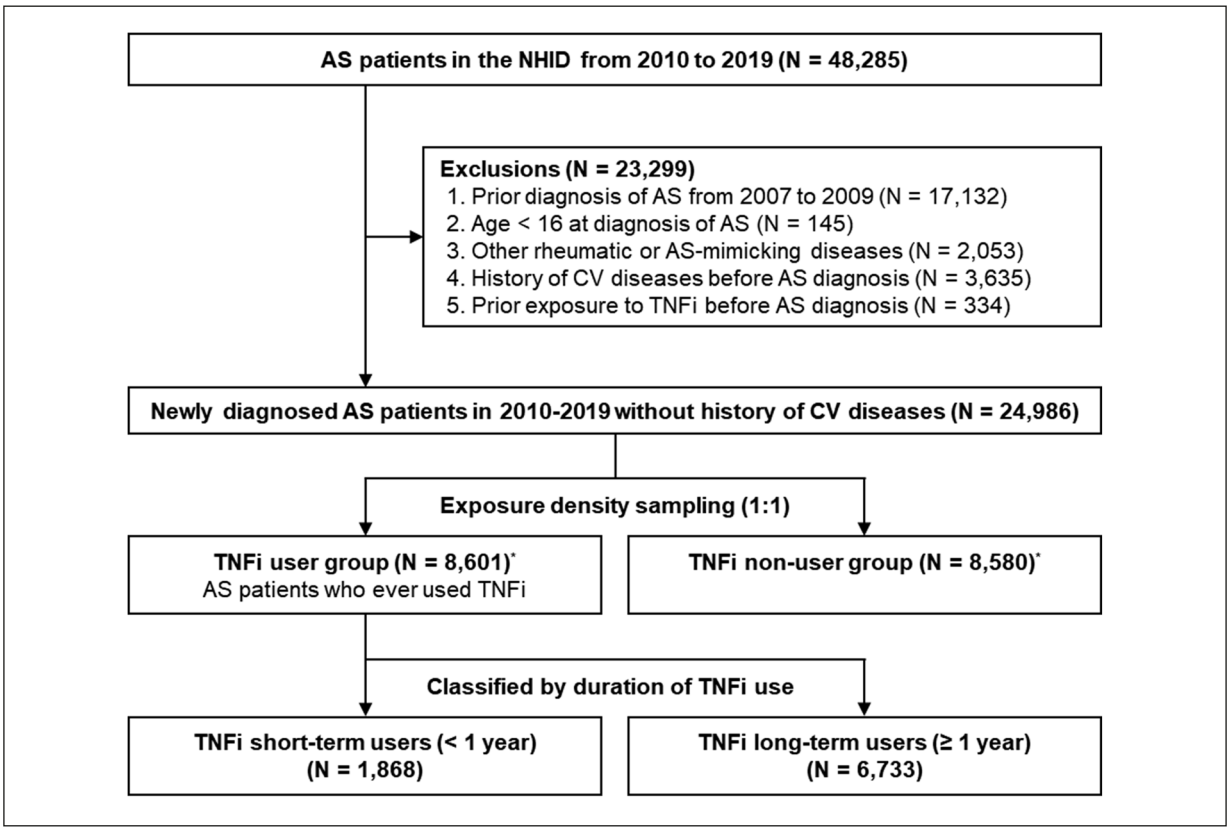

Figure 1. Flow-chart of patients' selection. AS, ankylosing spondylitis; NHID, National Health Information Database; CV, cardiovascular; TNFi, tumor necrosis factor-α inhibitor. *Patients with a history of CV disease before the index date were excluded from both groups.

agent (infliximab, etanercept, adalimumab, golimumab, and certolizumab pegol) during the study period. Non-users were those who did not receive a TNFi prescription. For the TNFi user group, the index date was the first day of TNFi use. For the TNFi non-user control group, the index date was the date equivalent to the index date of the TNFi user group in the disease duration of AS. The control group was selected using 1:1 exposure density sampling, a dynamic matching method, at the time of exposure (**Supplementary Figure 1**)[19].

