

ORIGINAL RESEARCH

Patients With Rheumatoid Arthritis With an Inadequate Response to Disease-Modifying Antirheumatic Drugs at a Higher Risk of Acute Coronary Syndrome

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BACKGROUND: Cardiovascular disease is the most common cause of death in patients with rheumatoid arthritis. It is believed that using disease-modifying antirheumatic drugs (DMARDs) to control inflammation can reduce the risk of cardiovascular disease. In this study, we investigated whether patients who responded differently to DMARDs might sustain different cardiovascular events.

METHODS AND RESULTS: We designed a cohort study using the Chang Gung Research Database. We identified 7114 patients diagnosed with rheumatoid arthritis. After strict exclusion criteria, we collected 663 individuals as an inadequate response to DMARDs group. Then, 2034 individuals were included as the control group. The end point was composite vascular outcomes, including acute coronary syndrome or ischemic stroke. We used the inverse probability of treatment weighting to keep the covariates between these 2 groups well balanced. We compared the risk of these outcomes using the Cox proportional hazards model. The mean follow-up time was 4.7 years. During follow-up, there were 7.5% and 6.4% of patients with composite vascular outcomes in the DMARD-inadequate response and control groups, respectively. There was no significant difference in the risk of composite vascular outcomes (95% CI, 0.94–1.41) and ischemic stroke (95% CI, 0.84–1.36). The risk of acute coronary syndrome was significantly higher in the DMARD-inadequate response group (hazard ratio, 1.45; 95% CI, 1.02–2.05).

CONCLUSIONS: Patients with DMARD-inadequate response rheumatoid arthritis have a higher risk of developing acute coronary syndrome than those whose disease can be controlled by DMARDs.

Key Words: antirheumatic agents ■ cardiovascular disease ■ rheumatoid arthritis

Rheumatoid arthritis (RA) is a symmetrical inflammatory peripheral polyarthritis. If left untreated or unresponsive to treatment, inflammation and joint damage can lead to a loss of physical function and difficulty in performing daily tasks. In addition, because of chronic inflammation, the risk of cardiovascular events is higher than that in the general population.¹ In a large cohort of patients with RA, 30% of cardiovascular events were attributed to the clinical features of RA.² It is almost certain that this will lead to increased

mortality in these patients. In fact, circulatory diseases are one of the most common causes of death among people with RA.³ Therefore, the improvement of the cardiovascular risk in these patients is a top priority.

It is well known that a decrease in the average disease activity of RA is associated with fewer cardiovascular events.⁴ According to recent studies, low disease activity is sufficient to protect against cardiovascular disease (CVD) in RA.^{4–6} These studies also show that higher disease activity is a major

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CLINICAL PERSPECTIVE

What Is New?

- Although rheumatoid arthritis greatly increases the risk of cardiovascular disease, not all patients with rheumatoid arthritis have the same risk.
- Patients with inadequate response to disease-modifying antirheumatic drugs rheumatoid arthritis have a higher risk of developing acute coronary syndrome than those who are well controlled with disease-modifying antirheumatic drugs.

What Are the Clinical Implications?

- In addition to the traditional modifiable risk factors, how to identify patients with rheumatoid arthritis who will have an inadequate response to disease-modifying antirheumatic drugs later and how to switch to more effective treatments (such as biological agents) as soon as possible is also important for preventing cardiovascular disease.

Nonstandard Abbreviations and Acronyms

CGMH	Chang Gung Memorial Hospital
CGRD	Chang Gung Research Database
DMARD	disease-modifying antirheumatic drug
DMARD-IR	inadequate response to disease-modifying antirheumatic drugs
IPTW	inverse probability of treatment weighting
NHI	national health insurance

risk factor for CVD in patients with RA. Currently, methotrexate-based disease-modifying antirheumatic drug (DMARD) treatment is still the mainstay of RA treatment. Previous studies have shown that the use of methotrexate is associated with a reduced risk of CVD events in patients with RA.⁷ However, our knowledge is limited regarding the cardiovascular risk of patients with RA with an inadequate response to DMARDs (DMARD-IR).

To our knowledge, few studies have reported an increase in cardiovascular events in patients with RA in Taiwan.⁸ In Asia, there are few studies on the treatment and risk of CVD in patients with RA.^{9–11} Whether DMARD-IR increases the risk of CVD remains uncertain. Therefore, we designed a study to analyze CVD risk in patients with RA with an inadequate response to DMARD therapy in Taiwan.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Data Source

We designed a cohort study using the Chang Gung Research Database (CGRD), which includes inpatient and outpatient data. CGRD is a deidentification database extracted from the original medical records of Chang Gung Memorial Hospital (CGMH). CGMH provides the largest and most comprehensive medical services in Taiwan, including 7 hospital branches in Linkou, Taipei, Taoyuan, Keelung, Yunlin, Chiayi, and Kaohsiung. CGMH has 1050 beds, and at least 2.4 million people are hospitalized each year. CGMH receives an average of 8.2 million outpatient visits per year. Therefore, the CGRD is a huge medical database that can be used as a source of accurate data for medical research.^{12,13} The present study was approved by the Chang Gung Medical Foundation Institutional Review Board (No. 201900301B0). All the methods were carried out in accordance with relevant guidelines and regulations. Because the CGRD is a disconnected database, informed consent was not required.

Inclusion of Patients

We identified 7114 patients with a diagnosis of RA by the *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)* number 714.0 or *International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM)* number M05.70–M06.09, M06.20–M06.39, M06.80–M06.89, or M06.9 between January 1, 2002, and December 31, 2018, in the CGRD. To further confirm the diagnosis of RA, we excluded patients without catastrophic illness certification. According to Taiwan's National Health Insurance policy, RA is classified as a catastrophic disease, and if patients with RA pass the catastrophic disease certification audit, they do not need to make a copayment. We also excluded patients diagnosed with RA before January 2002 to ensure that we recruited new patients with RA. Patients with a diagnosis of RA before the age of 20 years were excluded under the Institutional Review Board regulations.

Patients diagnosed with certain diseases before the diagnosis of RA were also excluded. We excluded patients with acute coronary syndrome (ACS) or stroke because they were the end points of the study. Patients with a history of juvenile idiopathic arthritis were also excluded because they may have used a DMARD before the diagnosis of RA. We also excluded patients with chronic kidney disease and malignancies, as

these diseases may affect the selection and use of DMARDs (Figure 1).

