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ORIGINAL RESEARCH

Outcomes Associated with 50 mg/d and 100 mg/d Aspirin for the Prevention and Management of Cardiovascular Disease in Chinese Elderly: Single-Center Interim Analysis of a Multicenter, Prospective, Observational Study

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Purpose: Although aspirin can effectively reduce the occurrence of atherothrombosis, it is significantly associated with increased bleeding, with elderly individuals being at increased risk of cardiovascular diseases (CVD) and hemorrhage. This study aims to evaluate the efficacy and safety of aspirin 50 mg/d and 100 mg/d for the prevention and management of CVD in Chinese elderly.

Patients and Methods: The Low-dose Aspirin for Primary and Secondary Prevention of Cardiovascular Disease in the Elderly Study (LAPIS) is a multicenter, prospective, observational cohort study, this study was a single-center interim analysis of LAPIS. Patients aged ≥60 and required long-term aspirin for primary and secondary prevention of CVD were eligible. From Apr 1, 2019 to Feb 28, 2022, 165 patients who received 50 mg/d aspirin and 261 patients who received 100 mg/d aspirin were included in the study. The incidence of major cardiovascular events (MACEs), bleeding events, and gastrointestinal adverse events were compared between two groups.

Results: After adjusting for patient characteristics using propensity score matching, aspirin 100 mg/d was associated with increased incidence rates of total bleeding events (28.34 vs.17.25 events/100 patient-years, HR 1.671, 95% CI 1.024–2.712, P = 0.040) and minor bleeding events (27.63 vs.15.92 events/100 patient-years, HR 1.738, 95% CI 1.056–2.861, P = 0.031), whereas the incidence of MACE (6.35 vs 6.65 events/100 patient-years, HR 0.921, 95% CI 0.399–2.127, P = 0.848) and gastrointestinal adverse events (12.73 vs.10.42 events/100 patient-years, HR 1.206, 95% CI 0.623–2.337, P = 0.578) were similar between the two groups. Multivariate Cox analysis identified that aspirin dose (100 mg/d vs. 50 mg/d, HR 1.918, 95% CI 1.137–3.235, P = 0.015), concomitant use of other antiplatelets (HR 1.748, 95% CI 1.009–3.028, P = 0.046) and anticoagulants (HR 2.501, 95% CI 1.287–4.862, P = 0.007) were independently associated with bleeding events.

Conclusion: 50 mg/d aspirin may be preferred to balance the safety and effectiveness in Chinese individuals over 60 years of age who need long-term aspirin for the prevention and management of CVD.

Trial Registration: ChiCTR1900021980 (chictr.org.cn). Registered on 19 March 2019.

Keywords: low-dose aspirin, effectiveness outcome, safety outcome, Chinese elderly

Introduction

In China, the elderly population over 60 years old reached 254 million in 2020, accounting for approximately 18.70% of the total population and resulting in a demographic transition toward an aging society. Cardiovascular disease (CVD) is the leading cause of disability and death in the elderly and has become an increasingly severe public health issue in China. According to the Report on Cardiovascular Health and Disease Burden in China: An Updated Summary 2020,[1]

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330 million people suffer from CVD, accounting for 43.81% of deaths in urban residents and 46.66% of deaths in rural residents. Therefore, prevention and management of CVD are a high priority for the elderly in China.

Platelet activation and aggregation are the primary causes of arterial thrombosis. Aspirin, being a platelet aggregation inhibitor, can effectively reduce the occurrence of atherothrombosis,[2,3] although it is associated with a high risk of bleeding.[4] In elderly individuals, the risk of atherothrombosis is higher and the potential benefits of aspirin may accordingly be greater than in younger individuals.

However, an elevated risk of bleeding has also been documented in the older population,[5] which may limit the use of aspirin in the clinic, especially for elderly individuals with severe kidney impairment, as well as polypharmacy, frailty, previous falls, and other complicated comorbidities.

Currently, the recommended aspirin dose in China for the primary and secondary prevention of CVD is 75–100 mg/d,[6] based primarily on research in the Caucasian population. However, an increasing number of physicians may prescribe aspirin at dosages lower than recommendations in real-world clinical practice due to a significant bleeding risk in specific patients. Therefore, given the aging population, it is of significant clinical and socioeconomic benefits to investigate the effective and safe dose of aspirin for Chinese elderly in the prevention and management of CVD.

Materials and Methods

Study Design

The Low-dose Aspirin for Primary and Secondary Prevention of Cardiovascular Disease in the Elderly Study (LAPIS; chictr.org.cn, ChiCTR1900021980) was designed as a multicenter, prospective, observational cohort study that enrolled at least 10,000 Chinese elderly patients in real-world clinical practice with a 3-year follow-up to investigate the effectiveness and safety of 50 and 100 mg/d aspirin in the primary and secondary prevention of CVD. Patients were eligible if they matched the inclusion criteria, which comprised age ≥60 and required long-term aspirin for primary and secondary prevention of CVD. Critical exclusion criteria included a history of aspirin-sensitive asthma or allergies to aspirin, salicylic acid, or nonsteroidal anti-inflammatory medications. Patients with a life expectancy of ≤3 years were also excluded. The treating physicians determined the dosage and duration of aspirin medication. Participants were followed up at intervals of 30 days, 3 months, and 6 months and then every 6 months for the next 3 years (9 times). Outpatient/inpatient face-to-face or phone/WeChat visits were used for follow-up. All events were carefully checked and verified by an independent group of clinical physicians. Enrollment began in April 2019, and the final included patient will finish follow-up in April 2024.

