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ORIGINAL ARTICLE

Sulfasalazine might reduce risk of cardiovascular diseases in patients with ankylosing spondylitis: A nationwide population-based retrospective cohort study

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Abstract

Aim: To assess the effects of celecoxib and sulfasalazine on cardiovascular risk in patients with ankylosing spondylitis (AS).

Methods: We performed a 10-year population-based retrospective cohort study. A total of 1208 AS patients and 19 328 non-AS patients were sampled from the Taiwan National Health Insurance (NHI) database. We compared these two groups of patients to identify the differences in the exposure of non-steroidal anti-inflammatory drugs and sulfasalazine and their effects on cardiovascular risk. Univariate analyses were performed using Chi-squared tests for dichotomous variables and *t*-tests for continuous variables. Cox proportional hazard models were conducted to investigate the risk of developing cardiovascular diseases (CVD).

Results: AS patients had an adjusted hazard ratio (HR) of 1.72 (CI = 1.46–2.02, $P < 0.01$) for CVD compared with non-AS controls. The risk increased significantly with the progression of the disease. The use of celecoxib and sulfasalazine provided protective effects against CVD in both groups of patients. Both drugs at high cumulative defined daily doses (DDD) and celecoxib alone at high cumulative DDD showed significant protective effects against CVD in AS patients and the control group, respectively. Sulfasalazine at ≥ 0.5 DDD (1000 mg/day) reduced CVD risk in patients with AS (HR = 0.65, CI = 0.43–0.998, $P < 0.05$).

Conclusions: In this population-based retrospective cohort study, sulfasalazine at its optimal dose reduced CVD risk in patients with AS. Celecoxib was neutral regarding CVD risk in AS patients.

Key words: ankylosing spondylitis, cardiovascular disease, celecoxib, defined daily dose, sulfasalazine, Taiwan National Health Insurance database.

INTRODUCTION

Ankylosing spondylitis (AS) is a common chronic inflammatory arthritis affecting predominantly the axial skeleton and peripheral joints.[1] Characteristic symptoms usually seen in AS patients are lower back pain and stiffness which decrease the patient's quality of life. The onset age of AS is predominantly between 15 to 30 years old and AS is mostly associated with human leukocyte antigen (HLA)-B27.[2,3] AS is a systemic inflammatory disease associated with endothelial injury and dysfunction, which lead to higher risk of cardiovascular disease (CVD) including stroke and myocardial infarction.[4] In average, the mortality rate of AS patients

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is about 1.6–1.9 times higher than the general population, and those with CVD have an excess mortality rate of 20–40%.[5] Thus, it is essential to know how physicians can decrease AS patients' mortality rates associated with CVD.

Celecoxib is a cyclo-oxygenase (COX)-2 selective non-steroidal anti-inflammatory drug (NSAID). It is used to treat the signs and symptoms of inflammatory diseases such as AS and rheumatoid arthritis. Prior study has revealed that celecoxib showed significant pain-relieving effects in patients with AS.[6] However, some cardiovascular concerns were raised from the literature.[7]

Sulfasalazine is a disease-modifying antirheumatic drug (DMARD) used in AS. Study has shown that sulfasalazine may be helpful in relieving pain and improving peripheral arthritis associated with AS.[8] Another study revealed that sulfasalazine showed beneficial effects only in the early stage of AS.[9] However, the effect of sulfasalazine in CVD is unknown. Here we investigated the effects of celecoxib and sulfasalazine in a population-based cohort study.

OBJECTIVE

In this study, we aimed to investigate the effects of celecoxib and sulfasalazine on cardiovascular risk in patients with AS.

PATIENTS AND METHODS

Data sources

We analyzed the claims data of Taiwan National Health Insurance (NHI) database, a nationally representative