After including new patients with RA with the confirmation of catastrophic illness certification, we excluded patients who had not used DMARDs for 6 months. We also excluded patients who had a cardiovascular event before the index date. Patients were divided into a DMARD-IR group and a control group. The DMARD-IR group was defined as patients whose disease activity scores of 28 joints continued to exceed 5.1 after 6 months of methotrexate-based DMARD treatment.^{14,15} According to Taiwan’s National Health Insurance policy, after 6 months of methotrexate-based DMARD treatment, doctors should periodically assess disease activity scores of 28 joints. If the patient’s disease activity scores of 28 joints exceeds 5.1, it indicates that he or she has a high disease activity.¹⁴ The index date was defined as the date on which DMARD-IR occurred. The average time from the diagnosis of RA to the index date was 4.2 years. By definition, we assigned 663 individuals to the DMARD-IR group.

The control group was from the same cohort. Their treatment was not transferred to biologics because their disease activity scores of 28 joints was maintained below 5.1 after the administration of DMARDs for at least 6 months. The index dates of the control group participants were randomly assigned, corresponding to the index dates of patients in the DMARD-IR cohort. Since a patient is more likely to “fail” (finally in the DMARD-IR group) in the early stage (ie, year 2001) than in the later stage (ie, year 2010), we assigned the

index date of each patient in the DMARD-IR group to 3 or 4 counterparts in the control group. This can reduce the bias of the system; that is, the survival time of the control group is shorter or longer than that of the DMARD-IR group. Finally, according to the definition of the above control group, we selected 2034 individuals as the control group for this study.

Covariate Variables

Comorbidities including hypertension, diabetes mellitus, hyperlipidemia, and gout increase the risk of CVD. The existence of comorbidities was defined as a history of at least 2 outpatient visits or 1 hospital admission resulting in a diagnosis of comorbidities during the 6-month periods before and after the index date (Table S1). Drugs used in patients at a high risk of cardiovascular events include aspirin, clopidogrel, and statins. Within 6 months before the index date, the use of these drugs was identified on the basis of a prescription from the outpatient department for at least 28 days.

Outcome

The primary end point was hospitalization for composite vascular outcomes, including ACS or ischemic stroke. The secondary end point was a separate vascular event. These outcomes are defined according to *ICD-9-CM* and *ICD-10-CM*, codes and are listed in Table 1. The follow-up period was considered to be from the index date to the date of the vascular event or the last date of visit to the rheumatology clinic of CGMH.

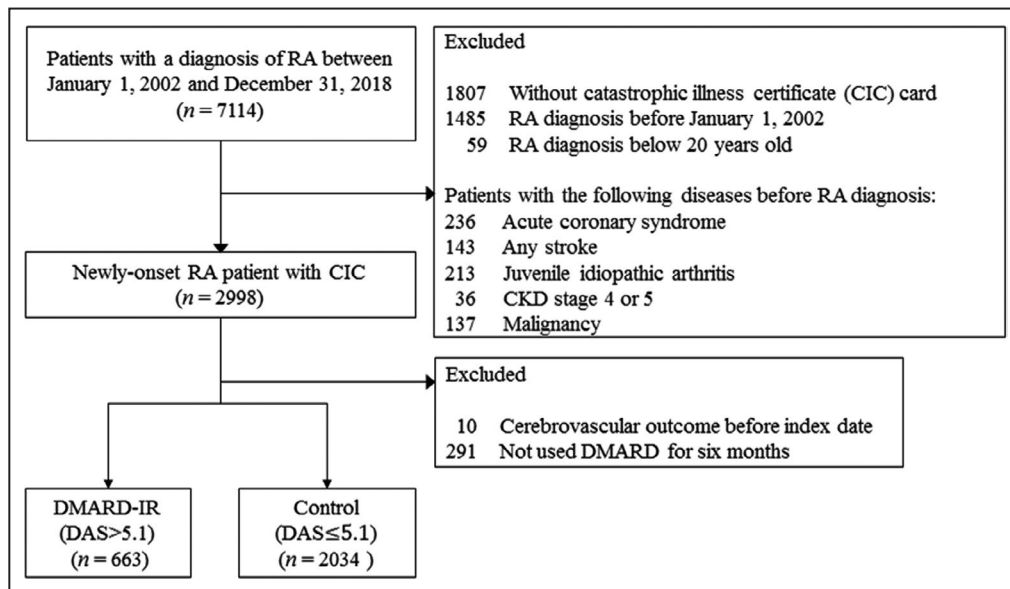


Figure 1. Enrollment of the study patients.

CKD indicates chronic kidney disease; DAS, disease activity score; DMARD, disease-modifying antirheumatic drug; DMARD-IR, inadequate response to disease-modifying antirheumatic drugs; and RA, rheumatoid arthritis.

Table 1. ICD-9-CM and ICD-10-CM Code for Outcome

Diagnosis	ICD-9	ICD-10			
Acute coronary syndrome					
Acute myocardial infarction	410.xx	I21.xx, I22.xx			
Unstable angina	411.8x 411.1	I20.0xx, I24.0xx, I24.8xx, I24.9xx			
Ischemic stroke	433.x	I66.x	I65.22x	I63.239x	I63.429x
	434.x	I65.1x	I65.23x	I63.011x	I63.431x
	435.x	I65.0x	I65.29x	I63.012x	I63.432x
	436.x	I65.8x	I63.59x	I63.019x	I63.439x
	437.x	I65.9x	I63.09x	I63.111x	I63.441x
		I63.6x	I63.19x	I63.112x	I63.442x
		I63.8x	I63.00x	I63.119x	I63.449x
		I63.9x	I63.10x	I63.211x	I63511x
		G45.0x	I63.20x	I63.212x	I63.512x
		G45.8x	I63.29x	I63.219x	I63.519x
		G45.1x	I63.30x	I63.311x	I63.521x
		G45.2x	I63.39x	I63.312x	I63.522x
		G46.0x	I63.40x	I63.319x	I63.529x
		G46.1x	I63.49x	I63.321x	I63.531x
		G46.2x	I63.50x	I63.322x	I63.532x
		G45.9x	I63.59x	I63.329x	I63.539x
		G45.4xx	I67.89x	I63.331x	I63.541x
		G46.3x	I67.81x	I63.332x	I63.542x
		G46.4x	I67.82x	I63.339x	I63.549x
		G46.5x	I63.031x	I63.341x	I67.841x
		G46.6x	I63.032x	I63.342x	I67.848x
		G46.7x	I63.039x	I63.349x	I63.31
		G46.8x	I63.131x	I63.411x	I63.33
	I63.02x	I63.132x	I63.412x	I63.34	
	I63.12x	I63.139x	I63.419x	I63.41	
	I63.22x	I63.231x	I63.421x	I63.42	
	I65.21x	I63.232x	I63.422x		

ICD-9-CM indicates International Classification of Diseases, Ninth Revision, Clinical Modification; and ICD-10-CM, International Classification of Diseases, Tenth Revision, Clinical Modification.

