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Aspirin use in central retinal arterial occlusion to prevent ischaemic stroke: a retrospective cohort study in Taiwan

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ABSTRACT

Objective To understand the efficacy of aspirin use for preventing ischaemic stroke after central retinal artery occlusion (CRAO).

Design The retrospective cohort study was conducted using the National Health Insurance Research Database from 1998 to 2013.

Setting A population-based study.

Participants A total of 9437 participants with newly diagnosed CRAO were identified. Participants who had a previous stroke and/or retinal vascular occlusion, were aged <20 years and used aspirin 3 months before the event were excluded. There were 3778 eligible participants matched by propensity score, and they were divided into aspirin (n=434) and aspirin-naive (n=1736) groups after the matching.

Methods Cox proportional hazard models and cumulative survival curves were used to assess ischaemic stroke in the study groups, along with log-rank tests to compare group differences.

Main outcome measures Incidence of ischaemic stroke in the aspirin and aspirin-naive groups 1 year after CRAO.

Results Of the 3778 patients with newly diagnosed CRAO, 151 (4%) had a subsequent ischaemic stroke within 1 year. The risk was especially high during the first week of the CRAO. No difference between the aspirin and aspirin-naive groups was found in risk of ischaemic stroke, haemorrhagic stroke, gastrointestinal bleeding, major bleeding, acute coronary syndrome, retinal vein occlusion, new-onset glaucoma, undergoing panretinal photocoagulation or all-cause mortality. Risk factors for ischaemic stroke within 1 year of CRAO included male gender (p=0.031; HR=1.46) and age (p=0.032; HR=1.14).

Conclusions Aspirin use after a CRAO showed no benefit on attenuating the risk of ischaemic stroke. The risk of ischaemic stroke was increased after CRAO especially during the first week. Male gender and age were risk factors for ischaemic stroke after CRAO.

Strengths and limitations of this study

► This is the first study analysing immediate aspirin use after central retinal artery occlusion (CRAO) to prevent ischaemic stroke.
► The population provided sufficient subjects with CRAO, which is a rare event, to conduct a propensity score matching.
► The data set provided comprehensive information of aspirin prescription.
► The lack of examination data limited the study to clarify visual outcome or disease severity.

INTRODUCTION

Since central retinal artery occlusion (CRAO) was first known in 1859, it has been one ocular emergency with many ocular complications and poor visual outcomes.[1 2] The typical presentation of CRAO is sudden onset of painless visual loss caused by a sudden stoppage of arterial blood supply to the retina.[3] The incidence of CRAO is low, approximately 1.5 in 100 000 patient-years, so randomised prospective studies on its treatment are difficult to conduct.[4 5] Therefore, there is no guideline-endorsed or agreed-upon treatment available for CRAO.[3 6]

CRAO was described as a risk factor for ischaemic stroke, coronary artery disease, critical carotid disease and peripheral arterial occlusive disease.[7 8] An increased incidence of stroke after all-cause retinal artery occlusion was found using a nationwide data set sample in Taiwan, and an increased incidence of stroke was observed even 0–3 years after the occlusion.[9] Park *et al* and French *et al* demonstrated a significantly increased incidence of ischaemic stroke after CRAO in Korea and the USA, especially during the first and second week of the CRAO event.[10 11] In addition to an increased risk of ischaemic stroke, the CRAO itself was thought to be an ocular analogue of ischaemic cerebral stroke. Therefore, immediate preventive treatment such as antiplatelet therapy for ischaemic stroke is crucial after CRAO.[3] CRAO can be divided into two groups: arteritic CRAO and non-arteritic CRAO (NA-CRAO).[12] Antiplatelet therapy alone may not be considered

a treatment for arteritic CRAO as it is always caused by giant cell arteritis. For current research, we did not classify the CRAO type, because arteritic CRAO accounts for only 4.5% of CRAO cases.[2]