The TNFi user group was further divided into short-term users (< 1 year) and long-term users (≥ 1 year) (Figure 1). This classification enabled an evaluation of the impact of TNFi usage duration on CV outcomes. Given that TNFi users generally have high disease severity due to the stringent reimbursement criteria in Korea, where patients must exhibit high disease activity of Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) ≥ 4, despite using at least two nonsteroidal anti-inflammatory drugs (NSAIDs) for ≥ 3 months[20], we sought to analyze CV outcomes based on the duration of TNFi use to better understand its effects.

Outcome Measures

The primary outcome was a composite CV outcome of ischemic stroke, heart failure, ischemic heart disease, and CV-caused death. Secondary outcomes included each component of the composite CV outcome and all-cause death. CV outcomes were defined using ICD-10 codes: ischemic stroke and heart failure were identified by at least one admission or outpatient clinic visit using codes I63 or I64 (ischemic stroke) and I50 (heart failure). Ischemic heart disease was defined by at least one admission or two outpatient visits using codes I20-I25. CV-caused death data were obtained from Statistics Korea and linked with the NHID. These definitions are summarized in **Supplementary Table I**.

Follow-up and Censoring

Follow-up began on the index date of each patient and continued until the earliest of the follow-

ing: occurrence of a CV outcome, death, or end of the study period (December 31, 2021). To maintain the integrity of the study, subjects initiating IL-17 inhibitors or TNFi non-user group subjects initiating TNFi during the follow-up were censored from the analysis.

Covariates

Baseline covariates were age, sex, disease duration, hypertension, diabetes, hyperlipidemia, chronic kidney disease, use of NSAIDs, body mass index (BMI), and smoking status. Data for these covariates were collected from January 1, 2007, to the index dates using diagnostic codes. Age and disease duration were assessed as of the index date. BMI and smoking status were obtained from national health examination data, using the results closest to the index date. In Korea, national health examinations are recommended at intervals of one or two years. NSAID use, defined as ≥ 4 continuous weeks of use, was treated as a time-varying variable in our analyses[21]. The Korean NHID drug codes for all medications used in the analyses of this study are summarized in **Supplementary Table II**.

Statistical Analysis

Descriptive statistics are expressed as numbers with percentages for categorical variables and medians with interquartile ranges (IQRs) for continuous variables. Incidence rates were calculated as the number of events per 1,000 person-years. Characteristics of the TNFi user and non-user groups were compared using the Mann-Whitney U test for continuous variables and the Chi-squared test for categorical variables.

The associations between TNFi use and CV outcomes were analyzed using Cox proportional-hazards regression analysis. Adjusted hazard ratios (aHRs) and 95% confidence intervals (CIs) were reported after adjusting for potential confounders of age, sex, disease duration, hypertension, diabetes, hyperlipidemia, chronic kidney disease, use of NSAIDs, BMI, and smoking status. Cumulative incidence curves for composite CV outcomes were generated using Kaplan-Meier survival analysis, and differences between groups were assessed using the log-rank test. To analyze the impact of TNFi usage duration on CV outcomes, we categorized users into short-term users (< 1 year) and long-term users (≥ 1 year). To accurately evaluate the effect of long-term TNFi use, we established a lag period, excluding any CV events occurring within the first year from the index date. For those in the short-term user group, data were censored at the point of TNFi re-initiation.

Subgroup analyses were performed to evaluate the consistency of the association between long-term TNFi use (≥ 1 year) and CV outcomes compared to short-term use (< 1 year) across various subgroups, including hypertension, diabetes, hyperlipidemia, and chronic kidney disease. Interaction tests were conducted to determine whether the effects of TNFi therapy on CV outcomes differed significantly between subgroups. These results are summarized in **Supplementary Figure 2**.

All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA) and R version 4.2.1 (R core Team, Vienna, Austria). A two-sided p-value < 0.05 was considered statistically significant.

Results

Baseline Characteristics

From among the initial 48,285 AS patients identified in the NHID, 24,986 newly diagnosed with AS from 2010 to 2019 without a history of CV disease were included in the study after applying the exclusion criteria. Following 1:1 matching and further exclusion of patients with a history of CV disease before the index date, the final study population consisted of 17,181 patients (8,601 TNFi users and 8,580 non-users) (Figure 1). The baseline characteristics of these groups are summarized in Table I.