In the current single-center interim analyses of the LAPIS study, we analyzed the effectiveness and safety outcomes in 426 patients recruited from Peking University First Hospital between Apr 1, 2019 and Feb 28, 2022, comparing those who received underdosed aspirin (50 mg/d) to those who received the recommended dose (100 mg/d).

Baseline Data Collection

Baseline and procedural data of all participants were collected into our database according to standard procedures. In the case report form (CRF), all essential information, including sociodemographic factors, personal and medical history, concomitant medications and routine laboratory testing in the past three months, was recorded in detail by independent clinical research coordinators. Current smoking was defined as regularly smoking one or more cigarettes daily for at least six months. Current drinking was defined as drinking once per week for at least six months. Patients without a history of coronary heart disease, stroke, transient ischemic attack (TIA), or peripheral artery disease (PAD), including aortic aneurysm, were defined as primary prevention. Gastrointestinal disease was defined as any self-reported history of reflux esophagitis, erosive gastritis, or gastric or duodenal ulcers. Hemorrhage history was defined as a history of any site and severity of bleeding events.

Effectiveness and Safety Outcomes

The effectiveness outcome was a composite of the first occurrence of major cardiovascular events (MACE), including nonfatal myocardial infarction, unstable angina, arteriosclerotic disease requiring surgery or intervention, nonfatal stroke,

transient ischemic attack, and cardiovascular death (excluding intracranial hemorrhage). The number of days from the date of enrollment to the confirmed date of the event was specified as the time to the event.

The safety outcome was the first occurrence of any bleeding event, which was defined as a composite of fatal bleeding (Bleeding Academic Research Consortium,[7] BARC, type 5), major bleeding (BARC, type 3–4), and minor bleeding (BARC, type 1–2). For safety analyses, data on the gastrointestinal adverse events associated with aspirin were collected as follows: new onsets of gastroduodenal ulcer, reflux esophagitis, erosive gastritis, stomach or abdominal discomfort, pain, or pressure, heartburn, and nausea.

Statistical Analysis

Data are presented as the mean ± standard deviation (SD) or median (interquartile range) for continuous variables and percentage (%) for categorical variables. Normally distributed continuous variables were compared using independent-samples T-tests. All categorical variables were compared using Pearson's χ^2 test or Fisher's exact test. Propensity score matching (PSM) with a 1:1 ratio was performed to adjust patient characteristics and enable direct comparison of outcomes between patients who received 100 mg/d aspirin and 50 mg/d aspirin. Propensity scores were estimated using logistic regression based on baseline characteristics which differed significantly between aspirin 50 mg/d and 100 mg/d groups, including age, sex, comorbidities such as prior cardiovascular disease (including primary prevention, coronary heart disease, myocardial infarction history, percutaneous coronary intervention/coronary artery bypass grafting history and unstable angina pectoris history), dyslipidemia, gastrointestinal disease (including current drinking, gastrointestinal disease) and hemorrhage history, concomitant medication (including prior use of aspirin, concomitant use of other antiplatelets and anticoagulants, β-blocker and proton pump inhibitors/histamine 2 receptor antagonist), and laboratory indication (low density lipoprotein cholesterol). Events are presented as both raw incidence proportions (patients with events/number of treated patients) and incidence rates (patients with events per 100 patient-years). Kaplan–Meier survival curves were generated and the Log rank test was used to assess for differences between the curves. Multivariate Cox proportional hazards models were developed to identify the independent predictors of bleeding events after adjusting for the variables that were known to be strongly associated with the risk of bleeding events or differed significantly by univariate analysis. Hazard ratio (HRs) and 95% confidence interval (CIs) were calculated. All P-values were 2-sided, and $P < 0.05$ was considered significant for all tests. Statistical analysis was performed using IBM SPSS Statistics version 23.0 (IBM, Armonk, NY, USA) software.

Ethical Approval

The LAPIS study protocol was approved by the institutional ethics committee (Peking University First Hospital, approval number 2018(248)) and was conducted in accordance with the Helsinki Declaration. Each participant signed a written informed consent form.

Results

Patient Characteristics

Of the 426 patients who participated in this study, 261 (61.27%) received 100 mg/d aspirin, among which 122 patients were concomitantly using other antiplatelet medications (91 clopidogrel, 31 ticagrelor) and 20 patients were concomitantly using anticoagulants (18 rivaroxaban, 2 dabigatran). A total of 165 (38.73%) patients received 50 mg/d aspirin, among which 40 patients were concomitantly using other antiplatelet medications (36 clopidogrel, 3 ticagrelor, and 1 cilostazol) and 29 patients were concomitantly using anticoagulants concurrently (2 edoxaban, 22 rivaroxaban, and 5 dabigatran). The study flow diagram is displayed in Figure 1, and the characteristics of the patients are detailed in Table 1. Patients who received 50 mg/d aspirin were significantly older and more likely to be female, had higher rates of gastrointestinal disease and hemorrhage history, and were more likely to use acid suppressants and anticoagulant medicines concurrently than those who received 100 mg/d aspirin. Patients who received 100 mg/d aspirin had higher rates of baseline cardiovascular comorbidities, including coronary heart disease, dyslipidemia, history of myocardial infarction, percutaneous coronary intervention/coronary artery bypass grafting (PCI/CABG), and unstable angina

