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ORIGINAL RESEARCH

Patients with Atrial Fibrillation are Unlikely to Benefit from Aspirin Monotherapy

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Background: Aspirin (ASA), the mainstay antiplatelet treatment in patients with cardiovascular disease (CVD), has been received by a considerable number of AF patients. This study sought to examine the association between ASA monotherapy and the risk of major adverse cardiac and cerebrovascular events (MACCE) in patients with atrial fibrillation (AF).

Methods: A total of 850 patients with AF were identified from a community-based Kailuan study. All patients were assigned to two groups according to their medicine history: an aspirin therapy group (ASA group) (n = 174), and a non-aspirin therapy group (non-ASA group) (n = 676). The clinical endpoints are MACCE, including myocardial infarction (MI), ischemic stroke (IS), and hemorrhagic stroke (HS). Incidence curves for MACCE were plotted using the Kaplan–Meier method, and the Log rank test was used to assess the differences in incidence rates. The hazard ratios (HR) and 95% confidence intervals (CI) for MACCE were analyzed using Cox proportional-hazards analysis regression models.

Results: During the 7.2-year follow-up, 30 MACCE occurred in the ASA group, and 101 in the non-ASA group, with a cumulative incidence of 19.88% vs 17.27%, $P = 0.511$; 3 cases of MI occurred in the ASA group, and 18 cases in the non-ASA group, with a cumulative incidence of 1.78% vs 2.90%, $P = 0.305$. Twenty-seven cases of IS occurred in the ASA group, and 84 cases in the non-ASA group, with a cumulative incidence of 1.78% vs 2.90%, $P = 0.305$. Eight cases of HS occurred in the ASA group, and 13 cases in the non-ASA group, with a cumulative incidence of 5.01% vs 2.34%, $P = 0.045$. Multivariate regression analysis showed that ASA therapy was not associated with MACCE (HR: 1.130, 95% CI: 0.747–1.710, $P = 0.562$). In addition, ASA therapy was not associated with IS (HR: 1.309, 95% CI: 0.843–2.034, $P = 0.231$). However, ASA therapy was significantly associated with HS (HR: 2.563, 95% CI: 1.024–6.418, $P = 0.044$).

Conclusion: ASA monotherapy is not associated with a lower risk of ischemic events, while significantly associated with a higher risk of bleeding events. Patients with AF are unlikely to benefit from aspirin monotherapy.

Keywords: atrial fibrillation, aspirin monotherapy, major adverse cardiac and cerebrovascular events, myocardial infarction, ischemic stroke, hemorrhagic stroke

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia, and the leading cause of cardioembolic stroke,[1,2] with a prevalence ranging from 0.1% in patients below 55 years to over 9% in octogenarian patients, and fivefold elevation in the risk of ischemic stroke (IS) among individuals with AF.[3] It has been well accepted that oral anticoagulants substantially reduce the risk for IS in patients with AF determined to be at intermediate to high risk for thromboembolism.[4] The latest guidelines consider that antiplatelet therapy is not recommended for stroke prevention in AF patients.[5,6] Despite that, aspirin (ASA), the mainstay antiplatelet treatment in patients with cardiovascular disease (CVD), has been received by a considerable number of AF patients.[7] It has been reported that AF patients with concomitant stable coronary artery disease are also likely to receive combined antiplatelet and anticoagulant therapy.[8–10] Therefore, this study sought the association

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between ASA monotherapy and the risk of major adverse cardiac and cerebrovascular events (MACCE) in patients with AF.

Methods

Study Participants and Grouping

The Kailuan study is an ongoing prospective community-based cohort study to investigate the risk factors for cardiovascular and cerebrovascular diseases in the city of Tangshan, China. The study participants are the employees and retirees from the Kailuan Group. Participants were originally recruited for physical examination. The present study is based on the data of Kailuan study from the year of 2014 to 2016. Based on the recorded medical histories, patients with AF were selected for our present study as per the relevant diagnostic criteria.[11]

Clinical Endpoints and Follow-Up

The clinical endpoints are MACCE, including myocardial infarction (MI), IS, and hemorrhagic stroke (HS). Follow-up started from the first physical examination and ended on December 31, 2022.