Median age at diagnosis was 36 years (IQR: 27-46), with a slightly higher median age in the non-user group (37 years) compared to the TNFi user group (36 years, $p < 0.001$). The majority of patients were male (76.03%). The median disease duration was 0.48 years (IQR: 0.25-1.71), with no significant difference between the TNFi user and non-user groups ($p = 0.862$).

Rates of hypertension, diabetes mellitus, hyperlipidemia, and chronic kidney disease as comorbidities were comparable between the two groups. However, the TNFi user group included a greater proportion of patients using NSAIDs during follow-up (87.45% *vs.* 82.79%, $p < 0.001$). BMI and smoking status showed differences between the groups, with a significant $p < 0.001$ for the overall distribution across categories. Specifically, the TNFi user group had a slightly high-

Table I. Baseline characteristics of the study population.

Variables	Total (N = 17,181)	TNFi user (N = 8,601)	TNFi non-user (N = 8,580)	p
Age (years)	36 (27-46)	36 (27-46)	37 (28-47)	< 0.001
Male sex	13,062 (76.03)	6,572 (76.41)	6,490 (75.64)	0.238
Disease duration (years)	0.48 (0.25-1.71)	0.48 (0.25-1.71)	0.48 (0.25-1.69)	0.862
Comorbidities				
Hypertension	2,288 (13.32)	1,138 (13.23)	1,150 (13.40)	0.740
Diabetes mellitus	792 (4.61)	399 (4.64)	393 (4.58)	0.855
Hyperlipidemia	2,014 (11.72)	1,012 (11.77)	1,002 (11.68)	0.858
Chronic kidney disease	115 (0.67)	61 (0.71)	54 (0.63)	0.521
BMI (kg/m^2)				< 0.001
< 25	6,699 (38.99)	3,225 (37.50)	3,474 (40.49)	
≥ 25	4,137 (24.08)	2,082 (24.21)	2,055 (23.95)	
Unknown	6,345 (36.93)	3,294 (38.30)	3,051 (35.56)	
Smoking				< 0.001
Non-smoker	7,799 (45.39)	3,861 (44.89)	3,938 (45.90)	
Current smoker	3,008 (17.51)	1,431 (16.64)	1,577 (18.38)	
Unknown	6,374 (37.10)	3,309 (38.47)	3,065 (35.72)	
NSAID use during follow-up	14,625 (85.12)	7,522 (87.45)	7,103 (82.79)	< 0.001

Values are presented as median (IQR) or frequency (%). TNFi, tumor necrosis factor-α inhibitor; BMI, body mass index; NSAID, nonsteroidal anti-inflammatory drug; IQR, interquartile range.

er proportion of patients with a BMI of ≥ 25 kg/m^2 (24.21% *vs*. 23.95%) and a lower proportion of current smokers (16.64% *vs*. 18.38%) compared to the non-user group.

Composite Cardiovascular Outcomes

General findings

Over a 12-year observation period, 578 composite CV events occurred in the TNFi non-user group, with an incidence rate of 15.48 per 1,000 person-years, compared to 691 events in the TNFi user group, with an incidence rate of 15.52 per 1,000 person-years. The aHR for composite CV outcomes in TNFi users *vs*. non-users was 1.11 (95% CI: 0.99-1.24, $p = 0.075$), indicating a non-significant trend toward increased CV events among TNFi users when not considering the duration of TNFi use (Table II).

Impact of duration of TNFi use

Cumulative incidence curves (Figure 2) revealed a significant divergence in CV outcomes starting from the one-year mark, which served as the starting point of observation. Long-term TNFi users (≥ 1 year) exhibited a lower incidence of composite CV outcomes than short-term users (< 1 year), and this difference was statistically significant ($p = 0.001$). Over the entire observa-

Table II. Risk of cardiovascular outcomes and all-cause death associated with TNFi use in patients with AS.