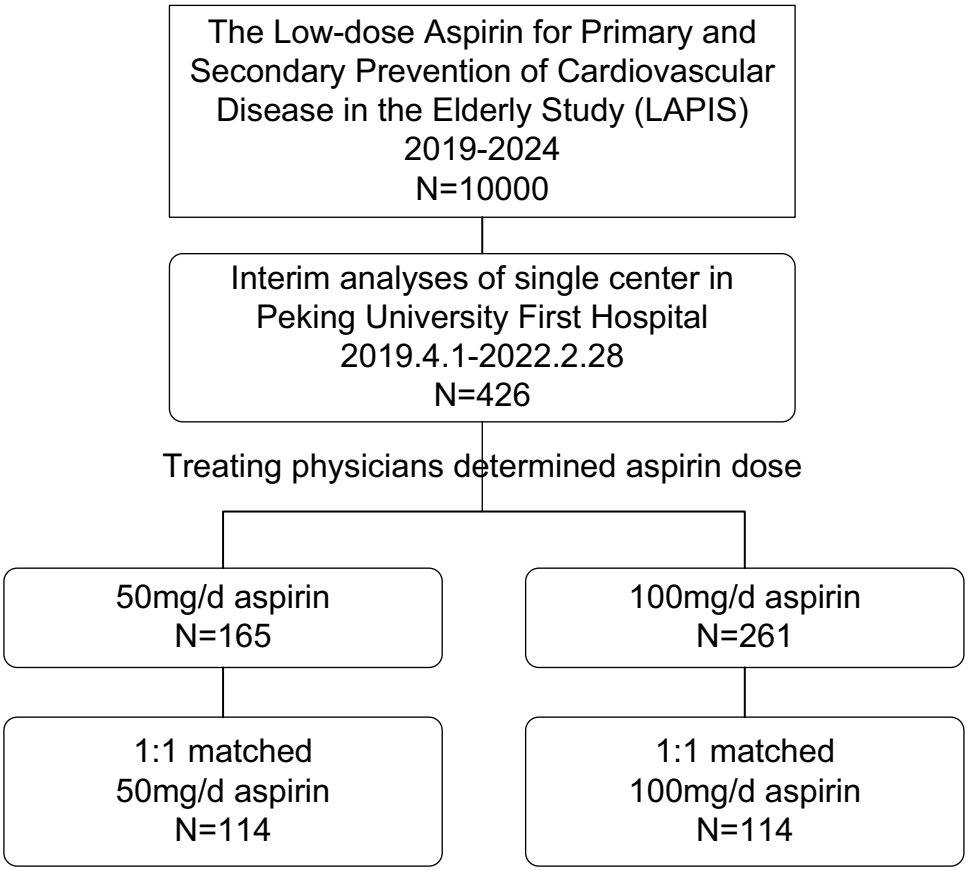

Figure 1 Study flow diagram displaying the process of cohort identification and matching.

pectoris, and were more likely to utilize dual antiplatelet medication concurrently. After adjustment, no statistical significance of the patients' characteristics was observed between the two groups.

Follow-Up

After a median of 691.0 days (interquartile range: 337.5, 745.0 days) of follow-up in all 426 patients without any lost, new-onset MACE occurred in 48 (11.27%) patients, bleeding events occurred in 101 (23.71%) patients, gastrointestinal adverse events occurred in 67 (15.73%) patients, and there were 13 (3.05%) deaths. Acute heart failure (1 case), sudden cardiac death (2 cases), fatal myocardial infarction (1 case), cerebral hemorrhage (1 case), stroke (1 case), malignant tumor (3 cases), septic shock (2 cases), multiple organ failure (1 case) and asphyxiation while eating (1 case) were the reasons for death. The median follow-up period for patients who received 50 mg/d aspirin was 519.0 days (interquartile range: 202.0, 742.0 days), which was significantly shorter than the median follow-up period of the 100 mg/d aspirin group (727.0 days, interquartile range: 377.0, 751.5 days, P = 0.007). After PSM adjustment, the median follow-up period was similar in both groups (696.0 days for 50 mg/d aspirin vs 701.0 days for 100 mg/d aspirin, P = 0.879). In AA-Ag, there was no statistically significant difference between the two groups before and after PSM adjustment, as demonstrated in Table 2.

Effectiveness Outcomes

After adjustment, there was no significant difference in the incidence rate of MACEs between patients who received 100 mg/d aspirin and those who received 50 mg/d aspirin (6.35 vs. 6.65 events/100 patient-years, HR 0.921, 95% CI 0.399–2.127, P = 0.848, Table 3). The incidence rates of unstable angina pectoris (events/100 patient-years, 2.89% for 100 mg/d aspirin vs. 1.81% for 50 mg/d aspirin; HR 1.562, 95% CI 0.373–6.544, P = 0.542), nonfatal myocardial infarction (events/100 patient-years, 0.58% for 100 mg/d aspirin vs. 1.21% for 50 mg/d aspirin; HR 0.464, 95% CI

Table 1 Baseline Characteristics for Patients Receiving 50 mg/d Aspirin and 100 mg/d Aspirin Before and After PSM Adjustment