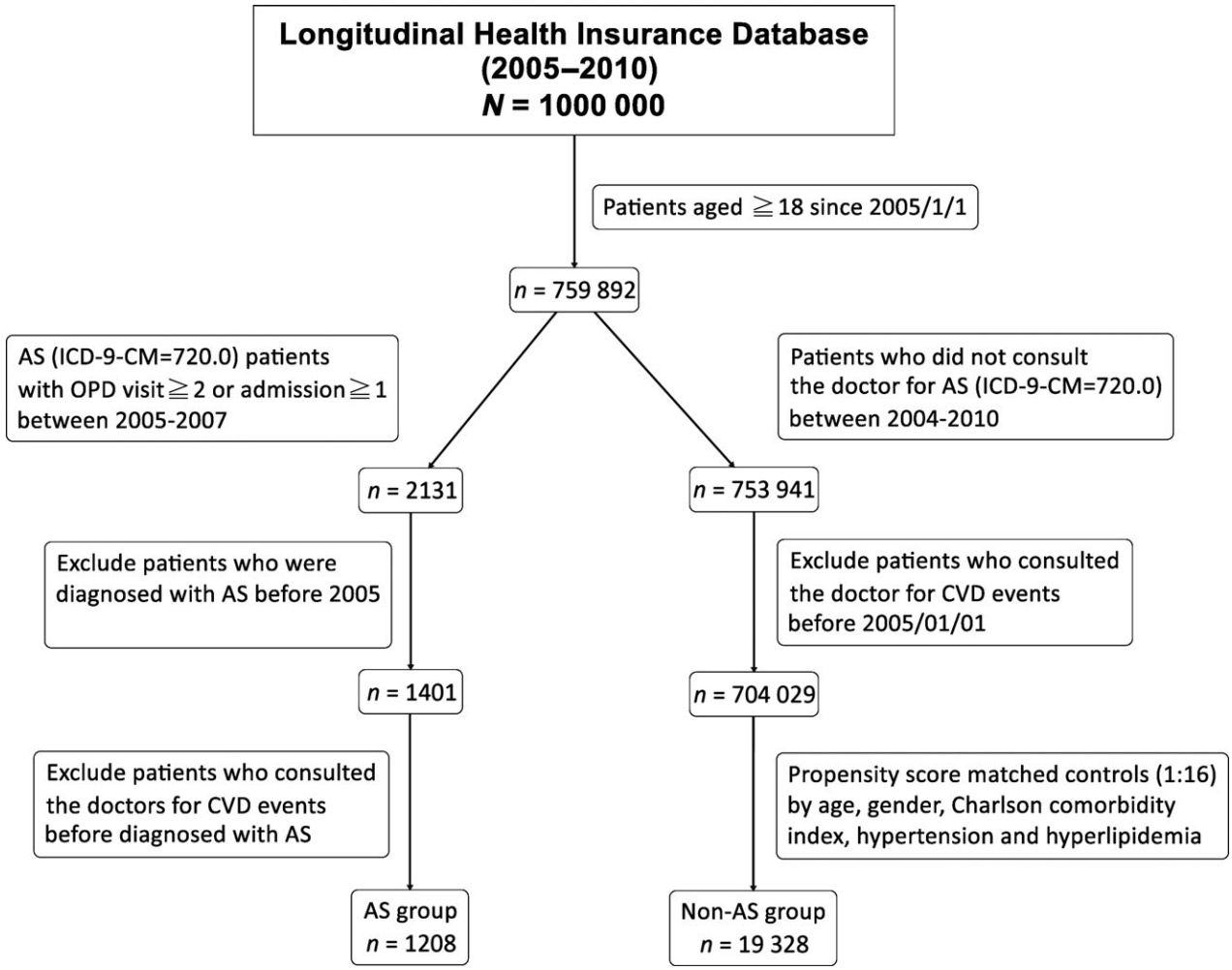

Figure 1 Consort diagram. AS, ankylosing spondylitis; OPD, Outpatient Department; CVD, cardiovascular disease.

data that contains the medical records of 23 million Taiwan residents. This database includes disease diagnosis, hospital admissions, outpatient visits and prescriptions from 99% of Taiwan residents. It utilizes International Classification of Diseases— Ninth Revision, Clinical Modification (ICD-9-CM) and thus enables us to estimate the incidence of CVD in both the general population and AS patients with different levels of NSAIDs and sulfasalazine exposure.

AS cohort

As shown in Figure 1, a total of 1 000 000 patients were randomly sampled from the Taiwan NHI database. Patients above the age of 18 and logged in the claims database between January 1, 2005, and December 31, 2010, were retrieved. In our study, patients who were diagnosed with AS using the ICD-9-CM (code 720.0) and had at least two outpatient visits or one inpatient care, were selected. After 730 patients who were diagnosed with AS before 2005 and 193 patients who had any CVD before the diagnosis of AS were excluded, 1208 AS patients were included as cases. Patients who were not diagnosed with AS were well-matched as the control group. In the control group, we excluded 49 912 patients who were diagnosed with CVD before 2005. Propensity score, a score commonly used in research to balance measured variables between treated and untreated subjects, was used to match the controls (1 : 16) by age, gender, Charlson comorbidity index, hypertension and hyperlipidemia. As a result, the control group encompassed 19 328 patients.