Aspirin, one of the most commonly used antiplatelet medication, has been recommended for the secondary prevention of recurrent ischaemic stroke in patients who have had a prior transient ischaemic attack or ischaemic cerebral infarction.[13 14] However, as a primary prevention of ischaemic stroke, aspirin has remained controversial for patients with different comorbidities or gender.[13 15 16] For example, aspirin has not been recommended for the primary prevention of ischaemic stroke in patients with atrial fibrillation (AF) and has no protective effect on ischaemic stroke in patients with diabetes, yet it could reduce the risk of stroke in diabetic women and myocardial infarction in diabetic men.[17 18] As for patients with CRAO, aspirin was used in some clinical practices after CRAO events for reducing the risk of subsequent thromboembolic occlusion that could affect other organs.[19] However, the effect of aspirin on ischaemic stroke prevention after CRAO is unclear.

There is limited research analysing the administration of aspirin in CRAO. Although a loading dose of 600 mg of aspirin was suggested in a textbook,[20] most recommendations for aspirin use were based on expert opinion.[3] Therefore, we conducted this population-based study using the National Health Insurance Research Database (NHIRD), which comprises Taiwanese population data, from 1998 to 2013. In the present study, we aimed to augment our understanding of the effect of aspirin in ischaemic stroke prevention after CRAO but also to clarify the additional factors associated with the occurrence of ischaemic stroke in patients who have had a CRAO.

METHODS
Data source
The current population-based retrospective cohort study was based on the NHIRD, which contains healthcare data from the Taiwan National Health Insurance (NHI) programme. The strengths of the NHIRD studies have been well discussed and mentioned elsewhere.[21 22] The Taiwan National Health Research Institute has encrypted all personal information in a data set to ensure the privacy of all participants. There is no way to identify any participant, and no leak of confidential information has been reported. The study was based on a data set from the NHIRD, provided by the Bureau of NHI, Department of Health and managed by the National Health Research Institutes in Taiwan. The interpretation and conclusions contained herein do not represent those of the Bureau of NHI. This study was approved by the Ethics Institutional Review Board of Chang Gung Memorial Hospital (IRB 201700418B1), and it also adhered to the tenet of the Declaration of Helsinki.

Patient enrolment, exclusion criteria and aspirin exposure
We identified patients had first-ever CRAO as principal diagnosis using the International Classification of Diseases, Revision 9, Clinical Modification (ICD-9-CM) code 362.31, from 1 January 1998 to 31 December 2013 (figure 1). We excluded patients who had a history of CRAO before enrolment and those aged <20 years. Furthermore, we excluded patients with a history of stroke (ICD-9-CM codes: 430–437) and retinal vascular occlusion (ICD-9-CM codes: 362.30, 362.32–362.36) within 1 year before the index date. The washout period was 3 months before enrolment, and any patient who had taken aspirin or any other antiplatelet agent (eg, clopidogrel,
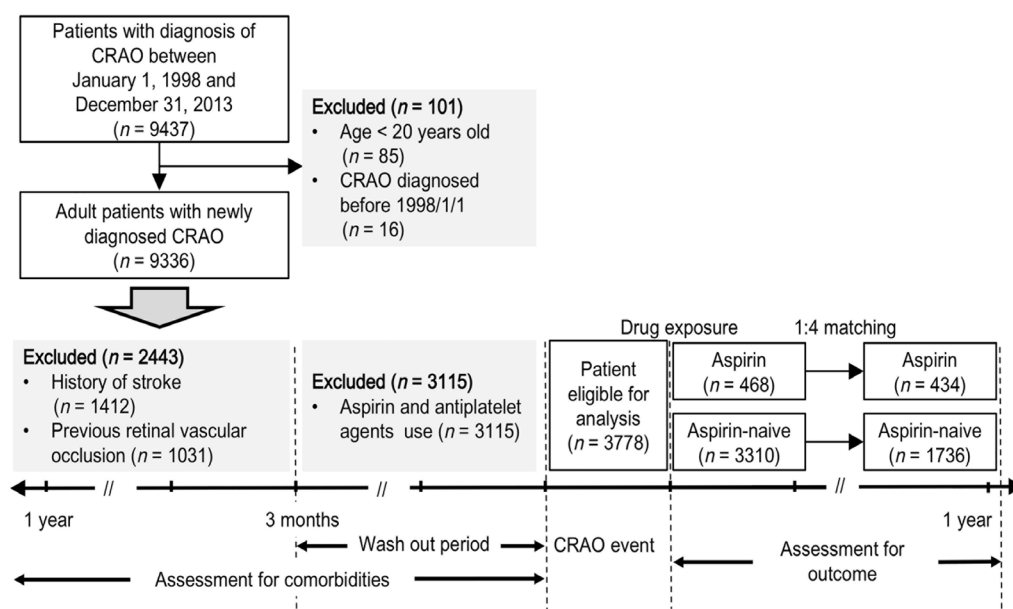
Figure 1 Enrolment of study patients. CRAO, central retinal arterial occlusion.