Characteristic	Before PSM Adjustment			After PSM Adjustment		
	Aspirin 50mg/d	Aspirin 100mg/d	P	Aspirin 50mg/d	Aspirin 100mg/d	P
Number of patients	165	261		114	114	
Demographics						
Age, years	77.84±9.11	73.31±8.23	<0.001*	76.77±9,36	75.44±8.10	0.251
≥75	101(61.21%)	113(43.30%)	<0.001*	65(57.02%)	65(57.02%)	1.000
Male,n(%)	128(77.58%)	231(88.51%)	0.002*	89(78.07%)	98(85.96%)	0.121
Current smoking,n(%)	15(9.09%)	34(13.03%)	0.139	11(9.65%)	10(8.77%)	0.819
Current drinking,n(%)	29(17.58%)	71(27.20%)	0.014*	22(19.30%)	22(19.30%)	1.000
Medical history						
Primary prevention,n(%)	28(16.70%)	9(3.45%)	<0.001*	10(8.77%)	8(7.02%)	0.623
CHD,n(%)	135(81.82%)	250(95.79%)	<0.001*	104(91.23%)	104(91.23%)	1.000
MI history,n(%)	26(15.76%)	71(27.20%)	0.004*	20(17.54%)	22(19.30%)	0.733
PCI/CABG history,n(%)	68(41.21%)	155(59.39%)	<0.001*	56(49.12%)	52(45.61%)	0.596
UA history,n(%)	32(19.39%)	89(34.10%)	0.001*	30(26.32%)	25(21.93%)	0.439
Stroke history,n(%)	18(10.91%)	21(8.05%)	0.204	11(9.65%)	12(10.53%)	0.826
TIA history,n(%)	5(3.03%)	7(2.68%)	0.526	3(2.63%)	5(4.39%)	0.722
Hypertension,n(%)	130(77.79%)	206(78.93%)	0.533	84(73.68%)	93(81.58%)	0.153
Diabetes Mellitus,n(%)	68(41.21%)	121(46.36%)	0.173	46(40.35%)	48(42.11%)	0.788
Dyslipidemia,n(%)	146(88.48%)	247(94.64%)	0.018*	104(91.23%)	106(92.98%)	0.623
Gastrointestinal disease,n(%)	106(64.24%)	125(47.89%)	0.001*	71(62.28%)	65(57.02%)	0.418
Hemorrhage history,n(%)	49(29.70%)	36(13.79%)	<0.001*	29(25.44%)	21(18.42%)	0.200
Concomitant medication						
Prior use of Aspirin	122(73.94%)	236(90.42%)	<0.001*	85(74.56%)	99(86.84%)	0.190
Concomitant use of other antiplatelets,n(%)	40(24.24%)	122(46.74%)	<0.001*	33(28.95%)	42(36.84%)	0.205
Concomitant use of anticoagulants,n(%)	29(17.58%)	20(7.66%)	0.008*	18(15.79%)	11(9.65%)	0.164
β-blocker,n(%)	96(58.18%)	186(71.26%)	0.004*	70(61.40%)	79(69.30%)	0.210
ACEI/ARB,n(%)	138(83.64%)	123(47.13%)	0.377	52(45.61%)	53(46.49%)	0.894
Statin,n(%)	40(26.5%)	60(25.0%)	0.742	103(90.35%)	104(91.22%)	0.819
PPI/H2RA,n(%)	23(13.94%)	20(7.66%)	0.028*	46(40.35%)	49(42.98%)	0.687
Laboratory indication						
AA-Ag(%)						
Not taking aspirin previously	77.41 (70.59,80.88)	74.15 (65.16,78.15)	0.125	75.91 (66.68,80.88)	73.99 (58.04,78.23)	0.060
Aspirin therapy before screening	6.03(4.39,7.89)	6.11(4.88,7.74)	0.566	5.46(4.22,7.80)	6.02(4.96,7.55)	0.274
HGB(g/L)	133.70±16.44	136.13±13.63	0.115	134.80±16.95	135.82±13.99	0.622
UA(μmol/L)	352.83±86.46	365.81±86.14	0.132	350.71±86.22	370.73±84.44	0.079
eGFR(mL/min.1.73m^2)	70.23±16.17	71.74±15.62	0.339	70.41±16.00	68.74±15.27	0.421
FBG(mmol/L)	5.98(5.19,7.07)	5.91(5.19,7.44)	0.761	5.93(5.16,6.99)	5.73(5.20,6.99)	0.889
TG(mmol/L)	1.22(0.89,1.71)	1.27(0.92,1.71)	0.756	1.22(0.89,1.71)	1.28(0.95,1.74)	0.540
TCHO(mmol/L)	3.63±0.79	3.51±0.77	0.134	3.58±0.75	3.66±0.85	0.456
LDL-C(mmol/L)	1.85(1.56,2.26)	1.80(1.47,2.07)	0.047*	1.84(1.56,2.22)	1.87(1.53,2.21)	0.935
HDL-C(mmol/L)	1.05(0.88,1.23)	1.05(0.89,1.26)	0.952	1.04(0.88,1.24)	1.06(0.90,1.26)	0.613
HbA1c(%)	6.00(5.70,6.60)	6.10(5.80,6.80)	0.068	6.00(5.70,6.70)	6.10(5.70,6.60)	0.621

Notes: Data are presented as mean±standard deviation or median (interquartile range) for continuous variables and percentage (%) for categorical variables. *P-value less than 5% was considered nominally statistically significant.

Abbreviations: PSM, propensity score matching; CHD, coronary heart disease; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; UA, unstable angina pectoris; TIA, transient Ischemic Attacks; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; PPI, proton pump inhibitors; H2RA, histamine 2 receptor antagonist; AA-Ag, arachidonic acid-induced platelet aggregation rate; HGB, hemoglobin; UA, uric acid; eGFR, estimated glomerular filtration rate; FBG, fasting blood-glucose; TG, triglyceride; TCHO, total cholesterol; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; HbA1C, glycosylated hemoglobin.