Outcomes	Events (n)	Incidence, Per 1,000 person-years	Adjusted HR (95% CI)	p
Composite CV outcomes				
TNFi non-user	578	15.48	1.00 (reference)	
TNFi user	691	15.52	1.11 (0.99-1.24)	0.075
All-cause death				
TNFi non-user	121	3.09	1.00 (reference)	
TNFi user	88	1.88	0.89 (0.67-1.19)	0.444

Adjusted for age, sex, disease duration, hypertension, diabetes, hyperlipidemia, chronic kidney disease, use of NSAID, BMI, and smoking status. TNFi, tumor necrosis factor-α inhibitor; AS, ankylosing spondylitis; HR, hazard ratio; CI, confidence interval; CV, cardiovascular; NSAIDs, nonsteroidal anti-inflammatory drug; BMI, body mass index.

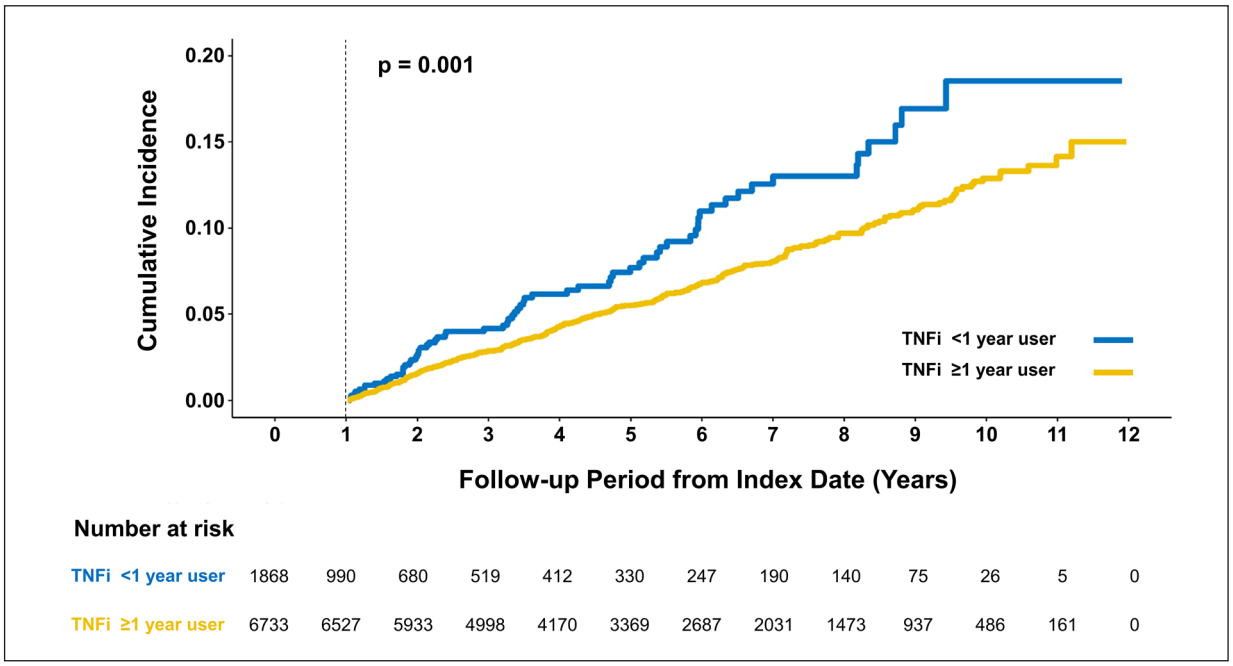

Figure 2. Cumulative incidence curves of composite cardiovascular outcomes over 11 years comparing short-term users of TNFi under one year and long-term users over one year. This figure illustrates the cumulative incidence of composite cardiovascular (CV) outcomes among AS patients. A lag period excluding any CV events occurring within the first year from the index date was established. The dashed line indicates the observation start point at one year. For TNFi < 1-year users, data were censored at the point of TNFi re-initiation. TNFi, tumor necrosis factor-α inhibitor.

tion period, the incidence of CV events was lower in long-term TNFi users than in short-term users. The aHR for composite CV outcomes in long-term TNFi users *vs.* short-term users was 0.72 (95% CI: 0.55-0.93, $p = 0.012$) (Table III). These analyses revealed a lower CV risk in patients who continued TNFi therapy for ≥ 1 year *vs.* those who discontinued it earlier.