ticlopidine and cilostazol) within the washout period was excluded. The remaining eligible cases were separated into aspirin and aspirin-naive groups. Patients in the aspirin group required aspirin administration on the same day of the CRAO diagnosis. Each patient obtained follow-up until the event date, death or 1 year was reached.

Outcome definitions

The primary outcome was an acute ischaemic stroke (ICD-9-CM codes: 433–437). Acute ischaemic stroke was recognised when the following two criteria were met: (1) hospitalisation; and (2) principal diagnosis of acute ischaemic stroke on admission. Secondary outcomes were safety and ocular outcomes. Safety outcomes analysed in the current study included acute haemorrhagic stroke (ICD-9-CM codes: 430–432), gastrointestinal (GI) bleeding (ICD-9-CM codes: 353–362, 530.21, 530.7, 530.82, 531–534 535, 537.83, 537.84, 578), major bleeding events (ICD-9-CM codes: 430–432, 578, 719.1, 423.0, 599.7, 626.2, 626.6, 626.8, 627.0, 627.1, 786.3, 784.7, 459.0) and all-cause mortality. Mortality was defined if an individual withdrew from the NHI programme; these details of the methodology for estimating safety outcomes and mortality are explained elsewhere.[23] Ocular outcomes included retinal vein occlusion (ICD-9-CM codes: 327.23 and 362.36), outpatient principal diagnosis of neovascularisation-related glaucoma (ICD-9-CM codes: 365.00–365.06, 365.1, 365.2, 365.61, 365.63, 365.7, 365.81, 365.82, 365.89, and 365.9) and underwent panretinal photocoagulation.

Confounding factors

An analysis of comorbidities was performed for all patients before matching (n=3778). Comorbidity was considered if patients had at least two outpatient diagnoses or one inpatient diagnosis 1 year before the index date, as the methodology indicated elsewhere.[24] Comorbidities investigated in the study included: hypertension (ICD-9-CM codes: 401–405), diabetes mellitus (DM) (ICD-9-CM code: 250), hyperlipidaemia (ICD-9-CM code: 272), chronic kidney disease (CKD) (ICD-9-CM codes: 580–589, 403–404), dialysis (ICD-9-CM codes of catastrophic illness certificate: 585) and AF (ICD-9-CM codes: 427.31 and 427.32).[25] We also included ocular history such as glaucoma and undergoing panretinal photocoagulation before the index date. Medication use (eg, statin and warfarin) was retrieved from the NHIRD claim data for the 3 months before the index date. Charlson Comorbidity Index (CCI) was recorded based on the scoring system established by Charlson et al.[26]

Statistical analysis

To minimise the threat of selection bias while comparing outcomes for the aspirin and aspirin-naive groups, we performed a propensity score matching, during which one patient in the aspirin group was matched with four patients in the aspirin-naive group. For the propensity score calculation, covariates included demographic information (eg, age and gender), clinical characteristics (eg, comorbidities, medication and ocular history) and index year of the CRAO occurrence. We compared patient clinical characteristics and demographic information using a χ^2 test for categorical variables or two-sample t-test for continuous variables. The risk of outcomes between groups (after matching) was compared using a Cox proportional hazard model in which the study group (aspirin vs aspirin-naive) was the only explanatory variable. We assessed cumulative Kaplan-Meier survival curves for ischaemic stroke against the study groups, along with a log-rank test to compare group differences. We also analysed multivariable Cox models for ischaemic stroke in patients with CRAO before matching to investigate the potential risk factors. Data analysis including propensity score matching was conducted using SAS software, V.9.4 (SAS Institute, Cary, North Carolina, USA).