Table 2 AA-Ag of Patients Receiving 50mg/d and 100mg/d Aspirin Before and After PSM Adjustment

	Before PSM Adjustment			After PSM Adjustment		
	Aspirin 50mg/d	Aspirin 100mg/d	P	Aspirin 50mg/d	Aspirin 100mg/d	P
Overall population	7.17(5.77,8.84)	7.72(6.04,9.27)	0.111	7.15(5.74,8.80)	7.77(6.34,10.17)	0.124
MACE	7.26(6.15,10.15)	7.75(5.19,10.36)	0.831	7.26(6.15,10.15)	8.58(7.19,11.29)	0.627
Any bleeding events	7.11(5.56,8.53)	7.59(6.20,9.07)	0.252	7.13(5.79,8.53)	7.67(7.00,10.21)	0.066
Gastrointestinal adverse events	6.53(5.10,8.41)	7.13(5.31,8.58)	0.460	6.75(5.64,8.27)	7.57(6.09,10.12)	0.268

Note: Data are presented as median (interquartile range) for AA-Ag.
Abbreviations: AA-Ag, arachidonic acid-induced platelet aggregation rate; PSM, propensity score matching; MACE, major cardiovascular events.

0.042–5.132, P = 0.532), nonfatal stroke (events/100 patient-years, 0.58% for 100 mg/d aspirin vs. 1.21% for 50 mg/d aspirin; HR 0.438, 95% CI 0.040–4.831, P = 0.500), arteriosclerotic diseases requiring surgery or intervention (events/100 patient-years, 1.15% for 100 mg/d aspirin vs. 1.21% for 50 mg/d aspirin; HR 0.934, 95% CI 0.131–6.641, P = 0.946) and cardiovascular death (events/100 patient-years, 1.15% for 100 mg/d aspirin vs. 0.60% for 50 mg/d aspirin; HR 1.818, 95% CI 0.164–20.180, P = 0.626) were similar in participants between the two groups.

Safety Outcomes

Bleeding events occurred in 27 (16.36%) patients in the 50 mg/d aspirin group and 74 patients (28.35%) in the 100 mg/d aspirin group. Of these bleeding events, 3 (2.97%) had severe gastrointestinal bleeding (BRAC type 3–4), 1 (0.99%) had fatal intracranial hemorrhage (BRAC type 5), and 97 patients (96.04%) had minor bleeding events (BARC type 1–2), including hematuria, gingival bleeding, ecchymosis, epistaxis, fecal occult blood, hemoptysis, scleral hemorrhage, and bloody sputum. After adjustment, 100 mg/d aspirin resulted in a higher incidence rate of any bleeding event (28.34 vs. 17.25 events/100 patient-years, HR 1.671, 95% CI 1.024–2.712, P = 0.040). In terms of hemorrhage severity, 100 mg/d aspirin significantly increased the incidence rate of minor bleeding events (27.63 events/100 patient-years) vs. 15.92 events/100 patient-years for 50 mg/d aspirin (HR 1.738, 95% CI 1.056–2.861, P = 0.031, Table 3 and Figure 2). However, due to the low occurrence rate, no significant differences were observed in major bleeding or fatal bleeding between patients who received 50 mg/d and 100 mg/d aspirin. The analysis of gastrointestinal adverse events of interest revealed no significant difference in the incidence rate of gastrointestinal adverse events between the two groups (events/100 patient-years, 12.73% for 100 mg/d aspirin vs. 10.42% for 50 mg/d aspirin; HR 1.206, 95% CI 0.623–2.337, P = 0.578, Table 3).

The results from the univariate Cox analysis were as follows: age, aspirin dose, hemorrhage history, use of proton pump inhibitors/histamine 2 receptor antagonist (PPI/H2RA), and concomitant use of other antiplatelets and anticoagulants were associated with a higher bleeding risk. After adjusting for covariates, we found that aspirin dose (100 mg/d vs. 50 mg/d, HR 1.918, 95% CI 1.137–3.235, P = 0.015), concomitant use of other antiplatelets (HR 1.748, 95% CI 1.009–3.028, P = 0.046) and anticoagulants (HR 2.501, 95% CI 1.287–4.862, P = 0.007) were independent risk factors for bleeding events (Table 4).

Discussion

Aspirin has been widely used for primary and secondary prevention of CVD for decades. The benefit of low-dose aspirin (75–100 mg/d) in secondary prevention of CVD is well established; however, the role of low-dose aspirin in primary prevention is still being debated.[8] Clinical trials of JPPP,[9] ARRIVE,[10] ASCEND,[11] and ASPREE,[12] as well as a previous systematic review and meta-analysis,[13] have shown inconsistent cardiovascular outcomes, with potential benefits offset by increased bleeding risk. Elderly individuals, are at higher risks for both atherosclerotic thrombosis and bleeding when compared to the general population.[8] In addition, this clinical dilemma is further complicated in elderly individuals with severe kidney impairment, for whom the risks of atherosclerotic thrombosis are higher, and hemostasis may be deranged in light of uraemic dysfunction,[14] a more tailored strategy for aspirin use is needed. Therefore, it is of great clinical

Table 3 Effectiveness and Safety Outcomes Before and After PSM Adjusting for Baseline Patient Characteristics