Statistical Analysis

The measurement data of normal distribution was expressed as mean ± standard deviation. A power analysis was used to estimate the smallest sample size needed in the current study. A propensity score matching was made to reduce the bias due to other cardiovascular risk factors-related variables. Kaplan–Meier curves were plotted for each of the two treatment groups and were compared using a Log rank test. The hazard ratios (HR) and 95% confidence intervals (CI) for MACCE were analyzed using Cox proportional-hazards analysis regression models. A *P*-value less than 0.05 was considered statistically significant.

Results

Clinical and Laboratory Baseline Characteristics

Figure 1. shows the flow chart of the current study. In total 171,086 participants were initially enrolled in the Kailuan study. 937 patients with AF were initially enrolled in this study, among which, 87 participants with medical histories with MI or stroke were further excluded. Finally, 174 AF patients with ASA monotherapy (ASA group) were 1:4 matched with 676 AF patients without ASA monotherapy (non-ASA group). Table 1 shows the baseline characteristics.

Incidence of MACCE

Figure 2. shows that during the 7.2-year follow-up, MACCE occurred 30 in the ASA group, and 101 in the non-ASA group, with a cumulative incidence of 19.88% vs 17.27%, $P = 0.511$; MI occurred 3 in the ASA group, and 18 in the non-ASA group, with a cumulative incidence of 1.78% vs 2.90%, $P = 0.305$. IS occurred 27 in the ASA group, and 84 in the non-ASA group, with a cumulative incidence of 1.78% vs 2.90%, $P = 0.305$. HS occurred 8 in the ASA group, and 13 in the non-ASA group, with a cumulative incidence of 5.01% vs 2.34%, $P = 0.045$. (Figure 2).

Regression Analysis of Factors Associated with Major Vascular Events

Table 2 shows that ASA therapy was not associated with MACCE in model 1 [hazard ratio (HR): 1.146, 95% confidence interval (CI): 0.763–1.723, $P = 0.511$], model 2 (HR: 1.152, 95% CI: 0.766–1.732, $P = 0.497$), and model 3 (HR: 1.130, 95% CI: 0.747–1.710, $P = 0.562$). Similarly, ASA therapy was not associated with MI in model 1 (HR: 0.635, 95% CI: 0.187–2.157, $P = 0.467$), model 2 (HR: 0.635, 95% CI: 0.187–2.155, $P = 0.466$), and model 3 (HR: 0.557, 95% CI: 0.161–1.931, $P = 0.356$). In addition, ASA therapy was not associated with IS in model 1 (HR: 1.254, 95% CI: 0.813–1.935, $P = 0.306$), model 2 (HR: 1.278, 95% CI: 0.828–1.973, $P = 0.269$), and model 3 (HR: 1.309, 95% CI: 0.843–2.034, $P = 0.231$). Except that, it shows that ASA therapy was not associated with HS in model 1 (HR: 2.393, 95% CI: 0.992–5.775, $P = 0.052$), and model 2 (HR: 2.387, 95% CI: 0.989–5.761, $P = 0.053$). However, it shows that ASA therapy was significantly associated with HS in model 3 (HR: 2.563, 95% CI: 1.024–6.418, $P = 0.044$).