RESULTS

Patient enrolment

From 1 January 1998 to 31 December 2013, a total of 9437 patients with CRAO were identified. We excluded 85 patients aged <20 years, 16 patients diagnosed with CRAO before 1998, 1412 patients with a history of ischaemic stroke, 1031 patients with a history of another retinal vascular occlusion and 3115 patients who used aspirin or any other antiplatelet agent within 3 months of the CRAO event, yielding a total of 3778 patients who were eligible for further analysis. Among the patients eligible for analysis, 468 patients had an aspirin prescription on the same day as the CRAO was diagnosed, and 3310 patients did not. Patients in the aspirin and aspirin-naive groups were propensity score matched based on a 1:4 ratio according to their covariates as previously mentioned. Finally, 434 patients in the aspirin group and 1736 patients in the aspirin-naive group were analysed (figure 1).

### Patient and public involvement

Patients and public were not involved in conducting or in the design of this study.

Incidence of ischaemic stroke

As for the 3778 patients eligible for analysis before propensity score matching, there were 151 (4.0%) patients who had an ischaemic stroke within 1 year after the CRAO. The number of post-CRAO ischaemic stroke events was stratified by weekly and monthly periods in separated time points (figure 2). The number peaked during the first week. After the first week, the number plunged and gradually decreased in frequency until the end of the first year.

Clinical characteristics of the study cohort

Clinical characteristics before and after matching are listed in table 1. In the aspirin and aspirin-naive groups before matching, men represented 62.6% and 58.5%, respectively, and their average ages were 62.7 and 61.9 years, respectively. In the aspirin and aspirin-naive groups,
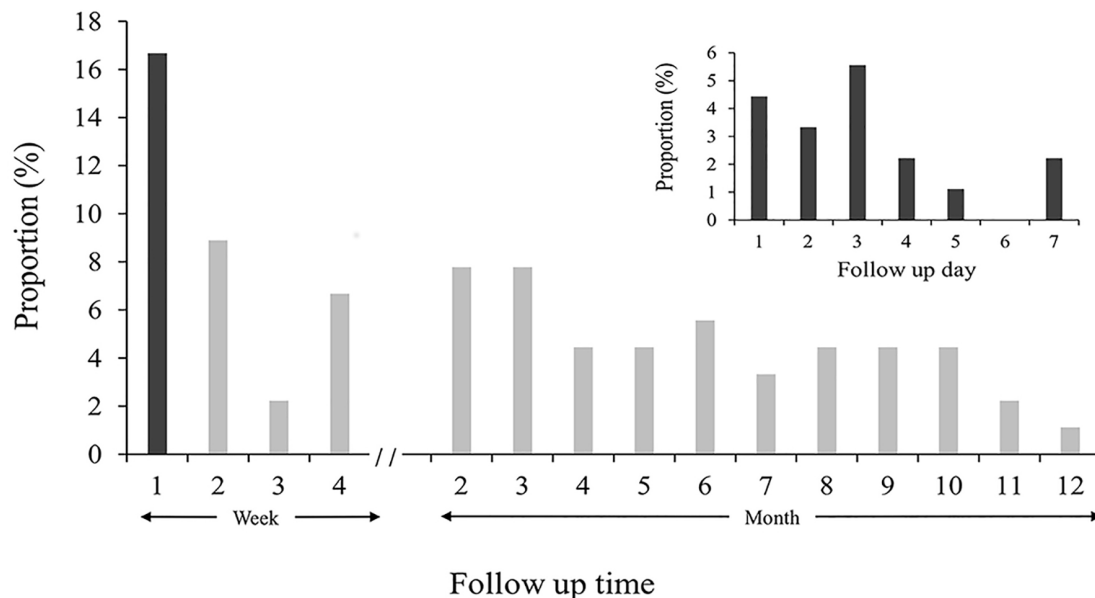
Figure 2 Distribution of stroke occurrence after new-onset central retinal arterial occlusion (n=3778).