	Before PSM Adjustment				After PSM Adjustment			
	No. of Patients with Event/No. of Treated Patients (Incidence Rate, Events/100 Patient-Years)		HR (95% CI) 100mg/d vs. 50mg/d	P	No. of Patients with Event/No. of Treated Patients (Incidence Rate, Events/100 Patient-Years)		HR (95% CI) 100mg/d vs. 50mg/d	*P*
	Aspirin 50mg/d (n=165)	Aspirin 100mg/d (n=261)			Aspirin 50mg/d (n=114)	Aspirin 100mg/d (n=114)		
Effectiveness outcomes								
MACE	11/165(6.24)	37/261(9.34)	1.773(0.904–3.478)	0.096	11/114(6.65)	11/114(6.35)	0.921(0.399–2.127)	0.848
UA	3/165(1.41)	16/261(4.04)	2.852(0.831–9.795)	0.096	3/114(1.81)	5/114(2.89)	1.562(0.373–6.544)	0.542
Nonfatal MI	2/165(0.94)	5/261(1.26)	1.375(0.266–7.102)	0.704	2/114(1.21)	1/114(0.58)	0.464(0.042–5.132)	0.532
Nonfatal stroke	2/165(0.94)	5/261(1.26)	1.250(0.242–6.452)	0.790	2/114(1.21)	1/114(0.58)	0.438(0.040–4.831)	0.500
Arteriosclerotic diseases requiring surgery or intervention	2/165(0.94)	7/261(1.77)	1.843(0.383–8.884)	0.446	2/114(1.21)	2/114(1.15)	0.934(0.131–6.641)	0.946
Cardiovascular death	1/165(0.47)	4/261(1.01)	2.017(0.225–18.067)	0.530	1/114(0.60)	2/114(1.15)	1.818(0.164–20.180)	0.626
TIA	1/165(0.47)	0	-	-	1/114(0.60)	0	-	-
Safety outcomes								
Any bleeding	27/165(13.53)	74/261(21.46)	1.620(1.042–2.518)	0.032*	26/114(17.25)	39/114(28.34)	1.671(1.024–2.712)	0.040*
Minor bleeding (BARC 1–2)	25/165(12.52)	72/261(20.88)	1.676(1.062–2.644)	0.027*	24/114(15.92)	38/114(27.63)	1.738(1.056–2.861)	0.031*
Major bleeding (BARC 3–4)	2/165(1.00)	1/261(0.29)	0.301(0.027–3.319)	0.327	2/114(1.33)	0	-	-
Fatal bleeding (BARC 5)	0	1/261(0.29)	-	-	0	1/114(0.73)	-	-
Gastrointestinal adverse events	21/165(10.71)	46/261(12.40)	1.166(0.695–1.958)	0.560	16/114(10.42)	20/114(12.73)	1.206(0.623–2.337)	0.578

Note: *P-value less than 5% was considered nominally statistically significant.

Abbreviations: PSM, propensity score matching; HR, hazard ratio; CI, confidence interval; MACE, major cardiovascular events; UA, unstable angina pectoris; MI, myocardial infarction; TIA, transient ischemic attacks; BARC, Bleeding Academic Research Consortium.

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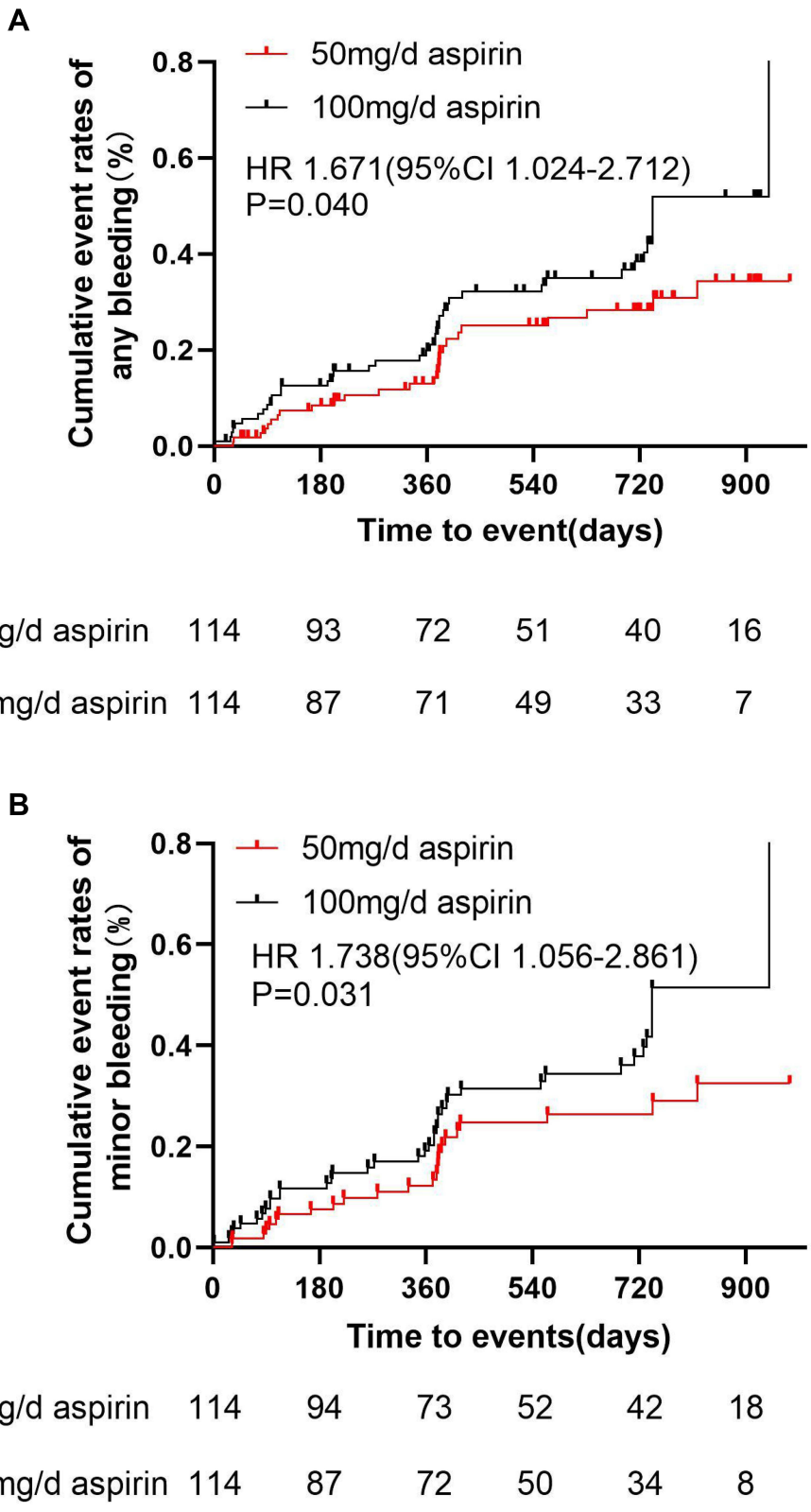