Secondary Cardiovascular Outcomes

Individual CV diseases (ischemic stroke, heart failure, ischemic heart disease, CV death) showed trends similar to those observed for the composite CV outcome but were not significant. Specifically, TNFi use was associated with a non-significant trend in increased risk of each CV disease compared to non-use (**Supplementary Table III**).

Table III. Risk of cardiovascular outcomes and all-cause death associated with duration of TNFi use: short-term (< 1 year) versus long-term (≥ 1 year) TNFi users.

Outcomes	Events (n)	Incidence, Per 1,000 person-years	Adjusted HR (95% CI)	*p*
Composite CV outcomes				
TNFi < 1 year user	68	14.89	1.00 (reference)	
TNFi ≥ 1 year user	430	11.92	0.72 (0.55-0.93)	0.012
All-cause death				
TNFi < 1 year user	17	3.50	1.00 (reference)	
TNFi ≥ 1 year user	46	1.22	0.37 (0.21-0.66)	< 0.001

Adjusted for age, sex, disease duration, hypertension, diabetes, hyperlipidemia, chronic kidney disease, use of NSAID, BMI, and smoking status. Data analysis applied a one-year lag period to exclude CV events occurring within the first year from the index date. For TNFi < 1-year users, data were censored at the point of TNFi re-initiation. TNFi, tumor necrosis factor-α; HR, hazard ratio; CI, confidence interval; CV, cardiovascular; NSAIDs, nonsteroidal anti-inflammatory drug; BMI, body mass index.

Conversely, long-term TNFi use (≥ 1 year) was associated with a non-significant trend in decreased risk of each CV disease compared to short-term use (< 1 year) (**Supplementary Table IV**). Due to limited data, reliable statistics for CV death could not be produced in the analysis comparing long-term and short-term TNFi use.

All-Cause Mortality

Analysis of all-cause death showed that long-term TNFi use (≥ 1 year) was associated with a significantly lower risk of all-cause death than short-term use (< 1 year), with an aHR of 0.37 (95% CI: 0.21-0.66, $p < 0.001$) (Table III). Furthermore, when comparing TNFi users to non-users, the aHR for all-cause death was 0.89 (95% CI: 0.67-1.19, $p = 0.444$), suggesting a trend toward reduced mortality among TNFi users, although this did not reach statistical significance.

Subgroup Analyses

Subgroup analyses showed that long-term TNFi use (≥ 1 year) compared to short-term use (< 1 year) was consistently associated with a trend toward decreased risk of the composite CV outcome across different subgroups of hypertension, diabetes mellitus, hyperlipidemia, and chronic kidney disease (**Supplementary Figure 2**). None of the interactions between comorbidity status and the effect of long-term TNFi use on CV outcomes were statistically significant except for one. Although a significant interaction was observed between hyperlipidemia status and the effect of long-term TNFi use on ischemic stroke, the wide CI indicates that this result is not reliable.

Discussion

The present study highlights the CV safety of TNFi and the potential CV protective effect of long-term (≥ 1 year) use of TNFi in AS patients. Analyses of a nationwide population-based cohort allowed us to explore associations between TNFi therapy and CV outcomes in AS, a relatively low-incidence disease. Our main findings are as follows: 1) overall, TNFi therapy had a neutral effect on CV outcomes in AS patients; 2) long-term TNFi use (≥ 1 year) is associated with a reduced risk of composite CV outcomes and all-cause death compared to short-term use (< 1 year).