hypertension (29.7% and 30.5%, respectively) was the most common comorbidity, followed by DM (13.7% and 15.6%, respectively) and CKD (8.5% and 10.0%, respectively). Further, 62.4% of the patients in the aspirin group and 60.3% of patients in the aspirin-naive group did not have any comorbidity before the CRAO. Regarding the

history of medication use, 7.3% and 7.4% of patients in the aspirin group and the aspirin-naive group had used statin, while only 0.2% and 0.9% of patients in the aspirin group and the aspirin-naive group had used warfarin. As for ocular history, 7.7% of the patients in the aspirin group and 10.1% of the patients in the aspirin-naive group

Table 1	Clinical characteristics of study cohorts					
	Before matching (%)			**After matching (%)**		
Variables	**Aspirin (n=468)**	**Aspirin-naive (n=3310)**	**P value**	**Aspirin (n=434)**	**Aspirin-naive (n=1736)**	**P value**
Male	293 (62.6)	1938 (58.5)	0.095	266 (61.3)	1034 (59.6)	0.511
Age (years)*	62.7±14.6	61.9±15.1	0.297	62.8±14.6	62.4±14.9	0.640
Age ≥65 years	224 (47.9)	1546 (46.7)	0.639	213 (49.1)	849 (48.9)	0.949
Comorbidity						
Hypertension	139 (29.7)	1008 (30.5)	0.740	134 (30.9)	505 (29.1)	0.465
Diabetes mellitus	64 (13.7)	517 (15.6)	0.275	62 (14.3)	251 (14.5)	0.927
CKD	40 (8.5)	332 (10.0)	0.313	40 (9.2)	145 (8.4)	0.564
Hyperlipidaemia	30 (6.4)	228 (6.9)	0.701	29 (6.7)	113 (6.5)	0.896
Dialysis	8 (1.7)	100 (3.0)	0.111	8 (1.8)	19 (1.1)	0.208
Atrial fibrillation	3 (0.6)	33 (1.0)	0.458	3 (0.7)	9 (0.5)	0.664
None of the above	292 (62.4)	1997 (60.3)	0.393	265 (61.1)	1094 (63.0)	0.451
Medication						
Statin	34 (7.3)	245 (7.4)	0.916	32 (7.4)	127 (7.3)	0.967
Warfarin	1 (0.2)	30 (0.9)	0.120	1 (0.2)	3 (0.2)	0.802
Ocular history						
Glaucoma	36 (7.7)	334 (10.1)	0.102	36 (8.3)	149 (8.6)	0.848
Intervention of PRP	32 (6.8)	275 (8.3)	0.276	31 (7.1)	124 (7.1)	1.000
CCI score*	0.72±1.30	0.85±1.48	0.074	0.77±1.34	0.72±1.32	0.476

*Presented as mean±SD.
CCI, Charlson Comorbidity Index; CKD, chronic kidney disease; PRP, panretinal photocoagulation.