Figure 2 Cumulative event rates of (**A**) any bleeding and (**B**) minor bleeding in patients who received 100 mg/d aspirin versus patients who received 50 mg/d aspirin.
Abbreviations: CI, confidence interval; HR, hazard ratio.

Table 4 Features Associated with Bleeding Events by Univariate and Multivariate Cox Analysis

	Univariate Cox Analysis		Multivariate Cox Analysis	
	HR (95% CI)	P	HR (95% CI)	P
Sex(male vs female)	0.835(0.425–1.640)	0.835		
Age(years)	1.030(0.999–1.061)	0.055	1.022(0.988–1.056)	0.204
Aspirin dose(100mg/d vs.50mg/d)	1.671(1.024–2.712)	0.040*	1.918(1.137–3.235)	0.015*
Diabetes Mellitus(yes vs. no)	0.842(0.510–1.388)	0.500		
Hypertension(yes vs. no)	1.707(0.868–3.355)	0.121		
Gastrointestinal disease(yes vs. no)	1.316(0.791–2.189)	0.290		
Hemorrhage history(yes vs. no)	1.732(1.034–2.900)	0.037*	1.614(0.937–2.780)	0.084
Current smoking(yes vs. no)	1.175(0.506–2.725)	0.708		
Current drinking(yes vs. no)	0.615(0.293–1.290)	0.198		
β-blocker(yes vs. no)	1.407(0.808–2.451)	0.228		
ACEI/ARB(yes vs. no)	0.950(0.579–1.557)	0.838		
Statin(yes vs. no)	1.144(0.415–3.152)	0.795		
PPI/H2RA(yes vs. no)	1.941(1.189–3.169)	0.008*	1.319(0.783–2.220)	0.298
Concomitant use of other antiplatelets(yes vs. no)	1.620(0.985–2.665)	0.057	1.748(1.009–3.028)	0.046*
Concomitant use of anticoagulants(yes vs. no)	2.514(1.425–4.434)	0.001*	2.501(1.287–4.862)	0.007*

Note: *P-value less than 5% was considered nominally statistically significant.
Abbreviations: HR, hazard ratio; CI, confidence interval; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; PPI, proton pump inhibitors; H2RA, histamine 2 receptor antagonist.

significance and socioeconomic value to establish a more accurate, individual, real-world-based assessment model and investigate the effective and safe dose of aspirin for elderly individuals in China.

The LAPIS study was designed as a multicenter, prospective, observational study to assess the efficacy and safety of 50 mg/d and 100 mg/d aspirin in the primary and secondary prevention of CVD in Chinese elderly individuals. The decision of aspirin dosage for each participant is left to the discretion of clinicians. In this interim analysis of Peking University First Hospital, the obtained data may, to some extent, reflect the real-world decision-making tendency of clinicians to utilize aspirin for antiplatelet therapy in elderly individuals. To balance the efficacy and safety of antithrombotic therapy for elderly patients, lower-dose aspirin (50 mg/d) is used more frequently in clinical applications for populations at high risk of bleeding, such as those with higher age, females, patients with a history of gastrointestinal diseases and bleeding, and those who require concomitant anticoagulant therapy. In comparison, aspirin at a recommended dose (100 mg/d) is preferable for patients with high cardiovascular risks, such as those with CVD, previous coronary events, alcohol consumption, dyslipidemia, and those requiring concomitant use of antiplatelet therapy. After propensity score matching for baseline data, the incidence rates of MACE, nonfatal myocardial infarction, unstable angina pectoris, vascular diseases requiring surgery or intervention, nonfatal stroke, and cardiovascular death (excluding intracranial hemorrhage) in the 100 mg/d aspirin group were similar to those in the 50 mg/d aspirin group. Meanwhile, in elderly individuals, aspirin could significantly inhibit AA-Ag independent of the dose used, which was also independent of the occurrence of MACE event, suggesting that aspirin at 50 mg/d could achieve an antithrombotic effect similar to a dosage of 100 mg/d.