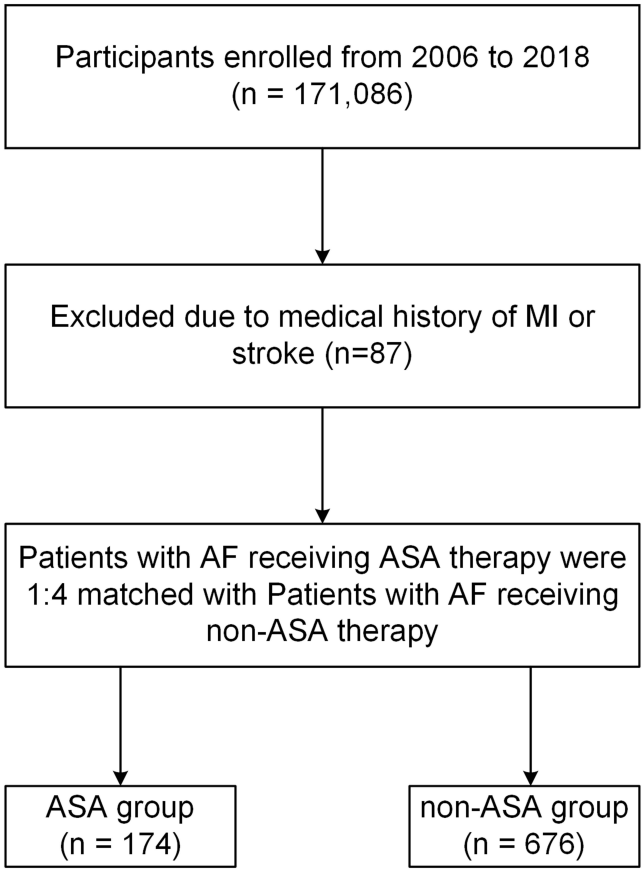

Figure 1 Flow chart of the prospective study.
Abbreviations: MI, myocardial infarction; ASA, aspirin; non-ASA, non-aspirin.

There is no difference between MACCE with ASA therapy as compared with non-ASA therapy in subgroups. However, it shows that the association between IS with ASA therapy was stronger in diabetes patients (HR: 2.442, 95% CI: 1.184–5.035) than nondiabetic patients (HR: 0.940, 95% CI: 0.522–1.693) (*P* for interaction = 0.037). Similarly, it

Table 1 Baseline Characteristics

Variables	Total (N=850)	Non-ASA (N=676)	ASA (N=174)	P value
Age, years	61.9±10.8	61.9±11.3	62.3±8.9	0.993
Male, n (%)	735 (86.47)	586 (86.69)	149 (85.63)	0.936
BMI, kg/m^2	25.88±3.83	25.83±3.89	26.08±3.59	0.750
SBP, mmHg	141.81±20.25	141.70±20.76	142.22±18.21	0.955
DBP, mmHg	84.87±12.02	84.93±11.78	84.61±12.92	0.951
FBG, mmol/l	6.36±2.02	6.32±1.99	6.50±2.16	0.599
TC, mmol/l	4.77±1.35	4.79±1.31	4.70±1.49	0.737
TG, mmol/l	1.33 (0.90–2.14)	1.33 (0.89–2.16)	1.32 (1.00–2.13)	0.714
HDL-C, mmol/l	1.25±0.31	1.25±0.31	1.24±0.28	0.999
LDL-C, mmol/l	2.81±0.83	2.80±0.82	2.86±0.86	0.653
hs-CRP, mg/l	1.10 (0.42–3.00)	1.05 (0.43–3.05)	1.20 (0.41–3.00)	0.999
Hypertension, n (%)	718 (84.47)	570 (84.32)	148 (85.06)	0.972
Diabetes, n (%)	239 (28.12)	189 (27.96)	50 (28.74)	0.980
Smoking, n (%)	218 (25.65)	165 (24.41)	53 (30.46)	0.265
Drinking, n (%)	64 (7.53)	47 (6.95)	17 (9.77)	0.454

Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; TC, total cholesterol; TG, triglyceride; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein.