Statistical Analysis

To compare the risk of time-to-event outcomes between the DMARD-IR group and the control group, first, the inverse probability of treatment weighting (IPTW) was performed, considering covariates including age at diagnosis of RA, age at index date, sex, comorbidities (4 items), medications (3 items), and the index date. A *P* value >0.05 between the 2 groups after the IPTW was considered well balanced. Second, the Cox proportional hazards model was used. Results were expressed as hazard ratios (HRs) and their 95% CIs. In addition, several subgroup analyses of cardiovascular events were performed using the prespecified subgroups of age, sex, comorbidity, and drugs. A *P* value <0.05 was considered statistically significant. Analyses were

conducted using SAS software, version 9.4 (SAS Institute Inc., Cary, NC).

RESULTS

Patient Characteristics

We assigned 663 patients to the DMARD-IR group and 2034 patients to the control group. As shown in Table 2, we list the patient profiles of the DMARD-IR and control groups before and after the IPTW. Before weighting (Table 2 left), the following observations were made: Patients in the DMARD-IR group were younger; they were more likely to be prescribed statins; and their follow-up was longer. After weighting, the characteristic distribution of the 2 groups of patients was homogeneous and was equivalent

Table 2. Characteristics of The Study Patients Before and After IPTW

Variable	Before IPTW			After IPTW		
	DMARD-IR (n=663)	Control (n=2034)	P value	DMARD-IR (n=663)	Control (n=2034)	P value
Characteristic						
Age, y	52.0±12.1	56.5±13.7	<0.0001	54.7±24.7	55.3±16.0	0.22
Female, n (%)	512 (77.2)	1628 (80.0)	0.12	79.8	79.4	0.70
Comorbidity, n (%)						
Hypertension	222 (33.5)	741 (36.4)	0.17	35.2	35.7	0.69
Diabetes mellitus	94 (14.2%)	311 (15.3%)	0.49	15.4	15.0	0.73
Dyslipidemia	82 (12.4)	293 (14.4)	0.19	13.7	13.9	0.78
Gout	49 (7.4)	180 (8.9)	0.24	8.7	8.5	0.83
Medication, n (%)						
Aspirin	115 (17.4)	381 (18.7)	0.42	18.4	18.4	0.98
Clopidogrel	45 (6.8)	130 (6.4)	0.72	6.6	6.5	0.85
Statin	124 (18.7)	302 (14.9)	0.02	15.8	15.8	0.95
Smoking	80 (12.1)	192 (9.4)	0.05	11.3	9.9	0.08
Duration between RA diagnosis and index date	4.7±3.9	3.7±3.2	<0.0001	3.8±3.0	3.7±3.0	0.59
Follow-up, y	5.4±3.8	4.5±3.6	<0.0001	4.8±4.1	4.7±4.2	0.63

DMARD-IR indicates inadequate response to disease-modifying antirheumatic drugs; IPTW, inverse probability of treatment weighting; and RA, rheumatoid arthritis.

to a *P* value >0.05 (Table 2, right). Noticeably, the duration between RA diagnosis and index date of the control group was still shorter than that of the DMARD-IR group (3.7 versus 4.7 years) in the original cohort before IPTW. However, this duration was similar between the 2 groups in the IPTW-adjusted cohort because the index date was included as one of the covariates obtained in the propensity score calculation.

Table 3 lists the details of the 2 groups of inflammatory markers and immune drugs. Higher acute-phase reactants, more glucocorticoids, and more DMARDs were found in the DMARD-IR group (*P*<0.05). Patients in the DMARD-IR group had used more different types of DMARDs than those in the control group (4.3 versus 2.9) (*P*<0.05).

The Occurrence of Outcomes

The average follow-up was 4.7±4.2 years. During follow-up, 7.5% and 6.4% of patients in the DMARD-IR group and control group, respectively, had composite vascular outcomes (Table 4). The results showed no significant difference in the risk of composite vascular outcomes between the 2 groups (HR, 1.16; 95% CI, 0.94–1.41). In addition, the risk of ACS was significantly higher in the DMARD-IR group (HR, 1.45; 95% CI, 1.02–2.05). There was no significant difference in the risk of ischemic stroke between the 2 groups (HR, 1.07; 95% CI, 0.84–1.36). The cumulative event rates of composite vascular outcome, ACS, and ischemic stroke during follow-up are shown in Figures 2A through 2C.

Subgroup Analyses

Subgroup analyses of the primary and secondary outcomes were further performed using the following predefined subgroups: age, sex, hypertension, diabetes mellitus, dyslipidemia, aspirin or clopidogrel, and statin. Compared with the control group, patients with

Table 3. Inflammatory Markers at the Time of the Index Date and Immunological Drugs Use of the Study Cohort After IPTW

	DMARD-IR	Control	P value
	(n=663)	(n=2034)	
Acute-phase reactant			
ESR	42.6±29.2	27.7±26.1	<0.0001
CRP	25.6±31.9	19.4±41.5	0.01
Glucocorticoid, %	95.8%	88.4%	<0.0001
DMARDs			
Azathioprine	10.1%	10.1%	0.97
Cyclosporine	22.8%	7.9%	<0.0001
Hydroxychloroquine	84.9%	73.0%	<0.0001
Leflunomide	45.7%	15.8%	<0.0001
Methotrexate	93.9%	50.9%	<0.0001
Sulfasalazine	73.2%	44.9%	<0.0001
Average DMARD number	4.3±1.2	2.9±1.7	<0.0001

DMARD-IR group was defined as disease activity scores for 28 joints (DAS 28)>5.1; Control group was defined as DAS 28≤5.1.