Table 2 Time to event outcome during a 1-year follow-up

Outcome	Number of events (%)		Aspirin *vs* Aspirin-naive	
	Aspirin (n=434)	Aspirin-naive (n=1736)	HR (95% CI)	P value
Ischaemic stroke				
Day 1–7	2 (0.5)	15 (0.9)	0.53 (0.12 to 2.33)	0.403
Day 1–14	4 (0.9)	19 (1.1)	0.84 (0.29 to 2.47)	0.752
Day 1–30	10 (2.3)	23 (1.3)	1.74 (0.83 to 3.64)	0.143
Day 1–90	15 (3.5)	37 (2.1)	1.63 (0.90 to 2.96)	0.111
Day 1–180	17 (3.9)	50 (2.9)	1.37 (0.79 to 2.37)	0.264
Day 1–365	20 (4.6)	70 (4.0)	1.15 (0.70 to 1.89)	0.581
Safety outcome				
Haemorrhagic stroke	1 (0.2)	8 (0.5)	0.50 (0.06 to 3.99)	0.513
GI bleeding	14 (3.2)	60 (3.5)	0.93 (0.52 to 1.67)	0.811
Major bleeding	5 (1.2)	31 (1.8)	0.64 (0.25 to 1.65)	0.359
Acute coronary syndrome	1 (0.2)	7 (0.4)	0.57 (0.07 to 4.64)	0.600
All-cause mortality	11 (2.5)	47 (2.7)	0.93 (0.48 to 1.79)	0.828
Ocular outcome				
Retinal vein occlusion	30 (6.9)	87 (5.0)	1.39 (0.92 to 2.11)	0.117
New-onset glaucoma	57 (13.1)	184 (10.6)	1.26 (0.94 to 1.70)	0.124
Undergoing PRP	46 (10.6)	218 (12.6)	0.83 (0.60 to 1.14)	0.242

GI, gastrointestinal; PRP, panretinal photocoagulation.

had glaucoma, and 6.8% of the patients in the aspirin group and 8.3% of the patients in the aspirin-naive group underwent panretinal photocoagulation. The CCI score was 0.72 and 0.85 in the aspirin and aspirin-naive groups, respectively. After matching, there was no significant difference between the aspirin and aspirin-naive groups.

Primary and secondary outcomes after matching

After matching, the number of event outcomes in the aspirin and aspirin-naive groups is listed in table 2. The mean aspirin dosage in the aspirin group was 93.4 mg/day (data not shown). Among the two groups, there were a total of 90 patients (4.1%) who had an ischaemic stroke within 1 year after the CRAO. As for safety outcomes, nine patients (0.4%) had a haemorrhagic stroke, 74 patients (3.4%) had a GI bleed, 36 patients (1.7%) had major bleeding events and eight patients (0.4%) had an acute coronary syndrome. The all-cause mortality rate was 2.7% (58 patients) during this period. As for ocular outcomes, 117 patients (5.4%) experienced a subsequent retinal vein occlusion, 241 patients (11.1%) developed a new-onset neovascularisation-related glaucoma, and 264 patients (12.2%) underwent panretinal photocoagulation within 1 year. No significant difference was demonstrated between the aspirin and aspirin-naive groups in ischaemic stroke, safety outcomes or ocular outcomes. The Kaplan-Meier survival curves were shown in online supplementary figure 1 to depict ischaemic stroke between the groups. Furthermore, prespecified

subgroup analyses were performed, and the observed neutral effect of aspirin was comparable within the subgroups regarding age, gender, DM, hypertension and AF (see online supplementary figure 2).

Risk factor analysis

We analysed the risk factors for ischaemic stroke within 1 year of CRAO using the population before matching (table 3). Significant risk factors for acute ischaemic stroke were male gender and age (male gender: HR 1.46; 95% CI 1.04 to 2.05; increasing age: HR 1.14; 95% CI 1.01 to 1.28). AF might have a trend to be associated with a

Table 3 Risk factor analysis for primary outcomes at a 1-year follow-up before matching (n=3778)

Predictor	HR	95% CI	P value
Ischaemic stroke (event number=151)			
Male	1.46	1.04 to 2.05	0.031
Age (per 10 years)	1.14	1.01 to 1.28	0.032
Atrial fibrillation	2.44	0.89 to 6.71	0.083
Hypertension	1.26	0.88 to 1.82	0.211
Diabetes mellitus	1.13	0.71 to 1.78	0.607
Hyperlipidaemia	0.73	0.31 to 1.71	0.469
Chronic kidney disease	0.80	0.45 to 1.41	0.432
Statin	1.47	0.70 to 3.10	0.313

higher risk of ischaemic stroke after CRAO (HR 2.44; p=0.083).