NSAIDs and sulfasalazine treatment

The NSAIDs prescribed in the claims database were categorized into non-selective NSAIDs and specific COX-2 inhibitors. Defined daily dose (DDD) was utilized as a tool to evaluate the dosage of NSAIDs and sulfasalazine. According to the World Health Organization (WHO), DDD is defined as the assumed average maintenance dose per day for a drug used for its main indication in adults.[10] Cumulative DDD was used to assess the cumulated dose of the respective drug. According to cumulative DDD, participants were divided into three groups: low, median and high dose. While according to DDD, patients taking celecoxib were divided into three groups: < 1 DDD, 1–1.5 DDD, > 1.5 DDD (1

Table 1 Demographic data and risk factors for cardiovascular disease

	Unmatched					Matched				
	Ankylosing spondylitis (*N* = 1208)		Comparison group (*N* = 704 029)		*P*-value	Ankylosing spondylitis (*N* = 1208)		Comparison group (*N* = 19 328)		*P*-value
	n	%	*n*	%		*n*	%	*n*	%	
Gender										
Female	484	40.1	362 494	51.5	< 0.001**	484	40.1	7744	40.1	1
Male	724	59.9	341 535	48.5		724	59.9	11 584	59.9	
Age										
18–39	587	48.6	359 492	51.1	0.229	587	48.6	9392	48.6	1
40–64	504	41.7	279 387	39.7		504	41.7	8064	41.7	
≥ 65	117	9.7	65 150	9.3		117	9.7	1872	9.7	
Mean ± SD	42.3 ± 15.0		41.5 ± 15.6		0.076	42.3 ± 15.0		42.6 ± 15.7		0.540
CCI										
0	765	63.3	561 507	79.8	< 0.001**	765	63.3	12 240	63.3	1
1	366	30.3	120 097	17.1		366	30.3	5856	30.3	
≥ 2	77	6.4	22 425	3.2		77	6.4	1232	6.4	
Hypertension	162	13.4	66 704	9.5	< 0.001**	162	13.4	2592	13.4	1
Hyperlipidemia	92	7.6	35 413	5.0	< 0.001**	92	7.6	1472	7.6	1
Celecoxib	330	27.3	27 936	4.0	< 0.001**	330	27.3	895	4.6	< 0.001**
Sulfasalazine	436	36.1	2351	0.3	< 0.001**	436	36.1	73	0.4	< 0.001**
Etoricoxib	72	6.0	6303	0.9	< 0.001**	72	6.0	205	1.1	< 0.001**
Naproxen	293	24.3	117 069	16.6	< 0.001**	293	24.3	3121	16.1	< 0.001**
Diclofenac	991	82.0	509 541	72.4	< 0.001**	991	82.0	14 009	72.5	< 0.001**

*$P < 0.05$, **$P < 0.01$. CCI, Charlson comorbidity index.

DDD = 200 mg/day); patients taking sulfasalazine were divided into two groups: < 0.5 DDD and ≥ 0.5 DDD (1 DDD = 2000 mg/day).

Outcomes

In this study, CVD including cerebral vascular diseases and coronary heart diseases (ICD-9 410–414, ICD-9 430–438) were used as the endpoint.

Statistical analyses

Univariate analyses were conducted to examine descriptive statistics and to determine the effects of different drugs on CVD outcomes. *t*-tests and Chi-squared tests were performed to compare continuous and dichotomous variables, respectively. Cox proportional hazards models were used to estimate the crude and adjusted hazard ratios (HRs) and 95% confidence interval (CI) for the CVD risk associated with drugs use. In this study, we utilized Charlson Comorbidity Index (CCI), a method that provides a total comorbidity score for predicting mortality, to measure the burden of comorbidities besides controlling for comorbid conditions in both the experimental and control groups. Important risk factors including age, gender, CCI, hypertension, hyperlipidemia and drugs used were integrated into the models. Kaplan-Meier analysis was performed to compare the 6-year cumulative incidence of CVD between AS and non-AS patients and the difference between the curves was evaluated by log-rank test. A CI of 95% was calculated for all mean values, and a *P*-value of < 0.05 was regarded as significant.

RESULTS

A total of 20 536 patients were recruited from the claims database. Demographic data and risk factors for CVD are listed in Table 1. About 60% of AS patients were men; 48.6% of AS patients were aged between 18 and 39 years. A small proportion of AS patients (6.4%) achieved a score of at least 2 on CCI. The uses of NSAIDs and sulfasalazine were significantly higher in AS patients than in the comparison group.