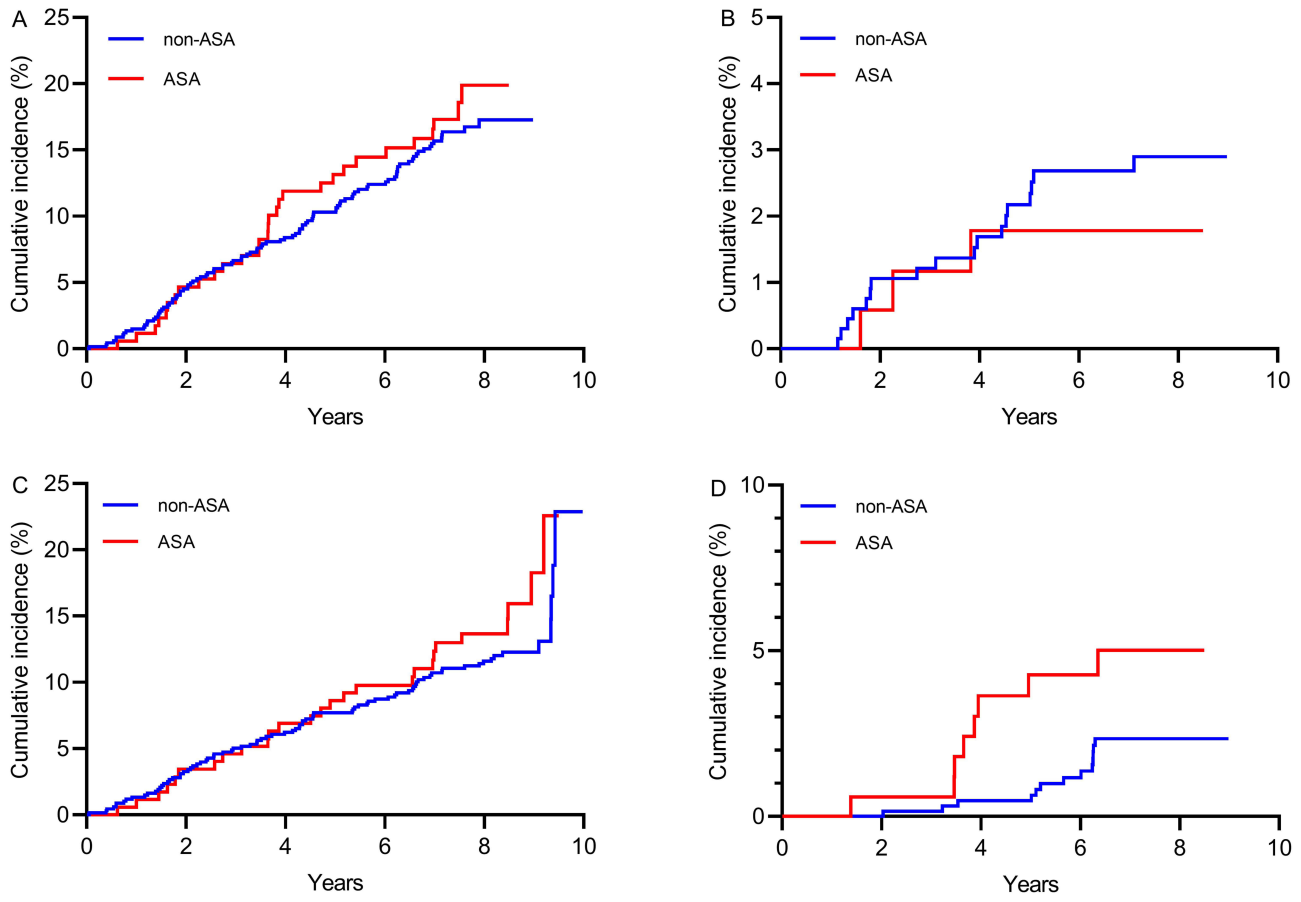

Figure 2 Cumulative incidence of (**A**) MACCE, (**B**) MI, (**C**) IS, (**D**) HS.
Abbreviations: MACCE, major cardiovascular and cerebrovascular events; MI, myocardial infarction; IS, ischemic stroke; HS, hemorrhagic stroke.

shows that the association between HS with ASA therapy was stronger in diabetes patients (HR: 6.857, 95% CI: 1.686–27.885) than nondiabetic patients (HR: 0.845, 95% CI: 0.158–4.513) (*P* for interaction = 0.045) (Table 3).

Discussion

Here, the results of our current study showed that there is no difference in the cumulative incidence of MACCE between the ASA therapy group and the non-ASA therapy group. ASA monotherapy is not significantly associated with MI and IS, but it is significantly associated with HS. Patients with AF are unlikely to benefit from ASA monotherapy.

In consist with our results, many studies suggested that ASA therapy is significantly associated with a higher risk of bleeding events, while without a lower risk of ischemic events in patients with AF. Here, Sato et al sought the efficacy of ASA for low-risk patients of AF, the superiority of ASA for prevention of primary end events (cardiovascular death, symptomatic brain infarction, or transient ischemic attack) was not confirmed. In addition, the risk of major bleeding in the ASA group was significantly higher than in the control group.[12] Dewilde et al investigated the efficacy and safety of clopidogrel alone compared with clopidogrel plus ASA in patients undergoing percutaneous coronary intervention and receiving oral anticoagulants. Their results showed that clopidogrel plus ASA significantly increased bleeding complications compared with clopidogrel alone.[13]