CRP indicates C-reactive protein; DMARD, disease-modifying antirheumatic drug; DMARD-IR, inadequate response to disease-modifying antirheumatic drugs; ESR, erythrocyte sedimentation rate; and IPTW, inverse probability of treatment weighting.

Table 4. Event Numbers and Incidence Density of the Outcomes Between the Study Patients After IPTW

Variable	DMARD-IR (n=663)	Control (n=2034)	Hazard ratio (95% CI)	P value
Composite vascular outcome*				
Event, %	7.5	6.4	1.16 (0.94–1.41)	0.16
Incidence†	15.78	13.66		
Acute coronary syndrome				
Event, %	2.9	2.0	1.45 (1.02–2.05)	0.04
Incidence†	5.91	4.07		
Ischemic stroke				
Event, %	5.1	4.7	1.07 (0.84–1.36)	0.60
Incidence†	10.47	9.82		

DMARD-IR indicates inadequate response to disease-modifying antirheumatic drugs; and IPTW, inverse probability of treatment weighting.

*Anyone with acute coronary syndrome or ischemic stroke.

†Incidence: Event numbers per 1000 person-years.

hypertension in the DMARD-IR group were at a higher risk for composite vascular outcomes (HR, 1.59; 95% CI, 1.22–2.08), while patients without hypertension showed the opposite trend (HR, 0.71; 95% CI, 0.51–0.99) (Figure 3) with the *P* value for this trend being 0.01. In these subgroups, other outcomes did not show a significant trend between the DMARD-IR and control groups, with *P* values >0.05 (Figures S1 and S2).

DISCUSSION

RA has been shown to increase the risk of cardiovascular events.¹ Our research further suggests that patients with DMARD-IR have a higher risk of ACS than controls. In addition, patients with hypertension with DMARD-IR may be at a greater risk. Therefore, our focus should be on how to identify patients who will become DMARD-IR later and to switch to more powerful treatments (such as biological agents) as soon as possible.

In the past few years, it has been discovered that RA is associated with an increased risk of CVD compared with the general population. This seems to be attributable not only to the increased incidence of classic CVD risk factors in RA but also to the inflammatory burden borne by RA itself.¹⁶ Thus, there are pitfalls when using traditional risk scores to assess CVD, which often underestimates the risk of CVD in the RA population. In fact, vascular age models that consider drug selection and disease activity have been developed to predict CVD in patients with RA.¹⁷

In our cohort, the period between RA diagnosis and the index date was approximately 4 years (Table 3). It is well known that the cumulative inflammation burden increases the risk of CVD.^{5,18} Early use of more effective drugs, such as biological agents, to control disease activity may reduce the risk of atherosclerosis

and cardiovascular events in patients with RA.¹⁹ Therefore, the initial prediction of the response to DMARDs is important. Indeed, review studies have shown that serologic features, including autoantibodies, smoking, disease duration, and compliance, affect the DMARD response. In addition, both soluble CD163 and the expression of CD39 in regulatory T cells are considered predictors.²⁰ Further, the machine learning method was applied to whole-blood transcript data to predict the response of RA to methotrexate.²¹ Testing of changes in gene expression before and after treatment may provide an early classification of response to methotrexate treatment. Therefore, patients with a poor response should upgrade treatment earlier, failure of which may further increase the risk of CVD.

Methotrexate is currently the most commonly used DMARD for reducing RA disease activity. Previous evidence suggests that the use of methotrexate reduces the risk of CVD events in patients with RA.²² However, these benefits depend on a good response to methotrexate. Therefore, if low-dose methotrexate was to be used to prevent CVD in the general population, it would be ineffective because the levels of these cytokines and acute-phase reactants would not drop further.²³ For patients with DMARD-IR, the expected benefits of using methotrexate do not occur, as shown in the present study. Even with biological agents, the risk of CVD is significantly reduced only in patients who respond well, but not in nonresponders.^{24,25} In other words, a good response to immunotherapy is the cornerstone of reducing the risk of CVD.

In the present study, the risk of ACS was significantly higher, but that of stroke was not. This inconsistency may be related to insufficient case numbers. According to previous studies, patients with RA are more likely than the general population to have a myocardial infarction, and it is reported that the incidence and prevalence of stroke in RA is usually similar to or slightly increased compared with that in the general population.^{26,27} Nevertheless, we believe that CVD in patients with RA has the same pathogenesis and should not be ignored when caring for patients with RA. In addition, the gap between the time curves of cumulative event rates between the 2 groups seems to be gradually widening. Therefore, if the follow-up time had been long enough, there might have been significant differences in composite vascular outcomes and ischemic stroke. In the subgroup analysis, for patients with hypertension, the DMARD-IR group had more composite vascular outcomes than the control group. One possible explanation is the link between systemic inflammation and blood pressure. Tumor necrosis factor- α can induce endothelial damage and oxidative stress, while interleukin-6 can increase arterial tension. Conceptually, patients with DMARD-IR who have hypertension may have a greater disease