The multivariate Cox proportional hazards regression analysis is reported in Table 2. For CVD as an endpoint, 1208 incident cases and 19 328 age-, gender-, CCI-, hypertension-, hyperlipidemia-matched controls were identified. AS patients had a significant increased risk of developing CVD compared with non-AS patients (HR = 1.72; 95% CI = 1.46–2.02; $P < 0.01$). CVD risk in AS patients increased with age in a statistically

Table 2 : Risk factors and their hazard ratios for cardiovascular events

	Crude HR	95% CI		Adjusted HR	95% CI	
		Lower	Upper		Lower	Upper
Ankylosing spondylitis						
No	1			1		
Yes	1.35**	1.16	1.56	1.72**	1.46	2.02
Age						
18–39	1			1		
40–64	5.96**	5.33	6.66	4.50**	4.01	5.05
≥ 65	17.63**	15.61	19.90	11.63**	10.18	13.29
Gender						
Female	1			1		
Male	0.72**	0.67	0.77	0.98	0.91	1.05
CCI						
0	1			1		
1	2.21**	2.04	2.38	1.62**	1.50	1.76
≥ 2	4.14**	3.71	4.62	1.71**	1.52	1.92
Hypertension	4.58**	4.26	4.94	1.98**	1.82	2.15
Hyperlipidemia	2.57**	2.33	2.83	1.35**	1.21	1.49
Celecoxib	1.75**	1.54	1.97	0.76**	0.66	0.86
Sulfasalazine	0.78	0.59	1.03	0.78	0.58	1.06
Etoricoxib	0.67*	0.47	0.97	0.36**	0.25	0.52
Naproxen	0.78**	0.70	0.87	0.82**	0.74	0.91
Diclofenac	0.52**	0.48	0.56	0.53**	0.49	0.57

*$P < 0.05$, **$P < 0.01$. CCI, Charlson comorbidity index; HR, hazards ratio.

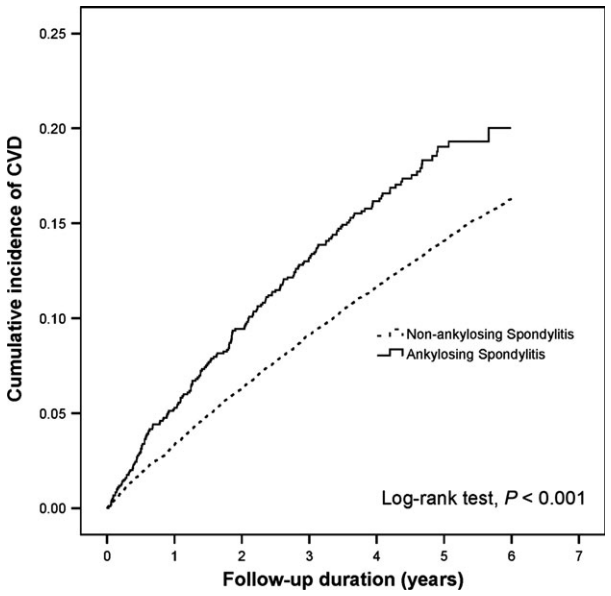

Figure 2 Cumulative incidence of cardiovascular disease (CVD) over 6 years.

significant fashion as shown in Figure 2. Patients older than 65 years had a CVD risk of 11.63 times higher than patients aged between 18 to 39 years (HR = 11.63; 95% CI = 10.18–13.29; $P < 0.01$).

Cardiovascular diseases risk was greater with higher CCI scores (CCI = 1: HR = 1.62, 95% CI = 1.50–1.76, $P < 0.01$; CCI ≥ 2: HR = 1.71, 95% CI = 1.52–1.92, $P < 0.01$). Patients with hypertension (HR = 1.98; 95% CI = 1.82–2.15; $P < 0.01$) and hyperlipidemia (HR = 1.35; 95% CI = 1.21–1.49; $P < 0.01$) were at increased risk for CVD as well. Both NSAID and sulfasalazine uses were associated with lower risk of CVD, but only NSAID use resulted in significant differences (celecoxib: HR = 0.76, 95% CI= 0.66–0.86, $P < 0.01$; etoricoxib: HR = 0.36, 95% CI = 0.25–0.52, $P < 0.01$; naproxen: HR = 0.82, 95% CI = 0.74–0.91, $P < 0.01$; diclofenac: HR = 0.53, 95% CI = 0.49–0.57, $P < 0.01$; sulfasalazine: HR = 0.78, 95% CI = 0.58–1.06).

As shown in Figure 3, celecoxib had protective effects against CVD in AS patients when administered in high cumulative DDD (HR = 0.39; 95% CI = 0.20–0.77; $P < 0.01$). Sulfasalazine at high cumulative DDD also decreased CVD risk in AS patients (HR = 0.44; 95% CI = 0.20–0.98; $P < 0.05$). For the control group which was exposed to celecoxib due to other medical conditions, there was a significant decrease in CVD risk when the drugs were administered in median and high cumulative DDD (median DDD: HR = 0.72, 95% CI = 0.58–0.91, $P < 0.01$; high DDD: HR = 0.69, 95% CI = 0.53–0.90, $P < 0.01$).