Our study, along with the meta-analysis by Karmacharya et al[11], demonstrates that TNFi use in AS patients does not significantly impact the overall risk of CV outcomes when comparing users to non-users. Specifically, the aHR for the composite CV outcome was 1.11 (95% CI: 0.99-1.24, $p = 0.075$), suggesting a non-significant trend toward increased CV events among TNFi users. While some studies[11-14], found no significant effects, other studies[9,10] have reported potential reductions in CV events with TNFi use. These mixed results may be due to differences in patient populations, disease severity, or TNFi use patterns. Shi et al[12,14] showed that a high inflammatory burden, as indicated by elevated ESR or C-reactive protein level, is associated with an increased risk of CV events in AS patients. In their recent study, the impact of TNFi on CV disease risk was attenuated and showed no significant association after adjusting for inflammatory burden[12]. These findings highlight the importance of inflammation control in reducing CV risk. Since TNFis are typically prescribed to patients with more active or severe AS[22,23], the outcomes related to AS activity or severity may be mistakenly attributed to the therapy instead of the disease itself. This concept, known as confounding by indication, can complicate the distinction between beneficial and harmful effects of treatments in non-randomized studies[24].

Considering that TNFi users in Korea generally exhibit high disease activity (BASDAI ≥ 4) at the initiation of therapy due to stringent reimbursement criteria[20], our study, based on the Korean population, compared TNFi usage patterns within a relatively homogeneous patient population. Specifically, we compared TNFi users based on the duration of TNFi use. Our study found that short-term TNFi users (< 1 year) had a higher incidence of CV events than long-term TNFi users (≥ 1 year) while they were off this drug ($p = 0.001$) (Figure 2). Notably, this divergence was evident from the beginning of the observation period, suggesting increased CV risk with early discontinuation of TNFi. Furthermore, long-term TNFi use (≥ 1 year) was associated with a significantly lower risk of the composite CV outcome than short-term use (< 1 year), with an aHR of 0.72 (95% CI: 0.55-0.93, $p = 0.012$) (Table III). This trend toward a decreased risk of the composite CV outcome was also observed in patients who used TNFi for ≥ 2 years compared to those who discontinued TNFi within two years, with an aHR of 0.82 (95% CI: 0.63-1.07, $p = 0.140$). While the risk reduction was not statistically significant for individual CV disease components, a consistent trend toward lower risk was observed, except for CV death, which had insufficient events for

analysis (**Supplementary Table IV**). Additionally, the protective effects of long-term TNFi use on the composite CV outcome appeared consistent across various comorbid conditions (**Supplementary Figure 2**). These findings suggest that long-term TNFi therapy is associated with reduced CV risk in AS patients.

No study has analyzed the association between TNFi use and CV outcomes by comparing TNFi usage patterns in patients with AS. A study[25] based on data from the Australian Rheumatology Association Database, which included patients with RA, psoriatic arthritis, or AS, showed that current biologic use was associated with a reduction in CV events compared to biologic-naïve patients. However, no reduction in CV risk was observed in those who had ceased biologic therapy. In a study[15] of RA patients, TNFi therapy reduced the incidence of MI in those who responded clinically to the treatment but not in non-responders. These findings suggest that, even among TNFi users, differences in response to TNFi or usage patterns may influence the association with CV outcomes. In Korea, TNFi usage patterns are guided by drug response according to insurance reimbursement criteria; only those patients who demonstrate a clinical response and maintain this response are allowed to continue TNFi therapy. Considering the Korean reimbursement criteria for the continuation of TNFi therapy (BASDAI improvement of $\geq$ 50% or a decrease of $\geq$ 2 units and its maintenance on periodic evaluations)[26], most long-term TNFi users analyzed in our study were more likely to be clinical responders than short-term users. In addition, a study of AS patients using data from the Korean College of Rheumatology Biologics (KOBIO) Registry (December 2012-June 2016) showed that the drug retention rate for first-line TNFi was approximately 80% at the one-year mark and few patients with AS switched to other TNFis during their median follow-up period of 14 months[27]. Taken together with previous findings, our study suggests that long-term TNFi use is associated with reduced CV risk, likely due to more effective inflammation control, compared to short-term TNFi use.