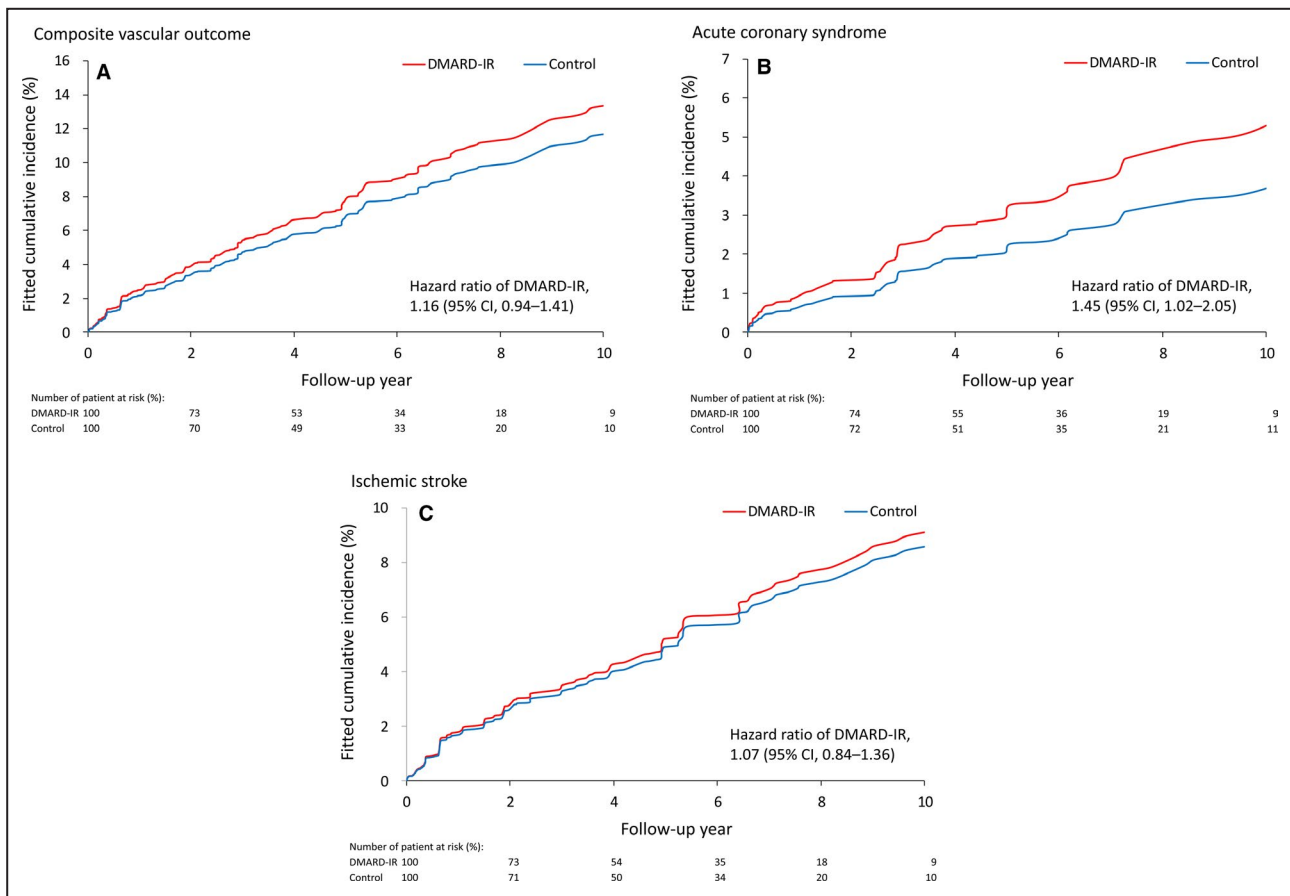


Figure 2. The fitted cumulative incidence (1 minus model-based estimated survival function) of composite vascular outcomes (A), acute coronary syndrome (B), and ischemic stroke (C) of the DMARD-IR and control groups in the IPTW-adjusted cohort.

DMARD-IR indicates inadequate response to disease-modifying antirheumatic drug; and IPTW, inverse probability of treatment weighting.

activity and therefore a higher cardiovascular risk. For the subgroups of diabetes mellitus and gout, there are similar findings; that is, patients with diabetes mellitus and gout are at a higher risk of composite vascular outcomes, possibly because these diseases may cause additional oxidative stress and chronic inflammation in addition to RA.^{28,29}

We noticed that for patients >65 years of age, the composite vascular outcomes and ACS risk of the DMARD-IR group were significantly higher than those of the control group (Figure 3 and Figure S1). Especially for the ACS results, we found a trend *P* value of 0.11, which indicates that the risk caused by DMARD-IR seems to be more significant in elderly patients. The longer duration of the disease and exposure to unrelieved inflammation can explain this.^{30,31} Therefore, more attention should be paid to the elderly.

In this study, we included patients taking drugs to reduce the risk of cardiovascular events, including aspirin, clopidogrel, and statins. Since we excluded patients with ACS or stroke before the index date,

the prescription of these drugs to some enrolled participants implies that they were at a high risk of CVD. Therefore, a higher outcome rate in these patients is predictable. In the subgroup analyses of patients with or without the use of these drugs, the outcome between DMARD-IR and the control group did not show a clear trend (Figure 3).

The current study has some limitations. First, although these patients can be classified according to insurance policies, which are based on whether patients are still at a high disease activity at least 6 months after receiving DMARD treatment, there is no clear individual disease activity score in the CGRD. However, we have some indirect evidence that the DMARD-IR group has a higher disease activity, including higher acute-phase reactants, and the need for higher doses of glucocorticoids and DMARDs (Table 3). In line with previous studies, the above findings relating to the goal of prevention of CVD in patients with RA might be corroborated by future cohort studies using information derived from the registry.⁵