DISCUSSION

To our knowledge, this is the first population-based retrospective cohort study that examined the use of aspirin as a primary prevention for acute ischaemic stroke after CRAO. In this project, immediate aspirin use in patients who had CRAO did not reduce the risk of ischaemic stroke within 1 year. Meanwhile, it had no effect on safety outcomes including haemorrhagic stroke, bleeding events, acute coronary syndrome or all-cause mortality. Aspirin use had neutral effects on ocular outcomes. The risk of ischaemic stroke was highest during the first week. Male patients and older patients had a higher risk of ischaemic stroke within 1 year after the CRAO.

In these patients, CRAO was associated with a risk of stroke, especially during the early stages of a CRAO.[8 10 11 27 28] Park et al reported an increased risk of ischaemic stroke after CRAO, and the risk was especially high during the first week.[10] In the USA, French et al also reported that incidence of ischaemic stroke peaked 2 weeks after CRAO.[11] According to other research, an increased risk was observed up to 3 years after the CRAO event.[9] Therefore, CRAO might be a predictor of subsequent acute ischaemic stroke, which may have a great impact on quality of life for both patients and their families. An ophthalmologist should focus on not only visual outcomes but also prevention of a subsequent vascular event, especially ischaemic stroke. From our study, the number of patients who experienced an ischaemic stroke was elevated during the first 2 weeks, especially the first 7 days, and gradually decreased after the second week. This finding was compatible with Park and French's investigations.[10 11] This issue affirms the importance of immediate management for stroke prevention after CRAO.[29]

In our study, an add-on strategy involving immediate aspirin use with an average daily dosage of 93.4 mg had no benefit on the primary prevention of ischaemic stroke in patients with CRAO. Aspirin, also known as acetylsalicylic acid, has been commonly used as an antipyretic, analgesic and anti-inflammatory agent.[30] It reduces the occurrence of atherosclerotic cardiovascular disease (ASCVD) events because its antithrombotic properties can effectively suppress platelet aggregation.[14] As previously discussed, aspirin use is recommended for secondary prevention of ischaemic stroke based on previous meta-analysis and randomised trials.[13 14] Moreover, as for the treatment of CRAO, most early studies focused mainly on the reperfusion of the ischaemic retina after CRAO, but the role of aspirin in stroke prevention after CRAO has rarely been investigated.[3] Park et al indicated that the window of time for stroke prevention is very short, especially during the first week of CRAO,[10] yet aspirin may still have an effect, as its onset takes only 45 min, and its impact lasts for about 10 days.[28 31] In this population-based cohort study, aspirin had no benefit as an immediate primary prevention of ischaemic stroke in patients with CRAO. Although the generally agreed-upon aspirin dose remains controversial for CRAO,[3 20] the daily aspirin dose for recurrent stroke prevention is 75 to 100 mg/day, as recommended by the American College of Chest Physicians Evidence-Based Clinical Practice Guidelines.[32] In this study, in the aspirin group, during the visit when CRAO was diagnosed, the mean aspirin dose was 93.4 mg/day, which met the guideline. However, aspirin therapy with this dose failed to reduce ischaemic stroke risk after patient experiencing CRAO in our study.

Although aspirin is effective for secondary prevention of recurrent ischaemic stroke, it is not suitable for stroke prevention in all situations. For example, using aspirin as monotherapy for primary ischaemic stroke prevention in patients with AF is not recommended.[17 33] According to the latest European guideline, aspirin can only be used as part of a combination therapy for patients with AF.[34] Instead of aspirin, an anticoagulant such as warfarin or novel oral anticoagulants was recommended in the latest studies.[34–36] A possible reason for the major modification of medication use was that AF-related ischaemic stroke is caused by thromboembolic events instead of an ASCVD.[37] Aspirin is effective for the prevention of ASCVD rather than thromboembolic events.[14] According to earlier papers, the behaviour of CRAO is more similar to thromboembolic diseases than an ASCVD.[1 6 12] This could explain why the add-on strategy involving immediate aspirin use failed to prevent an ischaemic stroke in patients with CRAO.