Figure 4 indicated that all doses of both celecoxib and sulfasalazine exerted protective effects against CVD in AS patients in a dose-dependent manner, but only the administration of sulfasalazine at ≥ 0.5 DDD resulted in significant differences (HR = 0.65; 95% CI = 0.43–0.998; $P < 0.05$).

DISCUSSION

Our results showed that AS patients had higher risk of CVD than non-AS controls. Surprisingly, sulfasalazine at certain doses demonstrated a protective effect against CVD in AS patients.

In our study, only celecoxib and sulfasalazine were analyzed with respect to DDD. This is because in Taiwan, all NSAIDs besides celecoxib were manufactured under different trade names and are further categorized into different dosages. At the same time, celecoxib was manufactured under only the brand name of Celebrex. Therefore, the possibility of making biased evaluation of the other NSAIDs has led to the decision to analyze only the effects of celecoxib at different dosages.

In recent years, concerns have arisen about the cardiovascular safety of selective COX-2 inhibitors due to initial reports of adverse effects of rofecoxib. In Cardiovascular Events Associated with Rofecoxib in a Colorectal Adenoma Chemoprevention Trial, a two-fold increase in cardiovascular risk was seen after 18 months of treatment with rofecoxib.[11] Does celecoxib have the same adverse cardiovascular effects as well? Some researchers provided evidence that the use of celecoxib may increase cardiovascular risk. In the APC study, the HR was 2.5 for celecoxib 200 mg twice daily and 3.4 for celecoxib 400 mg twice daily compared to placebo for the composite endpoint of death from cardiovascular causes, myocardial infarction or stroke.[12] In other words, the use of celecoxib is associated with dose-related increase in CV risk. However, in the Celebrex Long-Term Arthritis Safety Study (CLASS), no difference was observed for serious adverse cardiovascular events between celecoxib, ibuprofen and diclofenac.[13] In comparison to the CLASS study, our study further revealed that celecoxib had protective effects against CVD. This is possibly due to the anti-inflammatory effects of celecoxib on reducing CVD risk, since systemic inflammation is an independent predictor of CVD among AS patients.[14] Further, CVD risk caused by NSAIDs is associated with the extent to which the NSAID inhibits