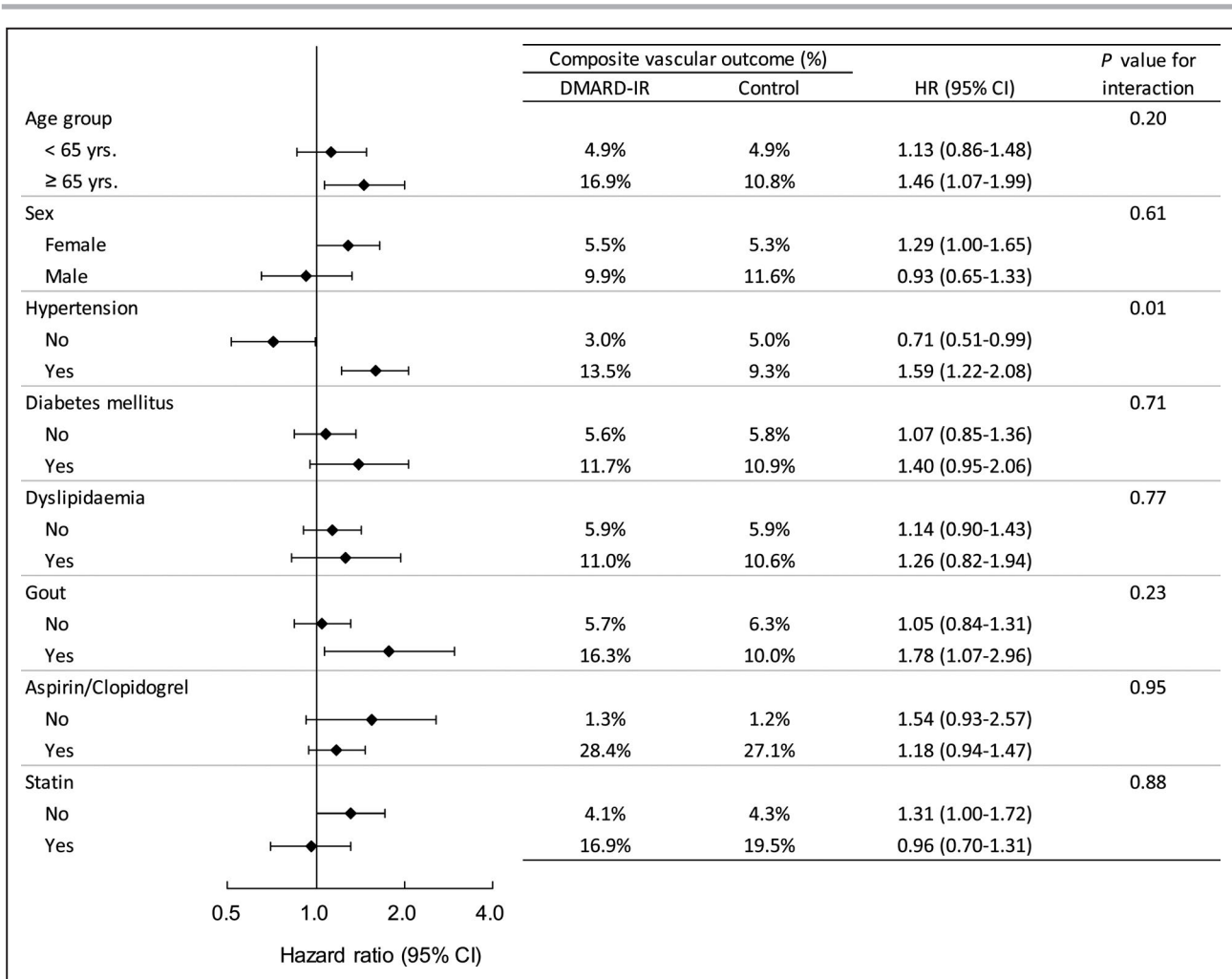


Figure 3. Prespecified subgroup analysis of composite vascular outcomes. DMARD-IR indicates inadequate response to disease-modifying antirheumatic drug.

Second, there are multiple factors associated with CVD risk in patients with RA, such as long-term course of illness, smoking status, obesity, and seropositivity.³² However, this is a database-based study that does not provide body mass index and autoantibodies information, so we cannot describe and analyze these factors. Therefore, in addition to general variables such as age, sex, and comorbidities, we also matched drugs that may be related to CVD, including antiplatelet drugs and statins. Considerable efforts have been made to use the IPTW to minimize the impact of this limitation. Nonetheless, because of the lack of complete information about patient habits and some underlined data, there may be bias in the analysis.

Third, we cannot avoid the impact of missing information. Because the study relied on information from a database, if a patient who suffered from CVD was treated in another hospital, his or her treatment data would not have reached us in time. Therefore, the event code may be missing if our doctors did not add a code to the medical records in our hospital. We believe that

this missing information would result in the underestimation of the incidence of CVD events and may further complicate the results.

In conclusion, patients with DMARD-IR RA have a higher risk of ACS than those whose disease activity could be controlled by DMARDs. Physicians should focus on cardiovascular risk during follow-up in patients with DMARD-IR RA, especially those with hypertension. In addition, the early identification of these patients would mean that they are deemed to be in the DMARD-IR cohort, and the timely use of biological agents may help prevent cardiovascular events. Subsequent prospective studies using the registry are necessary to confirm the conclusions of the present study.

ARTICLE INFORMATION

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Disclosures

None.