One of the major safety concerns regarding TNFi therapy is its potential association with HF. Early post-marketing surveillance data gathered by the U.S. Food and Drug Administration reported cases of worsening and new-onset HF among TNFi users[28]. Consequently, caution is advised when prescribing TNFi to patients with existing HF[29]. In our study, TNFi use did not increase the risk of HF when comparing TNFi users to non-users (aHR: 1.07, 95% CI: 0.88-1.30, p = 0.501) (**Supplementary Table III**). Additionally, when comparing long-term ($\geq$ 1 year) *vs*. short-term (< 1 year) TNFi users, long-term use was not associated with an increased risk of HF (aHR: 0.85, 95% CI: 0.53-1.36, p = 0.494) (**Supplementary Table IV**). While our study did not assess the impact of TNFi on patients with pre-existing HF, our findings suggest that TNFi use does not elevate the risk of new-onset HF in AS patients without prior CV disease, nor does it increase the risk with prolonged use. These findings align with previous observational studies of RA patients that found no increase in HF risk with TNFi therapy[29-31]. Furthermore, our study demonstrated that TNFi use was not associated with an increased risk of ischemic stroke, ischemic heart disease, CV mortality, or all-cause mortality in AS patients without CV history (**Supplementary Table III** and Table II). Notably, long-term TNFi use ($\geq$ 1 year) was associated with a non-significant trend toward a reduced risk of ischemic stroke, heart failure, and ischemic heart disease compared to short-term use (**Supplementary Table IV**). Importantly, long-term TNFi use significantly lowered the risk of all-cause mortality compared to short-term use, with an aHR of 0.37 (95% CI: 0.21-0.66, p < 0.001) (Table III). Overall, TNFi therapy appears to be safe in AS patients without pre-existing CV conditions, showing no significant association with serious CV outcomes and demonstrating a potential benefit in reducing all-cause mortality with long-term use.

Limitations of the Study

This study has several limitations that need to be acknowledged. First, the retrospective nature of our study inherently limited our ability to establish causality between TNFi use and CV outcomes. However, a strength of our study was our ability to observe CV outcomes over a relatively long period and across a large cohort of patients, providing valuable insights despite the inherent limitations of retrospective analysis. Second, due to the constraints of claims data, we lacked access to detailed clinical information, such as levels of inflammatory markers and AS disease severity, which could influence the risk of CV events in AS patients[2,12,14]. Nevertheless, we took a novel approach in our study by not merely comparing TNFi users to non-users but by ana-

lyzing CV outcomes within TNFi users. This approach allowed us to observe CV outcomes in a relatively homogeneous patient population with presumably high disease activity due to Korea's strict TNFi reimbursement policies[20]. Third, we were unable to distinguish between different types of TNFis due to policy constraints of the NHID system. Consequently, we could not assess the differential impact of individual TNFi agents on CV outcomes. It is also possible that some long-term TNFi users in our study were serial users due to non-response or adverse effects. However, a study[27] using the KOBIO registry, which overlaps with our observation period, reported that most Korean AS patients who maintained TNFi therapy continued with their first TNFi during the median follow-up period of 14 months. Fourth, the definition of AS based on ICD codes may not be accurate. To mitigate this concern, we only included patients enrolled in the RID registration program, which requires a verified diagnosis based on the modified New York criteria[17,18], and we restricted our cohort to those with at least two claims with AS diagnostic codes. A previous study using Korean NHID data that enrolled AS patients using this method reported a positive predictive value of 91.7% when validated in a single center[13]. Finally, our analysis did not include AS patients with pre-existing CV conditions, limiting the generalizability of our findings to a broader AS population. Although the exclusion of these patients was necessary to reduce confounding, it may overlook the potential risks and benefits of TNFi therapy in a high-risk group.

Conclusions

In conclusion, this nationwide retrospective cohort study demonstrated that, while TNFi use did not significantly influence overall cardiovascular outcomes in AS patients, long-term TNFi therapy (≥ 1 year) was associated with a reduced risk of the composite cardiovascular outcome and all-cause mortality compared to short-term use. These findings support the cardiovascular safety and potential cardiovascular benefits of sustained TNFi therapy in AS management.

Conflict of Interest
The authors have no potential conflicts of interest to disclose.

Ethics Approval
This study was approved by the Institutional Review Board of Wonju Severance Christian Hospital (IRB No. CR 322304) on April 5, 2022.

Informed Consent
The requirement for informed consent was waived due to the retrospective nature of the study and the use of de-identified data.

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