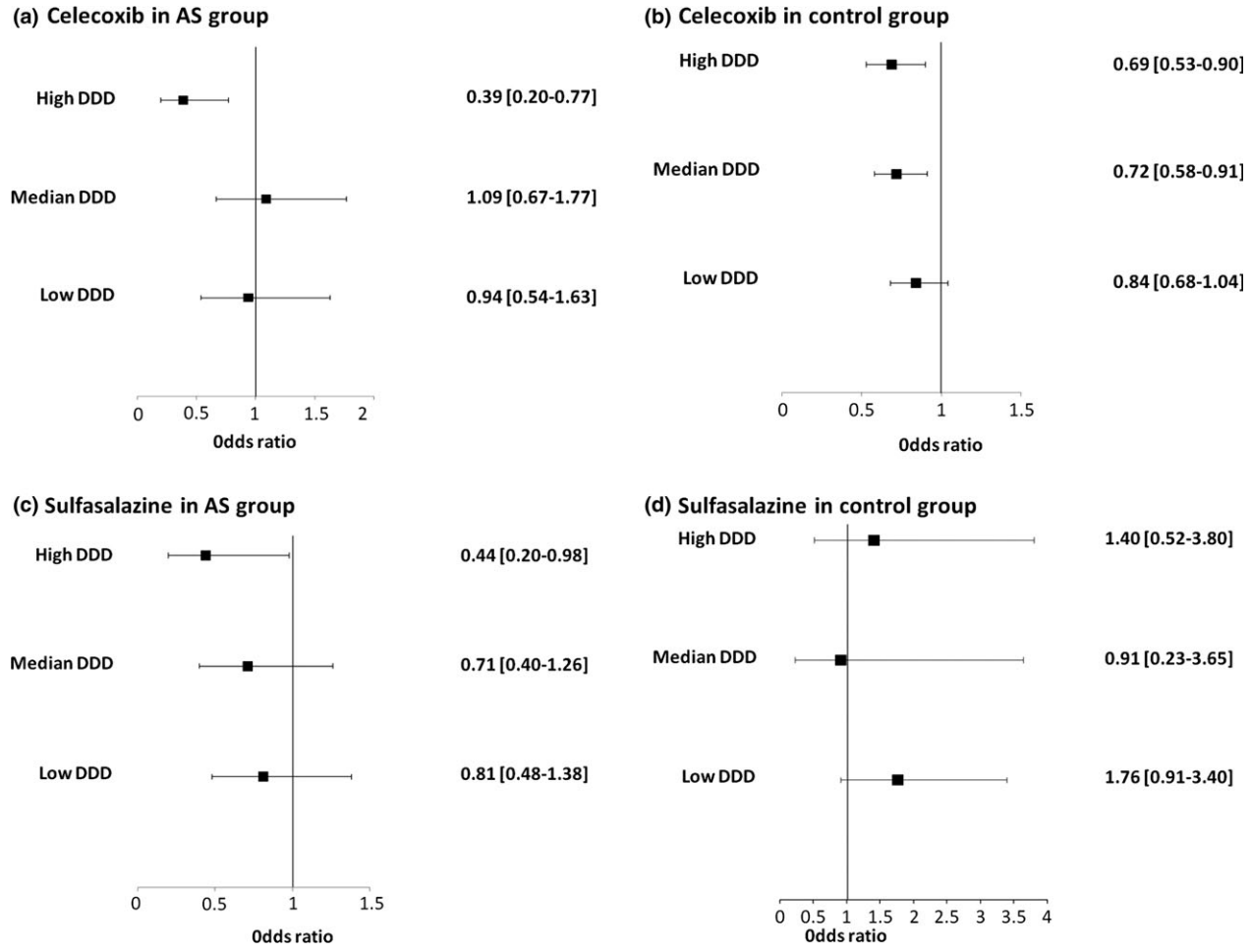

Figure 3 Risks of cardiovascular diseases associated with celecoxib and sulfasalazine use which were measured in cumulative defined daily dose (DDD). (a) Celecoxib in ankylosing spondylitis (AS) group, (b) celecoxib in control group, (c) sulfasalazine in AS group, (d) sulfasalazine in control group. Drug exposure was categorized into high, median and low dose.

COX-2 dependent prostacyclin production.[15] As celecoxib exhibits a lesser inhibition of COX-2 when compared with rofecoxib, its risk for CVD is presumed to be reasonably lower.

Our results showed that sulfasalazine conferred protective effects against CVD in a dose-dependent manner. This is in accordance with previous research that revealed the protective role of DMARDs in CVD among AS patients.[16,17] Several mechanisms have been proposed for this association. First, DMARD relieves arthritic symptoms and allows patients to increase physical activity which is good for cardiovascular health. Second, patients treated with DMARDs showed significant improvement in dyslipidemia after 1 year.[18] Also, it is commonly known that CVD is associated with inflammation. As an anti-inflammatory drug, sulfasalazine may have beneficial effect on stable coronary heart disease by controlling carotid arterial remodeling and inflammation-induced endothelial dysfunction.[19] Similarly, methotrexate, an important DMARD agent that has been used in rheumatoid arthritis for years has also been proven to be associated with decreased risk for CVD in RA patients.[20] Since both sulfasalazine and methotrexate have potent anti-inflammatory effects in common, it is reasonable to suggest that the anti-inflammatory effect plays an important role in protecting against CVD.

One limitation of this study was the short-term follow-up periods of 5 years after the patients were diagnosed with AS. Due to the possibility that CVD may have an induction period of more than 5 years, we might have underestimated the incidence rate of CVD