Supplementary Material

Table S1
Figures S1–S2

REFERENCES

- del Rincon ID, Williams K, Stern MP, Freeman GL, Escalante A. High incidence of cardiovascular events in a rheumatoid arthritis cohort not explained by traditional cardiac risk factors. *Arthritis Rheum*. 2001;44:2737–2745. DOI: 10.1002/1529-0131(200112)44:12<2737:ART460>3.0.CO;2-#.
- Crowson CS, Rollefstad S, Ikdahl E, Kitas GD, van Riel P, Gabriel SE, Matteson EL, Kvien TK, Douglas K, Sandoo A, et al. Impact of risk factors associated with cardiovascular outcomes in patients with rheumatoid arthritis. *Ann Rheum Dis*. 2018;77:48–54. DOI: 10.1136/annrheumdis-2017-211735.
- Widdifield J, Paterson JM, Huang A, Bernatsky S. Causes of death in rheumatoid arthritis: how do they compare to the general population? *Arthritis Care Res (Hoboken)*. 2018;70:1748–1755. DOI: 10.1002/acr.23548.
- Solomon DH, Reed GW, Kremer JM, Curtis JR, Farkouh ME, Harrold LR, Hochberg MC, Tsao P, Greenberg JD. Disease activity in rheumatoid arthritis and the risk of cardiovascular events. *Arthritis Rheumatol*. 2015;67:1449–1455. DOI: 10.1002/art.39098.
- Arts EE, Fransen J, Den Broeder AA, van Riel P, Popa CD. Low disease activity (DAS28≤ 3.2) reduces the risk of first cardiovascular event in rheumatoid arthritis: a time-dependent Cox regression analysis in a large cohort study. *Ann Rheum Dis*. 2017;76:1693–1699. DOI: 10.1136/annrheumdis-2016-210997.
- Arts EE, Fransen J, den Broeder AA, Popa CD, van Riel PL. The effect of disease duration and disease activity on the risk of cardiovascular disease in rheumatoid arthritis patients. *Ann Rheum Dis*. 2015;74:998–1003. DOI: 10.1136/annrheumdis-2013-204531.
- Greenberg JD, Kremer JM, Curtis JR, Hochberg MC, Reed G, Tsao P, Farkouh ME, Nasir A, Setoguchi S, Solomon DH, et al. Tumor necrosis factor antagonist use and associated risk reduction of cardiovascular events among patients with rheumatoid arthritis. *Ann Rheum Dis*. 2011;70:576–582. DOI: 10.1136/ard.2010.129916.
- Chung WS, Lin CL, Peng CL, Chen YF, Lu CC, Sung FC, Kao CH. Rheumatoid arthritis and risk of acute myocardial infarction—a nationwide retrospective cohort study. *Int J Cardiol*. 2013;168:4750–4754. DOI: 10.1016/j.ijcard.2013.07.233.
- Hsieh M-J, Chang S-H. Tocilizumab & abatacept were associated with lower risk of cardiovascular events than rituximab in rheumatoid arthritis patients failing tumor necrosis factor inhibitors in a national study. *J Am Coll Cardiol*. 2019;73:1777. Abstract.
- Tang CH, Yu F, Huang CY, Chen DY. Potential benefits of biologics on stroke and mortality in patients with rheumatoid arthritis: a nationwide population-based cohort study in Taiwan. *Int J Rheum Dis*. 2019;22:1544–1552. DOI: 10.1111/1756-185X.13611.
- Cho SK, Kim D, Won S, Lee J, Park B, Jang EJ, Bae SC, Sung YK. Impact of anti-rheumatic treatment on cardiovascular risk in Asian patients with rheumatoid arthritis. *Semin Arthritis Rheum*. 2018;47:501–506. DOI: 10.1016/j.semarthrit.2017.08.002.
- Tsai MS, Lin MH, Lee CP, Yang YH, Chen WC, Chang GH, Tsai YT, Chen PC, Tsai YH. Chang Gung Research Database: a multi-institutional database consisting of original medical records. *Biomed J*. 2017;40:263–269. DOI: 10.1016/j.bj.2017.08.002.
- Shao SC, Chan YY, Kao Yang YH, Lin SJ, Hung MJ, Chien RN, Lai CC, Lai EC. The Chang Gung research database—a multi-institutional electronic medical records database for real-world epidemiological studies in Taiwan. *Pharmacoepidemiol Drug Saf*. 2019;28:593–600. DOI: 10.1002/pds.4713.
- Wells G, Becker JC, Teng J, Dougados M, Schiff M, Smolen J, Aletaha D, van Riel PL. Validation of the 28-joint disease activity score (DAS28) and European League Against Rheumatism response criteria based on C-reactive protein against disease progression in patients with rheumatoid arthritis, and comparison with the DAS28 based on erythrocyte sedimentation rate. *Ann Rheum Dis*. 2009;68:954–960. DOI: 10.1136/ard.2007.084459.
- Buckley F, Finckh A, Huizinga TW, Dejonckheere F, Jansen JP. Comparative efficacy of novel DMARDs as monotherapy and in combination with methotrexate in rheumatoid arthritis patients with inadequate response to conventional DMARDs: a network meta-analysis. *J Manag Care Spec Pharm*. 2015;21:409–423. DOI: 10.18553/jmcp.2015.21.5.409.
- Fragoulis GE, Panayotidis I, Nikiphorou E. Cardiovascular risk in rheumatoid arthritis and mechanistic links: from pathophysiology to treatment. *Curr Vasc Pharmacol*. 2020;18:431–446. DOI: 10.2174/1570161117666190619143842.
- Wibetoe G, Sexton J, Ikdahl E, Rollefstad S, Kitas GD, van Riel P, Gabriel S, Kvien TK, Douglas K, Sandoo A, et al. Prediction of cardiovascular events in rheumatoid arthritis using risk age calculations: evaluation of concordance across risk age models. *Arthritis Res Ther*. 2020;22:90. DOI: 10.1186/s13075-020-02178-z.
- Meissner Y, Zink A, Kewow J, Rockwitz K, Liebhaber A, Zinke S, Gerhold K, Richter A, Listing J, Strangfeld A. Impact of disease activity and treatment of comorbidities on the risk of myocardial infarction in rheumatoid arthritis. *Arthritis Res Ther*. 2016;18:183. DOI: 10.1186/s13075-016-1077-z.
- Georgiadis AN, Voulgari PV, Argyropoulou MI, Alamanos Y, Elisaf M, Tselepis AD, Drosos AA. Early treatment reduces the cardiovascular risk factors in newly diagnosed rheumatoid arthritis patients. *Semin Arthritis Rheum*. 2008;38:13–19. DOI: 10.1016/j.semarthrit.2007.09.008.
- Ling S, Bluett J, Barton A. Prediction of response to methotrexate in rheumatoid arthritis. *Expert Rev Clin Immunol*. 2018;14:419–429.
- Plant D, Maciejewski M, Smith S, Nair N, Hyrich K, Ziemek D, Barton A, Verstappen S. Profiling of gene expression biomarkers as a classifier of methotrexate nonresponse in patients with rheumatoid arthritis. *Arthritis Rheumatol*. 2019;71:678–684. DOI: 10.1002/art.40810.
- Westlake SL, Colebatch AN, Baird J, Kiely P, Quinn M, Choy E, Ostor AJ, Edwards CJ. The effect of methotrexate on cardiovascular disease in patients with rheumatoid arthritis: a systematic literature review. *Rheumatology (Oxford)*. 2010;49:295–307. DOI: 10.1093/rheumatology/kep366.
- Ridker PM, Everett BM, Pradhan A, MacFadyen JG, Solomon DH, Zaharris E, Mam V, Hasan A, Rosenberg Y, Iturriga E, et al. Low-dose methotrexate for the prevention of atherosclerotic events. *N Engl J Med*. 2019;380:752–762. DOI: 10.1056/NEJMoa1809798.
- Dixon WG, Watson KD, Lunt M, Hyrich KL, Silman AJ, Symmons DP. Reduction in the incidence of myocardial infarction in patients with rheumatoid arthritis who respond to anti-tumor necrosis factor alpha therapy: results from the British Society for Rheumatology Biologics register. *Arthritis Rheum*. 2007;56:2905–2912. DOI: 10.1002/art.22809.
- Ljung L, Rantapää-Dahlqvist S, Jacobsson LT, Askling J. Response to biological treatment and subsequent risk of coronary events in rheumatoid arthritis. *Ann Rheum Dis*. 2016;75:2087–2094. DOI: 10.1136/annrheumdis-2015-208995.
- Turesson C, Jarenros A, Jacobsson L. Increased incidence of cardiovascular disease in patients with rheumatoid arthritis: results from