In addition, Steinberg et al reported that 35% of 10,126 AF patients received a concomitant oral anticoagulant agents (OAC) and ASA therapy, in which, 39% of patients had no history of atherosclerotic disease. More major bleeding events were recorded in patients receiving combined OAC and ASA therapy.[7] Lip et al demonstrated that the risks of stroke and bleeding events in low-risk patients are truly low. With 1 additional stroke risk factor, the event rates significantly increased in patients receiving anticoagulant therapy compared to patients without

Table 2 Cox Proportional Hazards Regression Analysis

	β	SE	χ2	P value	HR	95% CI
MACCE						
Model 1						
ASA	0.137	0.208	0.431	0.511	1.146	0.763–1.723
Model 2						
ASA	0.141	0.208	0.461	0.497	1.152	0.766–1.732
Gender (Male)	0.079	0.254	0.096	0.757	1.082	0.658–1.779
Age	0.045	0.009	26.566	<0.001	1.046	1.029–1.065
Model 3						
ASA	0.123	0.211	0.336	0.562	1.130	0.747–1.710
Gender (Male)	0.138	0.269	0.265	0.607	1.148	0.678–1.944
Age	0.039	0.010	13.815	<0.001	1.040	1.018–1.061
MI						
Model 1						
ASA	−0.454	0.624	0.529	0.467	0.635	0.187–2.157
Model 2						
ASA	−0.455	0.624	0.531	0.466	0.635	0.187–2.155
Gender (Male)	0.452	0.744	0.369	0.544	1.571	0.366–6.746
Age	0.033	0.021	2.381	0.123	1.034	0.991–1.078
Model 3						
ASA	−0.585	0.635	0.851	0.356	0.557	0.161–1.931
Gender (Male)	0.565	0.779	0.527	0.468	1.760	0.383–8.098
Age	0.010	0.026	0.139	0.709	1.010	0.960–1.062
IS						
Model 1						
ASA	0.226	0.221	1.047	0.306	1.254	0.813–1.935
Model 2						
ASA	0.245	0.222	1.225	0.269	1.278	0.828–1.973
Gender (Male)	−0.022	0.270	0.007	0.934	0.978	0.576–1.661
Age	0.042	0.009	20.703	<0.001	1.043	1.024–1.063
Model 3						
ASA	0.269	0.225	1.435	0.231	1.309	0.843–2.034
Gender (Male)	0.124	0.290	0.184	0.668	1.133	0.642–1.999
Age	0.040	0.011	13.176	<0.001	1.040	1.018–1.063
HS						
Model 1						
ASA	0.873	0.449	3.772	0.052	2.393	0.992–5.775
Model 2						
ASA	0.870	0.450	3.747	0.053	2.387	0.989–5.761
Gender (Male)	−0.843	0.483	3.039	0.081	0.431	0.167–1.111
Age	0.025	0.023	1.267	0.260	1.026	0.981–1.072
Model 3						
ASA	0.941	0.468	4.040	0.044	2.563	1.024–6.418
Gender (Male)	−1.049	0.561	3.489	0.062	0.350	0.117–1.053
Age	−0.007	0.030	0.055	0.815	0.993	0.935–1.054

Notes: Model 1 was a univariate model. Model 2 was adjusted for age and gender. Model 3 was adjusted for age, gender, BMI, SBP, DBP, FBG, TC, TG, HDL-C, LDL-C, hs-CRP, history of hypertension, history of diabetes, smoking status, drinking status.

Abbreviations: ASA, aspirin; MI, myocardial infarction; IS, ischemic infarction; HS, hemorrhagic stroke.

anticoagulation therapy. The superiority of the ASA treatment versus no treatment for the prevention of stroke was not confirmed in this study. Whereas, the bleeding events significantly increased in the ASA group versus no treatment. Furthermore, the stroke and death events were reduced in the warfarin group compared to the ASA or