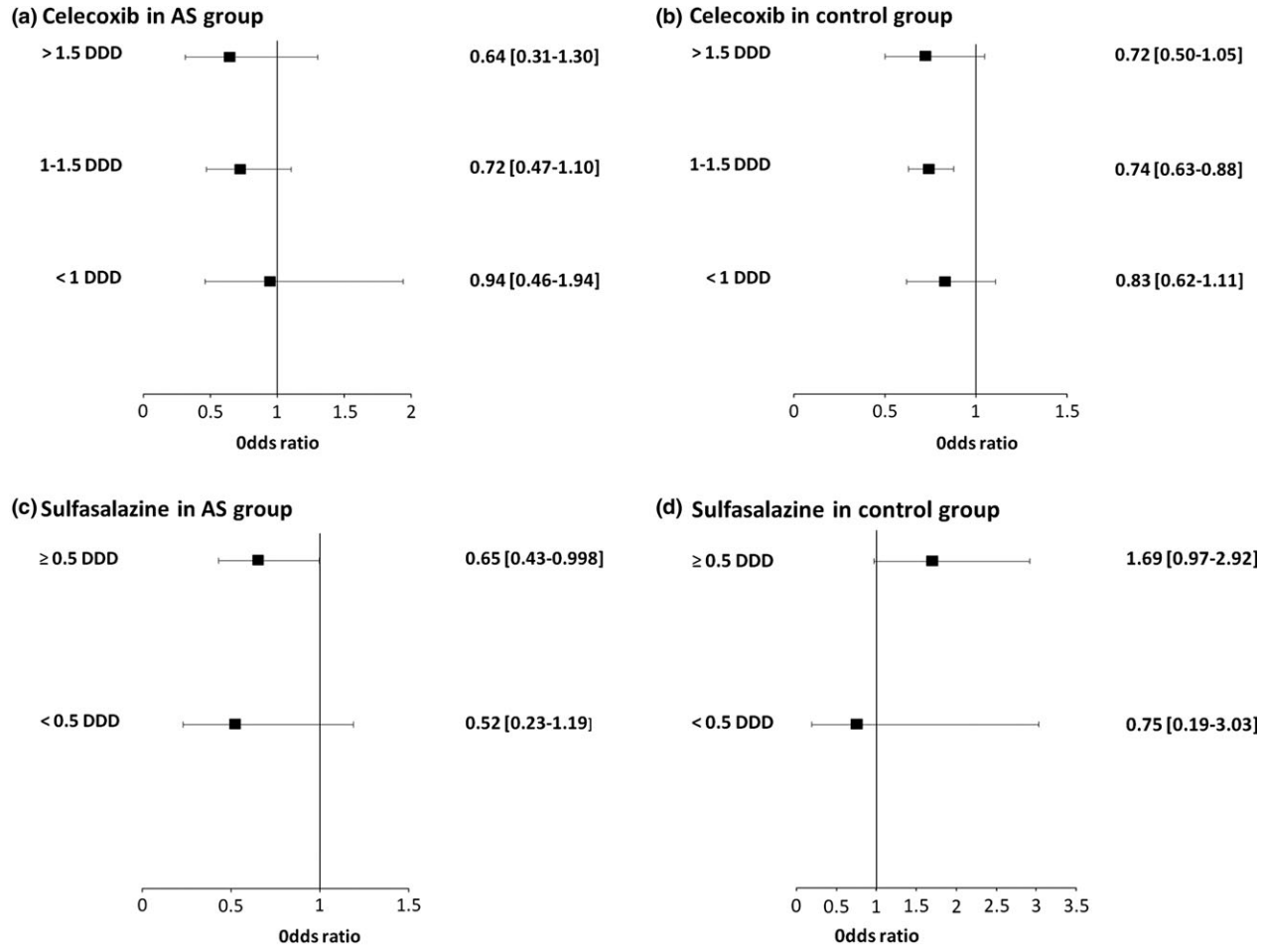

Figure 4 Risks of cardiovascular diseases associated with celecoxib and sulfasalazine use which were measured in defined daily dose (DDD). (a) Celecoxib in ankylosing spondylitis (AS) group, (b) celecoxib in control group, (c) sulfasalazine in AS group, (d) sulfasalazine in control group. For celecoxib users, drug exposure was categorized into < 1 DDD, 1–1.5 DDD, > 1.5 DDD; for sulfasalazine users, drug exposure was categorized into < 0.5 DDD, ≥ 0.5 DDD.

related to AS. Second, the diagnosis of AS in our study was established by clinicians using diagnostic codes from ICD-9-CM, rather than independent validation of the Assessment in AS International Working Group (ASAS) classification criteria. This is because the outpatient and inpatient claims data in Taiwan NHI research database was recorded using ICD-9-CM diagnostic codes. Nevertheless, every ICD code in the database was validated and has been continually reviewed by several NHI inspectors. Therefore, the diagnostic accuracy of our study is warranted.

Third, there stands a chance we missed some AS patients who were diagnosed and followed up at the local clinic and these data could not be traced in the database. The extent to which our results can be generalized to other countries is also an issue of concern.

Although much remains to be done, our work did provide concrete recommendations on optimal doses of sulfasalazine in people at risk for CVD. The evidence that sulfasalazine can be safely administered in AS patients and even benefits them is of great significance due to the fact that the drug is widely used in the population. As there have been relatively few studies addressing this issue, further research to examine the safety profiles of these two drugs are warranted.

CONCLUSION

At its optimal dose, sulfasalazine might reduce CVD risk in patients with AS. Celecoxib was neutral regarding CVD risk in AS patients.

Key messages

- Patients with AS are at increased risk for CVD.
- Sulfasalazine at its optimal dose reduces CVD risk in patients with AS.
- Celecoxib was neutral regarding CVD risk in AS patients.