The cumulative risk of stroke for all patients in the study cohort was 0.9% and 4.0% at 30 days and 1 year, respectively. As for safety and secondary outcomes, aspirin use did not increase the risk of haemorrhagic stroke, gastrointestinal bleeding or major bleeding in 1 year. Further, it did not affect the risk of common ocular complications after CRAO or all-cause mortality. A subgroup analysis was performed to evaluate the risk of ischaemic stroke in patients with different characteristics, but no difference between the aspirin and aspirin-naive groups was found in any characteristic including age, gender, DM, hypertension and AF. Previous studies have shown that a retinal artery occlusion had similar systemic risk factors for ischaemic stroke, including hypertension, DM and hyperlipidaemia.[1 10] In our study, we investigated the additional 1-year risk of ischaemic stroke after CRAO. We found that male gender and age were associated with the occurrence of ischaemic stroke after a CRAO event. Although AF did not reach statistical significance, a trend of increased risk of ischaemic stroke was observed. These findings suggest that CRAO is an early warning sign of ischaemic stroke for patients with risk factors, and efforts to prevent a subsequent stroke and cardiovascular events, including a thorough cardiovascular examination and an immediate referral, should be performed as soon as possible after a CRAO occurrence.[29]

This study had several strengths. First, this is the first cohort study that tested the hypothesis regarding an

add-on strategy involving immediate aspirin use for the prevention of ischaemic stroke in patients with CRAO. Although it is not a randomised controlled trial, it still could provide information for ophthalmologists to select possible medications to help avoid vascular events after CRAO. Second, this population provided numerous subjects with CRAO, and it allowed us to match the two groups by propensity score. In the real world, obtaining information on a sufficient number of patients for medication trials would have been difficult to accomplish, particularly for the patient group because of the low incidence of CRAO. Third, Taiwan NHIRD provides information on prescription medications. In our project, the use of aspirin, which is only available by prescription, could be obtained, and the dosage could be accurately calculated. Given these strengths, our investigation may be a close representation of an actual patient being treated with aspirin after a CRAO.

There were some limitations in the current study. First, the NHIRD coding system was based on ICD-9 CM codes that do not indicate information on diseases for which physicians provided care. For example, ICD-9 CM codes usually do not classify disease severity. For ophthalmic research, ophthalmologists may expect visual outcome such as visual acuity which NHIRD did not contain. However, we mainly focused on the occurrence of subsequent outcomes after CRAO, and visual outcomes from CRAO are usually poor. In Dr Hayreh's investigation, the initial visual acuity was counting fingers or worse in 93.2% of the patients with NA-CRAO, and the vision improved in only 9% of the patients 30 days after the event.[2] The visual outcomes did not affect our study result. Second, the study did not perform any validation to determine accuracy of the diagnosis based on ICD-9-CM codes. However, more than 2000 articles were published through 2015 using the NHIRD.[22] Major outcomes in this study such as ischaemic stroke and covariates such as diabetes and hypertension have already been validated.[38 39] Hence, the results of the present study should be faithful. Third, the NHIRD did not contain examination results such as blood tests or images. Regarding CRAO, readers may want to understand the association between carotid artery stenosis or atherosclerosis and subsequent ischaemic stroke, yet we were not able to analyse this issue. Although a carotid ultrasonography was suggested for patients with an incident CRAO and large artery atherosclerosis was found to be associated with retinal artery occlusion,[7 28 40] some of the previous studies found no association between a retinal embolus and carotid artery stenosis.[41 42] In addition, the effect of aspirin used in our study may not be affected whether result of blood test or image examination is available or not.

CONCLUSION

In conclusion, this is the first study analysing the effect of aspirin after CRAO based on a 16-year population-based data. An add-on strategy involving immediate aspirin use showed no benefit on attenuating the risk of ischaemic stroke, and it did not increase the risk of bleeding events. An elevated risk of ischaemic stroke after CRAO was observed especially during the first 7 days. Risk factors for an ischaemic stroke within 1 year of a CRAO were male gender and age.

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