Table 3 Relative Risks for Various Subgroups

	Total/Events	P value	HR	95% CI	P for Interaction
MACCE					
Age					0.958
≥60	520/106	0.725	0.918	0.572–1.475	
<60	330/25	0.138	2.022	0.798–5.118	
Gender					0.864
Male	735/113	0.540	1.150	0.736–1.796	
Female	115/28	0.922	0.941	0.280–3.166	
BMI					0.618
BMI≥28	210/47	0.941	1.028	0.495–2.134	
BMI<28	640/84	0.565	1.165	0.693–1.961	
Hypertension					0.312
Yes	718/123	0.389	1.204	0.789–1.837	
No	132/8	0.182	0.059	0.001–3.756	
Diabetes					0.107
Yes	239/51	0.098	1.719	0.906–3.264	
No	611/80	0.714	0.899	0.509–1.589	
MI					
Age					0.717
≥60	520/17	0.332	0.469	0.102–2.161	
<60	330/4	–	–	–	
Gender					–
Male	735/19	0.528	0.669	0.192–2.328	
Female	115/2				
BMI					0.977
BMI≥28	210/7	0.767	0.705	0.070–7.075	
BMI<28	640/14	0.417	0.497	0.092–2.689	
Hypertension					0.990
Yes	718/19	0.548	0.680	0.193–2.396	
No	132/2				
Diabetes					0.991
Yes	239/13	0.696	0.720	0.139–3.736	
No	611/8	0.965	1.051	0.115–0.961	
IS					
Age					0.756
≥60	520/90	0.835	1.055	0.639–1.740	
<60	330/21	0.206	1.931	0.697–5.352	
Gender					0.521
Male	735/95	0.274	1.306	0.810–2.106	
Female	115/16	0.590	1.421	0.395–5.113	
BMI					0.653
BMI≥28	210/40	0.593	1.241	0.563–2.733	
BMI<28	640/71	0.341	1.307	0.753–2.270	
Hypertension					0.463
Yes	718/105	0.173	1.367	0.872–2.144	
No	132/6	0.247	0.097	0.002–5.029	
Diabetes					0.037
Yes	239/38	0.016	2.442	1.184–5.035	
No	611/73	0.836	0.940	0.522–1.693	

(*Continued*)

Table 3 (Continued).

	Total/Events	P value	HR	95% CI	P for Interaction
HS					
Age					0.098
≥60	520/16	0.972	0.978	0.284–3.362	
<60	330/5	–	–	–	
Gender					0.281
Male	735/15	0.106	2.441	0.827–7.211	
Female	115/6	0.106	6.114	0.681–54.921	
BMI					0.978
BMI≥28	210/8	0.271	2.549	0.481–13.499	
BMI<28	640/13	0.182	2.261	0.682–7.503	
Hypertension					1.000
Yes	718/21	0.044	2.563	1.024–6.418	
No	132/0	–	–	–	
Diabetes					0.045
Yes	239/11	0.007	6.857	1.686–27.885	
No	611/10	0.843	0.845	0.158–4.513	

Abbreviations: ASA, aspirin; MI, myocardial infarction; IS, ischemic infarction; HS, hemorrhagic stroke.

no treatment group, while the bleeding events showed no significant difference between warfarin and ASA.[14] Flaker et al investigated the efficacy and safety of combining ASA and anticoagulant therapy in patients with AF, their results showed that the combination of ASA and anticoagulant therapy was not associated with any reduction in stroke, systemic embolism, or MI compared to anticoagulant therapy alone. In contrast, a combination of ASA and warfarin was associated with an increase in major bleeding events.[15] Hansen et al demonstrated that triple therapy of warfarin, ASA, and clopidogrel is associated with an increased risk of bleeding events, carrying a more than 3-fold higher risk of bleeding events than warfarin monotherapy.[16] In summary, concomitant anticoagulation and antiplatelet therapy are not suitable for AF patients without a recent cardiovascular event.[17]

Our study has several limitations. First, the ethnicity of people enrolled was Chinese Han, hence the results cannot apply to a general population. Second, the sample size is very limited. Third, patients were recruited consecutively, which may cause bias in research.

Conclusion

In summary, our study demonstrated that ASA therapy is significantly associated with a higher risk of bleeding events, while without a lower risk of ischemic events in patients with AF. Patients with atrial fibrillation are unlikely to benefit from aspirin monotherapy.

Data Sharing Statement

The original data are available from the corresponding author on reasonable request.

Statement of Ethics

The Kailuan study has been reviewed and approved by the ethics committee of Kailuan hospital (registration number in the Chinese clinical trial registry: ChiCTR-TNRC-11001489). An informed consent was obtained from the study participants. All procedures were performed in accordance with the declaration of Helsinki.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests in this work.

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