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- a community based study. *Ann Rheum Dis.* 2004;63:952–955. DOI: 10.1136/ard.2003.018101.
27. Wolfe F, Freundlich B, Straus WL. Increase in cardiovascular and cerebrovascular disease prevalence in rheumatoid arthritis. *J Rheumatol.* 2003;30:36–40.
 28. Tsalamandris S, Antonopoulos AS, Oikonomou E, Papamikroulis GA, Vogiatzi G, Papaioannou S, Deftereos S, Tousoulis D. The role of inflammation in diabetes: current concepts and future perspectives. *Eur Cardiol.* 2019;14:50–59. DOI: 10.15420/ocr.2018.33.1.
 29. Pagidipati NJ, Clare RM, Keenan RT, Chiswell K, Roe MT, Hess CN. Association of gout with long-term cardiovascular outcomes among patients with obstructive coronary artery disease. *J Am Heart Assoc.* 2018;7:e009328. DOI: 10.1161/JAHA.118.009328.
 30. van den Oever IA, van Sijl AM, Nurmohamed MT. Management of cardiovascular risk in patients with rheumatoid arthritis: evidence and expert opinion. *Ther Adv Musculoskelet Dis.* 2013;5:166–181. DOI: 10.1177/1759720X13491025.
 31. Urman A, Taklalsingh N, Sorrento C, McFarlane IM. Inflammation beyond the joints: rheumatoid arthritis and cardiovascular disease. *Scifed J Cardiol.* 2018;2:1000019.
 32. Roelsgaard IK, Ikdahl E, Rollefstad S, Wibetoe G, Esbensen BA, Kitas GD, van Riel P, Gabriel S, Kvien TK, Douglas K, et al. Smoking cessation is associated with lower disease activity and predicts cardiovascular risk reduction in rheumatoid arthritis patients. *Rheumatol.* 2020;59:1997–2004. DOI: 10.1093/rheumatology/kez557.

SUPPLEMENTAL MATERIAL

Table S1. ICD-9-CM and ICD-10-CM code for comorbidity.

Diagnosis	ICD-9	ICD-10
Hypertension	401.x 402.x 403.x 404.x 405.x	I10.x, I11.x, I12.x, I13.x, I15.x, N26.2x
Diabetes mellitus	250.x	E08.x, E09.x, E10.x, E11.x, E12.x, E13.x
Dyslipidemia	272.x	E77.x, E78.0x, E78.1x, E78.2x, E78.3x, E78.4x, E78.6x, E78.6x, E88.1x, E75.3x, E75.5x, E88.2x, E75.6x, E78.9x
Gout	274.x	M10.x, M1A.0x, M1A.2x, M1A.3x, M1A.4x, M1A.9x, N20.0x

Figure S1. Pre-specified subgroup analysis of acute coronary syndrome.

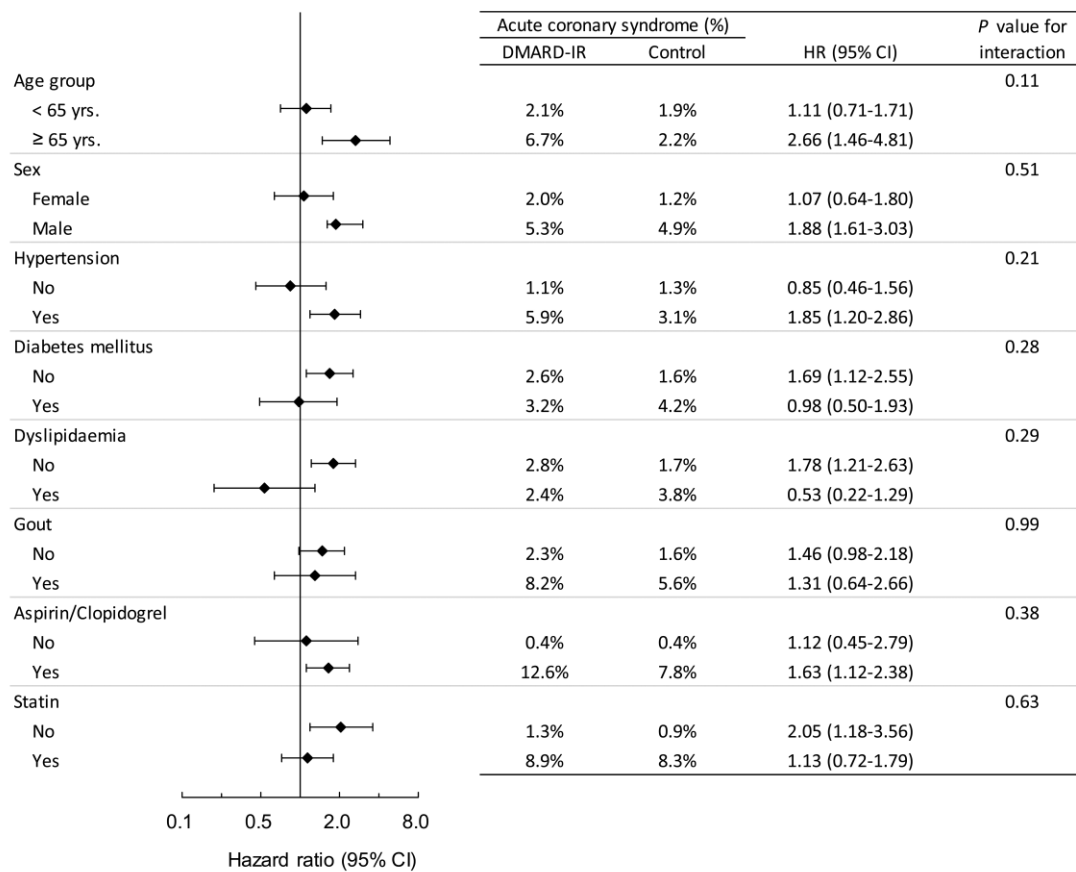


Figure S2. Pre-specified subgroup analysis of ischaemic stroke.