Aspirin-related bleeding is the focus of clinical attention. Consistent with the findings of previous studies, overall bleeding events occurred in 23.71% of all recruited participants in the present study, including patients on aspirin monotherapy and concomitant use of antiplatelet and anticoagulant medication. The bleeding risk associated with aspirin has been shown to increase with age and aspirin dose.[15,16] It was reported that 20–40 mg/d aspirin could effectively block the synthesis of thromboxane A2 (TXA2) and exert irreversible platelet inhibition,[17] and the adverse effects of aspirin therapy can be minimized by using the lowest effective dose.[18] Furthermore, the risk of bleeding increased when aspirin was combined with other antithrombotic agents.[19,20] In real-world clinical practice, many physicians remain reluctant to prescribe a standard dose of aspirin to older patients due to risk factors for bleeding in this patient group. The present

study extended these findings by demonstrating that after propensity score matching for baseline characteristics, the incidence rates of any bleeding events (28.34 vs. 17.25 events/100 patient-years, HR 1.671, 95% CI 1.024–2.712, P = 0.040) and minor bleeding events (27.63 vs. 15.92 events/100 patient-years, HR 1.738, 95% CI 1.056–2.861, P = 0.031) in the 100 mg/d aspirin group were considerably higher than that in the 50 mg/d aspirin group. However, due to the low incidence rates, there was no significant difference in major and fatal bleeding events between patients who received 50 mg/d aspirin and 100 mg/d aspirin. In the present study, multivariate analysis identified that both aspirin dose and concomitant use of other antiplatelets or anticoagulants were associated with a higher bleeding risk. Compared to the 50 mg/d aspirin group, those who received 100 mg/d aspirin had a 92% higher risk of bleeding events. Furthermore, there was no significant difference in AA-Ag levels between groups at different aspirin dosages. It is believed that lower-dose aspirin could effectively reduce the risk of bleeding and has higher safety in elderly individuals, particularly in individuals at high risk of bleeding, which is in line with previous studies.[21,22] Additionally, lower-dose aspirin means a lower price, which may relieve the pharmacoeconomic burden in China. However, this study was conducted in elderly Chinese individuals with a relatively high risk for bleeding, limiting extrapolation of current findings to nonelderly populations. Further research is needed to determine whether 50 mg/d aspirin is associated with a better net benefit than 100 mg/d aspirin in nonelderly individuals.

Aspirin decreases gastric mucosal prostaglandin levels and causes significant gastrointestinal mucosal damage,[23] furthermore, acid back diffusion and impaired platelet aggregation induce direct epithelial damage. It was reported that gastrointestinal adverse reactions were significantly more common than clinically overt bleeding in individuals on antiplatelet therapy.[24–26] Elderly age (aged >65 years), history of ulcer or upper gastrointestinal bleeding, *Helicobacter pylori* infection, aspirin dose, concomitant use of other antithrombotic medications, excessive smoking and drinking were all risk factors for aspirin-related gastrointestinal complications.[27] In the present study, gastrointestinal adverse reactions occurred in 15.73% of patients, with no significant differences between groups at different aspirin dosages, which may be related to the small sample size and bias. Further multivariate analysis revealed that the coexistence of gastrointestinal disease (HR = 3.751, 95% CI 1.990–7.069, P < 0.001) was an independent risk factor for the occurrence of gastrointestinal adverse events in elderly patients following aspirin administration. Understandably, patients with underlying gastrointestinal disease are more likely to be concerned about and report gastrointestinal symptoms. It is vital for patients with underlying gastrointestinal illnesses to thoroughly assess the risk of gastrointestinal injury while also implementing preventive measures.

The limitations of the study must be considered. First, it was a single-center interim analysis of the LAPIS study with a relatively short follow-up period. Due to the small sample size and short follow-up time, selection bias cannot be excluded, and the effectiveness and safety of aspirin in primary and secondary prevention were not analyzed separately. Second, most bleeding events were minor, and only 3 (0.70%) and 1 (0.23%) of 426 patients suffering from major and fatal bleeding events during follow-up, respectively, precluding the assessment of associations between severe clinical hemorrhage and aspirin dose. Third, to improve baseline data matching between the two groups of patients in our study, the approach of propensity score matching was utilized for multiple variables, resulting in the loss of some samples and endpoint events, which may have resulted in bias in this study. Fourth, due to the small sample size, the efficacy and safety of aspirin-plus-antithrombotic drugs were not independently assessed. Fifth, the median follow-up period for the 50 mg/d aspirin group was significantly shorter than that for the 100 mg/d aspirin group. Although the median follow-up period was similar in the two groups after PSM adjustment, bias could not be completely eliminated. Sixth, the renal function of patients participating in this study was relatively good, which may not be representative of a wider population that has other bleeding risk factors. Seventh, the majority of patients had taken aspirin already before participating in this study, which may have led to the underestimation of the incidence of bleeding events. Last, due to the unfavorable impact of the COVID-19 pandemic, it was inconvenient for some patients to visit the hospital for a face-to-face interview and could only be followed up by phone or WeChat, which may have influenced the reporting rate of endpoint events to some extent. More data from the larger multicenter clinical investigation of the LAPIS study are required to validate and expand on our findings.

Conclusion

Our findings may help determine the optimal evidence-based dose of aspirin therapy in Chinese elderly individuals. In this prospective study, we found that 50 mg/d aspirin achieved similar cardiovascular benefits but fewer bleeding events than 100 mg/d aspirin in Chinese individuals over 60 years of age. Given the need to evaluate all potential cardiovascular advantages against bleeding risks, cost, and other factors, aspirin at 50 mg/d may be more beneficial in balancing the efficacy and safety of antithrombotic therapy in Chinese elderly patients.

Data Sharing Statement

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

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 report no conflicts of interest in this work.

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