FINANCIAL SUPPORT

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CONFLICT OF INTEREST

There is no conflict of interest with regard to the work.

REFERENCES

1 Braun J, Sieper J (2007) Ankylosing spondylitis. *Lancet* **369**, 1379–90.
2 Bakland G, Nossent HC, Gran JT (2005) Incidence and prevalence of ankylosing spondylitis in Northern Norway. *Arthritis Care Res* **53**, 850–5.
3 Benjamin R, Parham P (1990) Guilt by association: HLA-B27 and ankylosing spondylitis. *Immunol Today* **11**, 137–42.
4 Lin C-W, Huang Y-P, Chiu Y-H, Ho Y-T, Pan S-L (2014) Increased risk of ischemic stroke in young patients with ankylosing spondylitis: a population-based longitudinal follow-up study. *PLoS One* **9** (4), e94027.
5 Mathieu S, Gossec L, Dougados M, Soubrier M (2011) Cardiovascular profile in ankylosing spondylitis: a systematic review and meta-analysis. *Arthritis Care Res* **63**, 557–63.
6 Dougados M, Béhier J-M, Jolchine I *et al.* (2001) Efficacy of celecoxib, a cyclooxygenase 2–specific inhibitor, in the treatment of ankylosing spondylitis: a six-week controlled study with comparison against placebo and against a conventional nonsteroidal antiinflammatory drug. *Arthritis Rheum* **44** (1), 180–5.
7 Trelle S, Reichenbach S, Wandel S *et al.* (2011) Cardiovascular safety of non-steroidal anti-inflammatory drugs: network meta-analysis. *BMJ* **342**, c7086.
8 Sieper J, Klopsch T, Richter M *et al.* (2008) Comparison of two different dosages of celecoxib with diclofenac for the treatment of active ankylosing spondylitis: results of a 12-week randomised, double-blind, controlled study. *Ann Rheum Dis* **67**, 323–9.
9 Gorman JD, Sack KE, Davis JC (2002) Treatment of ankylosing spondylitis by inhibition of tumor necrosis factor α. *N Engl J Med* **346**, 1349–56.
10 World Health Organization. Collaborating centre for drug statistics methodology. Available from URL: http://www.whocc.no/ddd/definition_and_general_considera/. Accessed November 6, 2015.
11 Bresalier RS, Sandler RS, Quan H *et al.* (2005) Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. *N Engl J Med* **352**, 1092–102.
12 Solomon SD, McMurray JJV, Pfeffer MA *et al.* (2005) Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention. *N Engl J Med* **352**, 1071–80.
13 Silverstein FE, Faich G, Goldstein JL *et al.* (2000) Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the class study: a randomized controlled trial. *JAMA* **284**, 1247–55.
14 Divecha H, Sattar N, Rumley A *et al.* (2005) Cardiovascular risk parameters in men with ankylosing spondylitis in comparison with non-inflammatory control subjects: relevance of systemic inflammation. *Clin Sci* **109** (2), 171–6.
15 García Rodríguez LA, Tacconelli S, Patrignani P (2008) Role of dose potency in the prediction of risk of myocardial infarction associated with nonsteroidal anti-inflammatory drugs in the general population. *J Am Coll Cardiol* **52**, 1628–36.
16 Naranjo A, Sokka T, Descalzo MA *et al.* (2008) Cardiovascular disease in patients with rheumatoid arthritis: results from the QUEST-RA study. *Arthritis Res Ther* **10** (2), R30.
17 van Halm VP, Nurmohamed MT, Twisk JW, Dijkmans BA, Voskuyl AE (2006) Disease-modifying antirheumatic drugs are associated with a reduced risk for cardiovascular disease in patients with rheumatoid arthritis: a case control study. *Arthritis Res Ther* **8** (5), R151.
18 Chatterjee S, Sarkate P, Ghosh S, Biswas M, Ghosh A (2013) Early, structured disease modifying anti-rheumatic drug (DMARD) therapy reduces cardiovascular risk in rheumatoid arthritis-a single centre study using non-biologic drugs. *J Assoc Physicians India* **61**, 531–4.
19 Vohra K, Krishan P, Varma S, Kalra HS (2015) Exploring the potential of low-dose sulfasalazine in stable coronary artery disease patients: randomized, double-blind, placebo-controlled study. *Eur Heart J Cardiovasc Pharmacother* **1**, 214–6.
20 Westlake S, Colebatch A, Baird J *et al.* (2010) The effect of methotrexate on cardiovascular disease in patients with rheumatoid arthritis: a systematic literature review. *Rheumatology* **49**, 295–307.